Original Article

Dupilumab in Adults and Adolescents with Eosinophilic Esophagitis

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Study Overview

- In two randomized trials, weekly subcutaneous dupilumab, which blocks interleukin-4 and interleukin-13 signaling, improved histologic outcomes and alleviated symptoms of eosinophilic esophagitis.

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RESEARCH SUMMARY

Dupilumab in Adults and Adolescents With Eosinophilic Esophagitis

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CLINICAL PROBLEM

Eosinophilic esophagitis is a chronic, progressive, type 2 inflammatory disease that substantially affects the quality of life. Current first-line treatments often lack efficacy or cause adverse events; treatments that address the underlying inflammatory processes are needed. Dupilumab, a monoclonal antibody, blocks the receptor for interleukin-4 and interleukin-13, which have key roles in the disease.

CLINICAL TRIAL

Design: A three-part, randomized, phase 3 trial assessed the efficacy and safety of subcutaneous dupilumab in adult and adolescent patients with eosinophilic esophagitis.

Intervention: Patients were ≥12 years old with a diagnosis of eosinophilic esophagitis by endoscopic biopsy and a Dysphagia Symptom Questionnaire (DSQ) score of ≥10 (range, 0 to 84; higher scores indicate a worse outcome). In Part A, 81 patients received 300 mg of dupilumab weekly or placebo for 24 weeks. In Part B, 240 patients received 300 mg of dupilumab either weekly or every 2 weeks or placebo weekly for 24 weeks. In Part C, 77 patients from Part A received 300 mg of dupilumab weekly for 28 weeks. Primary end points were histologic remission and change in DSQ score at week 24.

RESULTS

Efficacy: Histologic remission at week 24 was more common in the weekly dupilumab group than in the placebo group in Parts A and B. In Part C, histologic remission was observed at week 52 regardless of whether the patients received dupilumab or placebo in Part A. Reductions in dysphagia symptoms were observed with weekly dupilumab but not with dupilumab every 2 weeks.

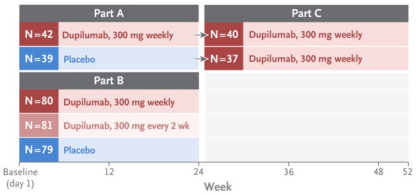
Safety: The incidence of adverse events during the treatment period was similar across trial groups and trial parts. Severe adverse events occurred in 10 patients.

LIMITATIONS AND REMAINING QUESTIONS

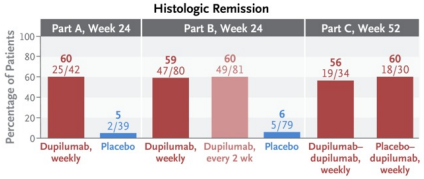
- The placebo-controlled treatment period, at 24 weeks, is relatively short given that eosinophilic esophagitis is a chronic, progressive disease.
- A high percentage of patients were White, which may limit generalizability of the results; however, the trial population was representative of the overall population with eosinophilic esophagitis.

Links: Full Article | NEJM Quick Take | Editorial

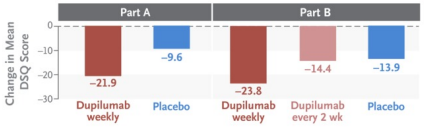
Phase 3 Trial Design
(all doses delivered subcutaneously)



Histologic Remission



Change in Mean DSQ Score at Week 24



Incidence of Adverse Events at Week 24

Adverse Event	Part A		Part B		
	Dupilumab, weekly (N=42)	Placebo (N=39)	Dupilumab, weekly (N=80)	Dupilumab, every 2 wk (N=81)	Placebo (N=78)
	no. of patients (%)				
Death	0	0	0	0	0
Any adverse event	36 (86)	32 (82)	67 (84)	63 (78)	55 (71)
Serious adverse event	2 (5)	0	5 (6)	1 (1)	1 (1)

CONCLUSIONS

Among adults and adolescents with eosinophilic esophagitis, weekly dupilumab was associated with histologic improvement and reductions in symptoms.

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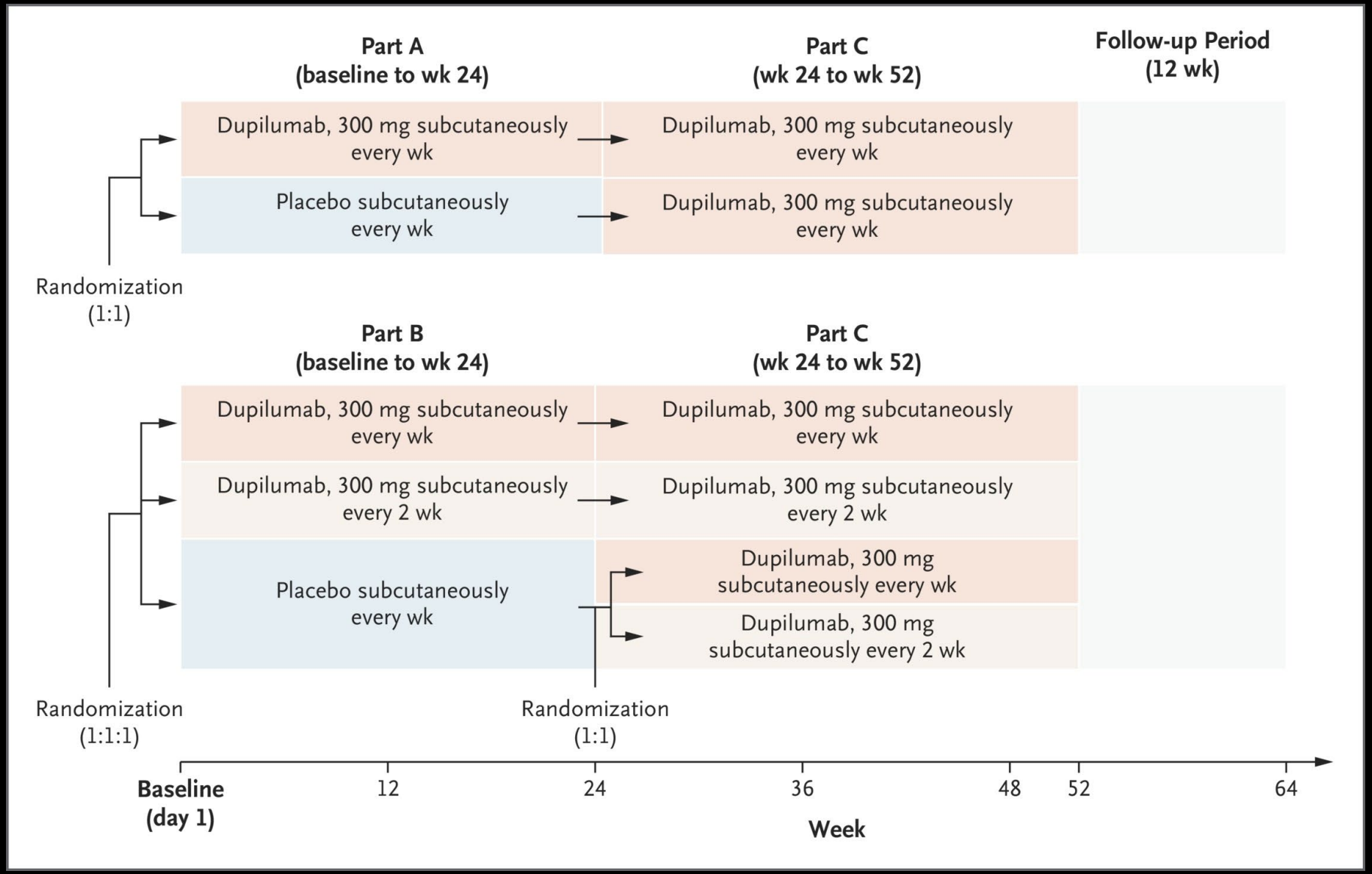
Phase 3 Trial Design.



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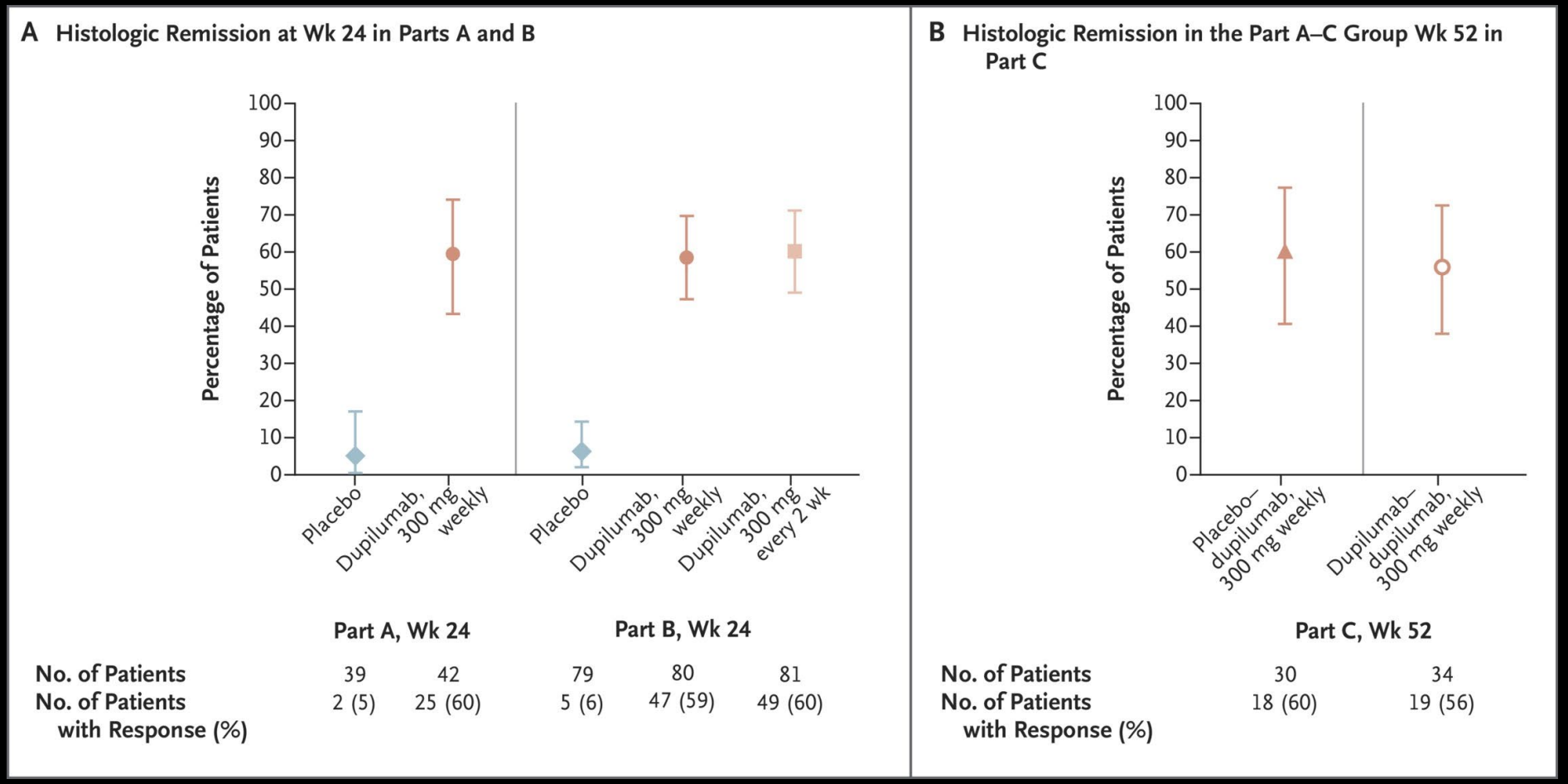
Histologic Remission at Weeks 24 and 52.



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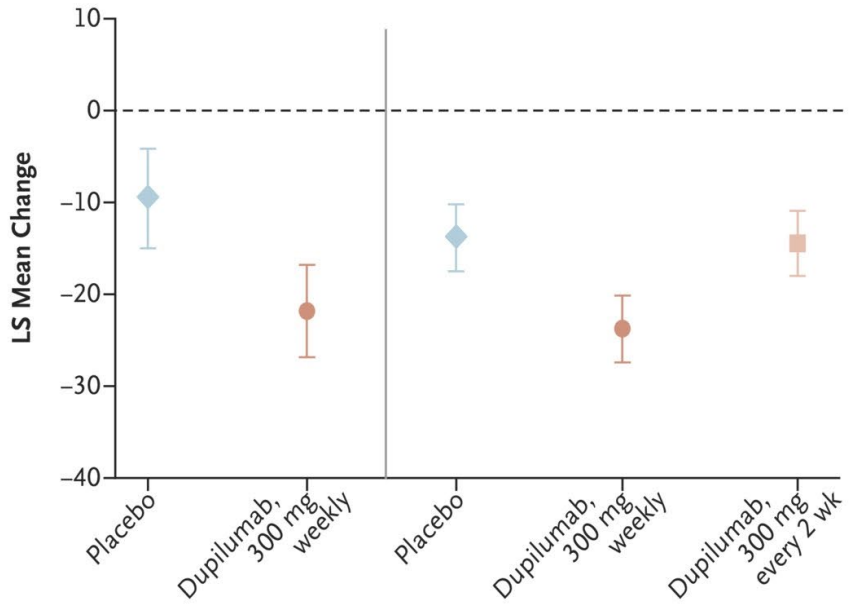
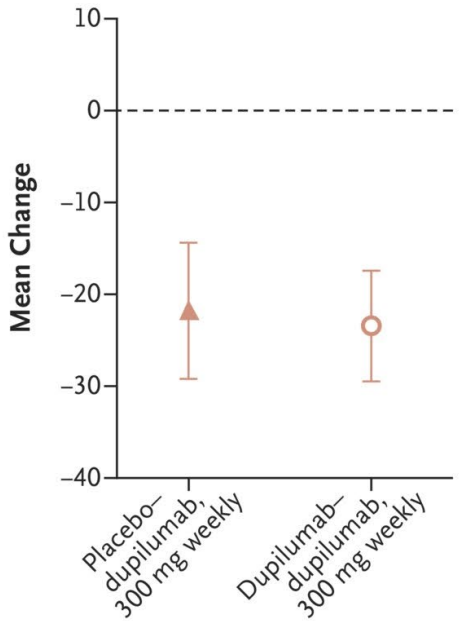
Change in DSQ Score at Weeks 24 and 52.

A Change from Baseline in DSQ Score in Parts A and B



	Part A, Wk 24		Part B, Wk 24		
No. of Patients/No. with Imputed Values	28/11	38/4	59/19	63/17	62/19
LS Mean Change (95% CI)	−9.6 (−15.06 to −4.12)	−21.9 (−26.87 to −16.97)	−13.9 (−17.61 to −10.12)	−23.8 (−27.43 to −20.13)	−14.4 (−18.02 to −10.72)

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



	Part C, Wk 52	
No. of Patients	23	29
Mean Change (95% CI)	−21.7 (−29.13 to −14.30)	−23.4 (−29.58 to −17.30)

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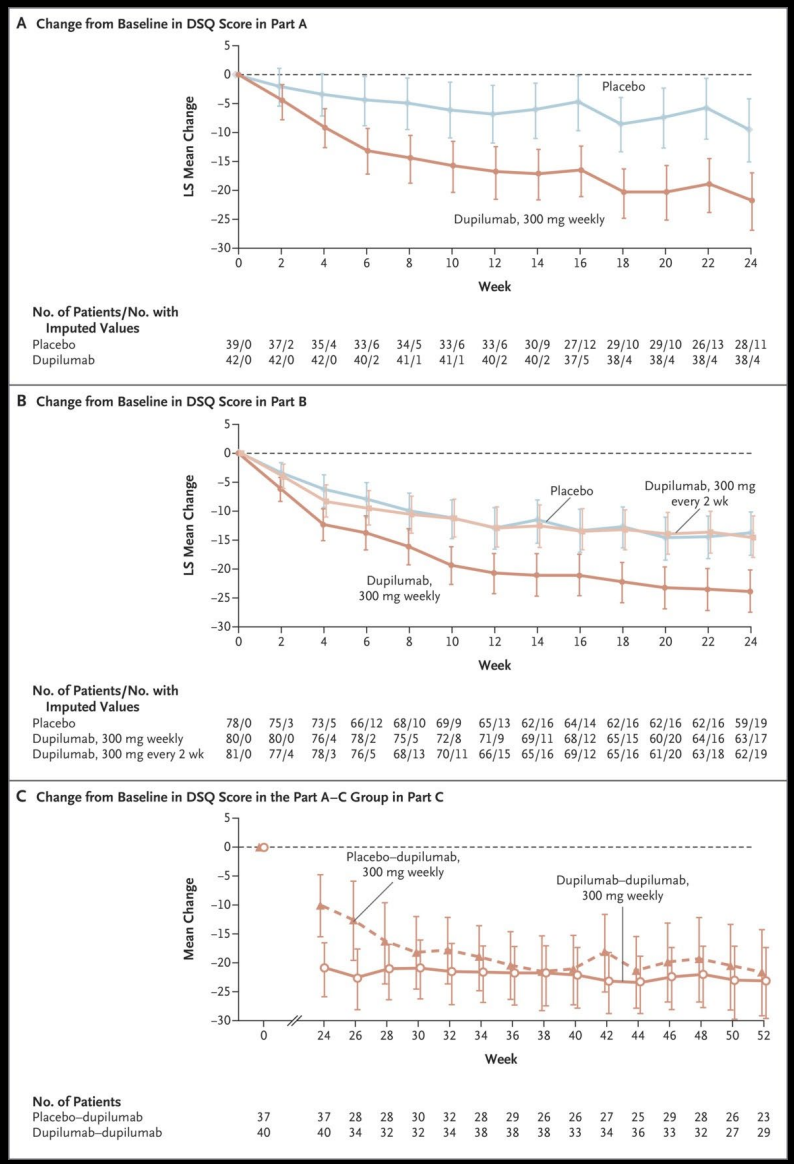
Change in DSQ Score over Time.



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

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.

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

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.

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Conclusions

- Among patients with eosinophilic esophagitis, subcutaneous dupilumab administered weekly improved histologic outcomes and alleviated symptoms of the disease.