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

Short title: Dupilumab in Eosinophilic Esophagitis

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Abbreviations used in this paper:

ANCOVA, analysis of covariance; CI, confidence interval; EEsAI, Eosinophilic Esophagitis Activity Index; EoE, eosinophilic esophagitis; EoE-HSS, eosinophilic esophagitis histology scoring system; EoE-QOL-A, Adult Eosinophilic Esophagitis Quality of Life; eos/HPF, eosinophils per high-power field; EREFS, Endoscopic Reference Score; HLT, high-level term; HSS, histology scoring system; LS, least squares; MedDRA, Medical Dictionary for Regulatory Activities; PPI, proton pump inhibitor; PRO, patient-reported outcome; PT, preferred term; qw, once a week; SAE, serious adverse event; SD, standard deviation; SDI, Straumann Dysphagia Instrument; SE, standard error; TEAE, treatment-emergent adverse event.

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Conflicts of interest

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ABSTRACT

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 4 (IL4) receptor, inhibits IL4 and IL13 signaling. Dupilumab is effective in 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 dysphagia 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. Subjects 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 patient-reported outcome (SDI-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 vs a mean reduction of 1.3 in the placebo group ($P=.0304$). At week 12, dupilumab reduced peak esophageal intraepithelial eosinophil count by a mean 86.8 eosinophils per high-power field (reduction of 107.1%; $P<.0001$ compared with baseline), the EoE-HSS severity score by 68.3% ($P<.0001$ vs baseline), and the endoscopic reference score by 1.6 ($P=.0006$ compared with baseline). Dupilumab increased esophageal distensibility by 18% compared with baseline ($P<.0001$). 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 no: NCT02379052

KEY WORDS: 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-4, interleukin-5, and interleukin-13.^{4,5} Chronic esophageal inflammation leads to remodeling, stricture formation, and fibrosis, with commensurate worsening of dysphagia.⁶⁻⁸ Patients with EoE demonstrate a marked reduction in esophageal 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 around the world (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

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 VelocImmune[®]-derived monoclonal antibody^{16,17} directed against the interleukin-4 receptor- α component of the type 2 receptor, and inhibits signaling of both interleukin-4

and interleukin-13.¹⁸ The efficacy of dupilumab in several settings of allergic/atopic/type 2 disease demonstrates that interleukin-4 and interleukin-13 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 is also being studied as an adjunct for peanut and grass allergy desensitization.²⁷ Therapeutics targeting interleukin-5 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} Following the efficacy of dupilumab observed 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 multi-center, 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, Inc.). 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 guidelines³⁰ were eligible to participate. Active esophageal inflammation was to be evident at screening (ie, a peak cell count ≥ 15 eosinophils per high-power field [eos/HPF]: 400X magnification of a 0.3mm² 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' 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 screen-failed 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 prior to screening. Detailed inclusion and exclusion criteria are provided in the Supplementary Appendix, Section 1.

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 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 Appendix, Section 2), while continuing study treatment. Patients using stable doses of PPIs at screening were permitted to continue on the same dosing regimen until the end-of-treatment visit; those not using PPIs in the 8 weeks prior to 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 score³¹ from baseline to Week 10. Secondary SDI PRO endpoints included percentage change in SDI PRO score from baseline to Week 10 and percentage of patients with a SDI PRO score decrease of ≥ 3 points relative to baseline at Week 10, which was proposed by Straumann and colleagues 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 anatomical measures of esophageal disease (ie, exudate, rings, edema, furrows, and strictures), distensibility measures of esophageal function, as well as additional PROs. These endpoints were assessed by measuring percentage 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 percentage change in weekly Eosinophilic Esophagitis Activity Index (EEsAI) PRO score³³ from baseline to Week 10, percentage of patients with $\geq 40\%$ improvement³³ 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 v.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 (SAEs) from baseline to Week 28.

Exploratory histology endpoints were change in LS mean peak esophageal intraepithelial eosinophil count (eos/HPF) (calculated 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/HPF³⁷ and < 15 eos/HPF (post hoc analysis), and change in EoE histology scoring system (EoE-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 Taking into account an assumed 15% dropout rate, 22 patients per treatment arm were to be enrolled. The primary and secondary efficacy endpoints were analyzed in the full analysis set, which included all randomized patients. The analysis was conducted 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). Due to a substantial imbalance at baseline in the number of patients in the 2 randomization strata (only 13% of patients in the strata 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. SAEs 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 using SAS software, version 9.4 (SAS Institute, Cary, NC). The full statistical methodology is summarized in Supplementary Appendix, Section 3.

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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 screen failure (32/33 patients [97%]), in particular, inadequate frequency of dysphagia, failure to meet histologic criteria, failure to meet stabilized diet for at least 6 weeks criteria, and failure to meet signing informed consent criteria; one 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 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 (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 prior to 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; $n = 17$ of 23 dupilumab-treated patients).

At Week 10, dupilumab significantly improved the SDI PRO score from baseline (least squares [LS] mean change, -3.0 vs -1.3 for placebo; $P=.0304$) (Figure 1A 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, outcomes of 3 prespecified sensitivity analyses, which include different imputation methods (ie, LOCF and WOCF) and all observed values regardless of rescue treatment use, were similar to those of the primary analysis (Supplementary Table 5).

SECONDARY SDI PROs

At Week 10, the LS mean percentage change from baseline in SDI score was also significantly improved with dupilumab (-45.1 vs -18.6 for placebo; $P=.0312$) (Figure 1B 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% 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; Supplementary Figure 5). The LS mean (SE) 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; 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, Figure 1C).

Compared with placebo, dupilumab treatment led to a reduction in total EoE-HSS severity score (grade; LS mean % change -68.3 [95% CI, -86.2 to -50.3; $P < .0001$]) and total EoE-HSS extent score (stage; LS mean % change -54.6 [95% CI, -68.1 to -41.0; $P < .0001$]) that take into account histologic findings for all regions (proximal, mid, and distal) of the esophagus at Week 12 (Table 2 and Figures 1D and 1E). The representative esophageal mucosal pinch biopsies collected at baseline and Week 12 are shown in Supplementary 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 1F). Analyses for all observed values are provided in Supplementary Table 5.

SECONDARY PROs AND QUALITY-OF-LIFE OUTCOMES

Dupilumab treatment provided a numerical improvement in percentage change in weekly EEsAI PRO score of -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, Supplementary Figure 7). The proportion of patients with $\geq 40\%$ 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 to 41.6; $P=.0479$] and 21.7% [95% CI, 4.9 to 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 comprise the EoE-QOL-A. No patient in either treatment group received rescue medication or any other interventional procedure such as esophageal dilatation 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) as well as 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 as well as 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 term) occurring in ≥ 3 patients in either the dupilumab or placebo groups were nonserious injection-site erythema (35% vs 8%, respectively) and nasopharyngitis (17% vs 4%, respectively) (Table 3). Injection-site reactions by MedDRA high-level terms were reported in 13 (57%) dupilumab-treated patients vs 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 due to a TEAE (nail disorder; see Supplementary Appendix 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 Appendix for patient narrative). During the treatment period, conjunctivitis was observed in neither dupilumab- nor placebo-treated patients, despite a prior history of 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 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 demonstrate that interleukin-4 and interleukin-13 are central pathological mediators of esophageal inflammation and dysfunction in adult patients with active EoE. Studies with other targeted biologic agents have failed to demonstrate 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-interleukin-5) reduced esophageal intraepithelial eosinophil counts, but did not significantly improve symptoms compared with placebo.^{13,28,29} Interleukin-13-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 mAb) did not improve either dysphagia or histologic features of EoE compared with placebo, suggesting pathogenesis is not mediated by IgE, despite the association of EoE with comorbid allergies.⁴⁴

In this proof-of-concept study, dual blockade of interleukin-4 and interleukin-13 signaling with dupilumab improved both esophageal inflammation and clinical symptoms in patients with EoE. These data provide further evidence for the importance of interleukin-4/interleukin-13 pathways in type 2 inflammation and suggest that their dual inhibition may be a more effective inhibitor of type 2 inflammation than interleukin-5, interleukin-13, or IgE-targeted agents alone. The more fundamental roles of interleukin-4 and interleukin-13 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 asthma patients.

The high rate of screen failures observed in our study (41%) is consistent with other recently published, randomized controlled trial data in eosinophilic esophagitis. The United States 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 screen failures. In our study, the most common reason for screen failure was failing to meet eligibility criteria (32 of 33 patients), in particular, inadequate frequency of dysphagia, failure to meet histologic criteria, failure to meet stabilized diet for at least 6 weeks criteria, and failure to meet signing informed consent criteria.

This study has a number of limitations and strengths. At the time 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, since at baseline there was an imbalance in the

recruitment of patients with an SDI score >7 (only 13% of all recruits); interpretation of the findings in patients with more severe disease should therefore be made with caution. In addition, some patients had missing data for evaluation of SDI and EEAI 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, which were consistent across a range of sensitivity analyses. Though 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, EEAI 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 characteristic (SDI total score and frequency/number of dysphagia episodes vs disease activity at baseline [EREFS, EoE-HSS, peak eosinophils]).⁴⁶ While these findings support the concept of evaluating both the severity and extent of multiple pathologic features in EoE biopsies, the sample size is small. Further correlation analyses are planned in a larger patient population with broader disease activity.

In conclusion, dupilumab is the first targeted biologic agent to improve dysphagia, histologic and endoscopic measures of disease, as well as 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.

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.e8.
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.e1-2.
8. **Dellon ES, Hirano I**. Epidemiology and natural history of eosinophilic esophagitis. *Gastroenterology* 2018; 154:319-322.e3.
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.e1.
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.e3.
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. Available from: https://www.ema.europa.eu/en/documents/product-information/jorveza-epar-product-information_en.pdf.
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 6Mb 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. American Academy of Dermatology meeting, March 2017.
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; 389:2287-2303.
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; 387:40-52.
 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 β 2 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. Available at: <https://www.prnewswire.com/news-releases/regeneron-reports-second-quarter-2018-financial-and-operating-results-300690715.html>.
 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; American College of Gastroenterology. 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.e21.
34. Bajaj S, Taft T, Keefer L, et al. Validity, usability, and acceptability of the Eosinophilic Esophagitis Quality of Life scale for adults (EoE-QOL-A). *Gastroenterology* 2012; 142:S-434. Abstract.
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; International Eosinophilic Esophagitis Activity Index Study Group. Symptoms have modest accuracy in detecting endoscopic and histologic remission in adults with eosinophilic esophagitis. *Gastroenterology* 2016; 150:581-590.e4.

37. **Dellon ES**, Katzka DA, Collins MH, et al; MP-101-06 Investigators. Budesonide oral suspension improves symptomatic, endoscopic, and histologic parameters compared with placebo in patients with eosinophilic esophagitis. *Gastroenterology* 2017; 152:776-786.e5.
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; 30:1-8.
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, Boeckstaens 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 and 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. 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-Dayana 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. 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. Presented at Digestive Disease Week, June 2-5, 2018; Washington, DC.

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FIGURES

Figure 1. (A) LS mean change from baseline in SDI PRO score at Week 10. (B) LS mean percentage change in peak esophageal intraepithelial eosinophil count. (C) LS mean change in EoE-EREFS. (D) LS mean percentage change in EoE-HSS total grade score. (E) LS mean percentage change in EoE-HSS total stage score. (F) LS mean percentage change in distensibility at Week 12. Data EoE-EREFS, Eosinophilic Esophagitis Endoscopic Reference Score; EoE-HSS, eosinophilic esophagitis histology scoring system; LS, least squares; PRO, patient-reported outcome; SDI, Straumann Dysphagia Instrument; SE, standard error; n, number of patients with observed data; N, number of patients with imputed data. Missing data were imputed with multiple imputations.

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

TABLES

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

Characteristic	Placebo (n = 24)	Dupilumab 300 mg qw (n = 23)
Age, mean (SD) — yr	36.1 (12.75)	33.1 (8.70)
Male sex — no. (%)	10 (42)	13 (57)
White race — no. (%)	21 (87.5)	23 (100)
Prior esophageal dilations, mean (SD) — no.	3.9 (3.31)	5.7 (8.03)
Any prior use of a glucocorticoid for EoE — no. (%)	9 (38)	7 (30)
Prior history of treatment with high-dose PPIs at baseline — no. (%)	24 (100)	23 (100)
PPI treatment ongoing at baseline	15 (62.5)	14 (60.9)
Duration of eosinophilic esophagitis, mean (SD) — yr	5.0 (3.33)	3.6 (3.74)
>1 comorbid atopic disease — no. (%)	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, mean (SD) — $\times 10^9/L$	0.43 (0.29)	0.31 (0.18)
Total IgE, mean (SD) — kU/L	486.2 (900.7)	217.8 (288.8)
SDI PRO score, mean (SD) — scale 0–9 ^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 (eos/HPF) of proximal, mid, distal regions, mean (SD)	101.1 (57.12)	102.1 (53.46)
Proximal eosinophil count (eos/HPF), mean (SD)	50.5 (47.16)	49.2 (45.76)
Mid eosinophil count (eos/HPF), mean (SD)	96.0 (59.73)	77.3 (41.67)
Distal eosinophil count (eos/HPF), mean (SD)	69.2 (33.10)	75.2 (59.62)
EoE-EREFS total score, mean (SD) — scale 0–8 ^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, mean (SD), mm	17.6 (2.88)	18.7 (3.80)

Weekly EEsAI PRO score, mean (SD) — scale 0–100 ^e	62.2 (16.45)	62.0 (18.36)
EoE-QOL-A ^f	3.11 (0.995)	3.02 (0.899)

EEsAI, symptom-based Eosinophilic Esophagitis Activity Index; EoE-EREFS, Eosinophilic Esophagitis Endoscopic Reference Score; EoE-HSS, eosinophilic esophagitis histology scoring system; eos/HPF, eosinophils per high-power field; PRO, patient-reported outcome; SD, standard deviation; SDI, Straumann Dysphagia Instrument; qw, once a week.

^aThe 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.

^bSDI 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

^cThe 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).

^dThe 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).

^eEEsAI 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).

^fEoE-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 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.

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Table 2. Primary, Secondary, and Exploratory Endpoints

	Placebo (n = 24)	Dupilumab 300 mg qw (n = 23)	Difference vs placebo (95% CI)	P value vs placebo
SDI PRO score ^a				
Week 10 — no./imputed no.	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 percentage 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 — no. (%)	3 (13)	9 (39)	27 (-3 to 51)	.0490
Peak esophageal intraepithelial eosinophil count (eos/HPF)				
Week 12 — no./imputed no.	22/2	23/0		
LS mean change from baseline (SE)	-8.0 (9.6)	-94.8 (9.4)	-86.8 (-113.2 to -60.5)	<.0001

	Placebo (n = 24)	Dupilumab 300 mg qw (n = 23)	Difference vs placebo (95% CI)	P value vs placebo
LS mean % 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 — no. (%)	0.0	3 (13.0)	13.0 (-15.72 to 39.73)	.1092
Patients with response ≤6 eos/HPF — no. (%)	0.0	15 (65.2)	65.2 (38.31 to 83.62)	<.0001
Patients with response <15 eos/HPF — no. (%)	0.0	19 (82.6)	82.6 (59.18 to 95.05)	<.0001
EoE-EREFS total score ^b				
Week 12 — no./imputed no.	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 — no./imputed no.	20/4	22/1		
All LS mean percentage change from baseline	3.2 (6.7)	-65.1 (6.3)	-68.3 (-86.2 to -50.3)	<.0001

	Placebo (n = 24)	Dupilumab 300 mg qw (n = 23)	Difference vs placebo (95% CI)	P value vs placebo
(SE)				
Total stage (extent) score at Week 12 — no./imputed no.	20/4	23/0		
All LS mean percentage 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 — no./imputed no.	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 percentage 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 — no./imputed no.	13/11	17/6		

	Placebo (n = 24)	Dupilumab 300 mg qw (n = 23)	Difference vs placebo (95% CI)	P value vs placebo
LS mean change from baseline (SE)	-9.0 (5.6)	-22.9 (5.0)	-13.9 (-28.5 to 0.8)	.0635
LS mean percentage change from baseline (SE)	-11.3 (9.9)	-34.6 (9.1)	-23.2 (-49.7 to 3.2)	.0850
Patients with $\geq 40\%$ improvement — no. (%)	2 (8.3%)	6 (26.1%)	17.8 (-11.5 to 43.6)	.1365
Patients with ≥ 15 -point score improvement — no. (%)	6 (25.0)	11 (47.8)	22.8 (-7.22 to 48.72)	.1351
Patients with ≥ 30 -point score improvement — no. (%)	2 (8.3)	6 (26.1)	17.8 (-11.54 to 43.55)	.1365
Patients with EEsAI score ≤ 20 — no. (%)				
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				

	Placebo (n = 24)	Dupilumab 300 mg qw (n = 23)	Difference vs placebo (95% CI)	P value vs placebo
Week 12 — no./imputed no.	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

Missing data were imputed using multiple imputation. EEsAI, symptom-based Eosinophilic Esophagitis Activity Index; EoE-EREFS, Eosinophilic Esophagitis Endoscopic Reference Score; EoE-HSS, eosinophilic esophagitis histology scoring system; EoE-QOL-A, Adult Eosinophilic Esophagitis Quality of Life; eos/HPF, eosinophils per high-power field; LS, least squares; PRO, patient-reported outcome; SD, standard deviation; SDI, Straumann Dysphagia Instrument; SE, standard error; qw, once a week.

^aSDI 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

^bThe 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).

^cThe 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).

^dEEsAI 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).

^eEoE-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 scale. The scores for EoE-QOL-A score is the average score, equaled the total score/number of questions ($120/30 = 4$ for patients without disease). Total scores range from 1 to 5.

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

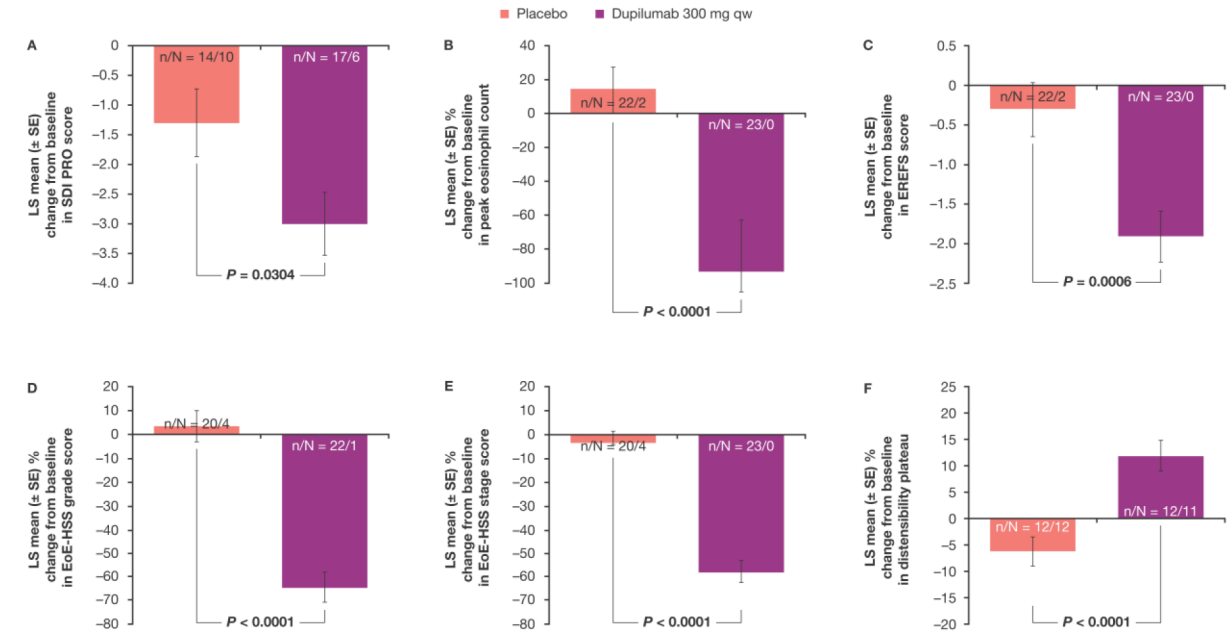
n (%)	Placebo (n = 24)	Dupilumab 300 mg qw (n = 23)
≥1 TEAE	15 (63)	18 (78)
≥1 SAE ^a	0	0
AEs leading to treatment discontinuation	0	1 (4)
Deaths	0	0
Terms with a difference of number of patients between two groups ≥3		
Injection-site reactions (HLT)	7 (29)	13 (57)
Injection-site erythema (PT)	2 (8)	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)

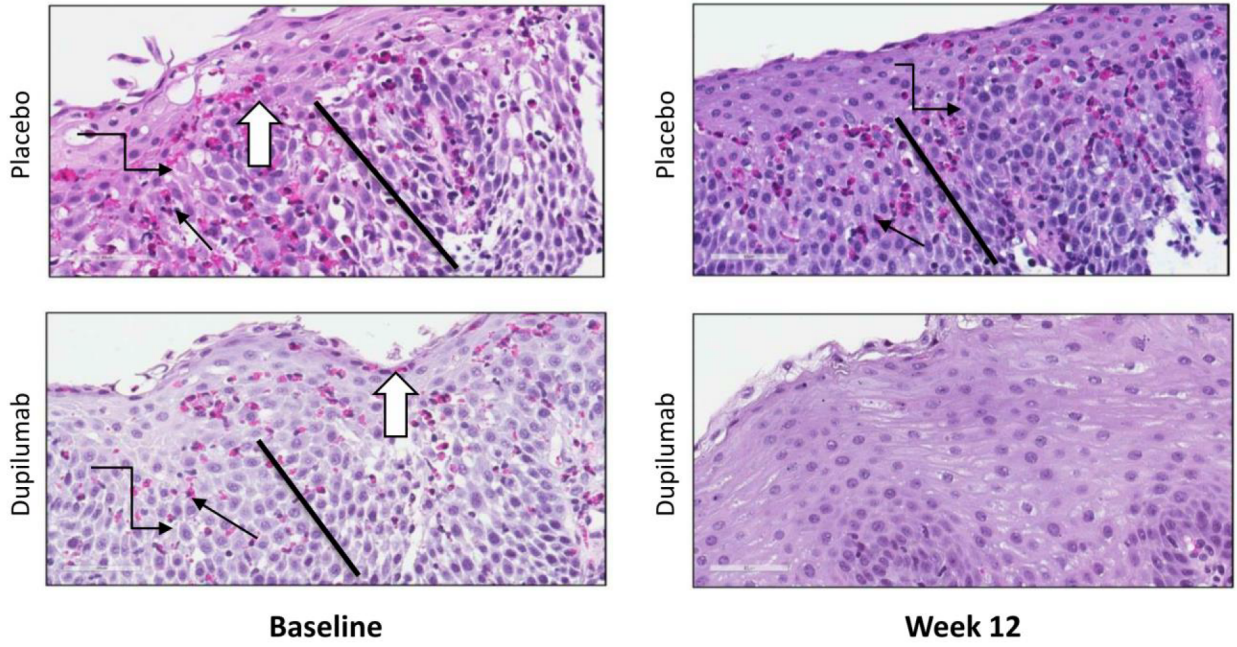
AE, adverse event; HLT, MedDRA high-level term; MedDRA, Medical Dictionary for Regulatory Activities; PT, MedDRA preferred term; SAE, serious AE; TEAE, treatment-emergent adverse event; qw, once a week.

^aSAEs 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 (aged 30 years) 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.

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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.

LAY SUMMARY Dupilumab is safe and effective for treatment of EoE, reducing symptoms and also correcting clinical and structural abnormalities associated with this disease.

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Hirano I, Dellon ES, Hamilton JD, et al. Dupilumab Efficacy in Adults With Active Eosinophilic Esophagitis: A Randomized, Placebo-Controlled Phase 2 Trial.

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**Dupilumab Efficacy in Adults With Active Eosinophilic Esophagitis: A
Randomized, Placebo-Controlled Phase 2 Trial**

Ikuo Hirano, Evan S. Dellon, Jennifer D. Hamilton, Margaret H. Collins, Kathryn Peterson,
Mirna Chehade, Alain M. Schoepfer, Ekaterina Safroneeva, Marc E. Rothenberg, Gary W. Falk,
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Author names in bold designate shared co-first authors.

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1. Patient eligibility criteria

1.1 Inclusion criteria

1. Male or female, 18 to 65 years old
2. Documented diagnosis of EoE by endoscopy prior to or at screening

Note: Must include a demonstration of intraepithelial eosinophilic infiltration (peak cell count ≥ 15 eosinophils/high power field [eos/HPF] [400X, 0.3mm²]) 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) proton pump inhibitors (PPIs)
3. 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 prior to 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
4. Must remain on a stabilized diet for at least 6 weeks prior to 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
5. SDI PRO score ≥ 5 at screening and baseline
6. Documented history of or presence of 1 or more of any of the following:
 - Allergic disease (eg, allergic asthma, allergic rhinitis, atopic dermatitis, or food allergies)
 - Blood eosinophil count ≥ 0.25 GI/L
 - Serum total immunoglobulin E (IgE) ≥ 100 kU/L
7. Willing and able to comply with all clinic visits and study-related procedures
8. Able to understand and complete study-related questionnaires
9. Provide signed informed consent
10. Endoscopy with photographs performed at screening, with a demonstration of intraepithelial eosinophilic infiltration (peak cell count ≥ 15 eos/HPF) in at least 2 of the 3 biopsied esophageal regions (proximal, mid, or distal)

1.2 Exclusion criteria

1. Prior participation in a dupilumab (anti–interleukin-4R) 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 prior to screening
4. Any esophageal stricture unable to be passed with a standard, diagnostic, adult (9mm to 10mm) 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 prior to 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, prior to screening
8. Use of systemic glucocorticoids within 3 months or swallowed topical glucocorticoids within 6 weeks prior to screening
9. Use of inhaled or nasal glucocorticoids within 3 months prior to screening and during the study, except stable dose for at least 3 months prior to screening biopsy (which cannot be changed during the study)
10. Treatment with oral immunotherapy (OIT) within 6 months prior to screening
11. Allergen immunotherapy (sublingual immunotherapy [SLIT] and/or subcutaneous immunotherapy [SCIT]), unless on stable dose for at least 1 year prior to 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 [IFN- γ], Janus kinase inhibitors, azathioprine, methotrexate, leukotriene inhibitors (except stable dose for at least 3 months prior to screening))

13. Diagnosed with active parasitic infection; 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 prior to screening
15. Use of oral antibiotics/anti-infectives within 2 weeks prior to screening
16. Known or suspected immunosuppression, including history of invasive opportunistic infections (eg, tuberculosis, non-tuberculous mycobacterial infections, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis) despite infection resolution, or 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 (HIV) infection
18. Positive or indeterminate hepatitis B surface antigen (HBsAg) or hepatitis C antibody at screening
19. Elevated transaminases (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]) more than 3 times the upper limit of normal (ULN) at screening
20. History of malignancy within 5 years prior to 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 prior to screening
22. Any other medical or psychological condition including relevant laboratory abnormalities at screening that, in the opinion of the investigator, suggest a new and/or insufficiently understood disease, may present an unreasonable risk to the study patient as a result of his/her participation in this clinical trial, may make the patient's participation unreliable, or may interfere with study assessments; the specific justification for patients excluded under this criterion will be noted in study documents (chart notes, case report form [CRF], 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 prior to 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 last dose of study drug; these include hormonal contraceptives, an intrauterine device, or double barrier contraception (ie, condom + diaphragm), or male partner with documented vasectomy
- * For females, menopause is defined as at least 12 consecutive months without menses (if in question, follicle stimulating hormone of ≥ 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

2. 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 prior to screening could not start PPI therapy prior to the end-of-treatment visit.

3. 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 (FAS) was imputed 50 times to generate 50 complete datasets by using the SAS MI procedure following 2 steps: 1) 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 the patient; 2) the missing data at subsequent visits were imputed 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 analysis of covariance (ANCOVA) model (consisting of the treatment group and the baseline SDI value), and observed post-baseline efficacy values up to Week

10. Data from each of the 50 complete datasets were analyzed using ANCOVA with treatment group as fixed effect and baseline SDI value as 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 least squares (LS) mean changes from baseline to Week 10, and other time points for each treatment group, with the corresponding standard error, confidence interval, 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 dataset to missing after the use of rescue medication, then the post-baseline last observation carried forward (LOCF) method was used to impute missing data; 3) ANCOVA with efficacy dataset to missing after the use of rescue medication, then the post-baseline worst observation carried forward (WOCF) method was used to impute missing data; and 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, while 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 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.

4. 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 female patient with eosinophilic esophagitis was randomized to receive study drug REGN668 (loading dose 600 mg SC, followed by 300 mg SC 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 her 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.

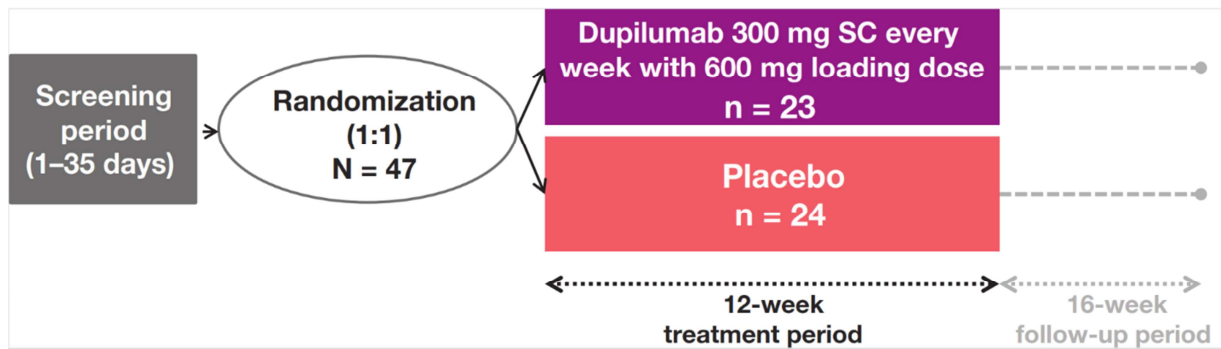
5. Patient narrative 2

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

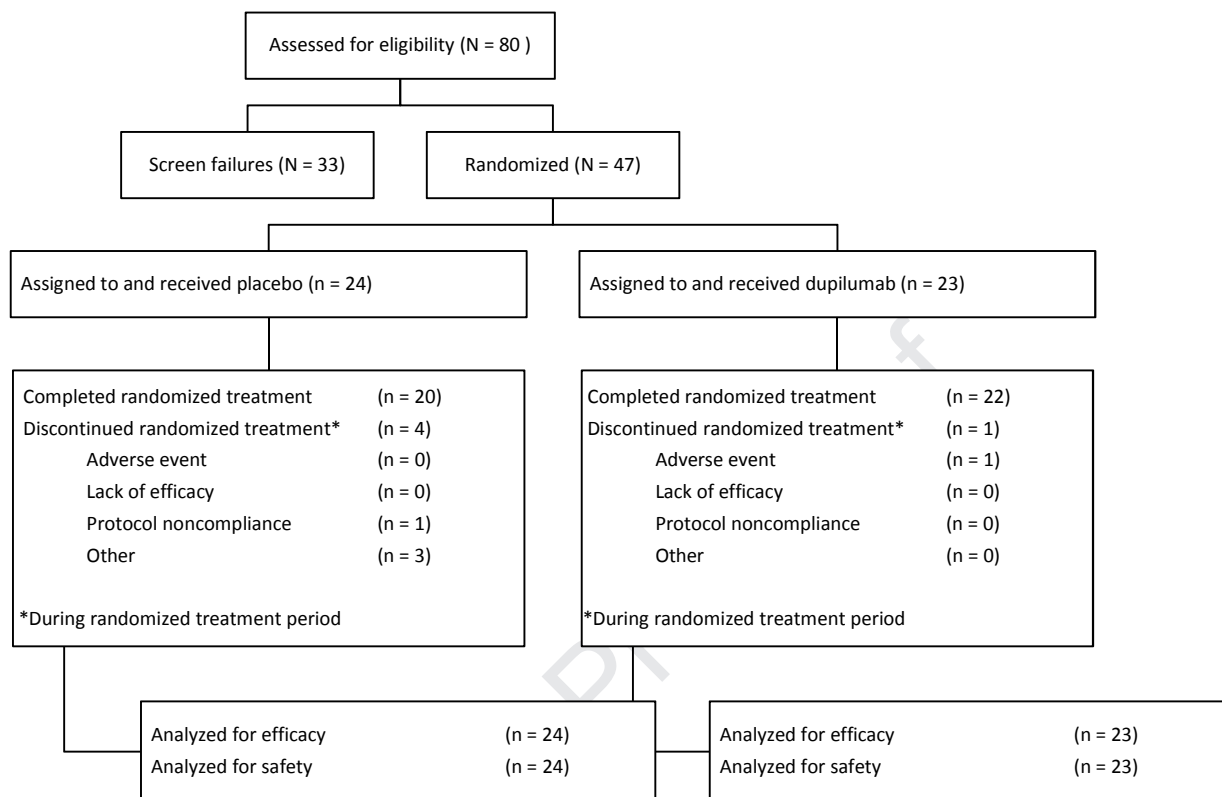
A 44-year-old female patient with eosinophilic esophagitis was randomized on September 30, 2016 to receive study drug REGN668 (loading dose 600 mg SC, followed by 300 mg SC weekly thereafter). The patient's medical history included cervical cancer, cervix removal, attention deficit disorder, dry eye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

On December 22, 2016, after 83 days of study treatment, the patient had an initial positive serum, urine pregnancy test with serum human chorionic gonadotropin 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 delivery 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 prior to 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 to have 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 was negative.

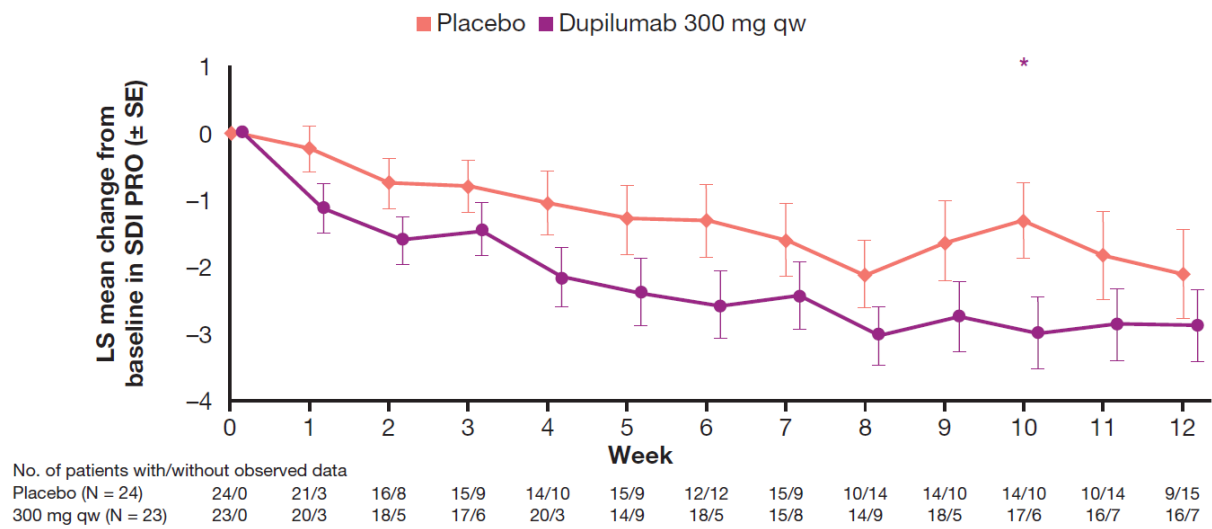
6. Tables and figures



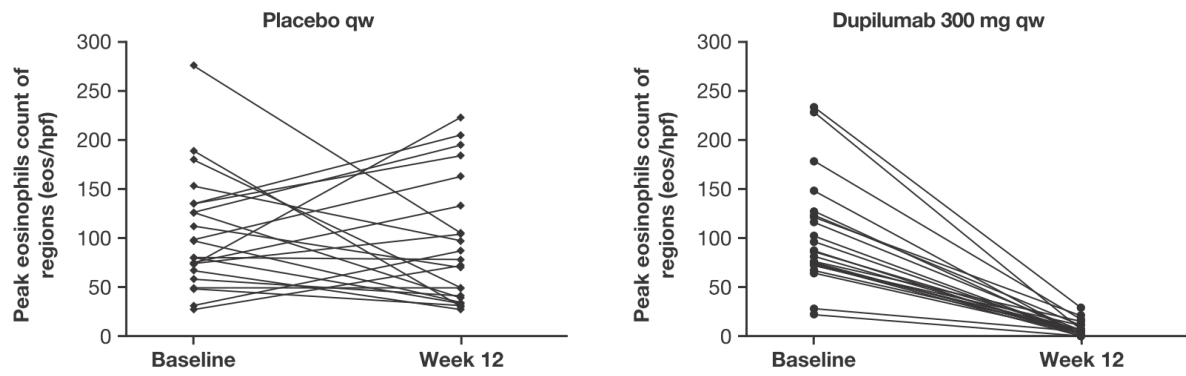
Supplementary Figure 1. Study design. Patients received weekly injections of study drug from Day 1 to Week 12 (with the last dose at Week 11). Follow-up visits occurred every 4 weeks. SC, subcutaneous.



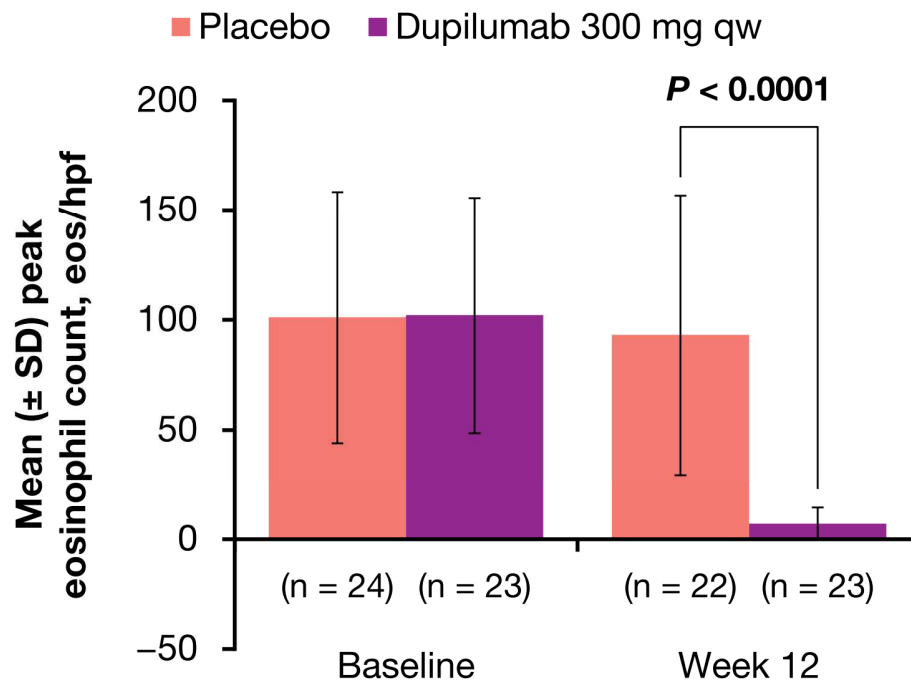
Supplementary Figure 2. CONSORT diagram.



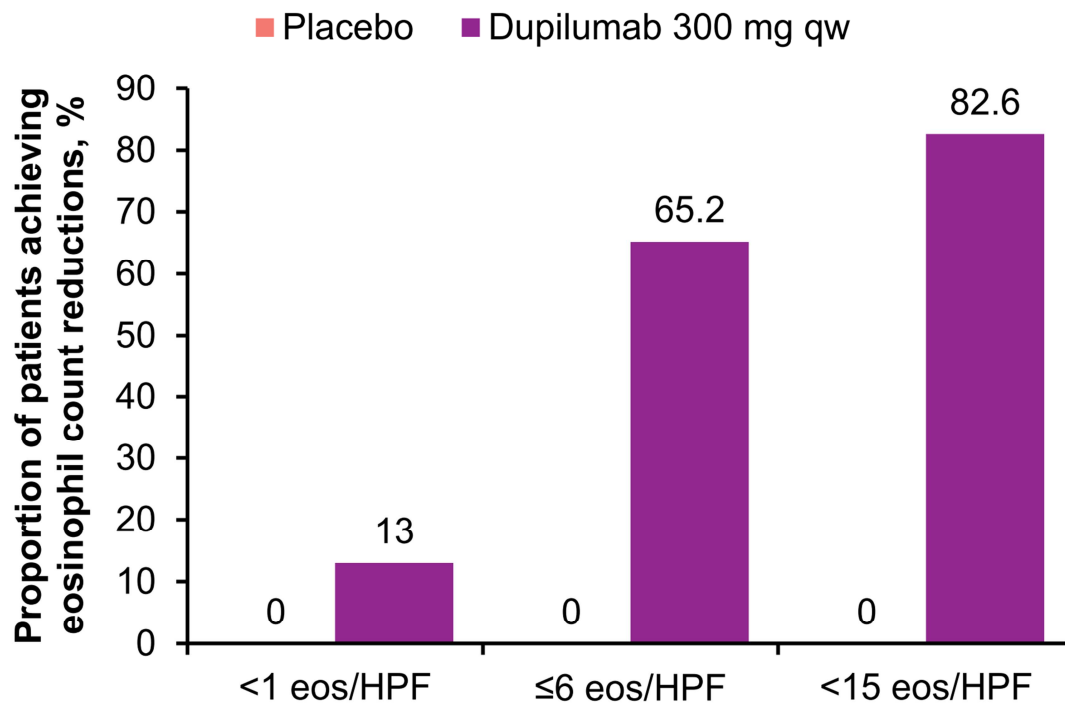
Supplementary Figure 3. SDI PRO change from baseline during the 12-week analysis period. * $P < .05$ vs placebo. LS, least squares; PRO, patient-reported outcome; qw, weekly; SE, standard error; SDI, Straumann Dysphagia Instrument. Missing data were imputed using multiple imputation.



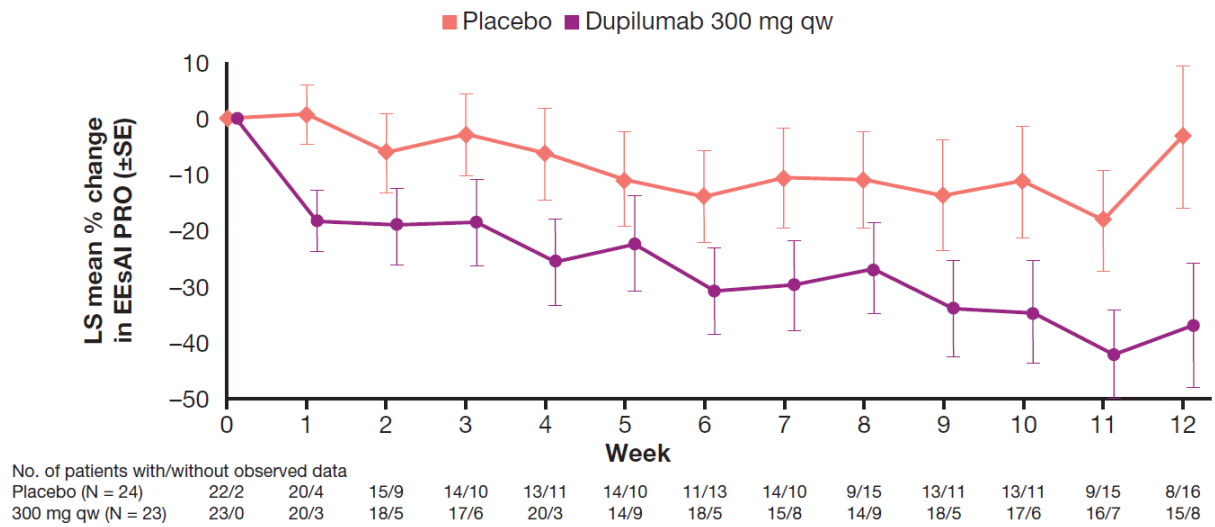
Supplementary Figure 4. Individual peak eosinophil count (eos/HPF) at baseline and Week 12. Eos/HPF, eosinophils per high-power field; qw, weekly.



Supplementary Figure 5. Peak eosinophil count (eos/HPF) at baseline and Week 12. P = comparison of change from baseline to Week 12. Eos/HPF, eosinophils per high-power field (0.3 mm^2); qw, weekly; SD, standard deviation.



Supplementary Figure 6. Proportion of patients with esophageal intraepithelial eosinophil count reductions at Week 12. Eos/HPF, eosinophils per high-power field; qw, weekly.



Supplementary Figure 7. EEAI PRO percent change from baseline during the 12-week analysis period. EEAI, symptom-based Eosinophilic Esophagitis Activity Index; LS, least squares; PRO, patient-reported outcome; qw, weekly; SE, standard error. Missing data were imputed using multiple imputation.

Supplementary Table 1. Summary of Study Endpoints^d

Endpoint	Timeframe
PRIMARY ENDPOINT	
Change in SDI PRO score ^b	Week 10
SECONDARY ENDPOINTS	
Percentage change in weekly EEsAI PRO score ^c	Weeks 10 and 12
Change in weekly EEsAI PRO score ^c	Weeks 10 and 12
Percentage 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 ≥ 3 points compared with baseline ^b	Week 10
Percentage of patients with $\geq 40\%$ improvement in EEsAI PRO score ^c	Week 10
Percentage change in overall peak esophageal intraepithelial eos/HPF (400X)	Week 12
Change in EoE-EREFS (endoscopy visual anatomical score) ^e	Week 12
Percentage of patients with use of rescue medication or procedure (eg, esophageal dilation)	Week 12
Safety	
Incidence of treatment-emergent AEs	12-week treatment period and follow-up (Week 28)
Exploratory endpoints	

Change in mean esophageal intraepithelial eosinophil count (eos/HPF) (calculated 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

EoE, eosinophilic esophagitis; EEsAI, symptom-based Eosinophilic Esophagitis Activity Index; EoE-EREFS, Eosinophilic Esophagitis Endoscopic Reference Score; EoE-HSS, eosinophilic esophagitis histology scoring system; EoE-QOL-A, Adult Eosinophilic Esophagitis Quality of Life Questionnaire; PRO, patient-reported outcome; SDI, Straumann Dysphagia Instrument.

^aThere was no adjustment of multiplicity for the secondary efficacy endpoints.

^bSDI 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 3.¹

^cEEsAI 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

^dEoE-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 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

^eThe 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).⁴

^fThe 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

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Supplementary Table 2. History of Food Allergy

Condition, n (%)	Placebo qw (n = 24)	Dupilumab 300 mg qw (n = 23)
Patients with at least one 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 shell fish	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

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	N 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 qw	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 qw	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 qw	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 qw	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 qw	23	23 (100)	1 (4)	0 (0)

Efficacy variable	Time point	Treatment	N at baseline	Patients with observed value, n (%)	Patients discontinued from the study treatment, n (%)	Patients with missing value, n (%)
Distensibility	Week 12	Placebo	24	12 (50)	4 (17)	12 (50)
	Week 12	Dupilumab 300 mg qw	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 qw	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 qw	23	23 (100)	1 (4)	0 (0)

EoE, eosinophilic esophagitis; EEsAI, symptom-based Eosinophilic Esophagitis Activity Index; EoE-EREFS, Eosinophilic Esophagitis Endoscopic Reference Score; EoE-HSS, eosinophilic esophagitis histology scoring system; EoE-QOL-A, Adult Eosinophilic Esophagitis Quality of Life Questionnaire; qw, weekly; PRO, patient-reported outcome; SDI, Straumann Dysphagia Instrument.

^aSDI 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 3.¹

^bThe 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).⁴

^cThe 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

^dEESAI PRO is a 5-component (10 or 11 item) measure of dysphagia, swallowing-associated pain, and strategies aimed at avoiding dysphagia episodes; total score range 0–100 (higher scores indicate worse symptoms).²

^eEoE-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 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

	Placebo (n = 24)	Dupilumab 300 mg qw (n = 23)	Difference vs placebo (95% CI)	P value versus placebo
SDI PRO score ^a				
Week 10 — no.	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 percentage 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 (eos/HPF)				
Week 12 — no.	22	23		
LS mean change from baseline (SE)	-9.7 (9.65)	-96.4 (9.44)	-86.7 (-114.00 to -59.37)	<.0001
LS mean % change from baseline (SE)	12.3 (12.31)	-93.3 (12.04)	-105.6 (-140.47 to -70.79)	<.0001

	Placebo (n = 24)	Dupilumab 300 mg qw (n = 23)	Difference vs placebo (95% CI)	P value versus placebo
EoE-EREFS total score ^b				
Week 12 — no.	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 — no.	20	22		
All LS mean percentage 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 — no.	20	23		
All LS mean percentage change	-3.4 (4.92)	-58.6 (4.58)	-55.1 (-68.76 to - 41.53)	<.0001

	Placebo (n = 24)	Dupilumab 300 mg qw (n = 23)	Difference vs placebo (95% CI)	P value versus placebo
from baseline (SE)				
Distensibility plateau, mm				
Week 12 — no.	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 percentage 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 — no.	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 percentage change from baseline (SE)	-16.7 (11.21)	-42.2 (9.80)	-25.6 (-56.23 to 5.06)	.0981

	Placebo (n = 24)	Dupilumab 300 mg qw (n = 23)	Difference vs placebo (95% CI)	P value versus placebo
EoE-QOL-A total score ^e				
Week 12 — no.	21	23		
LS mean change from baseline (SE)	0.44 (0.143)	0.79 (0.137)	0.35 (–0.054 to 0.751)	.0879

EEsAI, symptom-based Eosinophilic Esophagitis Activity Index; EoE-EREFS, Eosinophilic Esophagitis Endoscopic Reference Score; EoE-HSS, eosinophilic esophagitis histology scoring system; EoE-QOL-A, Adult Eosinophilic Esophagitis Quality of Life; eos/HPF, eosinophils per high-power field; LS, least squares; PRO, patient-reported outcome; SD, standard deviation; SDI, Straumann Dysphagia Instrument; SE, standard error; qw, once a week.

^aSDI 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

^bThe 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).

^cThe 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).

^dEESAI 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).

^eEoE-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 scale. The scores for EoE-QOL-A score is the average score, equaled 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

SDI score at Week 10 by missing data imputation method	Placebo (n = 24)	Dupilumab 300 mg qw (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

^aLOCF method: data were set to missing after rescue treatment. Missing values were imputed using the LOCF method. In the event that patients only had baseline values without any post-baseline values, their baseline values were carried forward to impute post-baseline missing values.

^bWOCF method: data were set to missing after rescue treatment. Missing values were imputed using the WOCF method. In the event that patients only had baseline values without any post-baseline values, WOCF would not impute for post-baseline missing values.

^cAll observed values: all observed values regardless of whether rescue medication was used were included in the analysis, with no imputation for missing values.

LOCF, last observation carried forward; WOCF, worst observation carried forward; SDI, Straumann Dysphagia Instrument.

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

n (%)	Placebo (n = 24)	Dupilumab 300 mg qw (n = 23)
≥1 TEAE	16 (67)	21 (91)
≥1 SAE ^a	0	3 (13)
AEs leading to treatment discontinuation	0	1 (4)
Deaths	0	0
Terms with a difference of number of patients between two 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)

AE, adverse event; HLT, MedDRA high-level term; MedDRA, Medical Dictionary for Regulatory Activities;

PT, MedDRA preferred term; SAE, serious AE; TEAE, treatment-emergent adverse event; qw, once a week.

^aSAEs 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 (aged 30 years) 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.

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7. 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.

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