Gastroenterology 2020;158:111–122

Efficacy of Dupilumab in a Phase 2 Randomized Trial of Adults With Active Eosinophilic Esophagitis

Ikuo Hirano,[1,*] **Evan S. Dellon**,[2,*] Jennifer D. Hamilton,[3] Margaret H. Collins,[4] Kathryn Peterson,[5] Mirna Chehade,[6] Alain M. Schoepfer,[7] Ekaterina Safroneeva,[8] Marc E. Rothenberg,[4] Gary W. Falk,[9] Yehudith Assouline-Dayan,[10] Qiong Zhao,[3] Zhen Chen,[3] Brian N. Swanson,[11] Gianluca Pirozzi,[11] Leda Mannent,[12] Neil M. H. Graham,[3] Bolanle Akinlade,[3] Neil Stahl,[3] George D. Yancopoulos,[3] and Allen Radin[3]

[1]Northwestern University Feinberg School of Medicine, Chicago, Illinois; [2]Center for Esophageal Diseases and Swallowing, University of North Carolina School of Medicine, Chapel Hill, North Carolina; [3]Regeneron Pharmaceuticals, Inc, Tarrytown, New York; [4]Cincinnati Children's Hospital Medical Center and University of Cincinnati College of Medicine, Cincinnati, Ohio; [5]University of Utah School of Medicine, Salt Lake City, Utah; [6]Mount Sinai Center for Eosinophilic Disorders, Icahn School of Medicine at Mount Sinai, New York, New York; [7]Centre Hospitalier Universitaire Vaudois et Université de Lausanne, Lausanne, Switzerland; [8]Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland; [9]University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania; [10]University of Iowa Hospitals and Clinics, Iowa City, Iowa; [11]Sanofi, Bridgewater, New Jersey; and [12]Sanofi, Chilly-Mazarin, France

BACKGROUND & AIMS: Eosinophilic esophagitis (EoE) is an allergen-mediated inflammatory disease with no approved treatment in the United States. Dupilumab, a VelocImmune-derived human monoclonal antibody against the interleukin (IL) 4 receptor, inhibits IL4 and IL13 signaling. Dupilumab is effective in the treatment of allergic, atopic, and type 2 diseases, so we assessed its efficacy and safety in patients with EoE. **METHODS:** We performed a phase 2 study of adults with active EoE (2 episodes of dysphagia/week with peak esophageal eosinophil density of 15 or more eosinophils per high-power field), from May 12, 2015, through November 9, 2016, at 14 sites. Participants were randomly assigned to groups that received weekly subcutaneous injections of dupilumab (300 mg, n = 23) or placebo (n = 24) for 12 weeks. The primary endpoint was change from baseline to week 10 in Straumann Dysphagia Instrument (SDI) patient-reported outcome (PRO) score. We also assessed histologic features of EoE (peak esophageal intraepithelial eosinophil count and EoE histologic scores), endoscopically visualized features (endoscopic reference score), esophageal distensibility, and safety. **RESULTS:** The mean SDI PRO score was 6.4 when the study began. In the dupilumab group, SDI PRO 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 the peak esophageal intraepithelial eosinophil count by a mean 86.8 eosinophils per high-power field (reduction of 107.1%; $P < .0001$ vs placebo), the EoE-histologic scoring system (HSS) severity score by 68.3% ($P < .0001$ vs placebo), and the endoscopic reference score by 1.6 ($P = .0006$ vs placebo). Dupilumab increased esophageal distensibility by 18% vs placebo ($P < .0001$). Higher proportions of patients in the dupilumab group developed injection-site erythema (35% vs 8% in the placebo group) and nasopharyngitis (17% vs 4% in the placebo group). **CONCLUSIONS:** In a phase 2 trial of patients with active EoE, dupilumab reduced dysphagia, histologic features of disease (including eosinophilic infiltration and a marker of type 2 inflammation), and abnormal endoscopic features compared with placebo. Dupilumab increased esophageal distensibility and was generally well tolerated. ClinicalTrials.gov, Number: NCT02379052

Keywords: EREFS; HSS; Food Allergy; Esophagus.

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.[1,2]

Adult patients with EoE have substantially impaired quality of life due to, among other things, dysphagia and the risk of food impaction.[3] They have increased levels of esophageal inflammatory infiltrates, including eosinophils, T cells, mast cells, and basophils, as well as type 2–associated inflammatory chemokines and cytokines, including eotaxin 3, interleukin (IL) 4, IL5, and IL13.[4,5] Chronic esophageal inflammation leads to remodeling, stricture formation, and fibrosis, with commensurate worsening of dysphagia.[6–8] Patients with EoE show a marked reduction in esophageal

***Authors share co-first authorship.**

Abbreviations used in this paper: **ANCOVA, analysis of covariance; CI, confidence interval; EEsAI, Eosinophilic Esophagitis Activity Index; EoE, eosinophilic esophagitis; EoE-QOL-A, Adult Eosinophilic Esophagitis Quality of Life; eos/HPF, eosinophils per high-power field; EREFS, Endoscopic Reference Score; HSS, histology scoring system; IL, interleukin; LS, least squares; MedDRA, Medical Dictionary for Regulatory Activities; PPI, proton pump inhibitor; PRO, patient-reported outcome; SD, standard deviation; SDI, Straumann Dysphagia Instrument; TEAE, treatment-emergent adverse event.**

Most current article

0016-5085
https://doi.org/10.1053/j.gastro.2019.09.042

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Dupilumab, a monoclonal antibody against the interleukin 4 receptor, is effective in treatment of allergic, atopic, and type 2 diseases. We assessed its efficacy and safety in patients with eosinophilic esophagitis (EoE).

NEW FINDINGS

In a phase 2 trial of patients with active EoE, dupilumab reduced dysphagia, and histologic and endoscopic features of the disease compared with placebo. Dupilumab increased esophageal distensibility and was generally well tolerated.

LIMITATIONS

The study was small and of short duration (12 weeks). Further studies are required to determine the long-term efficacy and safety of dupilumab in treatment of EoE.

IMPACT

Dupilumab might be a new treatment approach for patients with EoE.

distensibility associated with adverse outcomes of food impaction and requirement for esophageal dilation.[9] The pooled incidence rate of EoE in a meta-analysis of 13 population-based studies from North America, Europe, and Australia on the epidemiology of EoE in adults and children was 3.7/100,000 persons/year, and the pooled prevalence was 22.7/100,000 inhabitants.[10] In the United States, the prevalence of EoE in adults ranges from 40 to 90 cases per 100,000 persons.[11]

The current standard of care for EoE consists of food-elimination diets, off-label use of swallowed topical corticosteroids, high-dose proton pump inhibitor (PPI) therapy in PPI-responsive phenotypes, and esophageal dilation.[1] However, these therapies can be limited by variable response rates, relapse after therapy cessation, and adverse effects on quality of life. These potential limitations highlight the need for new treatments targeting key pathways driving EoE inflammation.[12–14] To date, the US Food and Drug Administration has not approved pharmacologic therapies for EoE; the European Medicines Agency recently approved budesonide orodispersible tablets for the treatment of EoE in adults.[15]

Dupilumab is a fully human monoclonal antibody derived via VelocImmune (Regeneron Pharmaceuticals, Tarrytown, NY)[16,17] directed against the IL4 receptor-α component of the type 2 receptor, and it inhibits signaling of both IL4 and IL13.[18] The efficacy of dupilumab in several settings of allergic/atopic/type 2 disease shows that IL4 and IL13 are key initiators of type 2 inflammation. Dupilumab has shown efficacy in pediatric and adult atopic dermatitis,[19–22] asthma,[23–25] and chronic sinusitis with nasal polyposis,[26] and it is also being studied as an adjunct for peanut and grass allergy desensitization.[27] Therapeutics targeting IL5 have shown efficacy in asthma but have failed in other settings of allergic/atopic/type 2 disease, such as atopic dermatitis and EoE.[13,28,29] After observing the efficacy of dupilumab in multiple settings of allergic/atopic/type 2 diseases, we investigated the efficacy and safety of dupilumab vs placebo in adults with active EoE.

Methods

Study Design and Oversight

This was a multicenter, randomized, double-blind, parallel-group, placebo-controlled phase 2 study of dupilumab in adults with active EoE. The study was conducted between May 2015 and July 2017 at 14 study sites in the United States. The study consisted of a 35-day screening period, a 12-week randomized treatment period, and a 16-week post-treatment follow-up period (see Supplementary Figure 1). Efficacy was assessed based on clinical signs and symptoms evaluated using EoE-specific patient-reported outcome (PRO) measures and based on histologic and endoscopic findings, including distensibility assessment. Technical problems with the electronic diary used for collecting PROs resulted in data loss and required a change in the primary endpoint from week 12 to week 10; this amendment was made before unblinding and was included in both the study protocol and the statistical analysis plan. All other measures, including histologic endpoints, endoscopically visualized features, distensibility measures of esophageal function, and quality-of-life endpoints that were not captured electronically were evaluated at week 12.

The protocol (see Supplementary Appendix) was developed by the sponsors (Sanofi and Regeneron Pharmaceuticals). Data were collected by the investigators and analyzed by the sponsors. The study was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice guidelines, and applicable regulatory requirements. An independent data and safety monitoring committee conducted blinded monitoring of patient safety data. The local institutional review board or ethics committee at each study center oversaw trial conduct and documentation. All patients provided written informed consent before participating in the trial.

All authors had access to the study data and participated in the interpretation of the data. They each provided input and critical feedback to the drafting of the manuscript, approved the final manuscript, and take responsibility for the accuracy and completeness of the data and analyses. All investigators had confidentiality agreements with the sponsors, Sanofi and Regeneron Pharmaceuticals. The manuscript drafts were prepared with the assistance of a medical writer paid by the sponsors.

Patients

Adults (ages 18–65 years) with documented EoE who were nonresponsive to PPIs and were diagnosed in accordance with consensus guidelines[30] were eligible to participate. Active esophageal inflammation was to be evident at screening (ie, peak cell count $\geq$ 15 eosinophils per high-power field [eos/HPF]: $\times$400 magnification of a 0.3-mm^2 field) as indicated by esophageal pinch biopsy specimens from at least 2 of 3 esophageal sites from endoscopy performed no more than 2 weeks after at least 8 weeks of treatment with high-dose (or twice-daily dosed) PPIs. Patients were also required to have a

patient-reported history of an average of ≥2 episodes of dysphagia per week in the 4 weeks before screening, with a Straumann Dysphagia Instrument (SDI)[31] PRO score ≥ 5 at screening and baseline and a documented history or presence of ≥1 type 2 comorbid atopic disease. The presence of atopy was required because at the time of the study design, dupilumab had documented efficacy in atopic dermatitis, and so an EoE study population enriched for other type 2/allergic/atopic conditions was considered to be the most likely responsive population. No patients were excluded based on this criterion.

Key exclusion criteria included esophageal stricture unable to be passed with a standard adult upper endoscope, esophageal dilation required at screening, and use of systemic glucocorticoids <3 months or swallowed topical glucocorticoids <6 weeks before screening. Detailed inclusion and exclusion criteria are provided in the Supplementary Methods, "Patient Eligibility Criteria" section.

Treatment and Procedures

Patients were randomized 1:1 to receive weekly subcutaneous dupilumab 300 mg (loading dose, 600 mg on day 1) or matching placebo during the 12-week, double-blind treatment phase. Randomization, stratified by baseline SDI score (≥5 and ≤7 vs >7),[31] was conducted by using a central interactive voice/web response system. Study patients, principal investigators, central pathology review pathologists, and study site personnel remained blinded to all randomization assignments during the double-blind treatment period of the study. Blinded study drug kits coded with a medication numbering system were used, and lists linking these codes with product lot numbers were not accessible to individuals involved in study conduct. Patients were instructed not to modify their diets during the study. Patients could receive concomitant medications as needed at the investigator's discretion, except for those that were prohibited (Supplementary Methods, "Prohibited Concomitant Medications" section), while continuing study treatment. Patients using stable doses of PPIs at screening were permitted to continue the same dosing regimen until the end-of-treatment visit; those not using PPIs in the 8 weeks before screening were prohibited from starting them. If medically necessary, rescue medications or emergency esophageal dilation could be provided. Patients who received rescue therapy were discontinued from study treatment and considered nonresponders. Study assessments were performed weekly from weeks 1 to 12 and every 4 weeks during the 16-week follow-up.

Endpoints

The primary efficacy endpoint was the change in SDI PRO dysphagia score[31] from baseline to week 10. Secondary SDI PRO endpoints included percent change in SDI PRO score from baseline to week 10 and percentage of patients with an SDI PRO score decrease of ≥3 points relative to baseline at week 10, which was proposed by Straumann et al as evidence of a clinical response.[31] Other secondary endpoints, primarily evaluated at week 12, included histologic measures of type 2 inflammation in the esophagus (as measured by esophageal intraepithelial eosinophilia), endoscopically visualized anatomic measures of esophageal disease (ie, exudate, rings, edema, furrows, and strictures), distensibility measures of esophageal function, and additional PROs. These endpoints were assessed by measuring percent change in peak esophageal intraepithelial eos/HPF from baseline to week 12 and change in EoE Endoscopic Reference Scoring System (EREFS) score[6,32] from baseline to week 12.

Other secondary efficacy endpoints were percentage of patients requiring rescue medication or a procedure (eg, esophageal dilation) through week 12 and the PRO and quality-of-life endpoints of absolute and percent change in weekly Eosinophilic Esophagitis Activity Index (EEsAI) PRO score[33] from baseline to week 10, percentage of patients with ≥40% improvement[33] or ≥15- or ≥30-point improvement in EEsAI PRO score from baseline to week 10, and change in Adult Eosinophilic Esophagitis Quality of Life (EoE-QOL-A) score, version 3.0[34,35] from baseline to week 12. Symptomatic remission of EoE, defined as an EEsAI score of ≤20 at weeks 10 and 12, was also assessed in a post hoc analysis, as were the proportions of patients who achieved both histologic (<6 eos/HPF at week 12) and symptomatic remission (SDI score reduction of ≥3 points relative to baseline at week 10) and both histologic and endoscopic remission.[36] Safety was evaluated by incidence of treatment-emergent adverse events (TEAEs) and serious adverse events from baseline to week 28.

Exploratory histology endpoints were change in least squares (LS) mean peak esophageal intraepithelial eosinophil count (eos/HPF) (calculated by using peak counts from each esophageal site) from baseline to week 12, proportion of patients who achieved peak esophageal intraepithelial eosinophil count <1 eos/HPF at week 12, proportion of patients who achieved peak esophageal intraepithelial eosinophil count ≤6 eos/HPF[37] and <15 eos/HPF (post hoc analysis), and change in EoE histology scoring system (HSS) from baseline to week 12.[38] An exploratory endpoint was change in esophageal distensibility plateau, measured by functional luminal imaging probe (EndoFLIP; Medtronic, Minneapolis, MN),[39,40] from baseline to week 12.

The full list of protocol prespecified endpoints is provided in Supplementary Table 1.

Statistical Analysis

A sample size of 18 patients per treatment arm was calculated to provide 94% power to detect a clinically meaningful treatment effect, with an expected mean difference of a 3-point change from baseline to week 12 in SDI score between dupilumab and placebo in a 2-sided *t* test with 5% significance and an assumed standard deviation of 2.46.[31] An assumed 15% dropout rate meant that 22 patients should be enrolled per treatment arm. The primary and secondary efficacy endpoints were analyzed in the full analysis set, which included all randomized patients. The analysis was conducted by using multiple imputation for missing data, with an analysis of covariance (ANCOVA) model with treatment as a fixed effect and baseline SDI value and relevant baseline value as continuous covariates (only for secondary efficacy analysis). Because of a substantial imbalance at baseline in the number of patients in the 2 randomization strata (only 13% of patients in the stratum of baseline SDI > 7), the ANCOVA model did not use randomization strata as a factor but, instead, included baseline SDI value as a continuous covariate.

TEAEs were defined as any untoward medical occurrence during the treatment period. *Serious adverse events* were defined as any untoward medical occurrence that at any dose

resulted in death, was life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, or was an important medical event.

Categorical analyses were performed on responder data; comparisons between dupilumab and placebo used Fisher's exact test. Patients with early withdrawal or use of rescue medication or procedure were counted as nonresponders subsequent to the withdrawal or rescue.

All analyses were conducted with SAS software, version 9.4 (SAS Institute, Cary, NC). The full statistical methodology is summarized in the Supplementary Methods, "Statistical Analysis" section.

Results

Patients

Between May 12, 2015, and November 9, 2016, 80 patients were screened for study eligibility; of these, 47 (59%) were subsequently randomized (23 dupilumab, 24 placebo) at 14 study sites in the United States and received ≥1 dose of study medication (Supplementary Figure 2). Failing to meet eligibility criteria was the main reason for screening failure (32/33 patients [97%]), specifically, inadequate frequency of dysphagia, failure to meet histologic criteria, failure to meet stabilized diet for at least 6 weeks criterion, and failure to meet signing informed consent criterion; 1 patient withdrew consent. Baseline characteristics were generally well balanced between the groups, except for mean total immunoglobulin E (IgE), which was higher in the placebo group (Table 1 and Supplementary Table 2). Most patients (79% and 87% for the placebo and dupilumab groups, respectively) had ≥2 additional comorbid atopic diseases: 42% and 48%, respectively, had prior esophageal dilation, and 38% and 30% of placebo- and dupilumab-treated patients, respectively, had previously used oral or systemic glucocorticoids for their EoE treatment. Patients reported a history of an average ≥2 episodes of dysphagia per week in the 4 weeks before screening and in the time period between screening and baseline. In placebo- and dupilumab-treated patients, respectively, the mean (standard deviation [SD]) weekly baseline SDI PRO score was 6.4 (1.01) and 6.4 (1.04), mean (SD) baseline EREFS was 4.3 (1.46) and 3.9 (1.87), and mean (SD) baseline peak eosinophil count was 101.1 (57.12) and 102.1 (53.46) eos/HPF. The numbers of patients with missing values for the primary and secondary efficacy endpoints are provided in Supplementary Table 3.

Primary Outcome

As mentioned in the "Methods" section, technical problems with the electronic diary (identified before database lock) resulted in significant data loss by week 12 and necessitated assessment of the primary endpoint at week 10 rather than week 12. The number of patients with missing values for both the primary and secondary efficacy endpoints are provided in Supplementary Table 3. For completeness, an analysis of the primary endpoint is presented below for observed values only, with no imputation of missing data (ie, n = 14 of 24 placebo-treated patients and n = 17 of 23 dupilumab-treated patients).

At week 10, dupilumab significantly improved the SDI PRO score from baseline (LS mean change, −3.0 vs −1.3 for placebo; $P = .0304$) (Figure 1*A* and Table 2). In dupilumab-treated patients, improvements in SDI PRO scores were observed as early as week 1 (Supplementary Figure 3). This finding was supported by the analysis of the primary endpoint using observed values regardless of rescue treatment use, with no imputation of missing data. At week 10, dupilumab significantly improved the SDI PRO score from baseline (LS mean change, −3.2 vs −1.1 for placebo; $P = .0226$) (Supplementary Table 4).

Overall, the outcomes of the 3 prespecified sensitivity analyses, which include different imputation methods (ie, last observation carried forward and worst observation carried forward) and all observed values regardless of rescue treatment use, were similar to those of the primary analysis (Supplementary Table 5).

Secondary Straumann Dysphagia Instrument Patient-Reported Outcomes

At week 10, the LS mean percent change from baseline in SDI score was also significantly improved with dupilumab (−45.1 vs −18.6 for placebo; $P = .0312$) (Figure 1*B* and Table 2). Nine (39%) dupilumab-treated patients showed a reduction in SDI PRO score of ≥3 vs 3 (13%) patients in the placebo group at week 10: LS mean difference vs placebo, 26.6% (95% confidence interval [CI], −3.0 to 51.1); $P = .0490$ (Table 2).

Secondary Histology, Exploratory Histology, and Endoscopy Outcomes

Esophageal intraepithelial eosinophil counts relative to baseline were decreased at week 12 in all 23 (100%) dupilumab-treated patients (Supplementary Figure 4). Relative to placebo, the LS mean reduction from baseline to week 12 in peak esophageal intraepithelial eosinophil count was 86.8 eos/HPF (95% CI, −113.2 to −60.5; $P < .0001$) (Table 2 and Supplementary Figure 5). The LS mean (standard error) peak esophageal intraepithelial eosinophil count was reduced by 92.9% (12.1) in patients receiving dupilumab treatment and was increased by 14.2% (12.5) in patients receiving placebo ($P < .0001$ vs placebo). The proportions of dupilumab-treated patients with esophageal intraepithelial eosinophil counts of ≤6 eos/HPF and <15 eos/HPF vs placebo at week 12 were 65% vs 0% ($P < .0001$ vs placebo) and 83% vs 0% ($P < .0001$ vs placebo), respectively (Table 2 and Supplementary Figure 6). In dupilumab-treated patients, 13% had a response of <1 eos/HPF at week 12 vs 0% in the placebo arm ($P = .1092$ vs placebo).

Dupilumab treatment improved EoE-EREFS total scores by −1.6 (95% CI,−2.5 to −0.7; $P = .0006$) vs placebo at week 12 (Table 2 and Figure 1*C*).

Table 1. Demographics and Clinical Characteristics of the Patients at Baseline

Characteristics	Placebo (n = 24)	Dupilumab 300 mg weekly (n = 23)
Age, *y*, mean (SD)	36.1 (12.75)	33.1 (8.70)
Male sex, n (%)	10 (42)	13 (57)
White race, n (%)	21 (87.5)	23 (100)
Prior esophageal dilations, n, mean (SD)	3.9 (3.31)	5.7 (8.03)
Any prior use of a glucocorticoid for EoE, n (%)	9 (38)	7 (30)
Prior history of treatment with high-dose PPIs at baseline, n (%)	24 (100)	23 (100)
PPI treatment ongoing at baseline	15 (62.5)	14 (60.9)
Duration of eosinophilic esophagitis, *y*, mean (SD)	5.0 (3.33)	3.6 (3.74)
>1 comorbid atopic disease, n (%)	19 (79)	20 (87)
Food allergy[a]	17 (71)	14 (61)
Allergic rhinitis	15 (63)	16 (70)
Asthma	9 (38)	11 (48)
Chronic rhinosinusitis	8 (33)	2 (9)
Atopic dermatitis	5 (21)	3 (13)
Allergic conjunctivitis	3 (13)	3 (13)
Blood eosinophils × 10^9/L, mean (SD)	0.43 (0.29)	0.31 (0.18)
Total IgE, *kU/L*, mean (SD)	486.2 (900.7)	217.8 (288.8)
SDI PRO score (scale, 0−9), mean (SD)[b]	6.4 (1.0)	6.4 (1.0)
SDI PRO intensity score, mean (SD)	3.3 (0.46)	3.2 (0.39)
SDI PRO frequency score, mean (SD)	3.1 (0.93)	3.3 (0.86)
Peak esophageal eosinophil count of proximal, mid, and distal regions, *eos/HPF*, mean (SD)	101.1 (57.12)	102.1 (53.46)
Proximal eosinophil count	50.5 (47.16)	49.2 (45.76)
Mid eosinophil count	96.0 (59.73)	77.3 (41.67)
Distal eosinophil count	69.2 (33.10)	75.2 (59.62)
EoE-EREFS total score (scale, 0−8), mean (SD)[c]	4.3 (1.46)	3.9 (1.87)
EoE-HSS grade total score, mean (SD)[d]	27.6 (8.38)	28.5 (7.98)
EoE-HSS stage total score, mean (SD)[d]	27.4 (6.46)	27.9 (6.05)
Esophageal distensibility plateau, *mm*, mean (SD)	17.6 (2.88)	18.7 (3.80)
Weekly EEsAI PRO score (scale 0−100), mean (SD)[e]	62.2 (16.45)	62.0 (18.36)
EoE-QOL-A[f]	3.11 (0.995)	3.02 (0.899)

[a]The presence of food allergy was based on chart review and did not require formal allergy testing (see Supplementary Table 2 for breakdown). The specific foods queried would be expected to capture oral allergy syndrome (food-pollen syndrome) and not just food-related anaphylaxis.
[b]The SDI PRO total score is the sum of the scores of frequency of dysphagia and intensity of dysphagia; total score range, 0−9 (higher scores indicate worse symptoms). The minimal clinically important difference is 3.[30]
[c]The EoE-EREFS measures endoscopically identified EoE esophageal mucosal inflammatory and remodeling features; total scores for edema, rings, furrows, exudate, stricture range, 0−8 (higher scores indicate greater impairment).
[d]The EoE-HSS measures eosinophil density, basal zone hyperplasia, eosinophil abscesses, eosinophil surface layering, surface epithelial alteration, dyskeratotic epithelial cells, and dilated intercellular spaces; scale range, 0−63 (higher scores indicate more severe histologic findings).
[e]The EEsAI PRO is a 5-component (10-item) measure of dysphagia, swallowing-associated pain, and strategies aimed at avoiding dysphagia episodes; total score range, 0−100 (higher scores indicate worse symptoms).
[f]The EoE-QOL-A questionnaire includes 30 items related to 5 established domains (eating/diet impact, social impact, emotional impact, disease anxiety, and swallowing anxiety) of daily life experiences using a 5-point Likert-like scale. The EoE-QOL-A score is the average obtained by dividing the total score by the number of questions (for patients without disease, 120/30 = 4). Total scores range from 1 to 5.

Compared with placebo, dupilumab treatment led to a reduction in total EoE-HSS severity score (grade: LS mean percent change, −68.3; 95% CI, −86.2 to −50.3; $P < .0001$) and total EoE-HSS extent score (stage: LS mean percent change, −54.6; 95% CI, −68.1 to −41.0; $P < .0001$), which take into account histologic findings for all regions (proximal, mid, and distal) of the esophagus at week 12 (Table 2 and Figures 1*D* and *E*). The representative esophageal mucosal pinch biopsies collected at baseline and week 12 are shown in Figure 2.

Compared with placebo, dupilumab use also improved esophageal distensibility plateau by 18.0% (2.9 mm) (95% CI, 10.9 to 25.2; $P < .0001$) at week 12 (Table 2 and Figure 1*F*). Analyses for all observed values are provided in Supplementary Table 5.

Secondary Patient-Reported Outcomes and Quality-of-Life Outcomes

Dupilumab treatment provided a numerical improvement in percent change in weekly EEsAI PRO score of

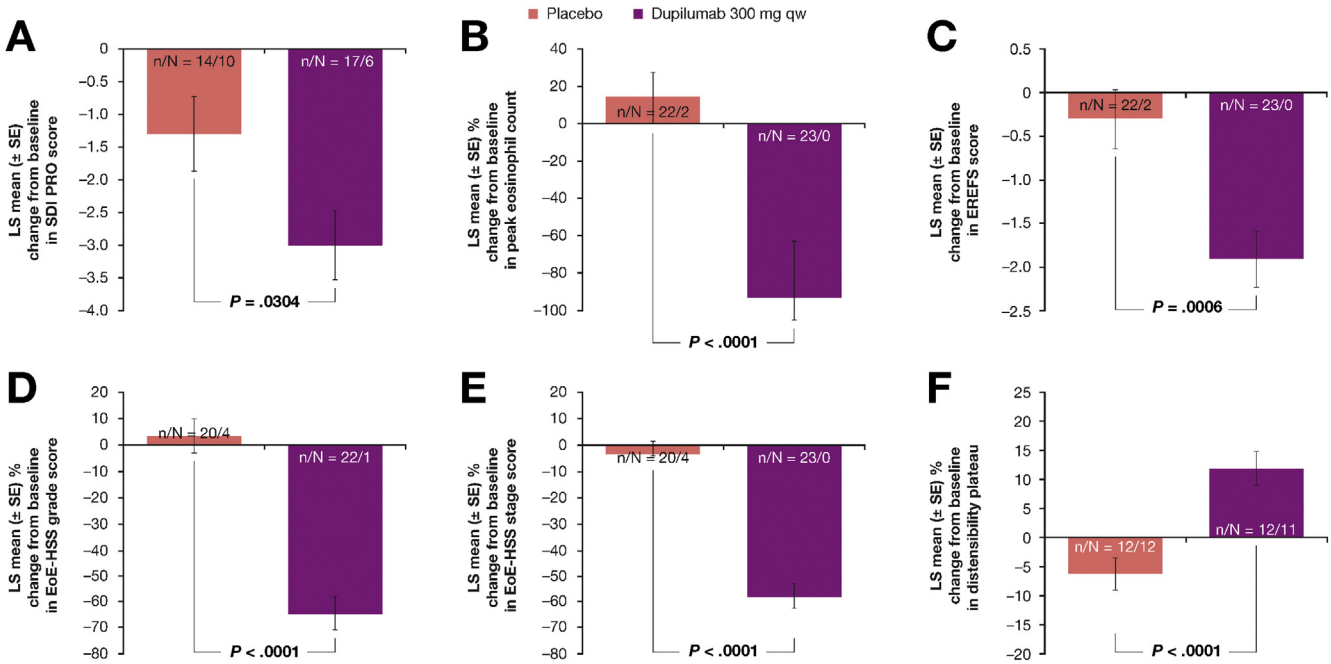


Figure 1. (*A*) LS mean change from baseline in SDI PRO score at week 10. (*B*) LS mean percent change in peak esophageal intraepithelial eosinophil count. (*C*) LS mean change in EoE-EREFS. (*D*) LS mean percent change in EoE-HSS total grade score. (*E*) LS mean percent change in EoE-HSS total stage score. (*F*) LS mean percent change in distensibility at week 12. Missing data were imputed with multiple imputations. n, number of patients with observed data; N, number of patients with imputed data; qw, weekly; SE, standard error.

−23.2% (95% CI, −49.7 to 3.2; $P = .0850$) vs placebo at week 10. These improvements were observed as early as week 1 (Table 2 and Supplementary Figure 7). The proportion of patients with ≥40% improvement from baseline to week 10 in EEsAI score was 26% with dupilumab vs 8% with placebo (difference vs placebo, 17.8%; 95% CI, −11.5 to 43.6; $P = .1365$) (Table 2). Significantly more dupilumab- vs placebo-treated patients were in symptomatic remission at weeks 10 and 12, as defined by an EEsAI score ≤20[35] (risk difference vs placebo, 21.9%; 95% CI, 2.3–41.6; $P = .0479$ and 21.7%; 95% CI, 4.9–38.6; $P = .0219$, respectively) (Table 2).

At week 12, a numerical improvement of 0.3 (95% CI, −0.1 to 0.7; $P = .0910$) was observed for total EoE-QOL-A scores with dupilumab vs placebo (Table 2). Numerical but nonsignificant improvements were also observed for each of the individual domains that make up the EoE-QOL-A. No patient in either treatment group received rescue medication or any other interventional procedure, such as esophageal dilation, during the 12-week treatment period or in the 16-week follow-up period.

Patients Achieving Histologic Plus Symptomatic Remission

The proportions of patients achieving histologic remission (3 regions with eos/HPF < 6 at week 12) and symptomatic remission (SDI score reduction of ≥3 points at week 10) were 13% and 0% for dupilumab- and placebo-treated patients, respectively (risk difference [95% CI] vs placebo, 13.0 [−0.7 to 26.8]; $P = .1092$). The proportions of patients with histologic remission at week 12 and symptomatic remission (EEsAI score ≤ 20 at week 10) were 4.3% and 0% for dupilumab- and placebo-treated patients, respectively (risk difference [95% CI] vs placebo, 4.3 [−4.0 to 12.7]; $P = .4894$).

Safety

Dupilumab was well tolerated during the study period. During the 12-week treatment period, the most frequently occurring TEAEs (as defined by the Medical Dictionary for Regulatory Activities [MedDRA] preferred terms) occurring in ≥3 patients in either the dupilumab or placebo groups were nonserious injection-site erythema (35% and 8%, respectively) and nasopharyngitis (17% and 4%, respectively) (Table 3). Injection-site reactions by MedDRA high-level terms were reported in 13 (57%) dupilumab-treated patients and 7 (29%) placebo-treated patients. There were no serious TEAEs or deaths during the 12-week treatment period. One dupilumab-treated patient (4.3%) discontinued treatment because of a TEAE (nail disorder; see Supplementary Materials for patient narrative). Three serious TEAEs that were considered to be unrelated to the investigational medicinal product occurred in dupilumab-treated patients during the safety follow-up phase after the 12-week treatment period: food allergy in 1 patient, creatine phosphokinase elevation in 1 patient, and spontaneous abortion in 1 patient (see Supplementary Materials for patient narratives). During the treatment period, conjunctivitis was observed in neither dupilumab- nor placebo-treated patients, despite a prior history of

Table 2. Primary, Secondary, and Exploratory Endpoints

Endpoints	Placebo (n = 24)	Dupilumab 300 mg weekly (n = 23)	Difference vs placebo (95% CI)	*P* value vs placebo
SDI PRO score[a]				
Week 10, n/imputed n	14/10	17/6		
LS mean change from baseline (SE)	−1.3 (0.6)	−3.0 (0.5)	−1.7 (−3.2 to −0.2)	.0304
LS mean percent change from baseline (SE)	−18.6 (9.0)	−45.1 (8.4)	−26.5 (−50.5 to −2.4)	.0312
Patients with decrease of ≥3 points on the SDI from baseline to week 10, n (%)	3 (13)	9 (39)	27 (−3 to 51)	.0490
Peak esophageal intraepithelial eosinophil count				
Week 12, n/imputed n	22/2	23/0		
LS mean change from baseline (SE), *eos/HPF*	−8.0 (9.6)	−94.8 (9.4)	−86.8 (−113.2 to −60.5)	<.0001
LS mean percent change from baseline (SE)	14.2 (12.5)	−92.9 (12.1)	−107.1 (−141.2 to −73.0)	<.0001
Patients with response <1 eos/HPF, n (%)	0.0	3 (13.0)	13.0 (−15.72 to 39.73)	.1092
Patients with response ≤6 eos/HPF, n (%)	0.0	15 (65.2)	65.2 (38.31 to 83.62)	<.0001
Patients with response <15 eos/HPF, n (%)	0.0	19 (82.6)	82.6 (59.18 to 95.05)	<.0001
EoE-EREFS total score[b]				
Week 12, n/imputed n	22/2	23/0		
LS mean change from baseline (SE)	−0.3 (0.3)	−1.9 (0.3)	−1.6 (−2.5 to −0.7)	.0006
EoE-HSS score (excluding lamina propria)[c]				
Total grade (severity) score at Week 12, n/imputed n	20/4	22/1		
All LS mean percent change from baseline (SE)	3.2 (6.7)	−65.1 (6.3)	−68.3 (−86.2 to −50.3)	<.0001
Total stage (extent) score at week 12, n/imputed n	20/4	23/0		
All LS mean percent change from baseline (SE)	−3.5 (5.0)	−58.1 (4.7)	−54.6 (−68.1 to −41.0)	<.0001
Distensibility plateau, *mm*				
Week 12, n/imputed n	12/12	12/11		
LS mean change from baseline (SE), *mm*	−1.2 (0.5)	1.8 (0.5)	2.9 (1.7 to 4.2)	<.0001
LS mean percent change from baseline (SE)	−6.2 (2.7)	11.8 (2.7)	18.0 (10.9 to 25.2)	<.0001
Weekly EEsAI PRO score[d]				
Week 10, n/imputed n	13/11	17/6		
LS mean change from baseline (SE)	−9.0 (5.6)	−22.9 (5.0)	−13.9 (−28.5 to 0.8)	.0635
LS mean percent change from baseline (SE)	–11.3 (9.9)	–34.6 (9.1)	–23.2 (–49.7 to 3.2)	.0850
Patients with ≥40% improvement, n (%)	2 (8.3%)	6 (26.1%)	17.8 (−11.5 to 43.6)	.1365
Patients with ≥15-point score improvement, n (%)	6 (25.0)	11 (47.8)	22.8 (−7.22 to 48.72)	.1351
Patients with ≥30-point score improvement, n (%)	2 (8.3)	6 (26.1)	17.8 (−11.54 to 43.55)	.1365
Patients with EEsAI score ≤ 20, n (%)				
At week 10	1 (4.2)	6 (26.1)	21.9 (2.3 to 41.6)	.0479
At week 12	0 (0)	5 (21.7)	21.7 (4.9 to 38.6)	.0219
EoE-QOL-A total score[e]				
Week 12, n (%)	21/3	23/0		
LS mean change from baseline (SE)	0.5 (0.1)	0.8 (0.1)	0.3 (−0.1 to 0.7)	.0910

NOTE. Missing data were imputed by using multiple imputation.
[a]The SDI PRO total score is the sum of scores of frequency of dysphagia and intensity of dysphagia; total score range, 0−9 (higher scores indicate worse symptoms). The minimal clinically important difference is 3.[30]
[b]The EoE-EREFS measures endoscopically identified EoE esophageal mucosal inflammatory and remodeling features; total scores for edema, rings, furrows, exudate, stricture range, 0−8 (higher scores indicate greater impairment).
[c]The EoE-HSS measures eosinophil density, basal zone hyperplasia, eosinophil abscesses, eosinophil surface layering, surface epithelial alteration, dyskeratotic epithelial cells, and dilated intercellular spaces; scale range, 0−63 (higher scores indicate more severe histologic findings).
[d]The EEsAI PRO is a 5-component (10-item) measure of dysphagia, swallowing-associated pain, and strategies aimed at avoiding dysphagia episodes; total score range, 0−100 (higher scores indicate worse symptoms).
[e]The EoE-QOL-A questionnaire includes 30 items related to 5 established domains (eating/diet impact, social impact, emotional impact, disease anxiety, and swallowing anxiety) of daily life experiences using a 5-point Likert-like scale. The scores for EoE-QOL-A score are the average score, equal to the total score/number of questions (120/30 = 4 for patients without disease). Total scores range from 1 to 5.

conjunctivitis in 3 patients in each group. In this study, no cases of hypereosinophilia were observed in dupilumab-treated EoE patients. TEAEs during the entire study period, including the 16-week follow-up period, are presented in Supplementary Table 6.

Discussion

Dupilumab treatment significantly improved dysphagia, severity of histologic and endoscopic features, esophageal intraepithelial eosinophil count, and esophageal distensibility, with a trend toward reducing symptoms and

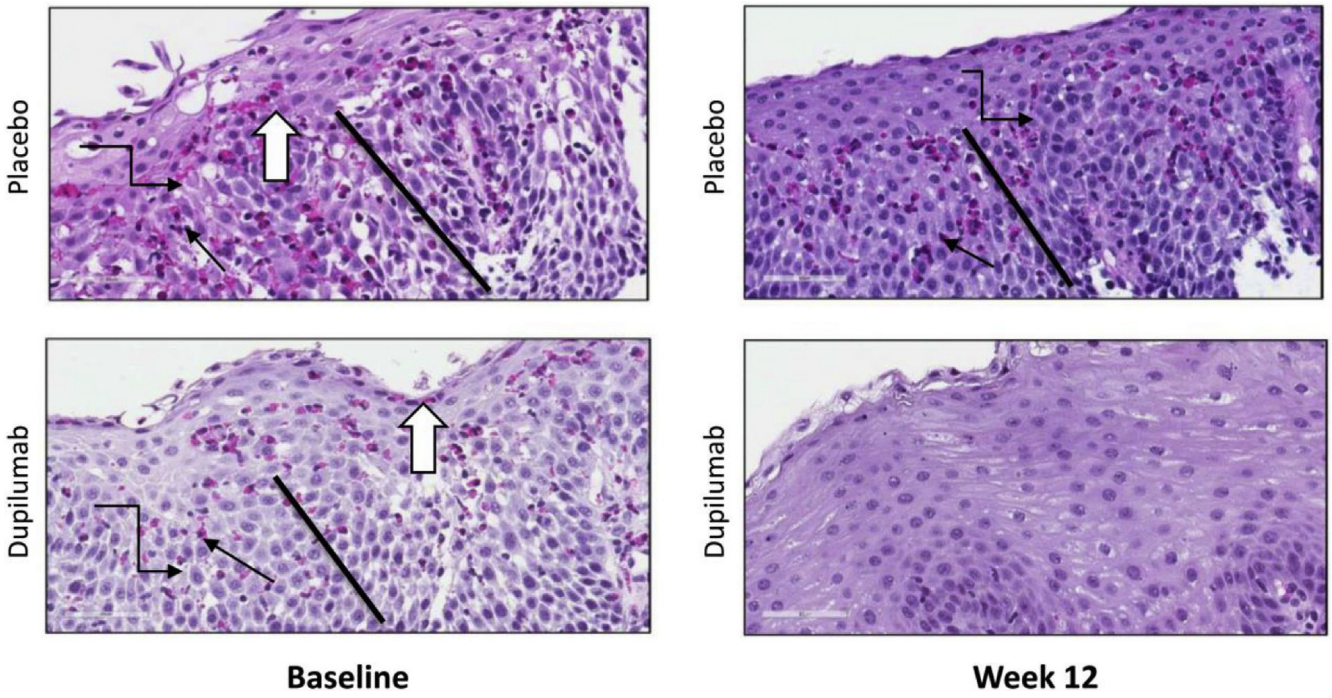


Figure 2. Esophageal mucosal pinch biopsies collected at baseline and week 12: basal zone hyperplasia (*black bar*), eosinophils (*black arrow*), surface layering (*white arrow*), and dilated intercellular spaces (*elbow connector arrow*). Note the apparent ablation of basal cell hyperplasia, complete depletion of eosinophils (and their surface layering), and elimination of dilated intracellular spaces at week 12 after dupilumab treatment.

improving quality of life compared with placebo. Dupilumab reduced both the frequency and severity of dysphagia events,[41] with concurrent reductions in mucosal eosinophil density and macroscopic manifestations ascertained by the validated EREFS endoscopic visualization score.[6,39] In addition, dupilumab improved most components of the EoE-HSS, a recently validated histologic score that measures other histologic abnormalities in addition to the density of eosinophilic inflammation.[38,42] Significant improvements in EEsAI PRO symptom score vs placebo were also observed with dupilumab treatment, which supported the histologic findings of decreased esophageal eosinophilia and increased distensibility with dupilumab treatment, consistent with a reduction in remodeling and improved esophageal function.[39] These results show that IL4 and IL13 are central pathologic mediators of esophageal inflammation and dysfunction in adult patients with active EoE.

Studies with other targeted biologic agents have failed to show significant improvement in dysphagia relative to placebo, even upon reduction of peak eosinophil count, suggesting that factors other than eosinophils are involved in the esophageal remodeling and dysfunction in adult EoE. Mepolizumab and reslizumab (anti-IL5) reduced esophageal intraepithelial eosinophil counts but did not significantly improve symptoms compared with placebo.[13,28,29] IL13-specific inhibitors (QAX576, RPC4046) improved histologic features of EoE but also did not resolve symptoms. QAX576 improved esophageal intraepithelial eosinophil counts and the EoE-associated transcriptome, but not dysphagia.[12] RPC4046 significantly reduced EoE-EREFS and esophageal eosinophil counts, with nonsignificant trends for dysphagia symptom improvement.[43] Omalizumab (anti-IgE monoclonal antibody) did not improve either dysphagia or histologic features of EoE compared with placebo, suggesting that pathogenesis is not mediated by IgE, despite the association of EoE with comorbid allergies.[44]

In this proof-of-concept study, dual blockade of IL4 and IL13 signaling with dupilumab improved both esophageal inflammation and clinical symptoms in patients with EoE. These data provide further evidence of the importance of IL4/IL13 pathways in type 2 inflammation and suggest that their dual inhibition may be a more effective inhibitor of type 2 inflammation than IL5, IL13, or IgE-targeted agents alone. The more fundamental roles of IL4 and IL13 in driving allergic/atopic/type 2 inflammation is similarly reflected by its broader activity in type 2 diseases (compared with other targeted agents), not only in EoE, but also in atopic dermatitis, as well as in its ability to significantly improve lung function in patients with asthma.

The high rate of screening failures observed in our study (41%) is consistent with other recently published randomized controlled trial data in eosinophilic esophagitis. The US trials are enrolling patients with very high levels of symptoms and histologic activity, who represent a discrete subset of patients with EoE. In the recent trial of budesonide oral suspension,[37] 203 patients were enrolled, and 81 patients were excluded at screening. In our study, the most common reason for screening failure was failure to meet eligibility criteria (32 of 33 patients), specifically, inadequate frequency of dysphagia, failure to meet histologic criteria, failure to meet the criterion of stabilized diet for at least 6

Table 3. Key TEAEs During the 12-Week Treatment Period

TEAEs	Placebo (n = 24), n (%)	Dupilumab 300 mg weekly (n = 23), n (%)
≥1 TEAE	15 (63)	18 (78)
≥1 serious adverse event[a]	0	0
Adverse events leading to treatment discontinuation	0	1 (4)
Deaths	0	0
Terms with a difference of number of patients between 2 groups ≥3		
Injection-site reactions (HLT)	7 (29)	13 (57)
Injection-site erythema (PT)	2 (8)	8 (35)
Injection-site inflammation (PT)	0	3 (13)
Injection-site rash (PT)	0	3 (13)
Upper respiratory tract infections (HLT)	3 (13)	7 (30)
Nasopharyngitis (PT)	1 (4)	4 (17)
Musculoskeletal, connective tissue pain and discomfort (HLT)	0	3 (13)

HLT, MedDRA high-level term; PT, MedDRA preferred term.
[a]Serious adverse events were considered to be unrelated to the investigational medicinal product; the 3 events in 3 patients in the dupilumab group were food allergy, creatine phosphokinase elevation, and spontaneous abortion. A female patient (30 years old) with a prior history of anaphylaxis to tree nuts and moderate allergy to milk and eggs developed a sudden episode of throat swelling after ingestion of a vegan shake; the episode was resolved with an epinephrine injection.

weeks, and failure to meet the criterion of signing informed consent.

This study has a number of limitations and strengths. When the study was designed, the only published data available for dysphagia response were for SDI PRO scores.[31] None were available for the EEsAI, a PRO measure designed and validated for use in EoE; therefore, size calculations could not be performed. Change from baseline in SDI PRO score was therefore chosen as the primary efficacy endpoint, and although the SDI is not a validated instrument, the results obtained were in line with those observed with the EEsAI. The study was small, and the results obtained are mainly limited to patients with mild to moderate esophageal symptoms, because at baseline there was an imbalance in the recruitment of patients with an SDI score >7 (only 13% of all recruits); therefore, findings in patients with more severe disease should be interpreted with caution. In addition, some patients had missing data for evaluation of SDI and EEsAI PRO scores due to an e-diary data capture issue. To diminish any potential bias as a result of data loss, we used multiple imputation methods, and even with the data loss, statistically significant symptom improvements were observed in the primary endpoint that were consistent across a range of sensitivity analyses. Although the functional lumen imaging probe procedure in EoE (EndoFLIP) was exploratory in nature, dupilumab treatment also significantly improved esophageal distensibility.[40] The study had a short treatment duration (12 weeks), so long-term efficacy remains to be evaluated. Enrollment of highly symptomatic patients from tertiary care centers limits the generalizability of these findings, and the prior glucocorticoid or elimination-diet responsiveness was not assessed. Furthermore, the great majority of patients (83%) had ≥2 comorbid atopic diseases, suggesting that the applicability of the data is likely restricted to EoE patients with comorbid type 2 conditions, rather than EoE alone. The strengths of this study include the use of centralized histologic assessment, multiple objective scoring systems (including the validated EoE-HSS, EEsAI PRO scores, and EREFS endoscopic grading and classification system), the use of the functional lumen imaging probe (EndoFLIP) to measure esophageal distensibility, and the highly consistent improvements across all assessments.

Dupilumab was generally well tolerated, although nonserious injection-site erythema and nasopharyngitis occurred more frequently in dupilumab-treated patients; increase in nasopharyngitis has not been noted across dupilumab studies involving thousands of patient years. Observed safety is consistent with published studies of dupilumab.[20–26]

To ascertain whether any relationships exist between clinical symptoms and endoscopic or histologic features in patients with EoE, we conducted a series of post hoc correlation analyses on the data from this study. Both endoscopic (EoE-EREFS) and histologic disease activity (EoE-HSS stage, EoE-HSS grade, peak eosinophil count) were found to be significantly correlated with reduced esophageal distensibility in all patients at week 12, suggesting an association between esophageal inflammation and function.[41] Significant correlations were also observed between EoE-EREFS and with both EoE-HSS stage and grade scores, but not with peak esophageal intraepithelial eosinophil count.[45] Nonsignificant negative correlations were observed between baseline characteristics (SDI total score and frequency/number of dysphagia episodes vs disease activity at baseline [EREFS, EoE-HSS, peak eosinophils]).[46] Although these findings support the concept of evaluating both the severity and extent of multiple pathologic features in EoE biopsy specimens, the sample size is small. Further correlation analyses are planned in a larger patient population with broader disease activity.

In conclusion, to our knowledge, dupilumab is the first targeted biologic agent to improve dysphagia, histologic and endoscopic measures of disease, and esophageal function and have an acceptable safety profile in adult patients with active EoE. Further studies are required to determine the long-term efficacy and safety of dupilumab in the treatment of EoE.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2019.09.042.

References

1. Furuta GT, Katzka DA. Eosinophilic esophagitis. N Engl J Med 2015;373:1640–1648.
2. Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. J Allergy Clin Immunol 2011;128:3–20.
3. Mukkada V, Falk GW, Eichinger CS, et al. Health-related quality of life and costs associated with eosinophilic esophagitis: a systematic review. Clin Gastroenterol Hepatol 2018;16:495–503.
4. O'Shea KM, Aceves SS, Dellon ES, et al. Pathophysiology of eosinophilic esophagitis. Gastroenterology 2018;154:333–345.
5. Rothenberg ME. Molecular, genetic, and cellular bases for treating eosinophilic esophagitis. Gastroenterology 2015;148:1143–1157.
6. Hirano I, Aceves SS. Clinical implications and pathogenesis of esophageal remodeling in eosinophilic esophagitis. Gastroenterol Clin North Am 2014;43:297–316.
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;145:1230–1236.
8. Dellon ES, Hirano I. Epidemiology and natural history of eosinophilic esophagitis. Gastroenterology 2018;154:319–322.
9. 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;11:1101–1107.
10. Arias Á, Pérez-Martínez I, Tenías JM, et al. Systematic review with meta-analysis: the incidence and prevalence of eosinophilic oesophagitis in children and adults in population-based studies. Aliment Pharmacol Ther 2016;43:3–15.
11. Dellon ES. Epidemiology of eosinophilic esophagitis. Gastroenterol Clin North Am 2014;43:201–218.
12. Rothenberg ME, Wen T, Greenberg A, et al. Intravenous anti-IL-13 mAb QAX576 for the treatment of eosinophilic esophagitis. J Allergy Clin Immunol 2015;135:500–507.
13. Spergel JM, Rothenberg ME, Collins MH, et al. Reslizumab in children and adolescents with eosinophilic esophagitis: results of a double-blind, randomized, placebo-controlled trial. J Allergy Clin Immunol 2012;129:456–463.
14. 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;112:1527–1535.
15. Jorveza® (budesonide). Summary of product characteristics. European Medicines Agency Website. https://www.ema.europa.eu/en/documents/product-information/jorveza-epar-product-information_en.pdf. Accessed November 24, 2019.
16. Murphy AJ, Macdonald LE, Stevens S, et al. Mice with megabase humanization of their immunoglobulin genes generate antibodies as efficiently as normal mice. Proc Natl Acad Sci U S A 2014;111:5153–5158.
17. Macdonald LE, Karow M, Stevens S, et al. Precise and in situ genetic humanization of 6 Mb of mouse immunoglobulin genes. Proc Natl Acad Sci U S A 2014;111:5147–5152.
18. Gandhi NA, Pirozzi G, Graham NMH. Commonality of the IL-4/IL-13 pathway in atopic diseases. Expert Rev Clin Immunol 2017;13:425–437.
19. Cork M, Thaci D, DiCioccio AT, et al. Pharmacokinetics, safety and efficacy of dupilumab in a pediatric population with moderate-to-severe atopic dermatitis: results from an open-label phase 2a trial. Paper presented at: The 75th Annual Meeting of The American Academy of Dermatology; March 3-7, 2017; Orlando, FL, USA. Abstract presentation (oral).
20. Blauvelt A, de Bruin-Weller M, Gooderham M, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. Lancet 2017;389(10086):2287–2303.
21. Simpson EL, Bieber T, Guttman-Yassky E, et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. N Engl J Med 2016;375:2335–2348.
22. Thaçi D, Simpson EL, Beck LA, et al. Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial. Lancet 2016;387(10013):40–52.
23. Wenzel S, Castro M, Corren J, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. Lancet 2016;388:31–44.
24. Castro M, Corren J, Pavord ID, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. N Engl J Med 2018;378:2486–2496.
25. Rabe KF, Nair P, Brusselle G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. N Engl J Med 2018;378:2475–2485.
26. Bachert C, Mannent L, Naclerio RM, et al. Effect of subcutaneous dupilumab on nasal polyp burden in patients with chronic sinusitis and nasal polyposis: a randomized clinical trial. JAMA 2016;315:469–479.

27. Regeneron reports second quarter 2018 financial and operating results. PR Newswire Website. https://www.prnewswire.com/news-releases/regeneron-reports-second-quarter-2018-financial-and-operating-results-300690715.html. Accessed November 24, 2019.
28. Assa'ad AH, Gupta SK, Collins MH, et al. An antibody against IL-5 reduces numbers of esophageal intraepithelial eosinophils in children with eosinophilic esophagitis. Gastroenterology 2011;141:1593–1604.
29. Straumann A, Conus S, Grzonka P, et al. Anti-interleukin-5 antibody treatment (mepolizumab) in active eosinophilic oesophagitis: a randomised, placebo-controlled, double-blind trial. Gut 2010;59:21–30.
30. Dellon ES, Gonsalves N, Hirano I, et al. ACG clinical guideline: evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). Am J Gastroenterol 2013;108:679–692.
31. Straumann A, Conus S, Degen L, et al. Budesonide is effective in adolescent and adult patients with active eosinophilic esophagitis. Gastroenterology 2010;139:1526–1537.
32. 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;62:489–495.
33. Schoepfer AM, Straumann A, Panczak R, et al. Development and validation of a symptom-based activity index for adults with eosinophilic esophagitis. Gastroenterology 2014;147:1255–1266.
34. Bajaj S, Taft T, Keefer L, et al. Su1135. Validity, usability, and acceptability of the Eosinophilic Esophagitis Quality of Life Scale for Adults (EoE-QOL-A) [abstract]. Gastroenterology 2012;142:S–434.
35. 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;34:790–798.
36. Safroneeva E, Straumann A, Coslovsky M, et al. Symptoms have modest accuracy in detecting endoscopic and histologic remission in adults with eosinophilic esophagitis. Gastroenterology 2016;150:581–590.
37. Dellon ES, Katzka DA, Collins MH, et al. Budesonide oral suspension improves symptomatic, endoscopic, and histologic parameters compared with placebo in patients with eosinophilic esophagitis. Gastroenterology 2017;152:776–786.
38. Collins MH, Martin LJ, Alexander ES, et al. Newly developed and validated eosinophilic histology scoring system and evidence that it outperforms peak eosinophil count for diagnosis and monitoring. Dis Esophagus 2017;30(3):1–8.
39. Hirano I, Spechler S, Furuta G, et al. White paper AGA: drug development for eosinophilic esophagitis. Clin Gastroenterol Hepatol 2017;15:1173–1183.
40. Hirano I, Pandolfino JE, 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;15:325–334.
41. Hirano I, Hamilton JD, Collins MH, et al. Correlation between esophageal distensibility and objective measures of disease in patients with active eosinophilic esophagitis: a post hoc analysis of a randomized, placebo-controlled, phase 2 dupilumab trial. Paper presented at: Digestive Disease Week; June 2–5, 2018; Washington, DC.
42. Warners MJ, Ambarus CA, Bredenoord AJ, et al. Reliability of histologic assessment in patients with eosinophilic esophagitis. Aliment Pharmacol Ther 2018;47:940–950.
43. **Hirano I**, Collins MH, Assouline-Dayan Y, et al. RPC4046, a monoclonal antibody against IL13, reduces histologic and endoscopic activity in patients with eosinophilic esophagitis. Gastroenterology 2019;156:592–603.
44. Clayton F, Fang JC, Gleich GJ, et al. Eosinophilic esophagitis in adults is associated with IgG4 and not mediated by IgE. Gastroenterology 2014;147:602–609.
45. Hirano I, Collins MH, Dellon ES, et al. Endoscopic features are significantly associated with histologic measures of disease activity in patients with active eosinophilic esophagitis: a post hoc analysis of a randomized, placebo-controlled, phase 2 dupilumab trial. Paper presented at: Digestive Disease Week; June 2–5, 2018; Washington, DC.
46. Collins MH, Hirano I, Dellon ES, et al. Baseline characteristics and correlation between dysphagia and disease activity in patients with eosinophilic esophagitis in a randomized, placebo-controlled, phase 2 dupilumab trial. Paper presented at: Digestive Disease Week; June 2–5, 2018; Washington, DC.

Author names in bold designate shared co-first authorship.

Received February 25, 2019. Accepted September 24, 2019.

Reprint requests
Address requests for reprints to: Ikuo Hirano, MD, Northwestern University Feinberg School of Medicine, 259 East Erie Street, 16th Floor, Chicago, Illinois, 60611. e-mail: i-hirano@northwestern.edu; fax: 312-695-3999.

Acknowledgments
Principal investigators: Oral Alpan, MD, Robert Hardi, MD, John Leung, MD, John Wo, MD, Charles Barish, MD, Glen Gordon, MD, John Garber, MD, Benjamin Mitlyng, MD, Tom Whitlock, MD, and Paul Hendrix, MD. Regeneron Pharmaceuticals, Inc, employees: Linda Williams, RPh, Marcella Ruddy, MD, Usman Chaudhry, Andrew Korotzer, PhD, Joseph Elassal MD, Richard Wu, PhD, Jingdong Chao, PhD, and Dharani Ajithdoss, DVM, MS, PhD. Sanofi employees: Dianne Barry, PhD, Paul Rowe, MD, and Heribert Staudinger, MD, PhD. Writing assistance: The authors received writing/editorial support in the preparation of this manuscript provided by Jennifer L. F. Port, PhD, and Xiomara V. Thomas, PhD, of Excerpta Medica, funded by Sanofi Genzyme and Regeneron Pharmaceuticals, Inc.

Author contributions: Ikuo Hirano, Evan S. Dellon, Jennifer D. Hamilton, and Allen Radin: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content. Margaret H. Collins, Kathryn Peterson, Mirna Chehade, Alain M. Shoepfer, Ekaterina Safroneeva, and Marc E. Rothenberg: study concept and design, acquisition of data, analysis and interpretation of data, and critical revision of the manuscript for important intellectual content. Gary W. Falk and Yehudith Assouline-Dayan: acquisition of data, analysis and interpretation of data, critical revision of the manuscript for important intellectual content. Qiong Zhao and Zhen Chen: statistical analysis, analysis, and interpretation of data; critical revision of the manuscript for important intellectual content. Brian N. Swanson, Gianluca Pirozzi, Leda Mannent, Neil M. H. Graham: analysis and interpretation of data, critical revision of the manuscript for important intellectual content. Bolanle Akinlade, Neil Stahl, George D. Yancopoulos: acquisition of data, analysis and interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content.

Conflicts of interest

These authors disclose the following: Ikuo Hirano has been a consultant for Adare, Allakos, Receptos/Celgene, Regeneron Pharmaceuticals, Shire, Gossamer, Esocap and has received research funding from Adare, Allakos, Meritage, Receptos/Celgene, Regeneron Pharmaceuticals, and Shire. Evan S. Dellon has been a consultant for Alivio, Adare, Allakos, Banner, Calypso, Enumeral, EsoCap, GlaxoSmithKline, Receptos/Celgene, Regeneron Pharmaceuticals, Robarts, and Shire; has received research funding from Adare, Allakos, Meritage, Miraca, Nutricia, Receptos/Celgene, Regeneron Pharmaceuticals, and Shire; and received educational grants from Banner and Holoclara. Jennifer D. Hamilton, Qiong Zhao, Zhen Chen, Neil N. M. Graham, Bolanle Akinlade, and Allen Radin are employees and shareholders of Regeneron Pharmaceuticals. Margaret H. Collins has been a consultant for Allakos, Receptos/Celgene, Regeneron Pharmaceuticals, and Shire and has received research funding from Receptos/Celgene, Regeneron Pharmaceuticals, and Shire. Kathryn Peterson has received research funding from Janssen, Receptos/Celgene, and Regeneron Pharmaceuticals. Mirna Chehade has been a consultant for Actelion, Allakos, and Shire and received research funding from Nutricia, Regeneron Pharmaceuticals, and Shire. Alain M. Schoepfer has been a consultant for Adare, Aptalis, Dr Falk Pharma, and Regeneron Pharmaceuticals and has received research funding from AstraZeneca, Aptalis, Dr Falk Pharma, GlaxoSmithKline, Nestlé, Novartis, Receptos/Celgene, and Regeneron Pharmaceuticals. Ekaterina Safroneeva has been a consultant for Aptalis, Novartis, Receptos/Celgene, and Regeneron Pharmaceuticals. Marc E. Rothenberg has been a consultant for AstraZeneca, Celgene, GlaxoSmithKline, NKT Therapeutics, Novartis, PulmOne, Shire, and Spoon Guru; holds equity interest in Immune Pharmaceuticals, NKT Therapeutics, PulmOne, and Spoon Guru; receives royalties from reslizumab from Teva Pharmaceutical; and is the inventor of patents owned by Cincinnati Children's Hospital Medical Center. Gary W. Falk has received research funding from Allakos; has been a consultant for Adare and Banner; and has received research funding from Adare, Meritage, Receptos/Celgene, Regeneron Pharmaceuticals, and Shire. Gianluca Pirozzi and Leda Mannent L are employees of Sanofi and may hold stock and/or stock options in the company. Brian N. Swanson is a former employee of Sanofi and may hold stock and/or stock options in the company. The remaining author discloses no conflicts.

Funding

This research was sponsored by Sanofi and Regeneron Pharmaceuticals,Inc.

Supplementary Methods

Patient Eligibility Criteria

Inclusion Criteria.

1. Male or female, 18–65 years old

   Documented diagnosis of EoE by endoscopy before or at screening. Note: Must include a demonstration of intraepithelial eosinophilic infiltration (peak cell count $\geq$ 15 eos/HPF [$\times$400, 0.3 mm^2]) from esophageal biopsy specimens from endoscopy performed no more than 2 weeks after at least 8 weeks of treatment with high-dose (or twice-daily dosing) PPIs.

2. History (by patient report) of, on average, at least 2 episodes of dysphagia (with intake of solids off anti-inflammatory therapy) per week in the 4 weeks before screening and, on average, at least 2 episodes of documented dysphagia per week in the weeks between screening and baseline. *Dysphagia* is defined as trouble swallowing solid food, or having solid food stick, by patient report.

3. Must remain on a stabilized diet for at least 6 weeks before screening and during the course of the study; *stable diet* is defined as no initiation of single or multiple elimination diets or reintroduction of previously eliminated food groups.

4. SDI PRO score $\geq$ 5 at screening and baseline

5. Documented history of or presence of 1 or more of any of the following:

   - Allergic disease (eg, allergic asthma, allergic rhinitis, atomic dermatitis, or food allergies)
   - Blood eosinophil count $\geq$ 0.25 GI/L
   - Serum total IgE $\geq$100 kU/L

6. Willing and able to comply with all clinic visits and study-related procedures

7. Able to understand and complete study-related questionnaires

8. Provide signed informed consent

9. Endoscopy with photographs performed at screening, with a demonstration of intraepithelial eosinophilic infiltration (peak cell count $\geq$ 15 eos/HPF) in at least 2 of the 3 biopsied esophageal regions (proximal, mid, or distal)

Exclusion Criteria.

1. Prior participation in a dupilumab (anti-IL4R) clinical trial

2. Other causes of esophageal eosinophilia or the following diseases: hypereosinophilic syndromes, Churg-Strauss vasculitis, or eosinophilic gastroenteritis

3. History of achalasia, active *Helicobacter pylori* infection, Crohn's disease, ulcerative colitis, celiac disease, or prior esophageal surgery before screening

4. Any esophageal stricture unable to be passed with a standard, diagnostic, adult (9–10 mm) upper endoscope, or any critical esophageal stricture that required dilation at screening

5. History of bleeding disorders or esophageal varices

6. Use of chronic aspirin, nonsteroidal agents, or anticoagulants within 2 weeks before screening; patients should not stop these agents solely to become eligible for entry into this study.

7. Treatment with an investigational drug within 2 months or within 5 half-lives (if known), whichever is longer, before screening

8. Use of systemic glucocorticoids within 3 months or swallowed topical glucocorticoids within 6 weeks before screening

9. Use of inhaled or nasal glucocorticoids within 3 months before screening and during the study, except stable dose for at least 3 months before screening biopsy (which cannot be changed during the study)

10. Treatment with oral immunotherapy within 6 months before screening

11. Allergen immunotherapy (sublingual immunotherapy and/or subcutaneous immunotherapy), unless receiving stable dose for at least 1 year before screening

12. The following treatments within 3 months before the screening visit, or any condition that, in the opinion of the investigator, is likely to require such treatment(s) during the 3 months of study treatment:

    - Systemic immunosuppressive/immunomodulating drugs (eg, omalizumab, cyclosporine, mycophenolate mofetil, interferon gamma, Janus kinase inhibitors, azathioprine, methotrexate, and leukotriene inhibitors [except stable dose for at least 3 months before screening])

13. Diagnosis of active parasitic infection or having suspected parasitic infection, unless clinical and (if necessary) laboratory assessments have ruled out active infection before randomization

14. Chronic or acute infection requiring treatment with systemic antibiotics, antivirals, or antifungals within 1 month before screening

15. Use of oral antibiotics/anti-infectives within 2 weeks before screening

16. Known or suspected immunosuppression, including history of invasive opportunistic infections (eg, tuberculosis, nontuberculous mycobacterial infections,

histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis) despite infection resolution, otherwise recurrent infections of abnormal frequency, or prolonged infections suggesting an immunocompromised status, as judged by the investigator

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

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

Prohibited Concomitant Medications

Prohibited concomitant medications included medications used for the treatment of EoE, allergen immunotherapy, live attenuated vaccines, and any investigational drug other than dupilumab. Patients who were not using a proton pump inhibitor (PPI) in the 8 weeks before screening could not start PPI therapy before the end-of-treatment visit.

Statistical Analysis

Efficacy data through week 12 were set to *missing* for all time points subsequent to the use of rescue treatment, and then the missing value imputed using multiple imputation (MI). Missing data from the full analysis set was imputed 50 times to generate 50 complete data sets by using the SAS MI procedure following 2 steps. First, the monotone missing pattern was induced by the Markov chain Monte Carlo method in the MI procedure: if a patient had a missing value for a variable at a visit, then the values at all subsequent visits for the same variable were all missing for that patient. Second, the missing data at subsequent visits were imputed by using the regression method for the monotone pattern with adjustment for covariates, including treatment groups and baseline SDI score. The imputation model included the covariates that were included in the ANCOVA model (consisting of the treatment group and the baseline SDI value) and observed postbaseline efficacy values up to week 10. Data from each of the 50 complete data sets were analyzed by using ANCOVA with treatment group as the fixed effect and baseline SDI value as the continuous covariate. The SAS MIANALYZE procedure was used to generate valid statistical inferences by combining results from these multiple analyses using Rubin's formula.

The ANCOVA model generated LS mean changes from baseline to week 10 and other time points for each treatment group, with the corresponding standard error, CI, and *P* value for treatment comparisons. Four prespecified sensitivity analyses were performed for the primary endpoint, with various methods to handle missing data:

(1) MI followed by ANCOVA based on all observed data regardless of the use of rescue medication.

(2) ANCOVA with the efficacy data set to *missing* after the use of rescue medication. Then, the postbaseline last observation carried forward (LOCF) method was used to impute missing data.

3) ANCOVA with the efficacy data set to *missing* after the use of rescue medication. Then, the postbaseline worst observation carried forward (WOCF) method was used to impute missing data.

4) ANCOVA based on all observed data regardless of the use of rescue medication.

Upon blinded data review, it was noted that there was an e-diary malfunction resulting in fewer data being collected at week 12 than at week 10 for SDI. Thus, although the study was still blinded, the SDI primary endpoint in the protocol was amended from week 12 to week 10.

The continuous secondary and exploratory efficacy endpoints were analyzed by using the same approach as that used for the primary endpoint, with the exception that the imputation (used to perform MI) and ANCOVA models included each endpoint's relevant baseline value in addition to the baseline SDI as continuous covariates.

Patient Narrative 1

The following adverse event of a nonserious moderate nail disorder leading to withdrawal from the study was received by an investigator on March 23, 2016.

A 27-year-old woman with eosinophilic esophagitis was randomly assigned to receive study drug REGN668 (loading dose of 600 mg subcutaneously, followed by 300 mg subcutaneously weekly thereafter).

On March 23, 2016, after 37 days of study treatment, the patient experienced a nonserious moderate nail disorder (verbatim term: left index fingernail indentation) after receiving 5 weekly doses of dupilumab. The patient received her sixth dose on day 38; however, the event led to permanent discontinuation of the study drug afterward. The event was not symptomatic and not associated with an infection or any other symptoms. The cause of the event was unknown. The event was assessed by the investigator to be unrelated to the study drug. The event was ongoing at the time of the patient's last study visit. Additional adverse events were reported for the patient during treatment, including injection site reactions and back acne, and the nail disorder was considered the deciding factor, leading to the patient choosing to withdraw from the study. The investigator was comfortable with her continuing with the study and did not withdraw her for any adverse event.

Patient Narrative 2

The following serious adverse event of a spontaneous abortion was received by an investigator on December 23, 2016.

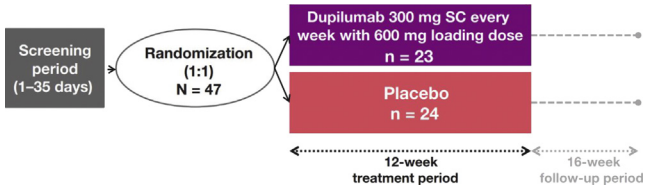
A 44-year-old woman with eosinophilic esophagitis was randomly assigned on September 30, 2016, to receive study drug REGN668 (loading dose of 600 mg subcutaneously, followed by 300 mg subcutaneously weekly thereafter). The patient's medical history included cervical cancer, cervix removal, attention deficit disorder, dry eye syndrome, and allergies (environmental and food).

On December 22, 2016, after 83 days of study treatment, the patient had an initial positive serum and urine pregnancy test result, with serum human chorionic gonadotropin level of 252.4 mIU/mL (normal range, 0–5 mIU/mL). Pregnancy was confirmed the same day. The number of weeks that the patient had been pregnant at the time of diagnosis was unknown. Use of contraceptives was not reported. The date of the patient's last menstrual period was not reported, and the estimated date of birth was unknown. Termination was reported as possible with more information pending. Information regarding previous pregnancies was not reported. On December 26, 2016, the patient had a spontaneous abortion. It was reported that the patient had planned a termination with her gynecologist but had spontaneously aborted before the planned termination. Based on the patient's history of cervical surgery, the abortion was not unexpected, and the patient stated that she had no intentions of having a child. The patient had an unspecified number of full-term births and an unknown number of spontaneous abortions. On January 20, 2017, a urine pregnancy test result was negative.

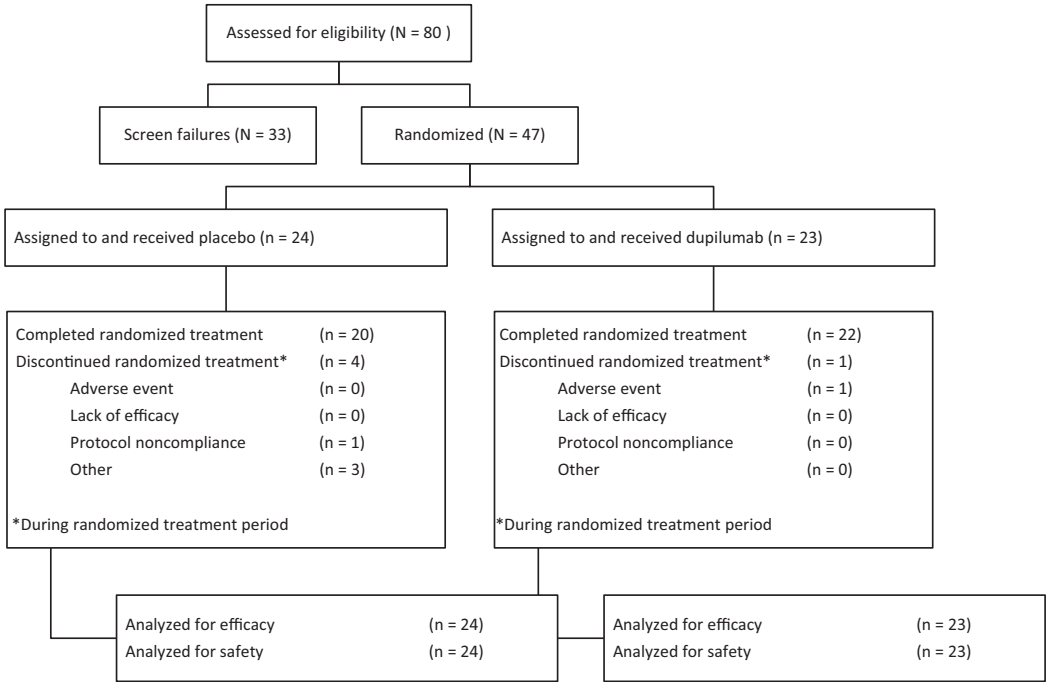
Supplementary References

1. Straumann A, Conus S, Degen L, et al. Budesonide is effective in adolescent and adult patients with active eosinophilic esophagitis. Gastroenterology 2010; 139:1526–1537.
2. **Schoepfer AM**, **Straumann A**, Panczak R, et al. Development and validation of a symptom-based activity index for adults with eosinophilic esophagitis. Gastroenterology 2014;147:1255–1266.e21.
3. Taft TH, Kern E, Keefer L, et al. Qualitative assessment of patient-reported outcomes in adults with eosinophilic esophagitis. J Clin Gastroenterol 2011; 45:769–774.
4. Hirano I, Aceves SS. Clinical implications and pathogenesis of esophageal remodeling in eosinophilic esophagitis. Gastroenterol Clin North Am 2014;43:297–316.
5. 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;30:1–8.

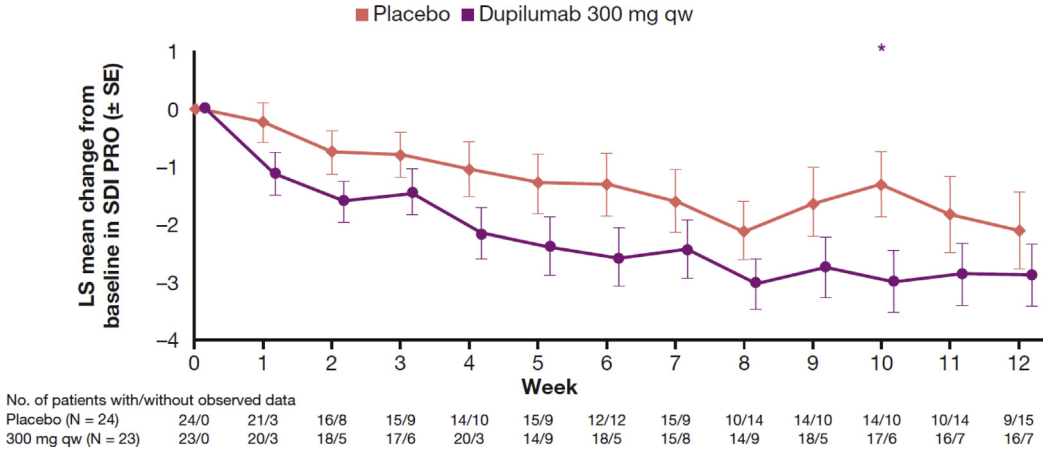
Author names in bold designate shared co-first authorship.



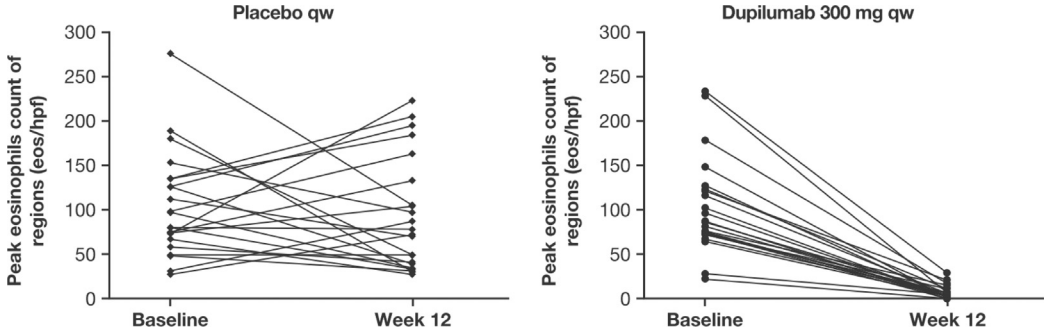
Supplementary Figure 1. Study design. Patients received weekly injections of the study drug from day 1 to week 12 (with the last dose at week 11). Follow-up visits occurred every 4 weeks. SC, subcutaneously.



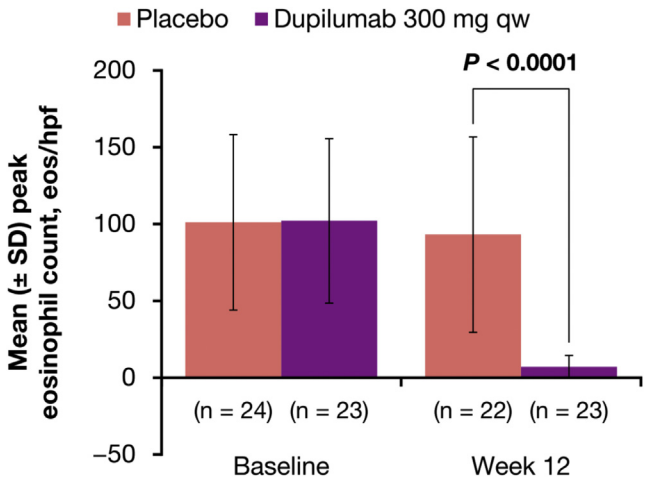
Supplementary Figure 2. Consolidated Standards of Reporting Trials (CONSORT) diagram.



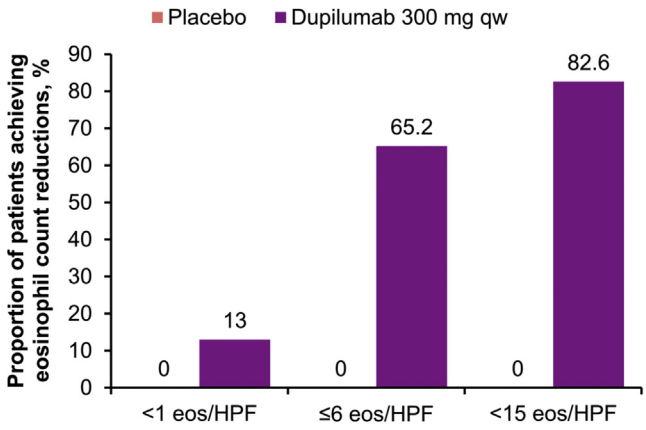
Supplementary Figure 3. SDI PRO change from baseline during the 12-week analysis period. *$P < .05$ vs placebo. Missing data were imputed using multiple imputation. qw, weekly; SE, standard error.



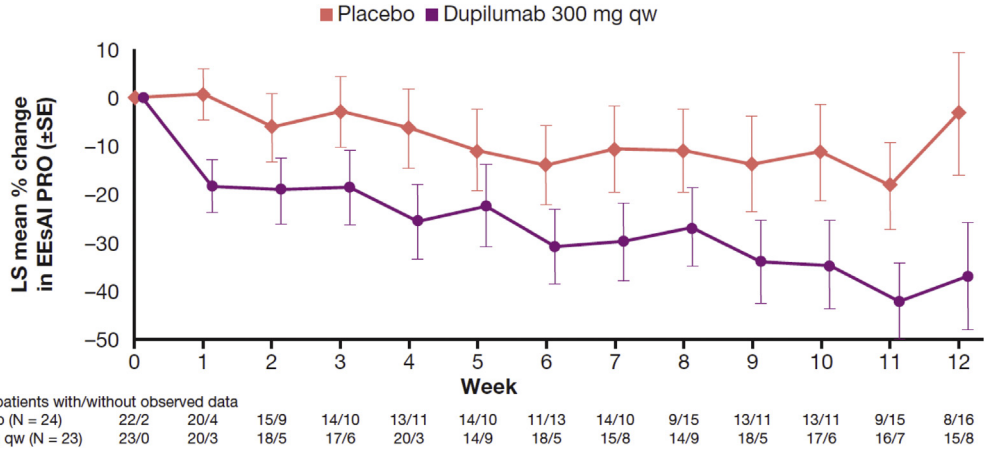
Supplementary Figure 4. Individual peak eosinophil count at baseline and week 12. qw, weekly.



Supplementary Figure 5. Peak eosinophil count (eos/HPF [× 400, 0.3 mm^2]) at baseline and week 12. *P* = comparison of change from baseline to week 12. qw, weekly; SD, standard deviation.



Supplementary Figure 6. Proportion of patients with esophageal intraepithelial eosinophil count reductions at week 12. qw, weekly.



Supplementary Figure 7. EEsAI PRO percent change from baseline during the 12-week analysis period. Missing data were imputed using multiple imputation. qw, weekly; SE, standard error.

Supplementary Table 1. Summary of Study Endpoints[a]

Endpoint	Time Frame
Primary endpoint	
Change in SDI PRO score[b]	Week 10
Secondary endpoints	
Percent change in weekly EEsAI PRO score[c]	Weeks 10 and 12
Change in weekly EEsAI PRO score[c]	Weeks 10 and 12
Percent change in SDI PRO score[b]	Weeks 10 and 12
Change in SDI PRO score[b]	Week 12
Change in EoE-QOL-A PRO score[d]	Week 12
Percentage of patients with SDI PRO response, where response is defined as a decrease of $\geq$3 points compared with baseline[b]	Week 10
Percentage of patients with $\geq$40% improvement in EEsAI PRO score[c]	Week 10
Percent change in overall peak esophageal intraepithelial eos/HPF ($\times$400)	Week 12
Change in EoE-EREFS (endoscopy visual anatomic score)[e]	Week 12
Percentage of patients with use of rescue medication or procedure (eg, esophageal dilation)	Week 12
Safety	
Incidence of TEAEs	12-week treatment period and follow-up (week 28)
Exploratory endpoints	
Change in mean esophageal intraepithelial eosinophil count (eos/HPF), calculated by using peak count from each esophageal site	Week 12
Proportion of patients with esophageal intraepithelial eosinophil count $<$ 1 eos/HPF	Week 12
Change in Collins histology score[f]	Week 12
Change in esophageal distensibility plateau as measured by functional lumen imaging	Week 12

[a]There was no adjustment of multiplicity for the secondary efficacy endpoints.
[b]The SDI PRO total score is the sum of the scores of frequency of dysphagia and intensity of dysphagia; total score range, 0−9 (higher scores indicate worse symptoms). The minimal clinically important difference is 3.[1]
[c]The EEsAI PRO is a 5-component (10 or 11 items) measure of dysphagia, swallowing-associated pain, and strategies aimed at avoiding dysphagia episodes; total score range, 0−100 (higher scores indicate worse symptoms).[2]
[d]The EoE-QOL-A questionnaire includes 30 items related to 5 established domains (eating/diet impact, social impact, emotional impact, disease anxiety, and swallowing anxiety) of daily life experiences using a 5-point Likert-like scale. The EoE-QOL-A score is the average obtained by dividing the total score by the number of questions (for patients without disease, 120/30 = 4). Total scores range from 1 to 5.[3]
[e]The EoE-EREFS measures endoscopically identified EoE esophageal mucosal inflammatory and remodeling features; total scores for edema, rings, furrows, exudate, and stricture range from 0 to 8 (higher scores indicate greater impairment).[4]
[f]The EoE-HSS measures eosinophil density, basal zone hyperplasia, eosinophil abscesses, eosinophil surface layering, surface epithelial alteration, dyskeratotic epithelial cells, and dilated intercellular spaces; scale, 0−63 (higher scores indicate more severe histologic findings).[5]

Supplementary Table 2. History of Food Allergy

Condition	Placebo weekly (n = 24), n (%)	Dupilumab 300 mg weekly (n = 23), n (%)
Patients with at least 1 food allergy history	17 (70.8)	14 (60.9)
Allergy to tree nuts	8 (33.3)	7 (30.4)
Allergy to soy	7 (29.2)	5 (21.7)
Allergy to milk	6 (25.0)	5 (21.7)
Allergy to wheat	6 (25.0)	5 (21.7)
Allergy to shellfish	7 (29.2)	3 (13.0)
Allergy to eggs	6 (25.0)	3 (13.0)
Allergy to peanuts	5 (20.8)	3 (13.0)
Allergy to fish	5 (20.8)	0
Allergy to any other food: corn	1 (4.2)	3 (13.0)
Allergy to sesame or mustard seed	2 (8.3)	2 (8.7)
Allergy to any other food: peas	2 (8.3)	1 (4.3)
Allergy to any other food: barley	1 (4.2)	1 (4.3)
Allergy to any other food: oat	1 (4.2)	1 (4.3)
Allergy to any other food: pea	1 (4.2)	1 (4.3)
Allergy to any other food: all fruit	0	1 (4.3)
Allergy to any other food: all melons	1 (4.2)	0
Allergy to any other food: apple	1 (4.2)	0
Allergy to any other food: avocado	1 (4.2)	0
Allergy to any other food: banana	1 (4.2)	0
Allergy to any other food: beef	1 (4.2)	0
Allergy to any other food: brewer's yeast	1 (4.2)	0
Allergy to any other food: carrot	0	1 (4.3)
Allergy to any other food: carrots	0	1 (4.3)
Allergy to any other food: cashew, walnut, coconut, avocado	1 (4.2)	0
Allergy to any other food: celery	0	1 (4.3)
Allergy to any other food: chocolate	0	1 (4.3)
Allergy to any other food: cinnamon, melon	1 (4.2)	0
Allergy to any other food: coconut, carrot, all melons, tomato	1 (4.2)	0
Allergy to any other food: cucumber	0	1 (4.3)
Allergy to any other food: green bean	0	1 (4.3)
Allergy to any other food: mushroom flavor	1 (4.2)	0
Allergy to any other food: oat	0	1 (4.3)
Allergy to any other food: pineapple, kiwi	0	1 (4.3)
Allergy to any other food: potato	0	1 (4.3)
Allergy to any other food: raspberry	1 (4.2)	0
Allergy to any other food: squash	0	1 (4.3)
Allergy to any other food: strawberry	0	1 (4.3)
Allergy to any other food: tomato	1 (4.2)	0
Allergy to any other food: turkey	0	1 (4.3)
Allergy to any other food: watermelon, tomato, garlic, coconut	1 (4.2)	0

NOTE. The table is sorted in descending order of overall frequency of food allergy.

Supplementary Table 3. Number of Patients With Available Data for the Primary, Secondary, and Exploratory Endpoints by Treatment

Efficacy variable	Time point	Treatment	Number at baseline	Patients with observed value, n (%)	Patients discontinued from the study treatment, n (%)	Patients with missing value, n (%)
SDI PRO[a]	Week 10	Placebo	24	14 (58)	4 (17)	10 (42)
	Week 10	Dupilumab 300 mg weekly	23	17 (74)	1 (4)	6 (26)
Peak esophageal intraepithelial eosinophil count	Week 12	Placebo	24	22 (92)	4 (17)	2 (8)
	Week 12	Dupilumab 300 mg weekly	23	23 (100)	1 (4)	0 (0)
EoE-EREFS[b]	Week 12	Placebo	24	22 (92)	4 (17)	2 (8)
	Week 12	Dupilumab 300 mg weekly	23	23 (100)	1 (4)	0 (0)
EoE-HSS grade[c]	Week 12	Placebo	24	20 (83)	4 (17)	4 (17)
	Week 12	Dupilumab 300 mg weekly	23	22 (96)	1 (4)	1 (4)
EoE-HSS stage[c]	Week 12	Placebo	24	20 (83)	4 (17)	4 (17)
	Week 12	Dupilumab 300 mg weekly	23	23 (100)	1 (4)	0 (0)
Distensibility	Week 12	Placebo	24	12 (50)	4 (17)	12 (50)
	Week 12	Dupilumab 300 mg weekly	23	12 (52)	1 (4)	11 (48)
EEsAI PRO[d]	Week 10	Placebo	24	13 (54)	4 (17)	11 (46)
	Week 10	Dupilumab 300 mg weekly	23	17 (74)	1 (4)	6 (26)
EoE-QOL-A[e]	Week 12	Placebo	24	21 (87.5)	4 (17)	3 (12.5)
	Week 12	Dupilumab 300 mg weekly	23	23 (100)	1 (4)	0 (0)

[a]The SDI PRO total score is the sum of the scores of frequency of dysphagia and intensity of dysphagia; total score range, 0−9 (higher scores indicate worse symptoms). The minimal clinically important difference is 3.[1]
[b]The EoE-EREFS measures endoscopically identified EoE esophageal mucosal inflammatory and remodeling features; total scores for edema, rings, furrows, exudate, and stricture range, 0−8 (higher scores indicate greater impairment).[4]
[c]The EoE-HSS measures eosinophil density, basal zone hyperplasia, eosinophil abscesses, eosinophil surface layering, surface epithelial alteration, dyskeratotic epithelial cells, and dilated intercellular spaces; scale range, 0−63 (higher scores indicate more severe histologic findings).[5]
[d]The EEsAI PRO is a 5-component (10 or 11 items) measure of dysphagia, swallowing-associated pain, and strategies aimed at avoiding dysphagia episodes; total score range, 0−100 (higher scores indicate worse symptoms).[2]
[e]The EoE-QOL-A questionnaire includes 30 items related to 5 established domains (eating/diet impact, social impact, emotional impact, disease anxiety, and swallowing anxiety) of daily life experiences using a 5-point Likert-like scale. The EoE-QOL-A score is the average obtained by dividing the total score by the number of questions (for patients without disease, 120/30 = 4). Total scores range from 1 to 5.[3]

Supplementary Table 4. Primary, Secondary, and Exploratory Endpoints: All Observed Values

Endpoints	Placebo (n = 24)	Dupilumab 300 mg weekly (n = 23)	Difference vs placebo (95% CI)	*P* value vs placebo
SDI PRO score[a]				
Week 10, n	14	17		
LS mean change from baseline (SE)	–1.1 (0.67)	–3.2 (0.61)	–2.2 (–4.06 to –0.33)	.0226
LS mean percent change from baseline (SE)	–15.3 (10.57)	–49.3 (9.59)	–34.1 (–63.34 to –4.84)	.0240
Peak esophageal intraepithelial eosinophil count				
Week 12, n	22	23		
LS mean change from baseline (SE), *eos/HPF*	–9.7 (9.65)	–96.4 (9.44)	–86.7 (–114.00 to –59.37)	<.0001
LS mean percent change from baseline (SE)	12.3 (12.31)	–93.3 (12.04)	–105.6 (–140.47 to –70.79)	<.0001
EoE-EREFS total score[b]				
Week 12, n	22	23		
LS mean change from baseline (SE)	–0.3 (0.33)	–1.9 (0.32)	–1.6 (–2.53 to –0.65)	.0015
EoE-HSS score (excluding lamina propria)[c]				
Total grade (severity) score at Week 12, n	20	22		
All LS mean percent change from baseline (SE)	2.3 (6.48)	–65.4 (6.17)	–67.7 (–85.84 to –49.51)	<.0001
Total stage (extent) score at week 12, n	20	23		
All LS mean percent change from baseline (SE)	–3.4 (4.92)	–58.6 (4.58)	–55.1 (–68.76 to –41.53)	<.0001
Distensibility plateau				
Week 12, n	12	12		
LS mean change from baseline (SE), *mm*	–1.01 (0.46)	1.85 (0.46)	2.85 (1.48 to 4.22)	.0003
LS mean percent change from baseline (SE)	–5.6 (3.02)	13.0 (3.02)	18.5 (9.58 to 27.47)	.0003
Weekly EEsAI PRO score[d]				
Week 10, n	13	17		
LS mean change from baseline (SE)	–11.1 (6.65)	–27.8 (5.81)	–16.7 (–34.91 to 1.46)	.0699
LS mean percent change from baseline (SE)	–16.7 (11.21)	–42.2 (9.80)	–25.6 (–56.23 to 5.06)	.0981
EoE-QOL-A total score[e]				
Week 12, n	21	23		
LS mean change from baseline (SE)	0.44 (0.143)	0.79 (0.137)	0.35 (–0.054 to 0.751)	.0879

[a]The SDI PRO total score is the sum of scores of frequency of dysphagia and intensity of dysphagia; total score range, 0−9 (higher scores indicate worse symptoms). The minimal clinically important difference is 3.[30]
[b]The EoE-EREFS measures endoscopically identified EoE esophageal mucosal inflammatory and remodeling features; total scores for edema, rings, furrows, exudate, and stricture range, 0−8 (higher scores indicate greater impairment).
[c]The EoE-HSS measures eosinophil density, basal zone hyperplasia, eosinophil abscesses, eosinophil surface layering, surface epithelial alteration, dyskeratotic epithelial cells, and dilated intercellular spaces; scale range, 0−63 (higher scores indicate more severe histologic findings).
[d]The EEsAI PRO is a 5-component (10-item) measure of dysphagia, swallowing-associated pain, and strategies aimed at avoiding dysphagia episodes; total score range, 0−100 (higher scores indicate worse symptoms).
[e]The EoE-QOL-A questionnaire includes 30 items related to 5 established domains (eating/diet impact, social impact, emotional impact, disease anxiety, and swallowing anxiety) of daily life experiences using a 5-point Likert-like scale. The scores for the EoE-QOL-A are the average score, equal to the total score/number of questions (120/30 = 4 for patients without disease). Total scores range from 1 to 5.

Supplementary Table 5. Sensitivity Analyses for Primary Endpoint

LS mean change from baseline (SE) in SDI score at week 10 by missing data imputation method	Placebo (n = 24)	Dupilumab 300 mg every week (n = 23)	LS mean difference vs placebo (95% CI)	*P* value vs placebo
LOCF method[a]	−1.2 (0.48)	−3.0 (0.49)	−1.8 (−3.20 to −0.43)	.0112
WOCF method[b]	−0.9 (0.48)	−2.7 (0.48)	−1.8 (−3.16 to −0.40)	.0127
All observed values[c]	−1.1 (0.67)	−3.2 (0.61)	−2.2 (−4.06 to −0.33)	.0226

[a]LOCF method: data were set to *missing* after rescue treatment. Missing values were imputed by using the LOCF method. In the event that patients had only baseline values without any postbaseline values, their baseline values were carried forward to impute postbaseline missing values.
[b]WOCF method: data were set to *missing* after rescue treatment. Missing values were imputed by using the WOCF method. In the event that patients had only baseline values without any postbaseline values, WOCF would not impute for postbaseline missing values.
[c]All observed values: all observed values, regardless of whether rescue medication was used, were included in the analysis, with no imputation for missing values.

Supplementary Table 6. Key TEAEs During the Entire Study Period, Including the 16-Week Follow-Up Period

TEAEs	Placebo (n = 24), n (%)	Dupilumab300 mg weekly (n = 23), n (%)
≥1 TEAE	16 (67)	21 (91)
≥1 serious adverse event[a]	0	3 (13)
Adverse events leading to treatment discontinuation	0	1 (4)
Deaths	0	0
Terms with a difference of number of patients between 2 groups ≥3		
Injection-site reaction (HLT)	7 (29)	13 (57)
Injection-site erythema (PT)	2 (8)	8 (35)
Injection-site inflammation (PT)	0	3 (13)
Injection-site rash (PT)	0	3 (13)
Upper respiratory tract infection (HLT)	6 (25)	9 (39)
Nasopharyngitis (PT)	2 (8)	5 (22)
Musculoskeletal, connective tissue pain, and discomfort (HLT)	0	4 (17)

HLT, MedDRA high-level term; PT, MedDRA preferred term

[a]SAEs were considered to be unrelated to the investigational medicinal product; 3 events in 3 patients in the dupilumab group were food allergy, creatine phosphokinase elevation, and spontaneous abortion; a female patient (30 years old) with a prior history of anaphylaxis to tree nuts and moderate allergy to milk and eggs developed a sudden episode of throat swelling after ingestion of a vegan shake; the episode was resolved with an epinephrine injection.