ORIGINAL ARTICLE

Dupilumab in Adults and Adolescents with Eosinophilic Esophagitis

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ABSTRACT

BACKGROUND

Dupilumab, a fully human monoclonal antibody, blocks interleukin-4 and interleukin-13 signaling, which have key roles in eosinophilic esophagitis.

METHODS

We conducted a three-part, phase 3 trial in which patients 12 years of age or older underwent randomization in a 1:1 ratio to receive subcutaneous dupilumab at a weekly dose of 300 mg or placebo (Part A) or in a 1:1:1 ratio to receive 300 mg of dupilumab either weekly or every 2 weeks or weekly placebo (Part B) up to week 24. Eligible patients who completed Part A or Part B continued the trial in Part C, in which those who completed Part A received dupilumab at a weekly dose of 300 mg up to week 52 (the Part A–C group); Part C that included the eligible patients from Part B is ongoing. The two primary end points at week 24 were histologic remission (≤6 eosinophils per high-power field) and the change from baseline in the Dysphagia Symptom Questionnaire (DSQ) score (range, 0 to 84, with higher values indicating more frequent or more severe dysphagia).

RESULTS

In Part A, histologic remission occurred in 25 of 42 patients (60%) who received weekly dupilumab and in 2 of 39 patients (5%) who received placebo (difference, 55 percentage points; 95% confidence interval [CI], 40 to 71; P<0.001). In Part B, histologic remission occurred in 47 of 80 patients (59%) with weekly dupilumab, in 49 of 81 patients (60%) with dupilumab every 2 weeks, and in 5 of 79 patients (6%) with placebo (difference between weekly dupilumab and placebo, 54 percentage points; 95% CI, 41 to 66 [P<0.001]; difference between dupilumab every 2 weeks and placebo, 56 percentage points; 95% CI, 43 to 69 [not significant per hierarchical testing]). The mean (±SD) DSQ scores at baseline were 33.6±12.41 in Part A and 36.7±11.22 in Part B; the scores improved with weekly dupilumab as compared with placebo, with differences of –12.32 (95% CI, –19.11 to –5.54) in Part A and –9.92 (95% CI, –14.81 to –5.02) in Part B (both P<0.001) but not with dupilumab every 2 weeks (difference in Part B, –0.51; 95% CI, –5.42 to 4.41). Serious adverse events occurred in 9 patients during the Part A or B treatment period (in 7 who received weekly dupilumab, 1 who received dupilumab every 2 weeks, and 1 who received placebo) and in 1 patient in the Part A–C group during the Part C treatment period who received placebo in Part A and weekly dupilumab in Part C.

CONCLUSIONS

Among patients with eosinophilic esophagitis, subcutaneous dupilumab administered weekly improved histologic outcomes and alleviated symptoms of the disease. (Funded by Sanofi and Regeneron Pharmaceuticals; ClinicalTrials.gov number, NCT03633617.)

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N Engl J Med 2022;387:2317-30.
DOI: 10.1056/NEJMoa2205982

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Eosinophilic esophagitis, a chronic, progressive, type 2 inflammatory disease that has a substantial effect on quality of life, is increasing in incidence and prevalence.[1-5] If untreated, esophageal fibrosis and remodeling can lead to strictures, food impaction, and associated medical complications.[4,6-9] The diagnosis of eosinophilic esophagitis is made on the basis of findings in esophageal mucosa on biopsy (≥15 tissue eosinophils per high-power field with no alternative causes) and clinical symptoms.[4,10]

Standard-of-care treatments for eosinophilic esophagitis include food elimination diets, proton-pump inhibitors (PPIs), swallowed topical glucocorticoids (applied to the esophagus by swallowing), and, in the case of strictures, esophageal dilation.[11,12] However, the rates of response are variable (30 to 40% of patients may not have a response to first-line treatments), and side effects or complications are possible.[13,14] Treatments that address the underlying inflammatory processes and prevent or control disease progression are needed. Growing evidence suggests that type 2 cytokines play key roles in eosinophilic esophagitis,[15] which is characterized by esophageal infiltration of eosinophils, mast cells, and type 2 inflammatory cytokines. Moreover, patients with this condition often have coexisting type 2 clinical complications.[16-18]

Dupilumab, a fully human monoclonal antibody,[19,20] blocks the shared receptor component for interleukin-4 and interleukin-13, key and central drivers of type 2 inflammation.[18,21,22] Dupilumab is approved for the treatment of multiple type 2 inflammatory diseases, including atopic dermatitis, asthma, chronic rhinosinusitis with nasal polyps, and eosinophilic esophagitis.[23,24] In a phase 2 trial involving adults with active eosinophilic esophagitis, dupilumab at a weekly dose of 300 mg reduced symptoms and improved histologic, molecular, and endoscopic aspects of the disease.[25,26] The current phase 3 trial was designed to assess the efficacy and safety of dupilumab at a dose of 300 mg weekly or every 2 weeks, as compared with placebo in patients with eosinophilic esophagitis who were 12 years of age or older.

METHODS

TRIAL DESIGN AND OVERSIGHT

The trial consisted of three parts (Fig. 1). Parts A and B were independent, 24-week, randomized, double-blind, placebo-controlled trials. Eligible patients who had completed Part A or Part B continued the trial in Part C, an extended active treatment period of 28 weeks. Here, we report the findings from Part A and Part B and from Part C that involved the eligible patients from Part A (the Part A–C group); Part C involving the eligible patients from Part B (the Part B–C group) is currently ongoing.

The trial was performed at 96 sites across Australia (4 sites), Canada (4 sites), Europe (25 sites), and the United States (63 sites). The protocol, available with the full text of this article at NEJM.org, was developed by the sponsors (Sanofi and Regeneron Pharmaceuticals) and the lead investigators. Data were collected by the investigators and analyzed by the sponsors. The trial was conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Council for Harmonisation. An independent data and safety monitoring committee reviewed patient safety data in a blinded manner (see the Supplementary Appendix, available at NEJM.org). The local institutional review board or ethics committee at each trial center oversaw the conduct and documentation of the trial. Written informed consent or assent (or both) was obtained from all the patients or their parent or legal guardian before enrollment. The tenth author conducted the statistical analyses. All the authors had access to and participated in the interpretation of the data presented herein and provided input into the drafting of the manuscript, critical feedback, and final approval of the manuscript for submission. A total of 21 authors (see the Supplementary Appendix) had access to the data included in the clinical trial report and vouch for the completeness and accuracy of the data and for adherence of the trial to the protocol. All the investigators had confidentiality agreements with the sponsors.

PATIENTS

Eligible patients were at least 12 years of age and had a documented diagnosis of eosinophilic esophagitis by endoscopic biopsy (peak eosinophil count, ≥15 per high-power field) despite 8 weeks of high-dose PPI therapy. All the patients had a score of 10 or greater on the Dysphagia Symptom Questionnaire (DSQ) at baseline (scores range from 0 to 84, with higher scores indicating more frequent or more severe dysphagia).

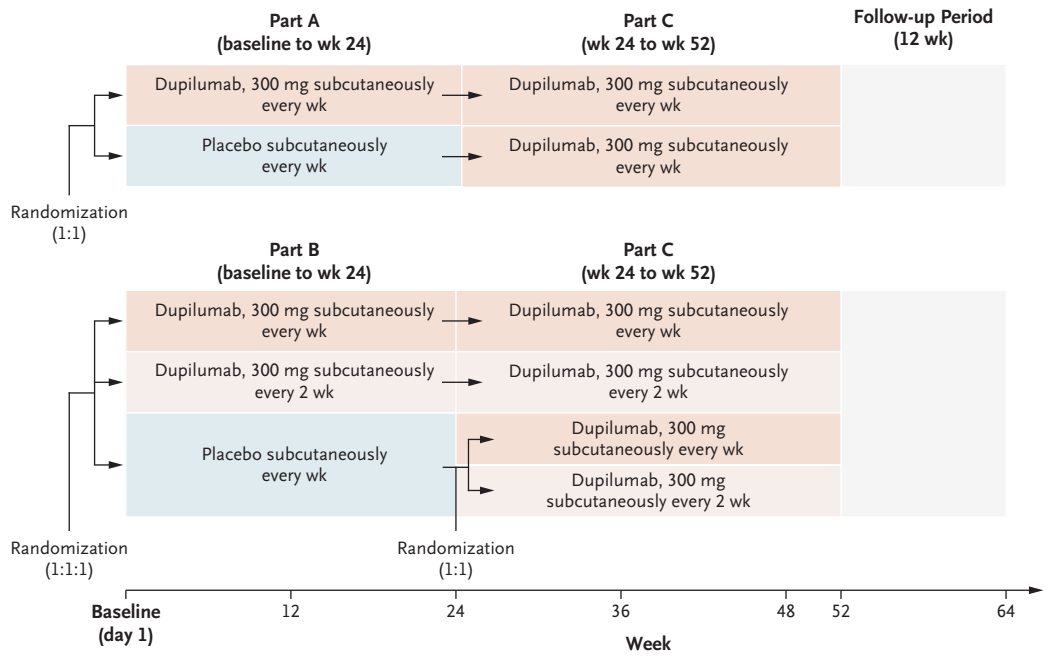


Figure 1. Phase 3 Trial Design.

The patients who received 300 mg of dupilumab every 2 weeks in Parts B and C also received placebo every 2 weeks, alternating with dupilumab, for regimen-blinding purposes. Enrollment in Part B began immediately after the last patient was enrolled in Part A; patients who were enrolled in Part A were not eligible for Part B. The patients entered a 12-week follow-up period at the end of Part C or immediately after Part A or B if they were ineligible for Part C. Part C involving the eligible patients from Part B is currently ongoing. In Part A, the assigned trial regimen was extended in four patients who could not attend the week 24 appointment because of restrictions related to coronavirus disease 2019 (three who were receiving weekly dupilumab and one who was receiving placebo). These four patients continued their assigned Part A trial regimen after the 24-week treatment period, until the time that the week-24 endoscopy visits could be performed; therefore, entry into Part C was delayed for these patients.

Inclusion and exclusion criteria were identical in Parts A and B.

INTERVENTIONS AND PROCEDURES

Randomization was stratified according to age group (≥12 to <18 years and ≥18 years) and current use of PPIs. In Part A, patients were randomly assigned in a 1:1 ratio to receive subcutaneous dupilumab at a weekly dose of 300 mg or matching placebo up to week 24. In Part C, the patients in the Part A–C group received dupilumab at a weekly dose of 300 mg for an additional 28 weeks (up to week 52). In Part B, the patients were randomly assigned in a 1:1:1 ratio to receive 300 mg of dupilumab either weekly or every 2 weeks or weekly placebo up to week 24. Patients receiving dupilumab every 2 weeks also received placebo every 2 weeks, alternating with dupilumab, for regimen-blinding purposes. In Part C, the patients in the Part B–C group who had received dupilumab in Part B followed the same regimen in Part C, whereas those who received placebo in Part B were randomly assigned in a 1:1 ratio to receive 300 mg of dupilumab either weekly or every 2 weeks for an additional 28 weeks in Part C (Fig. 1).

The patients who had been receiving PPIs at baseline continued to receive the same or a similar dose throughout the treatment period; initiation of new PPI therapy was prohibited. The patients who were on a stable food elimination diet for 6 weeks before screening could continue the diet without change throughout the treatment period. Use of swallowed topical glucocorticoids within 8 weeks before baseline or as background therapy during the treatment period was prohibited. Rescue medications (systemic or swallowed topical glucocorticoids or both) or procedures (esophageal dilation) were permitted if medically necessary.

END POINTS

In Parts A and B, the two primary end points at week 24 were histologic remission (defined as a peak esophageal intraepithelial eosinophil count of ≤6 per high-power field[27,28]) and the absolute change from baseline in the DSQ score. The DSQ scores were collected by means of a daily electronic diary assessing the frequency and severity of dysphagia; the scores were calculated over a 14-day period.[29,30]

Key secondary end points at week 24 were the percentage change from baseline in the peak esophageal intraepithelial eosinophil count; the absolute change from baseline in the grade and stage scores on the Eosinophilic Esophagitis Histology Scoring System (EoE-HSS — both scores range from 0 to 3, with higher scores indicating greater severity of histologic changes or greater extent of abnormal tissue, respectively[31]); and the absolute change from baseline in the score on an endoscopic reference scoring system referred to as EREFS, which stands for edema, rings, exudates, furrows, and strictures (scores range from 0 to 18, with higher scores indicating greater severity[32]). Other secondary end points at week 24 were a peak esophageal intraepithelial eosinophil count of less than 15 per high-power field and a count of 1 or less per high-power field; the percentage change from baseline in the DSQ score; the change from baseline in the Eosinophilic Esophagitis Impact Questionnaire (EoE-IQ) score (a measure of effect on quality of life; scores range from 1 to 5, with higher scores indicating a more negative effect); change from baseline in the Eosinophilic Esophagitis Symptom Questionnaire (EoE-SQ) frequency and severity scores (a measure of symptoms other than dysphagia; frequency scores range from 5 to 25 and severity scores range from 0 to 30, with higher scores indicating greater symptom frequency or severity, respectively). Normalized enrichment scores (a measure reflecting the degree to which a gene signature is up- or down-regulated using a gene set enrichment analysis tool) for the relative change from baseline after treatment in the eosinophilic esophagitis diagnostic panel (EDP) transcriptome signature (a published gene set that differentiates the gene expression profiles of esophageal-biopsy samples from the patients with eosinophilic esophagitis as compared with healthy controls)[33] and a type 2 inflammation transcriptome signature (a gene set curated from the literature and preclinical experiments performed at Regeneron) were assessed as secondary end points at week 24. The use of rescue medications or procedures, trough concentrations of dupilumab, and antidrug antibodies were also assessed as secondary end points during the treatment periods. A central reader performed all histologic assessments in a blinded manner. A full list of all prespecified primary and secondary end points is provided in Table S1 in the Supplementary Appendix. Among the patients in the Part A–C group in Part C, all primary and secondary end points were assessed as secondary end points at week 52.

The incidence of adverse events and serious adverse events during the treatment period are reported. Prespecified descriptive analyses were performed for the two primary end points at week 24 to assess treatment effects in subgroups with or without a history of esophageal dilation before randomization. Other prespecified subgroups analyses are not reported here.

STATISTICAL ANALYSIS

On the basis of data from previous phase 2 trials involving patients with eosinophilic esophagitis[25,34] and assuming a dropout rate of 15%, we calculated that a sample of 40 patients per trial group would provide Part A of the trial with more than 99% power to detect a between-group difference of 62 percentage points with respect to histologic remission at week 24 (65% with dupilumab and 3% with placebo) at a two-sided significance level of 5% using Fisher's exact test. We also calculated that the enrollment of 40 patients in each group would provide 80% power to detect a between-group difference in the absolute change from baseline in DSQ score at week 24 of –9.0 points, with a common standard deviation of 13.0, at a two-sided significance level of 5%, using a two-sample t-test. On the basis of the results in Part A, we calculated that 70 patients per trial group would provide Part B of the trial with more than 99% power to detect a between-group difference of 55 percentage points with respect to histologic remission at week 24 (60% with dupilumab and 5% with placebo) at a two-sided significance level of 5% using Fisher's exact test. We also calculated that the enrollment of 70 patients per trial group would provide more than 99% power to detect a between-group difference in the absolute change from baseline in the DSQ score at week 24 of

–12.3 points, with a common standard deviation of 15.0, at a two-sided significance level of 5%, using a two-sample t-test.

Efficacy analyses were performed in the full analysis set (all the patients who had undergone randomization). Safety analyses were performed in the safety analysis set (all the patients who had undergone randomization and received at least one dose or part of a dose of dupilumab or placebo). The between-group differences in the percentage of patients with histologic remission and all binary secondary end points were analyzed with the use of the Cochran–Mantel–Haenszel test adjusted for randomization stratification factors (i.e., age [12 to <18 years or ≥18 years] and use of PPIs at randomization [yes or no]). Differences between the dupilumab and placebo groups in the absolute change from baseline in the DSQ score and all continuous secondary end points were analyzed with the use of analysis of covariance, with trial group, randomization stratification factors, and score at baseline (i.e., baseline DSQ score in the case of absolute change in DSQ score) as covariates included in the model. Safety analyses were descriptive.

Parts A and B were carried out as two separate trials with no overlapping patients. Each trial part had a separate and independent two-sided alpha level of 0.05 and was considered to be positive independently on the basis of the significance of the findings with respect to the two primary end points. For each trial part, a hierarchical procedure was applied to control the type I error. The hierarchical order for each trial part is provided in Tables S2 and S3. A P value of less than 0.05 was required for both primary endpoint measures to consider the results for either to be significant. The testing would proceed to the next end point only if the difference was significant for the previous one.

In Parts A and B, to account for the use of rescue treatment in the primary analysis for a peak esophageal intraepithelial eosinophil count of 6 or fewer eosinophils per high-power field, patients were considered to have had no response after the use of rescue treatment. For the primary end point of absolute change from baseline in the DSQ score, data were imputed with the use of multiple imputation for all time points subsequent to the use of rescue treatment. Patients with missing values for the peak esophageal intraepithelial eosinophil count at week 24 were classified as having no response if data were missing for reasons other than those related to coronavirus disease 2019 (Covid-19), or data were imputed with the use of multiple imputation if they were missing because of restrictions related to Covid-19. The missing DSQ scores at week 24 were imputed with the use of multiple imputation. The 95% confidence intervals for the absolute change from baseline in the DSQ score were calculated according to Rubin's formula. In Part C, analyses in the Part A–C group were purely descriptive and were based on all observed data regardless of the use of rescue treatment. Full details of the statistical methods are provided in the Supplementary Appendix and the statistical analysis plan (available with the protocol).

RESULTS

TRIAL PATIENTS

In Part A, 81 patients underwent randomization; 42 were assigned to receive dupilumab at a weekly dose of 300 mg and 39 were assigned to receive placebo. In Part B, 240 patients underwent randomization; 80 were assigned to receive dupilumab at a weekly dose of 300 mg, 81 to receive dupilumab at a dose of 300 mg every 2 weeks, and 79 to receive placebo. A flow chart of the trial is provided in Fig. S1. A total of 40 patients (98%) who received weekly dupilumab in Part A continued the same regimen in Part C, and 37 patients (95%) who received placebo in Part A switched to dupilumab at a weekly dose of 300 mg in Part C.

The demographic and clinical characteristics of the patients at baseline were similar across trial groups (Table 1 and Table S4). The patients in Parts A and B had eosinophilic esophagitis for a mean of 5.0 and 5.6 years, respectively, had substantial symptom burden (mean DSQ score, 33.6 and 36.7, respectively), and had active eosinophilic esophagitis (mean peak eosinophil count, 89.3 and 87.1 per high-power field, respectively). The mean EREFS score was 6.3 among the patients in Part A and 7.2 among those in Part B; the mean EoE-HSS grade score was 1.29 and 1.26, respectively; and the mean EoE-HSS stage score was 1.34 and 1.25, respectively; most had received previous treatments. Across the trial groups, 23 to 33% of the patients were adolescents, and 89 to 98% were White. The patients were representative of the overall population with eosinophilic esophagitis (Table S5).

Table 1. Selected Demographic and Clinical Characteristics of the Patients at Baseline (Full Analysis Set).*

Characteristic	Part A			Part B			
	Dupilumab, 300 mg weekly (N=42)	Placebo (N=39)	Total (N=81)	Dupilumab, 300 mg weekly (N=80)	Dupilumab, 300 mg every 2 wk (N=81)	Placebo (N=79)	Total (N=240)
Age — yr	33.9±15.53	28.8±12.53	31.5±14.31	28.7±13.72	27.8±13.21	27.9±12.56	28.1±13.12
Female sex — no. (%)	14 (33)	18 (46)	32 (40)	30 (38)	36 (44)	21 (27)	87 (36)
Duration of eosinophilic esophagitis — yr†	5.23±4.18	4.77±4.55	5.01±4.34	5.89±4.66	5.92±5.18	4.88±4.48	5.57±4.79
Previous use of topical glucocorticoids for eosinophilic esophagitis — no. (%)	29 (69)	31 (79)	60 (74)	55 (69)	65 (80)	56 (71)	176 (73)
Refractory to previous therapy — no. (% of patients with previous use)	23 (79)	21 (68)	44 (73)	32 (58)	38 (58)	34 (61)	104 (59)
Inadequate response to or unacceptable side effects from previous therapy or current contraindication — no. (%)‡	—	—	—	38 (48)	41 (51)	39 (49)	118 (49)
History of esophageal dilation — no. (%)	18 (43)	17 (44)	35 (43)	26 (32)	26 (32)	33 (42)	85 (35)
Food elimination diet at screening — no. (%)	17 (40)	16 (41)	33 (41)	31 (39)	29 (36)	29 (37)	89 (37)
Presence of concurrent type 2 inflammatory disease — no. (%)	33 (79)	35 (90)	68 (84)	71 (89)	74 (91)	69 (87)	214 (89)
Allergic rhinitis	26 (62)	22 (56)	48 (59)	48 (60)	49 (60)	52 (66)	149 (62)
Food allergy	19 (45)	17 (44)	36 (44)	46 (58)	42 (52)	41 (52)	129 (54)
Asthma	10 (24)	15 (38)	25 (31)	32 (40)	31 (38)	27 (34)	90 (38)
Atopic dermatitis	6 (14)	9 (23)	15 (19)	12 (15)	17 (21)	19 (24)	48 (20)
DSQ score§	32.2±12.66	35.1±12.11	33.6±12.41	38.4±10.70	35.6±12.24	36.1±10.55	36.7±11.22
EREFS score¶	6.5±3.20	6.0±2.38	6.3±2.83	6.8±2.96	7.5±3.14	7.2±3.34	7.2±3.15
EoE-HSS grade score‖	1.26±0.41	1.32±0.47	1.29±0.44	1.31±0.39	1.25±0.37	1.23±0.40	1.26±0.39
EoE-HSS stage score‖	1.30±0.33	1.38±0.40	1.34±0.37	1.29±0.32	1.25±0.32	1.22±0.36	1.25±0.34
Peak eosinophil count per high-power field**	82.6±41.02	96.5±54.69	89.3±48.29	89.2±46.67	87.7±49.37	84.3±41.20	87.1±45.76
Median blood peripheral eosinophils (IQR) — IU/ml	430 (260–600)	450 (270–680)	440 (270–610)	420 (280–520)	380 (250–510)	430 (270–530)	400 (270–520)
Median IgE (IQR) — IU/ml	110 (51–463)	100 (47–294)	107 (50–306)	134 (48–302)	134 (47–362)	126 (52–416)	134 (48–330)

* Plus–minus values are means ±SD. The full analysis set included all the patients who had undergone randomization, regardless of whether an intervention was received. IQR denotes interquartile range.

† Disease duration was determined from the time of diagnosis of eosinophilic esophagitis, which could be based on either symptom (as reported by the patient) or histologic confirmation of disease, determined at the investigator's discretion.

‡ Data were not collected in Part A.

§ The Dysphagia Symptom Questionnaire (DSQ) was used to assess the frequency and severity of dysphagia. The biweekly DSQ score ranges from 0 to 84, with higher scores indicating more frequent or more severe dysphagia. The baseline DSQ score was calculated from the 14-day period before baseline, which was the day the first dose of the assigned trial regimen was administered.

¶ EREFS (edema, rings, exudates, furrows, and strictures), an endoscopic reference scoring system, was used to assess the severity of endoscopic features. Scores range from 0 to 18, with higher scores indicating greater severity. EREFS scores were measured from endoscopies of the proximal and distal esophageal regions.

‖ The Eosinophilic Esophagitis Histology Scoring System (EoE-HSS) was used to assess the grade (severity) and stage (extent) of histologic features. The grade and stage scores both range from 0 to 3, with higher scores indicating greater severity or greater extent, respectively. EoE-HSS scores were measured from esophageal biopsies from proximal, middle, and distal esophageal regions.

** Peak eosinophil count was the highest value measured from esophageal biopsies from proximal, middle, and distal esophageal regions.

HISTOLOGIC OUTCOMES OF EOSINOPHILIC ESOPHAGITIS

Efficacy end points are summarized in Table S6. In Part A, histologic remission at week 24 (a primary end point) occurred in 25 of 42 patients (60%) who received weekly dupilumab and in 2 of 39 patients (5%) who received placebo, for an adjusted between-group difference of 55 percentage points (95% confidence interval [CI], 40 to 71, P<0.001). In Part B, histologic remission occurred in 47 of 80 patients (59%) with weekly dupilumab, in 49 of 81 patients (60%) with dupilumab every 2 weeks, and in 5 of 79 patients (6%) with placebo (difference between weekly dupilumab and placebo, 54 percentage points; 95% CI, 41 to 66 [P<0.001]; difference between dupilumab every 2 weeks and placebo, 56 percentage points; 95% CI, 43 to 69 [not significant per hierarchical plan to adjust for multiple testing]) (Fig. 2).

In Part A, the percentage of patients who had fewer than 15 eosinophils per high-power field was greater among those who received weekly dupilumab than among those who received placebo, with an adjusted between-group difference of 58 percentage points (95% CI, 42 to 73; P<0.001). The reduction from baseline in peak eosinophil count at week 24 was greater among those who received weekly dupilumab than among those who received placebo, with a least-squares mean between-group difference of −68.3 percentage points (95% CI, −86.9 to −49.6; P<0.001) (Fig. S2A and S2B).

In Part B, the adjusted difference among patients with fewer than 15 eosinophils per high-power field at week 24 between those who received weekly dupilumab and those who received placebo was 75 percentage points (95% CI, 64 to 86), and the corresponding value between those who received dupilumab every 2 weeks and those who received placebo was 72 percentage points (95% CI, 61 to 84). The least-squares mean difference in the change from baseline in peak eosinophil count at week 24 between the patients who received weekly dupilumab and those who received placebo was −88.6 percentage points (95% CI, −112.2 to −65.0), and the corresponding value between the patients who received dupilumab every 2 weeks and those who received placebo was −79.2 percentage points (95% CI, −103.1 to −55.3).

In Part A, a reduction from baseline in the EoE-HSS grade score at week 24 was observed among the patients who received weekly dupilumab as compared with those who received placebo (least-squares mean between-group difference, −0.76 points [95% CI, −0.91 to −0.61, P<0.001]), as was a reduction from baseline in the EoE-HSS stage score (least-squares mean between-group difference, −0.74 points [95% CI, −0.88 to −0.60, P<0.001]) (Fig. S2C and S2D). In Part B, the least-squares mean difference in the EoE-HSS grade score between the patients who received weekly dupilumab and those who received placebo was −0.68 points (95% CI, −0.79 to −0.57), and the corresponding value between the patients who received dupilumab every 2 weeks and those who received placebo was −0.67 points (95% CI, −0.78 to −0.55). The least-squares mean difference in the EoE-HSS stage score between the patients who received weekly dupilumab and those who received placebo was −0.67 points (95% CI, −0.78 to −0.57), and the corresponding value between the patients who received dupilumab every 2 weeks and those who received placebo was −0.66 points (95% CI, −0.77 to −0.55).

Among the patients who received weekly dupilumab in Parts A and C, the treatment effects observed in Part A were sustained to week 52 in Part C. Histologic remission occurred in 19 of 34 patients (56%), and 28 of 34 patients (82%) had fewer than 15 eosinophils per high-power field (Fig. 2). Among these patients, the mean change from baseline (week 0 in Part A) in peak eosinophil count from was −88.6 percentage points (95% CI, −93.3 to −83.9), and the absolute changes from baseline in EoE-HSS grade and stage scores were −0.87 points (95% CI, −1.00 to −0.75) and −0.89 points (95% CI, −0.99 to −0.79), respectively. Among the patients who received placebo in Part A and weekly dupilumab in Part C, the treatment effects at week 52 were similar to those at week 24 among the patients who received weekly dupilumab in Part A. Histologic remission occurred in 18 of 30 patients (60%), and 21 of 30 patients (70%) had fewer than 15 eosinophils per high-power field. Among these patients, the mean change in peak eosinophil count from baseline was −83.8 percentage points (95% CI, −93.1 to −74.4), and the absolute changes from baseline in the EoE-HSS grade and stage scores were −0.87 points (95% CI, −1.08 to −0.67) and −0.87 points (95% CI, −1.05 to −0.70), respectively (Fig. 2).

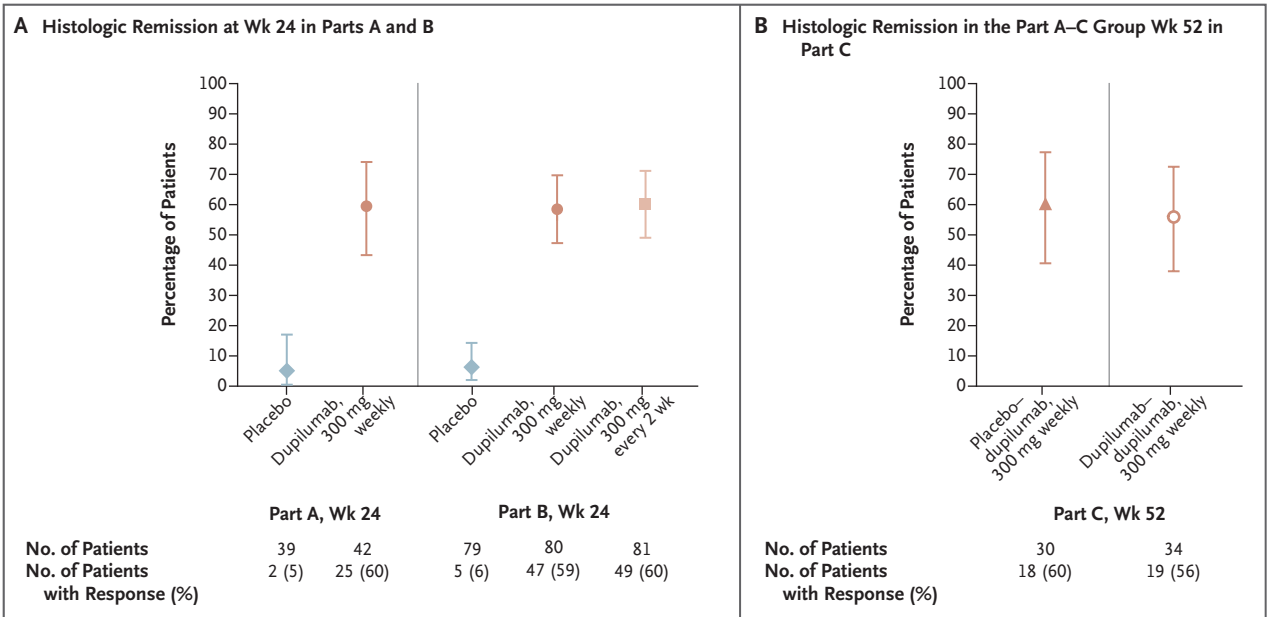


Figure 2. Histologic Remission at Weeks 24 and 52.

Shown are the percentages of patients with histologic remission at week 24 in Parts A and B of the trial (Panel A) and at week 52 in the Part A–C group, which comprised the eligible patients from Part A who continued the trial in Part C (Panel B). Histologic remission was defined as a peak esophageal intraepithelial eosinophil count of six or fewer eosinophils per high-power field. In Part C, placebo–dupilumab indicates the patients who received placebo in Part A and weekly dupilumab in Part C, and dupilumab–dupilumab indicates the patients who received dupilumab weekly in Parts A and C. The 95% confidence intervals (indicated by I bars) were calculated with the use of Rubin's method in Parts A and B of the trial and with the use of exact binomial distribution in Part C.

DYSPHAGIA SYMPTOMS

The reduction from baseline in the DSQ score at week 24 (a primary end point) was greater among the patients who received weekly dupilumab than among those who received placebo in Part A (least-squares mean change, –21.92 points vs. –9.60 points; difference, –12.32 points; 95% CI, –19.11 to –5.54 [P<0.001]) and in Part B (least-squares mean change, –23.78 points vs. –13.86 points; difference, –9.92 points; 95% CI, –14.81 to –5.02 [P<0.001]) (Figs. 3 and 4). The reduction from baseline in the DSQ score at week 24 did not differ significantly between the patients who received dupilumab every 2 weeks and those who received placebo (least-squares mean change, –14.37 points vs. –13.86 points; difference, –0.51 points; 95% CI, –5.42 to 4.41 [P=0.84]), which broke the testing hierarchy in Part B; therefore, the two primary end points and secondary outcomes in the hierarchy are considered to be not significant in the comparisons between the every-2-week dupilumab regimen and placebo. Trends for the percentage changes from baseline in the DSQ score were similar to the trends for the absolute changes (Fig. S3A and S3B). The number of days with dysphagia in Part A was reduced from a mean (±SD) of 9.7±3.36 at baseline to 3.1±3.60 at week 24 among the patients who received weekly dupilumab and from 10.3±3.01 to 6.3±4.86 among those who received placebo; the results in Part B were similar to those in Part A (Table S7).

Among the patients who received weekly dupilumab in Parts A and C, the improvements in DSQ score observed in Part A were sustained to week 52 in Part C (mean change from baseline, –23.44 points; 95% CI, –29.58 to –17.30). The reduction in DSQ score at week 52 among the patients who received placebo in Part A and weekly dupilumab in Part C was similar to that observed among the patients who received weekly dupilumab at the end of Part A (–21.71 points; 95% CI, –29.13 to –14.30) (Fig. 3 and Fig. S3C).

In summary, in Part A, the two primary and all secondary end points included in the hierarchy were significant. In Part B, because the hierarchy was broken at the primary end point of absolute change from baseline in the DSQ score at week 24 in the group that received dupilumab every 2 weeks (number 3 in Table S3), for all

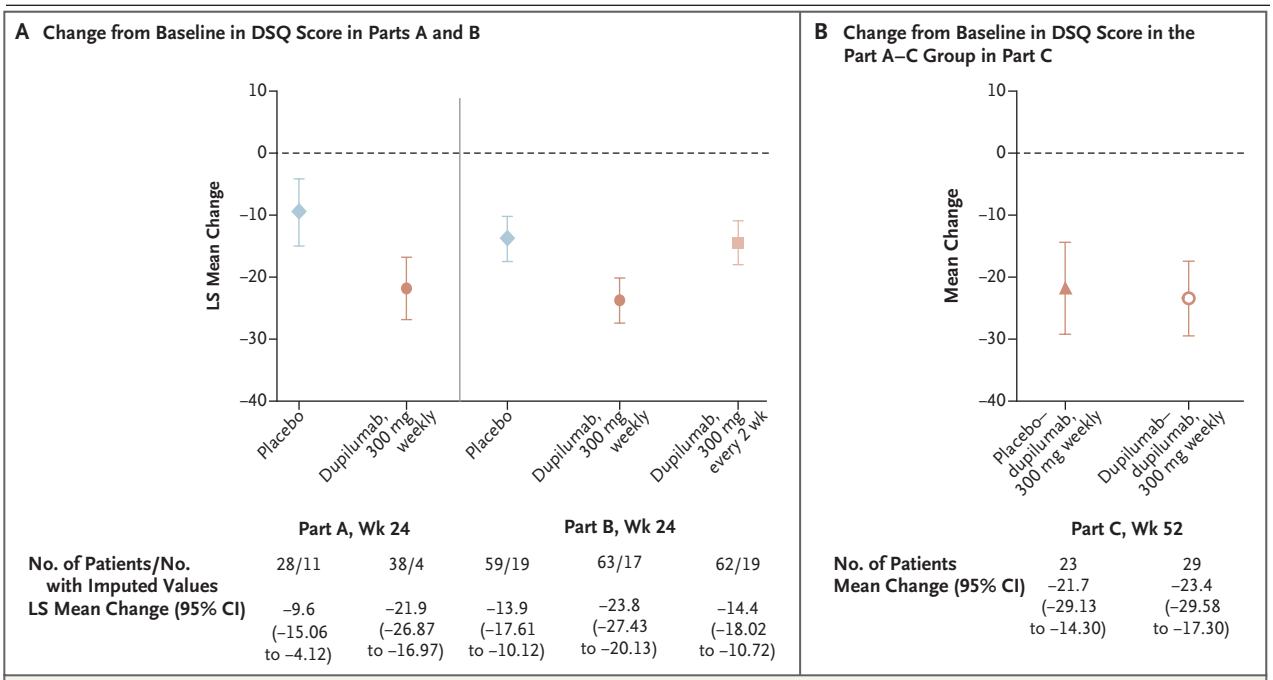


Figure 3. Change in DSQ Score at Weeks 24 and 52.

Shown are the least-squares (LS) mean changes from baseline in the Dysphagia Symptom Questionnaire (DSQ) score at week 24 in Parts A and B of the trial (Panel A) and the mean changes in the DSQ score at week 52 in the Part A–C group, which comprised the eligible patients in Part A who continued the trial in Part C (Panel B). Scores on the DSQ range from 0 to 84, with higher values indicating more frequent or more severe dysphagia. In Part C, placebo–dupilumab indicates the patients who received placebo in Part A and weekly dupilumab in Part C, and dupilumab–dupilumab indicates the patients who received dupilumab weekly in Parts A and C. I bars indicate 95% confidence intervals, which were calculated with the use of Rubin's method for the least-squares mean changes in Parts A and B and with the use of normal approximation for the mean changes in Part C.

subsequent end points in the hierarchy and for all end points not included in hierarchical plan, only estimates and confidence intervals are provided, with no hypothesis testing. The widths of the confidence intervals have not been adjusted for multiple testing and should not be used to infer definitive treatment effects.

ENDOSCOPIC MEASURES OF EOSINOPHILIC ESOPHAGITIS

At week 24 in Part A, the reduction from baseline in the EREFS score was greater among the patients who received weekly dupilumab than among those who received placebo (least-squares mean between-group difference, −2.9 points; 95% CI, −3.91 to −1.84 [P<0.001]) (Fig. S2E). In Part B, the least-squares mean difference in the EREFS score between the patients who received weekly dupilumab and those who received placebo was −3.8 points (95% CI, −4.77 to −2.93), and the corresponding value between the patients who received dupilumab every 2 weeks and those who received placebo was −3.9 points (95% CI, −4.86 to −3.02).

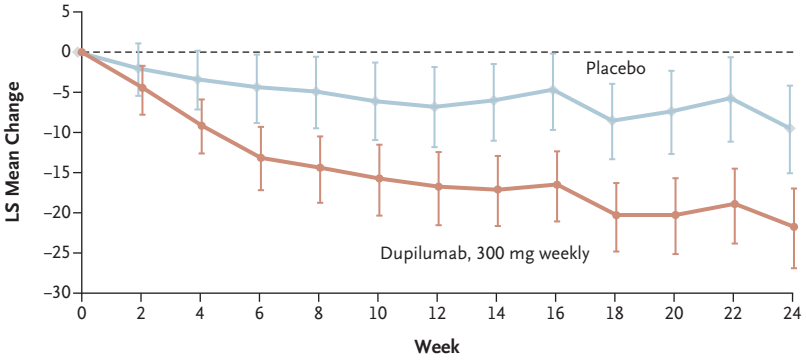
Among the patients who received weekly dupilumab in Parts A and C, the improvement in the EREFS score observed in Part A was maintained through week 52 in Part C (mean change from baseline, −4.1 points; 95% CI, −5.2 to −2.9). The improvement in the EREFS score by week 52 among the patients who received placebo in Part A and weekly dupilumab in Part C was similar to that among the patients who received weekly dupilumab in Parts A and C (mean change from the baseline, −3.9 points; 95% CI, −4.9 to −2.8).

QUALITY OF LIFE

In Part A, the change from baseline in the EoE-IQ score at week 24 favored weekly dupilumab over placebo, with a least-squares mean between-group difference of −0.37 points (95% CI, −0.64 to −0.10), as did the changes in the EoE-SQ frequency and severity scores, with least-squares mean between-group differences of −1.7 points (95% CI, −2.93 to −0.52) and −2.0 points (95% CI, −3.87 to −0.03), respectively.

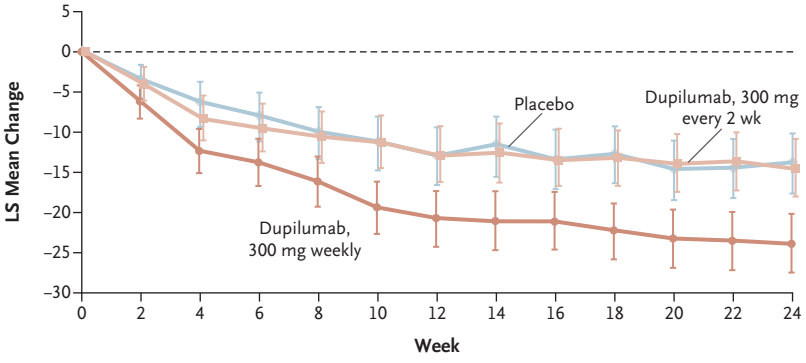
In Part B, the least-squares mean difference

A Change from Baseline in DSQ Score in Part A



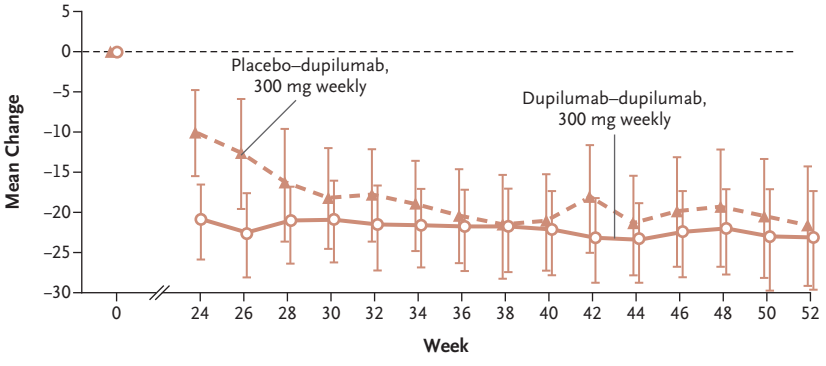
No. of Patients/No. with Imputed Values													
Placebo	39/0	37/2	35/4	33/6	34/5	33/6	33/6	30/9	27/12	29/10	29/10	26/13	28/11
Dupilumab	42/0	42/0	42/0	40/2	41/1	41/1	40/2	40/2	37/5	38/4	38/4	38/4	38/4

B Change from Baseline in DSQ Score in Part B



No. of Patients/No. with Imputed Values													
Placebo	78/0	75/3	73/5	66/12	68/10	69/9	65/13	62/16	64/14	62/16	62/16	62/16	59/19
Dupilumab, 300 mg weekly	80/0	80/0	76/4	78/2	75/5	72/8	71/9	69/11	68/12	65/15	60/20	64/16	63/17
Dupilumab, 300 mg every 2 wk	81/0	77/4	78/3	76/5	68/13	70/11	66/15	65/16	69/12	65/16	61/20	63/18	62/19

C Change from Baseline in DSQ Score in the Part A–C Group in Part C



No. of Patients																
Placebo–dupilumab	37	37	28	28	30	32	28	29	26	26	27	25	29	28	26	23
Dupilumab–dupilumab	40	40	34	32	32	34	38	38	38	33	34	36	33	32	27	29

Figure 4 (facing page). Change in DSQ Score over Time.
Shown are the LS mean changes from baseline in the DSQ score over time in Part A (Panel A) and Part B (Panel B) of the trial and the mean changes from baseline in the DSQ score over time in the Part A–C group, which comprised the eligible patients from Part A who continued the trial in Part C (Panel C). In Part C, baseline was week 0 in Part A. Placebo–dupilumab indicates the patients who received placebo in Part A and weekly dupilumab in Part C, and dupilumab–dupilumab indicates the patients who received dupilumab weekly in Parts A and C. I bars indicate 95% confidence intervals, which were calculated with the use of Rubin's method for the LS mean changes in Parts A and B and with the use of normal approximation for the mean changes in Part C.

in the change from baseline in the EoE-IQ score at week 24 between the patients who received weekly dupilumab and those who received placebo was −0.31 points (95% CI, −0.47 to −0.15), and the corresponding value between the patients who received dupilumab every 2 weeks and those who received placebo was −0.02 points (95% CI, −0.18 to 0.15). The least-squares mean difference in the change from baseline in the EoE-SQ frequency score at week 24 between the patients who received weekly dupilumab and those who received placebo was −1.4 points (95% CI, −2.30 to −0.45), and the corresponding value between the patients who received dupilumab every 2 weeks and those who received placebo was −0.5 points (95% CI, −1.38 to 0.44). The least-squares mean difference in the change from baseline in the EoE-SQ severity score between the patients who received weekly dupilumab and those who received placebo was −1.5 points (95% CI, −3.04 to 0.13), and the corresponding value between the patients who received dupilumab every 2 weeks and those who received placebo was −0.5 points (95% CI, −2.03 to 1.08). In the Part A–C group, improvements in the EoE-IQ score and the EoE-SQ frequency and severity scores at week 52 in Part C, as compared with the baseline scores in Part A, were reported for the patients who received weekly dupilumab in Parts A and C and for the patients who received placebo in Part A and weekly dupilumab in Part C.

RESCUE MEDICATIONS OR PROCEDURES

Small numbers of patients received rescue medications in Part A (4 patients who received placebo) and Part B (1 patient who received weekly dupilumab and 1 patient who received placebo), and small numbers of patients underwent rescue procedures in Part A (1 patient who received placebo) and Part B (1 patient who received weekly dupilumab, 1 patient who received dupilumab every 2 weeks, and 1 patient who received placebo). In Part C, no new patients in the Part A–C group received a rescue medication (1 patient discontinued the rescue medication before entering Part C, 2 patients who received placebo in Part A continued to receive rescue medications through Part C, and 1 patient who received placebo in Part A discontinued the rescue medication at the start of Part C). One patient who received dupilumab in Parts A and C underwent a rescue procedure in Part C. Among the 5 patients who underwent rescue esophageal dilation during Parts A, B, or C, 4 had a history of dilation before entering the trial.

MOLECULAR SIGNATURES

At baseline, type 2 inflammation and EDP transcriptome signatures qualitatively showed molecularly active disease, as reported previously.[33,35] In Part A, the relative change from baseline in the normalized enrichment score for type 2 inflammation transcriptome signature at week 24 was greater among the patients who received weekly dupilumab than among those who received placebo (median between-group difference, −1.59; 95% CI, −1.74 to −1.27 [P<0.001]), as was the relative change from baseline in the normalized enrichment score for EDP transcriptome signature (median between-group difference, −2.25 [−2.72 to −1.73]; P<0.001) (Fig. S4).

In Part B, the median difference in the change from baseline in the normalized enrichment score for type 2 inflammation transcriptome signature at week 24 between the patients who received weekly dupilumab and those who received placebo was −1.28 (95% CI, −1.82 to −1.07), and the corresponding value between the patients who received dupilumab every 2 weeks and those who received placebo was −1.26 (95% CI, −1.73 to −1.05). The median difference in the change from baseline in the normalized enrichment score for EDP transcriptome signature at week 24 between the patients who received weekly dupilumab and those who received pla-

cebo was –1.85 (95% CI, –2.44 to –1.15), and the corresponding value between the patients who received dupilumab every 2 weeks and those who received placebo was –1.84 (95% CI, –2.42 to –1.11). Among the patients who received weekly dupilumab in Parts A and C, the transcriptome changes were maintained through week 52.

TREATMENT EFFECTS ACCORDING TO DILATION HISTORY

In Parts A and B, the between-group differences in the results for the two primary end points did not differ substantially when stratified according to dilation status before randomization (Fig. S5). Other prespecified subgroups analyses are not reported here.

PHARMACOKINETICS AND IMMUNOGENICITY

In Parts A and B, mean serum concentrations of dupilumab at week 24 among the patients who received weekly dupilumab were more than two times as high as those among the patients who received dupilumab every 2 weeks; steady-state trough concentrations were reached by week 12 among the patients who received dupilumab every 2 weeks or by weeks 12 through 24 among the patients who received weekly dupilumab. In Part C, serum concentrations of dupilumab at week 52 were similar among the patients who received weekly dupilumab in Parts A and C and among those who received placebo in Part A and weekly dupilumab in Part C (Fig. S6). Antidrug antibody responses were observed during the treatment period in 0 to 3% of the patients across the active treatment groups; additional details are provided in Table S8.

SAFETY

The incidence of adverse events during the treatment period was 60 to 86% across the trial groups and trial parts (Table 2). The most frequently reported adverse event that occurred during the treatment period in the dupilumab groups was injection-site reaction (Table 2 and Tables S9 and S10). The incidence of conjunctivitis was low (in 1 of 39 patients who received placebo in Part A; 3 of 81 patients who received dupilumab every 2 weeks and 1 of 78 patients who received placebo in Part B; and in 1 of 37 patients who received placebo in Part A and weekly dupilumab in Part C). No clear trends in hematologic measures were observed except for the blood eosinophil count, which decreased over time in the dupilumab groups in Parts A and B and remained stable in the Part A–C group during the Part C treatment period (Fig. S7).

Adverse events that led to the discontinuation of dupilumab or placebo during the Part A or B treatment period were reported in 7 patients (3 who received weekly dupilumab, 2 who received dupilumab every 2 weeks, and 2 who received placebo), and 2 patients who received placebo in Part A and dupilumab in Part C had adverse events that led to discontinuation of dupilumab during the Part C treatment period. Serious adverse events occurred in 9 patients during the Part A or B treatment period (in 7 who received weekly dupilumab, 1 who received dupilumab every 2 weeks, and 1 who received placebo) and in 1 patient during the Part C treatment period who had received placebo in Part A and weekly dupilumab in Part C. No deaths occurred among the patients in Part A or Part B or among those in the Part A–C group in Part C.

DISCUSSION

In two phase 3, randomized trials, dupilumab at a weekly dose of 300 mg led to improvements in histologic outcomes and reductions in symptoms of eosinophilic esophagitis among adults and adolescents. The benefits with regard to histologic remission appeared to be qualitatively similar with the weekly and every-2-week dupilumab regimens, but the differences between the every-2-week regimen and placebo were not considered to be significant according to the hierarchical plan to adjust for multiple testing. The most common adverse event that occurred during the treatment period was injection-site reaction, which had a similar incidence across the trial groups. Such reactions did not lead to discontinuation of dupilumab or placebo in any patients.

Serum concentrations of dupilumab were higher with the weekly regimen than with the every-2-week regimen and may explain the greater benefits observed with the weekly dupilumab regimen.[24] Previous studies have shown that symptoms of eosinophilic esophagitis do not always correlate with histologic measures of disease.[36] The mechanism behind the discordance between symptoms and histologic features is not clear. A limitation of this trial is the high percentage of White patients; however, this percentage is representative of the overall population with eosinophilic esophagitis. Another limita-

Table 2. Incidence of Adverse Events during the Treatment Period (Safety Analysis Set).*

Event	Part A		Part B			Part A–C Group in Part C	
	Dupilumab, 300 mg weekly (N=42)	Placebo (N=39)	Dupilumab, 300 mg weekly (N=80)	Dupilumab, 300 mg every 2 wk (N=81)	Placebo (N=78)	Dupilumab–dupilumab (N=40)	Placebo–dupilumab (N=37)
	number of patients (percent)						
Deaths	0	0	0	0	0	0	0
Adverse event	36 (86)	32 (82)	67 (84)	63 (78)	55 (71)	24 (60)	27 (73)
Serious adverse event†	2 (5)	0	5 (6)	1 (1)	1 (1)	0	1 (3)
Adverse event leading to discontinuation†	1 (2)	0	2 (2)	2 (2)	2 (3)	0	2 (5)
Adverse event occurring in ≥10% of patients in any group‡							
Injection-site reaction	7 (17)	4 (10)	16 (20)	18 (22)	16 (21)	4 (10)	8 (22)
Injection-site erythema	3 (7)	5 (13)	8 (10)	18 (22)	9 (12)	4 (10)	5 (14)
Injection-site pain	4 (10)	3 (8)	7 (9)	10 (12)	4 (5)	2 (5)	3 (8)
Injection-site swelling	3 (7)	1 (3)	10 (12)	7 (9)	2 (3)	2 (5)	0
Nasopharyngitis	5 (12)	4 (10)	2 (2)	4 (5)	3 (4)	1 (2)	3 (8)
Headache	2 (5)	4 (10)	6 (8)	5 (6)	9 (12)	3 (8)	2 (5)
Acne	0	1 (3)	0	2 (2)	3 (4)	0	4 (11)
Rash	0	4 (10)	2 (2)	4 (5)	0	1 (2)	0

* The safety analysis set included all the patients who had undergone randomization and received at least one dose or part of a dose of dupilumab or placebo; data were analyzed according to whether the patients received dupilumab or placebo, regardless of trial group assignment. The Part A–C group comprised the eligible patients from Part A who continued the trial in Part C; placebo–dupilumab indicates those who received placebo in Part A and dupilumab at a weekly dose of 300 mg in Part C, and dupilumab–dupilumab indicates those who received dupilumab at a weekly dose of 300 mg in Parts A and C.

† None of the adverse events or serious adverse events that were assessed were considered by the trial investigators to be related to the trial regimen, with the exception of one serious adverse event of systemic inflammatory response syndrome; the patient with this event was continued to be followed in the trial, and the event did not recur (further details are provided in Table S9).

‡ Adverse events in this category were reported according to the preferred terms in the *Medical Dictionary for Regulatory Activities*, version 23.0.

tion was the relatively short placebo-controlled treatment period of 24 weeks for this chronic, progressive disease; however, Part C enabled assessment up to 52 weeks.

This three-part, phase 3 trial showed that weekly treatment with subcutaneous dupilumab improved histologic outcomes and alleviated symptoms of eosinophilic esophagitis in both adults and adolescents.

Supported by Sanofi and Regeneron Pharmaceuticals.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank Sara Hamon, Ph.D., and Zhen Chen, Ph.D., at Regeneron Pharmaceuticals for critical input and data analysis, respectively, and Grace Manley, Ph.D., and Jennifer L. F. Port, Ph.D., at Excerpta Medica for writing and editorial assistance in the development of earlier versions of the manuscript, including preparation of the first draft.

APPENDIX

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