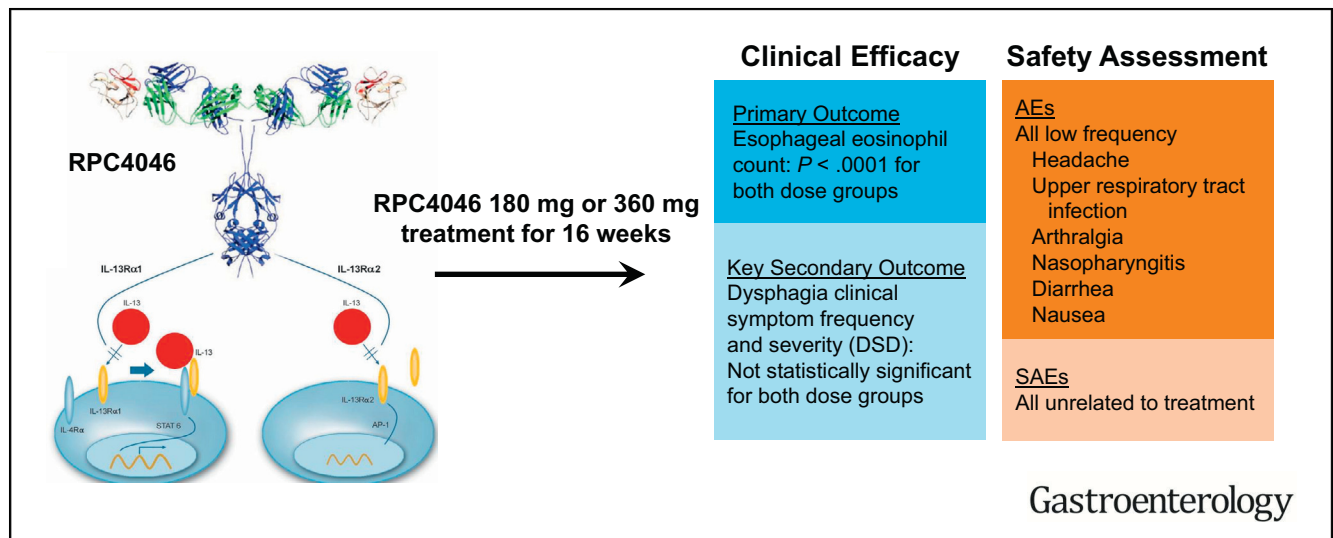




# RPC4046, a Monoclonal Antibody Against IL13, Reduces Histologic and Endoscopic Activity in Patients With Eosinophilic Esophagitis

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**BACKGROUND & AIMS:** Eosinophilic esophagitis (EoE) is a chronic, esophageal, type 2 inflammatory response associated with increased serum levels of interleukin 13 (IL13), which might contribute to its pathogenesis. RPC4046, a recombinant humanized monoclonal antibody against IL13, prevents its binding to the receptor subunits IL13RA1 and IL13RA2. We performed a phase 2 trial to evaluate the efficacy and safety of RPC4046 in patients with EoE. **METHODS:** We performed a multicenter, double-blind trial of 99 adults with active EoE randomly assigned (1:1:1) to groups given RPC4046 (180 or 360 mg) or placebo once weekly for 16 weeks, from September 2014 through December 2015. Patients were seen at day 1 (baseline) and weeks 2, 4, 8, 12, and 16. They underwent esophagogastroduodenoscopy and biopsies were collected at

baseline and week 16. Patients completed a daily dysphagia symptom diary through week 16 and patient-reported outcome data were collected. The primary outcome was change in mean esophageal eosinophil count in the 5 high-power fields (hpf) with the highest level of inflammation. **RESULTS:** At week 16, mean changes in esophageal eosinophil count per hpf were a reduction of  $94.8 \pm 67.3$  in patients who received 180 mg RPC4046 ( $P < .0001$ ) and a reduction of  $99.9 \pm 79.5$  in patients who received 360 mg RPC4046 ( $P < .0001$ ) compared with a reduction of  $4.4 \pm 59.9$  in patients who received placebo. The 360-mg RPC4046 group, compared with the placebo group, showed significant reductions in validated endoscopic severity score at all esophageal locations ( $P < .0001$ ), validated histologic grade and stage scores (both  $P < .0001$ ), and clinician's global assessment of disease severity ( $P = .0352$ ); they had a numerical reduction in scores from the dysphagia symptom diary ( $P = .0733$ ). Significant reductions in esophageal

eosinophil counts and histologic and endoscopic features were observed in patients with steroid-refractory EoE who received RPC4046. The most common adverse events were headache and upper respiratory tract infection. **CONCLUSIONS:** In a phase 2 trial of patients with EoE, we found RPC4046 (a monoclonal antibody against IL13) to reduce histologic and endoscopic features compared with placebo. RPC4046 was well tolerated. [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02098473) no: NCT02098473.

**Keywords:** Placebo-Controlled; Randomized; Esophagus; Immune Response.

**E**osinophilic esophagitis (EoE) is a chronic, allergic/immune-mediated clinicopathologic disease of the esophagus characterized histologically by eosinophil-predominant mucosal inflammation and clinically by signs and symptoms of esophageal dysfunction.<sup>1,2</sup> The prevalence of EoE has increased dramatically since the original description in 1993, with estimates of 0.5 to 1 cases per 1000 persons worldwide.<sup>3</sup> Complications of EoE, including strictures and food impaction, are related to esophageal remodeling and fibrostenosis, which are associated with a longer duration of untreated disease.<sup>4,5</sup> Presently, no therapies are approved for EoE in the United States, although an orodispersible budesonide tablet has recently been approved in Europe. Current management approaches include diet interventions designed to eliminate foods that trigger the inflammatory response and topically acting glucocorticosteroids that are swallowed to coat the esophageal mucosa. Although these therapies are effective in reducing eosinophilic inflammation, a significant proportion of patients are refractory, and the disease universally flares on weaning of therapy.<sup>6,7</sup> Furthermore, reduction in remodeling-associated alterations of the esophagus using steroids has been incomplete, necessitating use of esophageal dilation for strictures.<sup>8</sup>

Increased serum levels of interleukin 13 (IL13) might contribute to the pathogenesis of EoE. Preclinical in vitro modeling and human data have shown that IL13 is overexpressed in the esophageal mucosa of patients with EoE, induces a gene transcript profile that overlaps with the EoE-specific esophageal transcriptome,<sup>9</sup> and modulates cellular and molecular pathways involved in eosinophil recruitment,<sup>10</sup> esophageal barrier function,<sup>11</sup> and tissue remodeling and fibrosis.<sup>12</sup> Transgenic overexpression of IL13 in mice induces marked esophageal eosinophilia, extensive tissue remodeling, and an esophageal transcriptome that overlaps with the EoE transcriptome seen in patients.<sup>12</sup> IL13 also markedly induces the gene product encoded by the EoE major genetic susceptibility locus (2p23), calpain-14, which modifies esophageal epithelial barrier.<sup>13,14</sup> Furthermore, a small preliminary study using a monoclonal antibody against IL13 demonstrated reductions in esophageal eosinophil counts and EoE-related gene expression.<sup>15</sup> RPC4046 is a selective, high-affinity, humanized immunoglobulin G1 monoclonal antibody that recognizes wild-type and variant human IL13, and blocks its

## WHAT YOU NEED TO KNOW

### BACKGROUND AND CONTEXT

Eosinophilic esophagitis (EoE) is associated with elevated interleukin 13 (IL13), which may have a central role in disease pathogenesis. RPC4046, a recombinant humanized monoclonal antibody against IL13, prevents binding to both IL13 receptor subunits.

### NEW FINDINGS

This phase 2 trial provides evidence of the efficacy and safety of antibody against IL13 therapy with RPC4046 in adult patients with EoE, with improvement in histopathologic and endoscopic aspects of disease activity and global perception of disease severity.

### LIMITATIONS

The study was not powered to assess dysphagia symptom improvement. Furthermore, a validated patient-reported outcome measure for EoE symptoms was not available at the time the study was designed.

### IMPACT

The data from this phase 2 trial substantiate the potential contribution of IL13 in the pathogenesis of EoE and support the further study of RPC4046 as a novel, targeted approach for EoE.

binding to the receptor subunits IL13R $\alpha$ 1 and IL13R $\alpha$ 2.<sup>16</sup> We evaluated the efficacy and safety of RPC4046 in adult patients with clinically and histologically active EoE.

## Methods


### Trial Design

The double-blind period of this phase 2, randomized, placebo-controlled trial was conducted at 30 centers in 3 countries ([Supplementary Table 1](#)) from September 2014 to December 2015, with completion of the study marked by the last safety follow-up in February 2016. The protocol and amendments were approved by the institutional review board or ethics committee at each center. All patients gave written informed consent. See the [Supplementary Materials](#) for details regarding site information, study administration, and protocol amendments.

### Patient Population

Eligible patients were 18 to 65 years of age with a confirmed diagnosis of EoE. Patients were required to have

**Abbreviations used in this paper:** DSD, dysphagia symptom diary; EEsAI, eosinophilic esophagitis activity index; EoE, eosinophilic esophagitis; EoEHSS, Eosinophil Histologic Scoring System; eos, eosinophil count; EREFS, EoE endoscopic reference score; hpf, high-power field; IL13, interleukin 13; IV, intravenous; PRO, patient-reported outcome; SC, subcutaneous.

 Most current article

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symptoms of dysphagia for a minimum of 4 days over 2 weeks (within the 4-week screening period) and histologic evidence of EoE, defined as a peak count of  $\geq 15$  eosinophils per high-power field (eos/hpf; microscope hpf =  $0.3 \text{ mm}^2$ ) at any 2 of 3 levels of the esophagus (proximal, mid, distal) when off anti-inflammatory therapy for EoE. Patients must have previously received an adequate trial of a proton pump inhibitor to exclude gastroesophageal reflux disease and proton pump inhibitor-responsive esophageal eosinophilia as the primary cause of their symptoms. Prior treatment of patients with steroids for EoE was recorded, with steroid refractory defined as an adequate trial of systemic or swallowed topical steroids failing to result in a meaningful reduction in symptoms, as judged by the investigator. Key exclusion criteria were presence of generalized eosinophilic gastroenteritis, active *Helicobacter pylori* gastritis, Barrett's esophagus, severe esophageal stricture preventing passage of a standard adult diagnostic upper endoscope, and esophageal dilation within 4 months of screening. See the [Supplementary Material](#) for additional inclusion and exclusion criteria.

### Randomization and Masking

The trial included a 16-week, double-blind treatment period and an optional open-label period ([Figure 1](#)). This report describes the double-blind treatment period. Patients were randomly assigned (1:1:1) to groups given low-dose RPC4046 (5 mg/kg intravenous [IV] loading dose + 180 mg subcutaneously [SC]) on day 1, then 180 mg SC once weekly for 15 additional weeks, or matching placebo (IV loading dose + SC) on day 1, then SC dose once weekly for 15 additional weeks, or high-dose RPC4046 (10 mg/kg IV loading dose + 360 mg SC) on day 1, then 360 mg SC once weekly for 15 additional weeks ([Supplementary Material](#)). Randomization was done centrally on day 1 through an interactive voice response system/interactive Web-based response system using a computer-generated sequence that was programmed by an

independent, unmasked, statistical team at the contract research organization. Randomization allocation was stratified based on steroid-refractory status. The study drug, RPC4046, and placebo solutions were identical in physical appearance. The treatment each patient received was not disclosed to the investigator, trial center personnel, patient, sponsor, or their representatives. Each patient's treatment group assignment blind was not broken until all patients completed the double-blind treatment period.

### Procedures

Patients were seen at day 1 (baseline) and weeks 2, 4, 8, 12, and 16 during the double-blind treatment period. They underwent esophagogastroduodenoscopy and biopsies were collected at baseline and week 16 for esophageal eosinophil count and additional histopathologic assessment. Patients completed a daily dysphagia symptom diary (DSD) for at least the last 2 consecutive weeks during the 4-week screening period and daily from day 1 through week 16 ([Supplementary Materials](#)). Other patient-reported outcome (PRO) data were collected from the validated eosinophilic esophagitis activity index (EEsAI),<sup>17</sup> patient's global assessment of disease severity, and patient's global impression of change in EoE symptoms ([Supplementary Material](#)). Esophageal mucosal appearance was determined at the time of each endoscopic examination by the EoE endoscopic reference score (EREFS), a validated instrument for assessing the presence and severity of the major endoscopic signs of EoE, including esophageal edema, rings, exudates, furrows, and stricture ([Supplementary Material](#)).<sup>18</sup> A central pathologist blinded to treatment allocation determined EoE histologic changes. Mean (defined later in this article) esophageal eos/hpf and other parameters were assessed using the EoE histology scoring system, a validated measure for evaluating eosinophil density, basal zone hyperplasia, eosinophil abscesses, eosinophil surface layering, dilated intercellular spaces, surface epithelial alteration, dyskeratotic epithelial

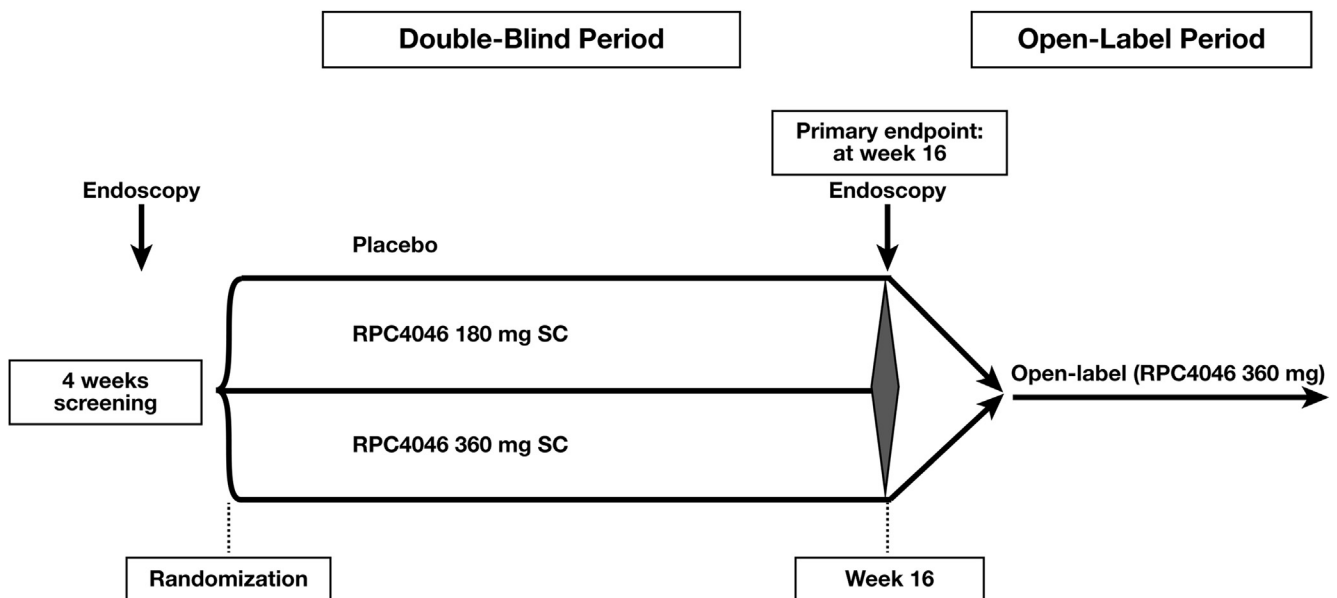
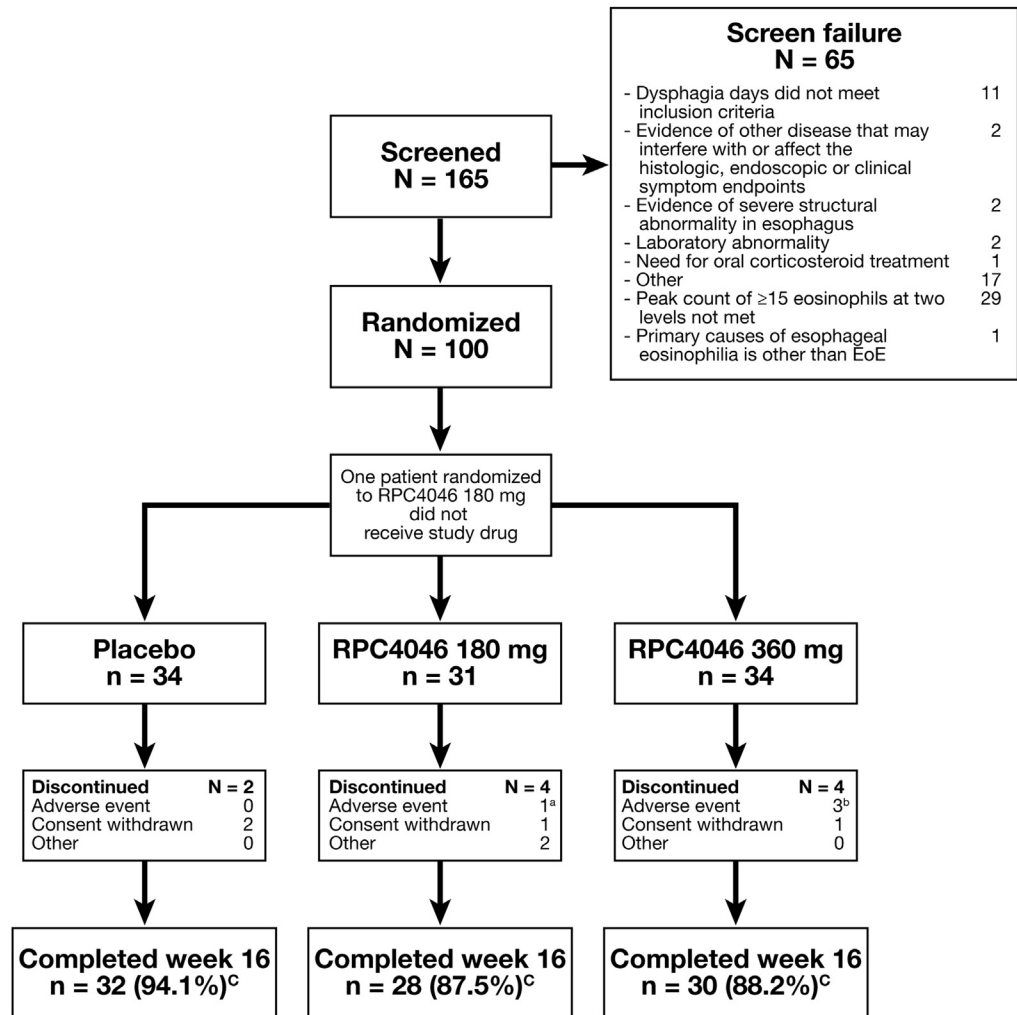


Figure 1. Study schematic.



**Figure 2.** Patient disposition and treatment through week 16. <sup>a</sup>Lightheadedness. <sup>b</sup>Flu-like symptoms; worsening EoE symptoms; pruritus and rash. <sup>c</sup>Based on number of patients randomized.

cells, and lamina propria fibrosis (Supplementary Material).<sup>19,20</sup> Adverse events and concomitant medication use were recorded through 16 weeks (24 weeks for patients who did not continue into the open-label extension). Blood samples were obtained at each clinic visit for clinical chemistry and hematology, serum RPC4046 assessment, and serum antibodies to RPC4046.

The primary efficacy outcome was change in mean esophageal eosinophil count in the 5 hpfs with the highest level of inflammation in the esophageal biopsies. The key secondary efficacy outcome was mean change in the dysphagia clinical symptom frequency and severity from baseline to week 16 as assessed by DSD completed over 2 weeks before the week 16 endpoint. Other secondary outcomes included change in EEsAI PRO score, peak esophageal eosinophil count, EREFS, patient’s and clinician’s global assessments of disease severity, patient’s global impression of change in EoE symptoms, and esophageal histologic severity (grade) and extent (stage).

**Statistical Analysis**

The trial was powered to determine the efficacy of 180 mg and 360 mg RPC4046 for the treatment of patients with EoE. The planned sample size of 90 randomized patients (30 patients/arm) was justified based on previous published trials of

other therapies for EoE. The baseline mean eosinophil count was expected to be in the range of 80 to 110 eos/hpf, with an estimated standard deviation of change from baseline in eosinophil counts of 30 to 50 eos/hpf. Using a 2-sided test at the  $\alpha = .05$  level of significance and a conservative standard deviation assumption of 50 eos/hpf, a sample size of 30 patients per arm provided 87% power to detect a treatment difference of 40 eos/hpf and 93% power to detect a treatment difference of 45 eos/hpf.

The trial had a parallel-group design; primary statistical analyses were performed using analysis of covariance with baseline mean esophageal eosinophil count measured in the 5 hpfs with the highest level of inflammation included as a covariate and treatment group and steroid-refractory status included as factors.

Comparisons between treatments and placebo were performed at 2-sided  $\alpha = 0.05$ . All efficacy analyses were performed using the intention-to-treat principle. The primary efficacy outcome was change in mean esophageal eosinophil count in the 5 hpfs with the highest level of inflammation at week 16. A Cochran-Mantel-Haenszel  $\chi^2$  test was performed at week 16 to compare the peak esophageal eosinophil count response ( $<15$  vs  $\geq 15$ ) by treatment group, controlling for steroid-refractory status.

**Table 1.** Patient Demographics and Disease Characteristics

	Placebo (n = 34)	RPC4046	
		180 mg (n = 31)	360 mg (n = 34)
Age, y			
Mean	38.6 ± 11.03	39.1 ± 9.87	33.9 ± 10.92
Median	38.5	40.0	31.5
Minimum, maximum	19, 64	19, 59	18, 63
Sex, n (%)			
Male	22 (64.7)	19 (61.3)	20 (58.8)
Female	12 (35.3)	12 (38.7)	14 (41.2)
Race, n (%)			
White	34 (100)	30 (96.8)	34 (100)
Black or African American	0	1 (3.2)	0
Years since EoE diagnosis, mean	4.26 ± 2.90	4.25 ± 3.82	3.92 ± 2.73
Steroid refractory, n (%)	16 (47.1)	14 (45.2)	16 (47.1)
Peak eosinophil count/hpf			
Mean	105.4 ± 60.42	131.9 ± 84.55	139.4 ± 79.94
Minimum, maximum	18, 212	24, 304	26, 389
Eosinophil count/hpf			
Mean	92.41 ± 54.11	116.65 ± 77.32	122.55 ± 71.08
Minimum, maximum	17.6, 189.8	21.4, 273.0	22.2, 369.2
Peripheral eosinophil count, 10 <sup>9</sup> /L			
Mean	0.44 ± 0.23	0.51 ± 0.28	0.39 ± 0.19
Minimum, maximum	0.1, 1.0	0.1, 1.4	0.1, 0.8
Total IgE, IU/mL			
Mean	96.2 ± 97.09	262.8 ± 289.60	190 ± 408.05
Minimum, maximum	1, 411	4, 1105	2, 2094
Daily symptom diary score			
Mean	29.44 ± 10.70	27.63 ± 13.18	29.03 ± 10.13
Minimum, maximum	11.0, 51.0	6.6, 52.0	11.0, 49.0
EEsAI PRO score (range 0–100)			
Mean	56.1 ± 13.19	58.1 ± 12.22	56.2 ± 13.21
Minimum, maximum	34, 94	27, 92	34, 94
EoE EREFS features, n (%)			
Edema	20 (62.5)	18 (66.7)	26 (78.8)
Rings	28 (87.5)	23 (85.2)	25 (75.8)
Exudates	16 (50.0)	21 (77.8)	20 (60.6)
Furrows	27 (84.4)	22 (81.5)	31 (93.9)
Stricture	13 (40.6)	9 (33.3)	9 (27.3)

Additional details regarding statistical methods, including prespecified subgroup analyses, exploratory analyses, sensitivity analyses, multiple post hoc subgroup analyses, and approaches to handling missing data, are provided in the [Supplementary Material](#).

All authors had access to the study data and reviewed and approved the final manuscript.

## Results

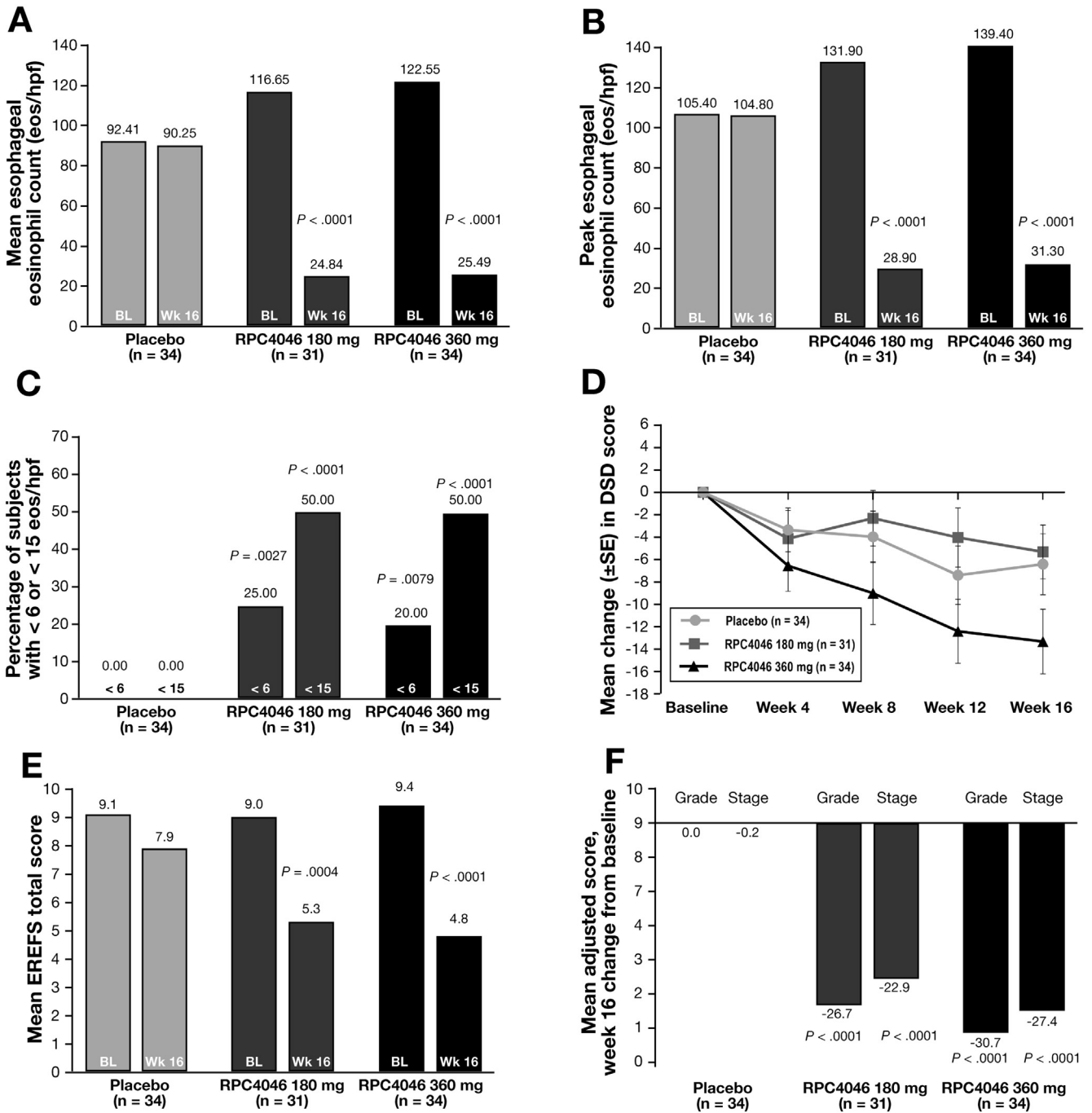
### Baseline Patient Characteristics

Of the total 100 patients randomly assigned to study groups, 99 patients received study drug or placebo ([Figure 2](#)). One patient in the 180 mg RPC4046 group was randomized in error, did not receive study drug, and was excluded from the analysis. Patient demographics were typical for an adult population with EoE, with male predominance and median age between 30 and 40 years. Study groups were generally balanced with respect

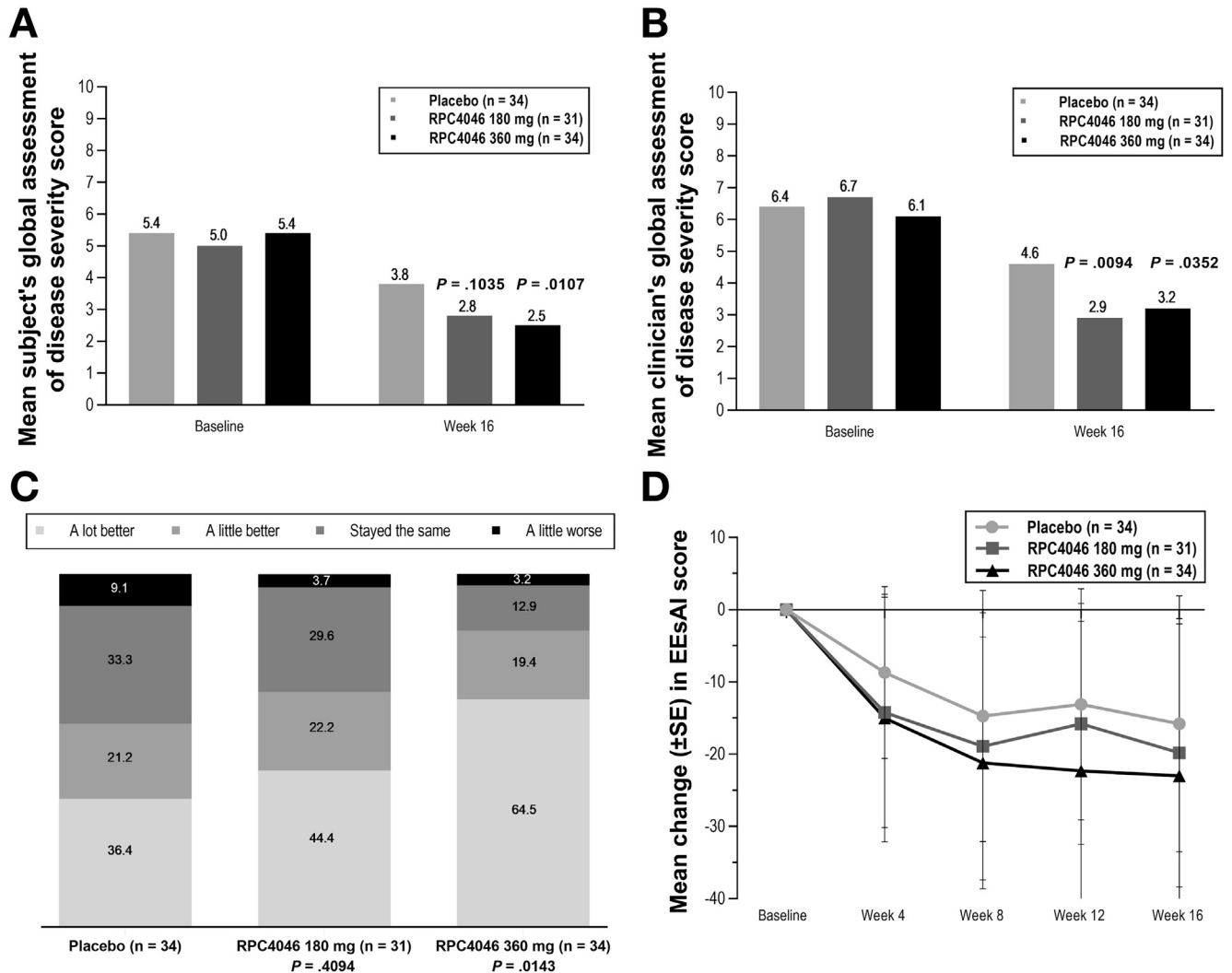
to demographic characteristics, except for slightly younger patients in the 360 mg RPC4046 group and higher baseline mean esophageal eosinophil count in the 180 mg (116.65 ± 77.32 eos/hpf) and 360 mg (122.55 ± 71.08 eos/hpf) groups compared with placebo (92.41 ± 54.11 eos/hpf) ([Table 1](#), [Supplementary Table 2](#)). Ninety of the 99 patients (90.9%) completed the 16-week treatment period.

### Clinical Efficacy

At week 16, mean reductions from baseline in esophageal eosinophil count were 4.42 ± 59.94, 94.76 ± 67.27, and 99.90 ± 79.53 eos/hpf in the placebo, 180 mg RPC4046, and 360 mg RPC4046 groups, respectively. Mean changes between either RPC4046 dose and placebo were statistically significant at week 16 ( $P < .0001$  for both comparisons; mean counts, [Figure 3A](#)). Peak esophageal eosinophil counts were significantly reduced, with 50% of patients treated



**Figure 3.** Clinical results for the overall EoE patient group include the following: the mean esophageal eosinophil count (eos/hpf) at baseline and week 16 (primary endpoint) (A); peak esophageal eosinophil count (eos/hpf) at baseline and week 16 (B); proportion of patients achieving peak esophageal eosinophil count <6 eos/hpf and <15 eos/hpf at baseline and week 16 (C); mean change over the 14 days preceding each study visit in dysphagia symptom diary (DSD) score (± standard error) at baseline and weeks 4, 8, 12, and 16 ( $P = .0733$  for 360 mg at week 16; daily DSD score range: 0–6, with higher scores indicating more severe dysphagia symptoms) (D); mean total EREFS at baseline and week 16 (endoscopic findings analyzed according to modified scoring system described by Hirano et al 2013<sup>18</sup>; total EREFS score range: 0–8 for each location [ie, total score range across 3 locations: 0–24]) (E); and mean changes from baseline to week 16 in eosinophilic histology grade (range: 0–3 for each of 8 features for proximal and distal biopsies [ie, total score range: 0–48]) and stage (range: same as for grade) scores (F).



**Figure 4.** For overall EoE patient group, mean patient's global assessment of disease severity was significantly reduced at week 16 for the 360-mg RPC4046 group compared with placebo; *P* values from an analysis of covariance model were adjusted for steroid-refractory status and baseline global assessment of disease severity score (A). Mean clinician's global assessment of disease severity was significantly reduced at week 16 for the 180-mg and 360-mg RPC4046 groups compared with placebo; *P* values from an analysis of covariance model were adjusted for steroid-refractory status and baseline global assessment of disease severity score (B). Categorical analysis of the patient's global impression of change from baseline in EoE symptoms at week 16; *P* values comparing 180 mg RPC4046 with placebo and 360 mg RPC4046 with placebo were based on the Wilcoxon rank-sum test (C). Mean change in the EEsAI score ( $\pm$  standard error) at weeks 4, 8, 12, and 16 (*P* = .1103 for 360 mg at week 16) (D).

with 180 mg and 360 mg having  $<15$  peak eos/hpf compared with 0% placebo (*P*  $<$  .0001 for both comparisons), and 25% of patients in the 180 mg RPC4046 group and 20% in the 360 mg RPC4046 group having  $<6$  peak eos/hpf after treatment (*P* = .0027 and *P* = .0079, respectively) (Figure 3B and C).

Mean reductions in the EREFS total score of  $1.2 \pm 1.18$  and  $1.3 \pm 1.22$  between either RPC4046 dose (180 mg, *n* = 24; 360 mg, *n* = 29) and placebo (*n* = 31) were statistically significant over all esophageal locations at week 16 (180 mg, *P* = .0004; 360 mg, *P*  $<$  .0001) (mean total scores, Figure 3E, Supplementary Table 3; stricture features, Supplementary Table 4). Reductions in mean adjusted Eosinophil Histologic Scoring System (EoEHSS) grade scores of  $26.651 \pm 14.737$  and  $30.737 \pm$

$15.520$  and stage scores of  $22.853 \pm 11.445$  and  $27.378 \pm 13.198$  between either RPC4046 dose (180 mg, *n* = 28; 360 mg, *n* = 30) and placebo (*n* = 33) were statistically significant at week 16 (*P*  $<$  .0001 for both comparisons) (Figure 3F).

Mean reductions in the patient's global assessment of disease severity score of  $2.01 \pm 1.68$  and  $2.8 \pm 2.71$  were significant at week 16 with the 360-mg dose (*n* = 27, *P* = .0107) but not with the 180-mg dose (*n* = 30, *P* = .1035) (Figure 4A). Mean reductions in the clinician's global assessment of disease severity score of  $3.6 \pm 2.71$  and  $2.9 \pm 2.70$  were significant at week 16 with the 180-mg (*n* = 27, *P* = .0094) and 360-mg doses (*n* = 30, *P* = .0352) (Figure 4B). Categorical analysis of patient's global impression of change in EoE symptoms at week 16

did not show significant improvements in either RPC4046 group (180 mg:  $n = 31$ ,  $P = .4094$ ; 360 mg:  $n = 34$ ,  $P = .0143$ ) (Figure 4C).

At week 16, mean reduction in the DSD composite score was greater in the 360-mg RPC4046 group compared with the placebo group ( $13.31 \pm 15.26$  vs  $6.41 \pm 15.40$ ), although this was not statistically significant ( $P = .0733$ ) (Figure 3D). Patients receiving 360 mg RPC4046 showed a trend toward greater reduction in the EEsAI PRO score vs placebo ( $P = .1103$ ) (Figure 4D).

### Steroid-Refractory Patient Subgroup

In the prespecified subgroup of steroid-refractory patients ( $n = 47$ ; Supplementary Table 2), mean reductions in esophageal eosinophil count of  $103.53 \pm 89.166$  and  $130.12 \pm 73.993$  between 180 mg ( $n = 14$ ) and placebo as well as 360 mg ( $n = 17$ ) and placebo ( $n = 16$ ) were observed at week 16 (180 mg,  $P = .0001$ ; 360 mg,  $P \leq .0001$ ) (Figure 5A, Supplementary Table 5; steroid-responsive subgroup, Supplementary Table 6). DSD composite scores for the 360-mg RPC4046 group approached significance ( $P = .054$ ); however, this trend was not observed for the 180-mg RPC4046 group (Figure 5B; Supplementary Table 7; steroid-responsive subgroup, Supplementary Table 6). Mean reductions in the EREFS total score of  $4.1 \pm 4.21$  and  $4.2 \pm 3.68$  over all measured locations at week 16 were reported in the 180-mg and 360-mg RPC4046 groups, respectively (180 mg,  $P = .0026$ ; 360 mg,  $P = .0016$ ; mean scores, Figure 5C, Supplementary Table 3). Mean reductions in adjusted EoEHSS grade scores of  $32.126 \pm 13.641$  and  $30.694 \pm 17.128$  and mean reductions in adjusted EoEHSS stage scores of  $25.529 \pm 12.660$  and  $27.374 \pm 14.669$  between either RPC4046 dose (180 mg,  $n = 12$ ; 360 mg,  $n = 15$ ) and placebo ( $n = 15$ ) were statistically significant at week 16 ( $P < .0001$  for all comparisons; Figure 5D; Supplementary Table 8). The reduction in EEsAI PRO score between the 360-mg RPC4046 and placebo groups was significant ( $P = .0393$ ), whereas the difference between the 180-mg RPC4046 and placebo groups was not (Figure 5E; Supplementary Table 9).

### Safety Assessment

The frequency of adverse events was numerically higher in the 360-mg RPC4046 group. The most common treatment-emergent adverse events observed were headache, upper respiratory tract infection, arthralgia, nasopharyngitis, diarrhea, and nausea (Table 2). Overall, the frequency of treatment-emergent adverse events in the RPC4046 treatment groups was low and similar to placebo. Four patients discontinued study drug due to a treatment-emergent adverse event (1 patient receiving 180 mg [dizziness], 3 patients receiving 360 mg [influenza-like illness, pruritus and rash, and worsening of EoE symptoms]). Three patients experienced a serious adverse event, all of which were considered unrelated to study drug (2 patients receiving placebo [umbilical hernia, appendicitis], 1 patient receiving 360 mg [appendicitis])

(Supplementary Table 6). Two patients receiving 180 mg and no patients receiving 360 mg developed anti-drug antibodies.

Serious adverse events and injection site treatment-emergent adverse events are shown in Supplementary Tables 10 and 11, respectively. One serious adverse event of umbilical hernia in the placebo group and 2 serious adverse events of appendicitis (1 in the placebo group and 1 in the 360-mg RPC4046 group) were reported. The most common injection site treatment-emergent adverse events were injection site pain (8.8%) in the placebo group and injection site erythema (8.8%) in the 360-mg RPC4046 group. Each injection site event that was reported in the 180-mg RPC4046 group occurred in no more than a single patient.

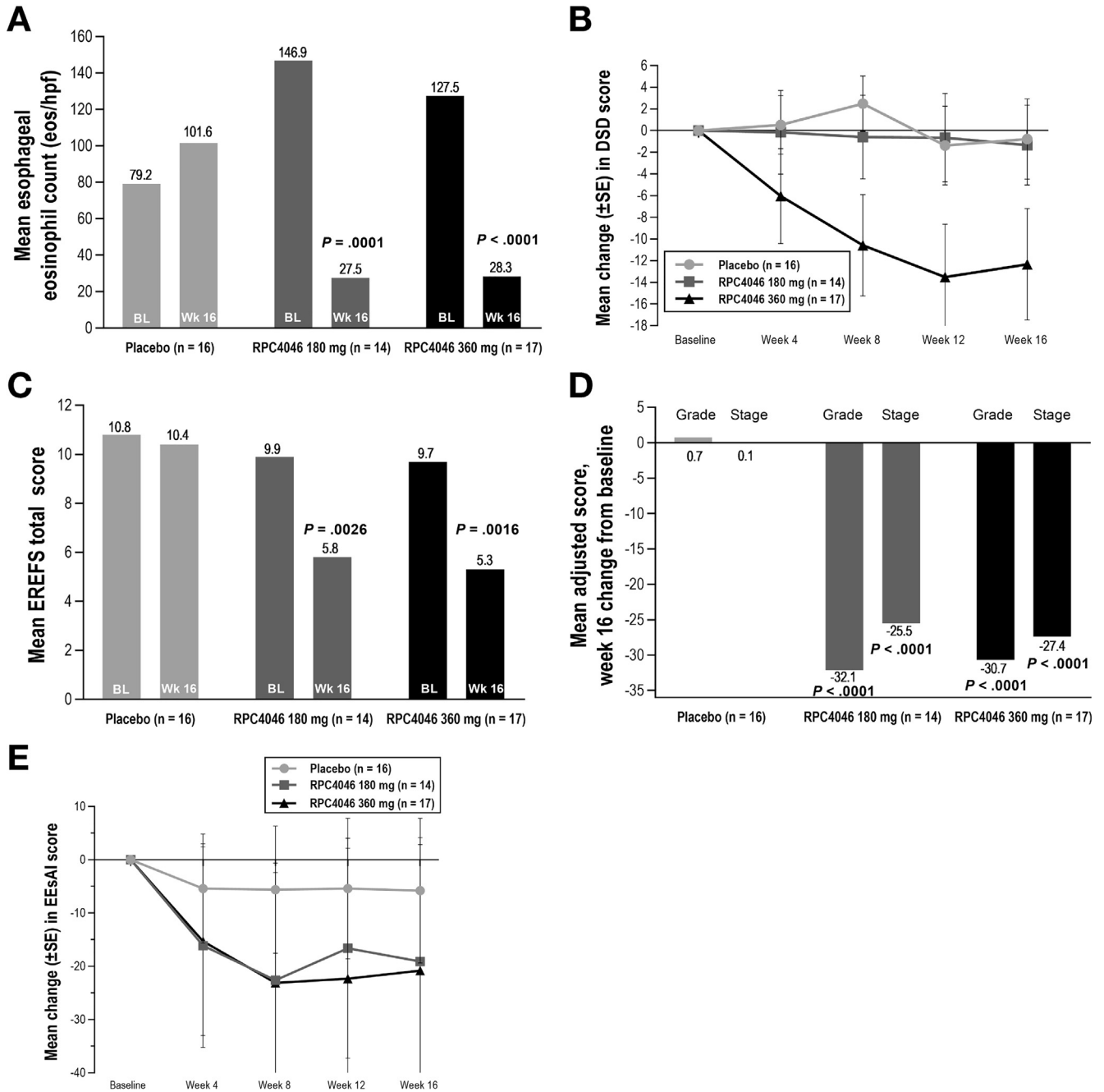
### Discussion

In this phase 2 trial of patients with active EoE, 180-mg and 360-mg RPC4046 demonstrated greater benefit than placebo in reducing esophageal eosinophil count at week 16. Furthermore, significant reductions in histologic and endoscopic assessment of disease activity were demonstrated using validated instruments. These results were seen both in the overall population and in the steroid-refractory subgroup.

IL13 has been implicated as a key cytokine in the pathogenesis of EoE. Significant reductions in EoE disease activity following RPC4046 treatment in this study highlight the clinical relevance of targeting IL13 as a therapeutic approach for this disorder. These results further extend and support preliminary data from a small proof-of-concept study in EoE using a different antibody against IL13,<sup>15</sup> as well as in vivo modeling in mice, in which IL13 overexpression has been shown to be sufficient to induce an EoE-like disease process.<sup>11</sup> Indeed, IL13 is markedly overexpressed in the esophagus of patients with EoE and induces EoE-like changes in esophageal epithelial cells,<sup>7</sup> including a subset of the EoE transcriptome, impaired barrier formation,<sup>10</sup> and production of the eosinophil chemoattractant and activating factor eotaxin-3<sup>7</sup> and induction of the gene product encoded by the primary EoE genetic risk factor, CAPN14, which regulates esophageal barrier function, which is impaired in EoE.<sup>13</sup>

Although reductions in dysphagia symptoms assessed by the DSD composite score and the EEsAI PRO score were not statistically significant with RPC4046 at either dose level compared with placebo, a strong trend was observed with the 360-mg RPC4046 dose. Furthermore, patient and clinician global PRO measures demonstrated significant reduction in overall perceptions of disease severity with RPC4046. These findings are notable, as the study was not powered to show differences in symptom metrics. Conceptually, reducing dysphagia symptoms may be more difficult to achieve than reducing mucosal inflammation owing to the contribution of subepithelial fibrostenotic remodeling. Nevertheless, the trend for a reduction in symptoms that was detected in spite of the small sample size is encouraging for further development of RPC4046.





**Figure 5.** For steroid-refractory subgroup, mean esophageal eosinophil count (eos/hpf) at baseline and week 16 (primary endpoint) (A). Mean change over the 14 days preceding each study visit in dysphagia symptom diary (DSD) score ( $\pm$  standard error) at baseline and weeks 4, 8, 12, and 16 ( $P = .0733$  for 360 mg at week 16; daily DSD score range: 0–6, with higher scores indicating more severe dysphagia symptoms) (B). Mean total EREFS at baseline and week 16 (endoscopic findings analyzed according to modified scoring system described by Hirano et al 2013<sup>18</sup>; total EREFS score range: 0–8 for each location [ie, total score range across 3 locations: 0–24]) (C). Mean changes from baseline to week 16 in eosinophilic histology grade (range: 0–3 for each of 8 features for proximal and distal biopsies [ie, total score range: 0–48]) and stage (range: same as for grade) scores (D). Mean change in the EEesAI score ( $\pm$  standard error) at weeks 4, 8, 12, and 16 ( $P = .0852$  for 180 mg and  $P = .0393$  for 360 mg at week 16) (E).

We did not identify any serious safety issues, although the trial was not large enough or of sufficient duration to fully assess the long-term safety of RPC4046 treatment of adults with EoE. A higher percentage of patients experienced adverse events with the 360-mg RPC4046 dose

compared with the 180-mg RPC4046 dose or placebo. The 3 most frequently reported events were headache, upper respiratory tract infection, and arthralgia.

Current EoE management relies primarily on off-label use of swallowed corticosteroids or dietary elimination of

**Table 2.** Summary of Safety Findings by Study Group During the Double-blind Treatment Period

	RPC4046		
	Placebo (n = 34)	180 mg (n = 31)	360 mg (n = 34)
No. of patients experiencing adverse events	103	99	127
Adverse event, n (%)	22 (64.7)	20 (64.5)	29 (85.3)
Serious adverse event <sup>a</sup> , n (%)	2 (5.9)	0	1 (2.9)
Adverse event leading to discontinuation of regimen, n (%)	0	1 (3.2)	3 (8.8)
Adverse event occurring in $\geq 2$ patients in either RPC4046 treatment group, n (%)			
Headache	5 (14.7)	5 (16.1)	7 (20.6)
Upper respiratory tract infection	3 (8.8)	5 (16.1)	5 (14.7)
Arthralgia	0	4 (12.9)	2 (5.9)
Nasopharyngitis	0	3 (9.7)	3 (8.8)
Diarrhea	2 (5.9)	3 (9.7)	2 (5.9)
Nausea	4 (11.8)	2 (6.5)	3 (8.8)
Abdominal pain	0	2 (6.5)	2 (5.9)
Dizziness	2 (5.9)	3 (9.7)	1 (2.9)
Oropharyngeal pain	0	1 (3.2)	3 (8.8)
Sinusitis	0	3 (9.7)	1 (2.9)
Vomiting	2 (5.9)	1 (3.2)	3 (8.8)
Contact dermatitis	0	1 (3.2)	2 (5.9)
Fatigue	1 (2.9)	2 (6.5)	1 (2.9)
Injection site erythema	2 (5.9)	0	3 (8.8)
Urticaria	0	2 (6.5)	1 (2.9)
Myalgia	0	1 (3.2)	2 (5.9)
Contusion	1 (2.9)	2 (6.5)	0
Cough	1 (2.9)	2 (6.5)	0
Gastroenteritis	1 (2.9)	2 (6.5)	0
Hypersensitivity	0	0	2 (5.9)
Injection site hematoma	0	0	2 (5.9)
Injection site pruritus	1 (2.9)	0	2 (5.9)
Ligament sprain	1 (2.9)	0	2 (5.9)

<sup>a</sup>A serious adverse event was defined as any untoward medical occurrence that resulted in death, was life-threatening (has an immediate risk of death), required admission to a hospital or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, or resulted in a congenital anomaly or birth defect.

putative allergic triggers.<sup>21</sup> Although steroids are effective at decreasing esophageal eosinophilia, their ability to reduce symptoms has been modest and variable. Furthermore, heterogeneity in the histologic response has been demonstrated with rates of corticosteroid resistance as high as 40% to 60% reported in several studies.<sup>6,7,22</sup> Drawbacks of steroid use include disease recurrence upon cessation of daily administration, esophageal candidiasis, possible loss of response with prolonged use,<sup>23,24</sup> as well as potential long-term side effects. It also remains uncertain if topical therapies will be effective for subepithelial remodeling. Diet therapies offer a nonpharmacologic strategy but lack an accurate test to identify trigger foods. Moreover, the prospect of long-term cessation of the most common food triggers, such as milk, wheat, soy, and egg, is unacceptable to many patients. Thus, alternative treatment options are needed.

Approximately half of the enrolled patients were categorized as being steroid refractory. Such patients represent an increasingly recognized, clinically relevant, and difficult-to-treat subgroup of EoE. Prospective studies have identified that >50% of patients treated with topical

steroids failed to sustain an initial histologic response with longer-term administration.<sup>23,24</sup> In the present study, it is notable that significant reductions in esophageal eosinophil counts, histologic features, and endoscopic features were observed in steroid-refractory patients following treatment with RPC4046. Interestingly, the reduction in dysphagia symptoms, as measured by the DSD and EEsAI, was more pronounced with the 360-mg RPC4046 dose in the steroid-refractory subset than in the overall patient group.

The potential role for biologic therapies such as RPC4046, in the management of EoE has yet to be defined. Patients refractory to corticosteroids are a logical initial target population in EoE. Increasing data support transmural inflammatory activity and remodeling consequences of EoE.<sup>8,25</sup> Systemically active therapeutics offer conceptual advantages over topical steroids that target the epithelium.<sup>8,26,27</sup> Finally, although yet unproven, the proposed benefits of IL13 blockade in terms of remodeling aspects of disease may prevent disease progression and disease complications, including esophageal strictures and food impactions.

Our study had several limitations. The study was not powered to assess reduction in dysphagia symptoms; however, a strong trend was observed with the 360-mg RPC4046 dose. Furthermore, a validated PRO for EoE symptoms was not available at the time the study was designed. Although steroid-refractory status was pre-specified for purposes of patient allocation, the designation was determined by the investigator. A uniform definition of steroid resistance would have provided better clarity in defining this important subgroup. Given the 16-week duration of observation and the small number of patients evaluated, we cannot establish the long-term efficacy or safety of RPC4046 in patients with EoE.

Important strengths of our study include the significant reduction in disease activity based on endoscopic (EREFS) and histologic (EoEHSS) outcome measures that were specifically designed and validated for EoE. In fact, the current study was the first clinical trial of biologic therapy in EoE to incorporate use of either the EREFS or the EoEHSS instruments. The study is the largest clinical trial of therapy targeting IL13 and the largest adult trial of a biologic agent in EoE. We also believe that the use of a centralized, blinded pathologist with expertise in eosinophilic disorders increases the accuracy of the histologic assessment with the EoEHSS.

In conclusion, data from this phase 2 trial provide evidence of the efficacy and safety of RPC4046 (a monoclonal antibody against IL13) in adult patients with EoE, with reduction in histopathologic and endoscopic aspects of disease activity and global perception of disease severity. These data substantiate the key contribution of IL13 to the pathogenesis of EoE and support the further study of RPC4046 as a novel, targeted approach for patients with EoE.

## Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at [www.gastrojournal.org](http://www.gastrojournal.org), and at <https://doi.org/10.1053/j.gastro.2018.10.051>.

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#### Acknowledgments

A complete list of investigators in the phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study evaluating the clinical efficacy and safety of RPC4046 in adult patients with eosinophilic esophagitis (HEROES) is provided in the [Supplementary Materials](#).

Author contributions: Ikuo Hirano, Margaret H. Collins, Yehudith Assouline-Dayyan, Larry Evans, Sandeep Gupta, Alain M. Schoepfer, Alex Straumann, Ekaterina Safroneeva, Marc E. Rothenberg, and Evan S. Dellon participated in the study design, data collection, data interpretation, writing, and editing of the manuscript. Michael Grimm, Heather Smith, Amy Woo, Robert Peach, Paul Frohna, Sheila Gujrathi, Gregory J. Opiteck, Allan Olson, and Richard Aranda participated in the study design, data interpretation, and editing of the manuscript. Cindy-ann Tompkins, Darryl N. Penenberg, and Caiyan Li participated in the data analysis, data interpretation, and editing of the manuscript. Study data were collected by a contract research organization (Agility Clinical, Inc.) and analyzed by the authors and Celgene Corporation. All authors had full access to the data and approved the final manuscript for submission.

Celgene is committed to responsible and transparent sharing of clinical trial data with patients, health care practitioners, and independent researchers for the purpose of improving scientific and medical knowledge as well as fostering innovative treatment approaches. For more information, please visit: <https://www.celgene.com/research-development/clinical-trials/clinical-trials-data-sharing/>.

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#### Conflicts of interest

These authors disclose the following: Ikuo Hirano has served as a consultant for Adare, Allakos, Celgene Corporation, Regeneron, and Shire, and has received grant/research support from Adare, Celgene Corporation, Regeneron, and Shire. Margaret H. Collins has served as a consultant for Celgene Corporation, Regeneron, and Shire and has received grant/research support from Celgene Corporation, Regeneron, and Shire. Sandeep Gupta has received grant/research support from Shire and served as a consultant for Abbott, Adare, Allakos, Celgene Corporation, and QOL. Alain M. Schoepfer has received grant/research support from Adare, Celgene Corporation, Falk, Merck Sharp & Dohme, and Regeneron, and has served as a consultant and advisor for AbbVie, Adare, Celgene Corporation, Falk, Merck Sharp & Dohme, and Regeneron. Alex Straumann has served as a consultant for Actelion, Calypso, Celgene Corporation, Falk, GlaxoSmithKline, Merck, Merck Sharp & Dohme, Novartis, Nutricia, Pfizer, Regeneron-Sanofi, Roche-Genentech, and Tillotts, and has received grant/research support from Celgene Corporation. Ekaterina Safroneeva has served as a consultant for Aptalis Pharma, Celgene Corporation, Novartis, and Regeneron. Michael Grimm, Heather Smith, Cindy-ann Tompkins, Amy Woo, Robert Peach, Paul Frohna, Sheila Gujrathi, Darryl N. Penenberg, Caiyan Li, and Richard Aranda were employees of Receptos at the time of the study; Receptos is now a wholly owned subsidiary of Celgene Corporation. Gregory J. Opiteck and Allan Olson are employees of Celgene Corporation. Marc E. Rothenberg has served as a consultant for Adare, Allakos, AstraZeneca, Celgene Corporation, GlaxoSmithKline, NKT Therapeutics, Novartis, Pulm One, Shire, and Spoon Guru; has an equity interest in Immune Pharmaceuticals, NKT Therapeutics, Pulm One, and Spoon Guru; has received royalties from Teva for reslizumab; and is an inventor of patents owned by Cincinnati Children's Hospital Medical Center. Evan S. Dellon has served as a consultant for Adare, Alivio, Allakos, Banner, Celgene Corporation, Enumeral, GSK, Regeneron, Robarts, and Shire, has received grant/research support from Adare, Banner, Celgene Corporation, Meritage, Miraca, Nutricia, Regeneron, and Shire, and has received educational grants from Banner and Holoclara. The remaining authors disclose no conflicts.

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This study was sponsored by Celgene Corporation.

## Supplementary Materials

### Study Investigators at Initiated Sites

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NOTE: The 40 listed sites were initiated for participation in this study; of these sites, 30 enrolled at least 1 subject.

### Study Administration

The members of the HEROES protocol committee designed the trial in collaboration with Celgene. Study data were collected by a contract research organization (Agility Clinical, Inc.) and analyzed by Celgene. Celgene and the HEROES study group interpreted the data jointly and safety data were reviewed by a safety review. All authors had full access to the data. The first author wrote the first draft of

the manuscript, and all authors contributed to subsequent drafts, made a collective decision to submit the manuscript for publication, and vouch for the completeness and veracity of the data and analyses and for the adherence to the protocol, available at [NEJM.org](http://NEJM.org). Editorial support was provided by Celgene. Confidentiality agreements were in place between Celgene and all authors.

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**Inclusion Criteria**

The following criteria were also required for study inclusion: Subjects with a partial response to a proton pump inhibitor (PPI) who met all other eligibility criteria could be enrolled; prospective subjects who discontinued use of a PPI had to wait at least 4 weeks before their screening endoscopy; if a prospective subject was receiving a PPI at

screening, the subject must have been receiving a stable dose for at least 4 weeks before the screening endoscopy and agreed to continue on the same dose through week 16; men and women of childbearing potential had to agree to use adequate birth control measures during the trial and for 5 months after their last dose of study drug; all women of childbearing potential must have had a negative serum pregnancy test at screening and a negative urine (or serum) pregnancy test before dosing on day 1.

**Exclusion Criteria**

Exclusion criteria included clinical or endoscopic evidence of the presence of any other disease that may have interfered with or affected the histologic, endoscopic, and clinical symptom endpoints for this trial (eg, erosive esophagitis grade 2 or above, Barrett's disease, upper gastrointestinal bleed, eosinophilic gastritis or gastroenteritis, duodenal or gastric eosinophilia on screening endoscopy, inflammatory bowel disease, significant hiatal hernia [ $>3$  cm]); presence of esophageal varices; evidence of severe endoscopic structural abnormality in esophagus (eg, high-grade stenosis where an 8- to 10-mm endoscope could not pass through the stricture without dilation at the time of endoscopy); primary causes of esophageal eosinophilia other than EoE; evidence of immunosuppression or were receiving systemic immunosuppressive or immunomodulating drugs (eg, methotrexate, cyclosporine, interferon alpha, tumor necrosis factor alpha inhibitors, antibodies to immunoglobulin E) within 5 drug half-lives before screening; were receiving systemic or swallowed topical corticosteroid medication; prospective subjects with EoE treated with a corticosteroid must have not received a systemic corticosteroid within 8 weeks or swallowed topical corticosteroids within 4 weeks of the screening endoscopy or the start of the daily clinical symptom diary data collection during screening, whichever was performed first; presence of any other disease making conduct of the protocol or interpretation of the trial results difficult or that would have put the prospective subject at risk by participating in the trial (eg, infection causing eosinophilia, gastritis, colitis, irritable bowel syndrome, and celiac disease, which have similar symptoms, neurologic or psychiatric illness that compromised the prospective subject's ability to accurately document symptoms of EoE); liver function impairment or persisting elevations of aspartate aminotransferase or alanine aminotransferase  $>2$  times the upper limit of normal (ULN), or direct bilirubin  $>1.5$  times the ULN; systemic or diarrheal illness following travel or residence in endemic areas of parasitic/helminthic infections, history of clinical schistosomiasis, history of travel to endemic areas within preceding 6 months; ongoing infection (eg, hepatitis B or C, human immunodeficiency virus, active tuberculosis); pregnancy or lactation; concurrent treatment with another investigational drug; prospective subjects could not have participated in a concurrent investigational drug trial or have received an investigational drug within 5 drug half-lives before signing the informed consent form for this trial; weight less than 40 kg (88.2 pounds) or greater than 125 kg (275 pounds); history of

idiopathic anaphylaxis or a known history of a major immunologic reaction (such as anaphylactic reaction, anaphylactoid reaction, or serum sickness) to an immunoglobulin G-containing agent; history of cancer or lymphoproliferative disease, other than a successfully treated nonmetastatic cutaneous squamous cell or basal cell carcinoma or adequately treated cervical carcinoma in situ, within 10 years of screening; esophageal dilation for symptom relief during the screening period and within 4 weeks before baseline assessment of dysphagia or anticipated to be performed during the trial.

### Protocol Amendments

The original protocol (dated March 13, 2014) was amended 3 times. The first amendment (dated May 16, 2014) was implemented before enrollment of the first patient in the study (September 3, 2014). Summaries of the major changes included in each amendment are provided as follows.

Protocol Amendment 1 (dated May 16, 2014):

- Removed the open-label extension (OLE) to shorten the total duration of treatment to 16 weeks to be consistent with the available toxicology data at that time, with the potential to add an OLE after completion of a then ongoing longer-term toxicology study
- Extended the duration of double-blind dosing from 12 weeks to 16 weeks, with the longer duration of double-blind treatment expected to have a greater impact on eosinophil count and increased clinical benefit
- Changed the time point for efficacy endpoints from week 12 to week 16 to be consistent with the increased duration of double-blind treatment
- Added a week 2 visit to assess antidrug antibody (ADA) and pharmacokinetic data to provide an earlier time point for these assessments
- Increased the lower limit of the eligible age range from 12 years to 18 years to address concerns about adolescents potentially receiving placebo and being exposed to more than minimal risk
- Increased the lower weight limit to 40 kg in alignment with removal of adolescents from the trial
- Added an exclusion criterion for subjects requiring esophageal dilation for symptom relief within 4 weeks before baseline assessment of dysphagia or anticipated to be performed during the trial; this change was made because use of esophageal dilation could ameliorate strictures in symptomatic subjects and would therefore confound efficacy assessment in this trial
- Reduced the number of biomarkers to be assessed
- Modified the restriction for concurrent medication to treat asthma or allergies during the trial to enable the Investigator to contact the Medical Monitor to discuss treatment options if changes to treatments are required,

providing more flexibility for the physician to treat without withdrawal of the subject

Protocol Amendment 2 (dated October 17, 2014):

- Updated data from nonclinical toxicology studies to report that no observed adverse effects levels were established at the highest dose evaluated in general toxicology studies in rats and cynomolgus monkeys and that once-weekly SC injection of 20, 60, or 300 mg/kg RPC4046 or IV administration of 300 mg/kg RPC4046 for 26 consecutive weeks (26 total doses) to cynomolgus monkeys was well tolerated at all dose levels
- Extended treatment by an optional 24-week OLE
- Removed the Esophageal String Test due to limited availability of the test
- Specified the requirement for collection of daily dysphagia symptom diary (DSD) for the past 2 consecutive weeks ( $\pm$  3 days) before day 1
- Added text regarding the day 1 IV loading dose + SC dose, and SC doses once weekly for 15 additional weeks to avoid confusion regarding the number of weekly SC doses to be administered in the double-blind treatment period
- Modified inclusion criteria as follows:
  - Criterion 1: clarification that diagnosis of EoE must be confirmed before randomization
  - Criterion 3: clarification that histological evidence of EoE can come from any 2 levels of the esophagus
  - Criterion 5: requirement for birth control use for 5 months after last dose of RPC4046 to coincide with elimination or clearance of the half-life of RPC4046 clearance (ie, 5 times the half-life of 1 month)
- Modified exclusion criteria as follows:
  - Criterion 10: specification that ongoing infections include active tuberculosis
  - Criterion 15: no history of cancer within 10 years of screening
- Changed IV stability dose to 8 hours at 2 to 8°C
- Clarified food restriction diet and added instruction regarding environmental therapy
- Clarified requirement to not use systemic or swallowed topical corticosteroids
- Specified that the blind in the trial was not to be broken until all subjects completed the double-blind treatment period (unless medically necessary)
- Added a coagulation panel during each hematology and chemistry assessment
- Extended the period of adverse event (AE) collection to 30 days after last dose or last visit

- Added text to clearly define the intent-to-treat and per-protocol populations  
Protocol Amendment 3 (dated June 22, 2015):
- Extended the OLE from 24 weeks to 52 weeks
- Removed the interim analysis from the protocol

## Methods

**Blinded Dosing Regimen.** The placebo and RPC4046 dose formulations were identical in appearance. All patients received an identical study drug regimen consisting of SC administration of placebo or RPC4046 180 mg or RPC4046 360 mg.

**Initial Study Dose.** The initial dose was administered as a 2-hour IV infusion (placebo or 5 mg/kg or 10 mg/kg) plus two 1.2-mL SC injections (placebo or RPC4046 180 mg or RPC4046 360 mg) in the clinic on day 1.

**Weekly Study Dose.** After day 1, dosing with two 1.2-mL SC injections of study drug continued weekly through week 15.

## Immunogenicity Assessment

A validated ECL-based assay was used to measure ADA response. A preliminary assessment was performed of the presence of neutralizing ADA through comparison of RPC4046 pharmacokinetics in ADA (+) and ADA (–) subjects.

Most subjects were ADA (–) at all visits. Two subjects, both in the RPC4046 180-mg group, tested positive for ADA during the study.

One subject was ADA (+) on day 1 and week 12 and was ADA (–) on weeks 2, 4, 8, and 16. This subject had a mild treatment-emergent AE (TEAE) of injection site pain (verbatim term: burning at all injection sites) on day 1 that was assessed as possibly related to study drug and had an unknown outcome. No other TEAEs were reported.

One subject was ADA (–) at all visits from day 1 through week 8 and was ADA (+) at weeks 12 and 16. This subject had the following TEAEs during the study: mild TEAE of feeling hot (verbatim term: feeling hot: no fever, no flushing, no sweating) assessed as probably related to study drug (day 1); 2 TEAEs of upper respiratory tract infection, 1 mild and unrelated (days 3–8) and 1 moderate and possibly related to study drug (days 25–36); a mild TEAE of gastroenteritis that was unlikely related to study drug (day 32); and a mild TEAE of nasopharyngitis that was unlikely related to study drug (days 99–108).

No subjects in the RPC4046 360-mg group were ADA (+) at any time during the study.

## Key Secondary Efficacy Endpoint: Daily Dysphagia Symptom Diary

The key secondary efficacy endpoint was the mean change from baseline to week 16 in the dysphagia clinical symptom frequency and severity as assessed by a daily DSD completed over 2 weeks before each visit. As with the primary endpoint,

analysis of subgroups for the key secondary endpoint was prespecified and included the following: subjects known to be steroid-refractory and subjects not known to be steroid-refractory; subjects with baseline daily DSD composite score of severity  $\leq$  median and  $>$  median; and subjects with  $\leq 5$  years and  $> 5$  years since EoE diagnosis.

## Daily Dysphagia Symptom Diary Questions

An interactive Web-based or phone response system was used by subjects to complete the DSD. Subjects were able to access the DSD by phone and/or by Internet.

The following questions were included in the DSD:

- Question 1: *Did you try to eat solid food today?*
  - Yes (go to Question 2)
  - No (go to Question 1a)
- Question 1a: *What is the primary reason you did not try to eat solid food today?*
  - EoE symptoms
  - Reason other than EoE symptoms
- Question 2: *During any meal today, did food go down slowly or get stuck in your throat or chest?*
  - Yes
  - No
- Question 3: *For the most difficult time you had swallowing today, did you have to do anything to make the food go down or to get relief?*
  - If Question 2 is no,
  - If Question 2 is yes:
    - No, it got better or cleared up on its own
    - Yes, I had to drink liquid to get relief
    - Yes, I had to cough and or gag to get relief
    - Yes, I had to vomit to get relief
    - Yes, the stuck food had to be removed by a doctor
- Question 4: *Did you have any pain associated with swallowing food today?*
  - Yes
  - No
- Question 4a: *How would you rate your pain associated with swallowing food today?*
  - Range 1 (minimal pain) – 10 (worst pain imaginable)

Subjects completed the DSD for at least the last 2 weeks  $\pm$  3 days during the screening period before day 1 and daily from day 1 through week 16. In addition, subjects completed the DSD for the 2 weeks before the safety follow-up visit on week 24 (if applicable).



### *Eosinophilic Esophagitis Endoscopic Reference Score (EREFS)*

The esophageal mucosal endoscopic features of EoE were assessed by each investigator using the EREFS<sup>1</sup> in 5 classification categories at screening, week 16, or if applicable at early termination. Grades for each feature and total scores were calculated for the following features:

- Fixed rings: 0 (none), 1 (mild), 2 (moderate), or 3 (severe)
- Exudates: 0 (none), 1 (mild), or 2 (severe)
- Furrows: 0 (none) or 1 (present)
- Edema: 0 (none) or 1 (present)
- Stricture: 0 (none) or 1 (present)

The EoE histology grade score was recorded independently in the proximal, mid, and distal esophagus as the sum of 8 features (basal zone hyperplasia, peak eosinophil count, abscesses, surface layering, dilated intercellular spaces, surface alteration, apoptotic epithelial cells, and lamina propria fibrosis). A total possible score was recorded based on features that were not evaluable. Each of the locations was standardized to a single score based on the following formula: Adjusted Score = (Total Score)/(Total Possible Score) × 100. The EoE histology stage score, which was recorded for the same 8 features, was calculated in the same manner.

### *Eosinophilic Esophagitis Endoscopic Histology Grade and Stage Score*

The esophageal histologic changes characteristic of EoE were assessed by examining 8 parameters<sup>2</sup>:

- Eosinophil inflammation was graded using peak eosinophil count obtained by counting eosinophils in the most densely inflamed high-power field
- Basal zone hyperplasia: >15% of the total epithelial thickness
- Eosinophil abscess: solid mass of intraepithelial eosinophils
- Eosinophil surface layering: linear alignment of eosinophils parallel to the epithelial surface
- Dilated intracellular spaces: spaces around squamous epithelial cells that exhibit intercellular bridges
- Surface epithelial alteration: surface epithelial cells that exhibit altered tinctorial properties, manifest as dark staining, with or without intraepithelial eosinophils

- Dyskeratotic epithelial cells: individual cells with deeply eosinophilic cytoplasm and hyperchromatic nuclei
- Lamina propria fibers: thickened connective tissue fibers in the lamina propria.

Each feature was scored separately for grade (severity) or stage (extent) of abnormality using a 4-point scale (0 = normal; 3 = most severe or extensive).

### *Eosinophilic Esophagitis Activity Index (EEsAI)*

The EEsAI is another paper-based PRO symptom instrument assessing changes in dysphagia caused by foods of various consistencies, behavioral adaptations to living with EoE, and swallowing-associated pain. The EEsAI uses a 7-day recall period. Based on summation of individual scores for EEsAI categories, a total score between 0 and 100 is possible. The mean change from baseline to week 16 in the dysphagia clinical symptoms frequency and severity as assessed by the EEsAI was a secondary endpoint.

### *Clinician and Subject Global Assessment of Disease Severity*

Clinicians assessed subject disease severity on a scale from 0 to 10, where 0 = no evidence of disease and 10 = worst possible evidence of disease. Subjects assessed their disease severity on a scale from 0 to 10, where 0 = no symptoms and 10 = worst symptoms possible.

### *Categorical Analysis of Subject's Global Impression of Change*

Subjects assessed their impression of change of their disease based on 5 categories, including a lot better, a little better, stayed the same, a little worse, and much worse.

## References

1. Hirano I, Moy N, Heckman MG, et al. Endoscopic assessment of the esophageal features of eosinophilic esophagitis: validation of a novel classification and grading system. *Gut* 2013;62:489–495.
2. 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.

**Supplementary Table 1.** Participants Across Study Sites by Country

Country	Site	Placebo (n = 34) n (%)	RPC4046 180 mg (n = 32) n (%)	RPC4046 180 mg (n = 32) n (%)	Total (N = 100) n (%)
United States	102	4 (11.8)	4 (12.5)	3 (8.8)	11 (11.0)
	104	1 (2.9)	2 (6.3)	4 (11.8)	7 (7.0)
	106	2 (5.9)	3 (9.4)	2 (5.9)	7 (7.0)
	107	4 (11.8)	1 (3.1)	0	5 (5.0)
	112	1 (2.9)	3 (9.4)	0	4 (4.0)
	115	2 (5.9)	2 (6.3)	1 (2.9)	5 (5.0)
	116	0	2 (6.3)	3 (8.8)	5 (5.0)
	118	0	1 (3.1)	1 (2.9)	2 (2.0)
	121	0	0	1 (2.9)	1 (1.0)
	122	1 (2.9)	0	0	1 (1.0)
	124	0	0	1 (2.9)	1 (1.0)
	125	2 (5.9)	0	3 (8.8)	5 (5.0)
	126	0	1 (3.1)	0	1 (1.0)
	130	1 (2.9)	2 (6.3)	0	3 (3.0)
	132	0	1 (3.1)	0	1 (1.0)
	133	1 (2.9)	0	0	1 (1.0)
	135	1 (2.9)	0	0	1 (1.0)
	136	1 (2.9)	1 (3.1)	1 (2.9)	3 (3.0)
	139	0	0	3 (8.8)	3 (3.0)
	140	1 (2.9)	0	0	1 (1.0)
	141	0	1 (3.1)	0	1 (1.0)
	143	4 (11.8)	1 (3.1)	1 (2.9)	6 (6.0)
	144	3 (8.8)	2 (6.3)	6 (17.6)	11 (11.0)
	145	1 (2.9)	2 (6.3)	0	3 (3.0)
146	0	1 (3.1)	1 (2.9)	2 (2.0)	
147	1 (2.9)	0	0	1 (1.0)	
148	0	0	1 (2.9)	1 (1.0)	
Canada	202	1 (2.9)	0	0	1 (1.0)
Switzerland	301	2 (5.9)	2 (6.3)	1 (2.9)	5 (5.0)
	302	0	0	1 (2.9)	1 (1.0)

**Supplementary Table 2.** Baseline Characteristics of Steroid-refractory and Non-steroid-refractory Patients

	Steroid refractory = Yes			Steroid refractory = No		
	Placebo (n = 16)	RPC4046 180 mg (n = 14)	RPC4046 360 mg (n = 17)	Placebo (n = 18)	RPC4046 180 mg (n = 17)	RPC4046 360 mg (n = 17)
Years since EoE Diagnosis						
Mean (SD)	5.2 (2.9)	6.0 (4.7)	4.1 (2.5)	3.4 (2.6)	2.8 (2.2)	3.7 (3.0)
Min, Max	0.20, 10.89	0.61, 15.52	0.60, 9.05	0.14, 9.12	0.12, 6.52	0.04, 9.53
Peak eosinophil count/hpf						
Mean (SD)	92.3 (55.6)	162.8 (91.0)	141.6 (82.5)	117.0 (63.7)	106.4 (71.8)	137.1 (79.8)
Min, Max	18, 201	42, 304	51, 389	31, 212	24, 281	26, 328
Mean eosinophil count/hpf						
Mean (SD)	79.2 (47.1)	146.9 (83.1)	127.5 (78.2)	104.1 (58.5)	91.8 (64.3)	117.6 (65.2)
Min, Max	17.6, 158.8	32.6, 273	42.2, 369.2	23.6, 189.8	21.4, 239.2	22.2, 264.4
DSD score						
Mean (SD)	32.7 (12.0)	26.9 (14.6)	29.3 (9.4)	26.9 (9.1)	28.5 (11.9)	28.8 (11.0)
Min, Max	11, 51	6.6, 52	11, 42	14, 48	12, 51	13, 49

DSD, daily dysphagia symptom diary; hpf, high-power field; Max, maximum; Min, minimum; SD, standard deviation.

**Supplementary Table 3.** Inflammatory Component (Edema, Exudate, Furrows) and Stenosis (Fixed Rings, Stricture) Component of Eosinophilic Esophagitis Endoscopic Reference Score (EREFS) for Total Population and Steroid-refractory Group

	Total population			Steroid-refractory subjects		
	Placebo (n = 34)	RPC4046 180 mg (n = 31)	RPC4046 360 mg (n = 34)	Placebo (n = 16)	RPC4046 180 mg (n = 14)	RPC4046 360 mg (n = 17)
<b>Total score</b>						
Baseline <sup>a</sup>	n = 32	n = 27	n = 31	n = 14	n = 14	n = 15
Mean (SD)	9.1 (4.3)	9.0 (4.4)	9.4 (4.3)	10.7 (3.8)	9.9 (4.8)	9.7 (3.9)
Week 16	n = 32	n = 27	n = 30	n = 14	n = 12	n = 15
Mean (SD)	7.9 (5.1)	5.3 (4.2)	4.8 (3.4)	10.4 (4.7)	5.8 (4.9)	5.3 (3.7)
P value <sup>b</sup>		.0004	<.0001		.0026	.0016
<b>Edema</b>						
Baseline <sup>a</sup>	n = 32	n = 27	n = 31	n = 14	n = 14	n = 15
Mean (SD)	1.7 (1.4)	1.9 (1.4)	2.1 (1.2)	2.1 (1.3)	2.1 (1.4)	2.1 (1.1)
Week 16	n = 32	n = 28	n = 30	n = 14	n = 12	n = 15
Mean (SD)	1.7 (1.4)	1.2 (1.4)	1.2 (1.4)	2.6 (0.9)	1.1 (1.4)	1.4 (1.3)
P value <sup>b</sup>		.0116	.0156		.0002	.0036
<b>Exudates</b>						
Baseline <sup>a</sup>	n = 32	n = 27	n = 31	n = 14	n = 14	n = 15
Mean (SD)	1.4 (1.7)	2.3 (1.9)	1.8 (2.0)	1.9 (1.9)	2.6 (1.6)	2.1 (1.8)
Week 16	n = 32	n = 27	n = 30	n = 14	n = 12	n = 15
Mean (SD)	1.2 (1.5)	0.5 (1.0)	0.5 (0.9)	1.7 (1.8)	0.3 (0.8)	0.9 (1.1)
P value <sup>b</sup>		.0022	.0159		.0045	.0665
<b>Furrows</b>						
Baseline <sup>a</sup>	n = 32	n = 27	n = 31	n = 14	n = 14	n = 15
Mean (SD)	2.3 (1.1)	2.1 (1.2)	2.4 (0.8)	2.6 (0.9)	1.9 (1.3)	2.7 (0.5)
Week 16	n = 32	n = 27	n = 30	n = 14	n = 12	n = 15
Mean (SD)	1.9 (1.1)	1.0 (1.2)	0.8 (1.0)	2.1 (1.0)	1.1 (1.2)	0.8 (1.2)
P value <sup>b</sup>		.0002	<.0001		.0328	.0018
<b>Fixed rings</b>						
Baseline <sup>a</sup>	n = 32	n = 27	n = 31	n = 14	n = 14	n = 15
Mean (SD)	3.0 (1.9)	2.1 (1.5)	2.8 (2.2)	3.1 (1.3)	2.6 (1.8)	2.5 (2.1)
Week 16	n = 32	n = 28	n = 30	n = 14	n = 12	n = 15
Mean (SD)	2.6 (2.2)	2.4 (1.8)	2.0 (1.6)	3.1 (2.3)	2.7 (2.2)	2.0 (1.7)
P value <sup>b</sup>		.6064	.2163		.9485	.2552
<b>Stricture</b>						
Baseline <sup>a</sup>	n = 32	n = 27	n = 31	n = 14	n = 14	n = 15
Mean (SD)	0.7 (1.0)	0.6 (1.0)	0.3 (0.5)	1.0 (1.2)	0.6 (1.1)	0.3 (0.5)
Week 16	n = 32	n = 27	n = 30	n = 14	n = 12	n = 15
Mean (SD)	0.5 (0.8)	0.4 (0.9)	0.2 (0.4)	0.7 (1.1)	0.7 (1.2)	0.2 (0.4)
P value <sup>b</sup>		.4043	.2151		.8925	.3689

SD, standard deviation.

<sup>a</sup>Baseline is defined as the last observed score before the first dose of study drug.<sup>b</sup>P values comparing RPC4046 180 mg with placebo and RPC4046 360 mg with placebo are based on an analysis of covariance model with treatment group as the factor and the baseline mean adjusted score as a covariate.

**Supplementary Table 4.** Stricture Features of Total Population

	Placebo (n = 34)	RPC4046 180 mg (n = 31)	RPC4046 360 mg (n = 34)
Number (%) of subjects with strictures			
Baseline <sup>a</sup>			
None	19/32 (59.4)	18/27 (66.7)	24/33 (72.7)
Present	13/32 (40.6)	9/27 (33.3)	9/33 (27.3)
Week 16			
None	20/33 (60.6)	22/28 (78.6)	24/30 (80.0)
Present	13/33 (39.4)	6/28 (21.4)	6/30 (20.0)
Stricture estimated diameter (mm)			
Baseline <sup>a</sup>			
None	19/32 (59.4)	18/27 (66.7)	24/33 (72.7)
4–6	0	0	0
7–9	1/32 (3.1)	2/27 (7.4)	1/33 (3.0)
10–12	7/32 (21.9)	3/27 (11.1)	2/33 (6.1)
13–15	4/32 (12.5)	4/27 (14.8)	1/33 (3.0)
16–18	1/32 (3.1)	0	4/33 (12.1)
>18	0	0	1/33 (3.0)
Week 16			
None	20/33 (60.6)	22/28 (78.6)	24/30 (80.0)
4–6	0	0	0
7–9	3/33 (9.1)	0	0
10–12	4/33 (12.1)	3/28 (10.7)	3/30 (10.0)
13–15	4/33 (12.1)	3/28 (10.7)	1/30 (3.3)
16–18	2/33 (6.1)	0	1/30 (3.3)
>18	0	0	1/30 (3.3)

<sup>a</sup>Baseline is defined as the last observed score before the first dose of study drug.

**Supplementary Table 6.** Exploratory Analyses of Mean Esophageal Eosinophil Count and Composite Diary Score in the Steroid-responsive Subgroup

	Steroid-responsive subjects		
	Placebo (n = 34)	RPC4046 180 mg (n = 31)	RPC4046 360 mg (n = 34)
Mean esophageal eosinophil count			
Baseline <sup>a</sup>			
Mean (SD)	n = 18 104.11 (58.46)	n = 17 91.75 (64.30)	n = 17 117.61 (65.24)
Week 16			
Mean (SD)	n = 18 80.78 (41.84)	n = 16 22.82 (35.59)	n = 15 22.69 (25.13)
P value <sup>b</sup>		<.0001	<.0001
Composite diary score			
Baseline <sup>c</sup>			
Mean (SD)	n = 18 26.88 (9.10)	n = 12 24.48 (11.95)	n = 16 28.81 (10.95)
Week 16			
Mean (SD)	n = 18 16.07 (17.60)	n = 16 18.75 (16.73)	n = 17 13.90 (15.76)
P value <sup>d</sup>		.8541	.5042

SD, standard deviation.

<sup>a</sup>Baseline is defined as the last observed mean esophageal eosinophil count before the first day of study drug.

<sup>b</sup>P values comparing RPC4046 180 mg with placebo and RPC4046 360 mg with placebo are based on an analysis of covariance model with treatment group and the baseline mean esophageal count as a covariate.

<sup>c</sup>Baseline is defined as the composite diary scores in the last 11–14 days during the screening period.

<sup>d</sup>P values comparing RPC4046 180 mg to placebo and RPC4046 360 mg to placebo are based on an analysis of covariance model with treatment group and the baseline composite diary score as a covariate.

**Supplementary Table 5.** Mean Esophageal Eosinophil Count in the Steroid-refractory Subgroup

	Steroid-refractory subjects		
	Placebo (n = 16)	RPC4046 180 mg (n = 14)	RPC4046 360 mg (n = 17)
Baseline <sup>a</sup>			
Mean (SD)	n = 16 79.2 (47.1)	n = 14 146.9 (83.1)	n = 17 127.5 (78.2)
Week 16			
Mean (SD)	n = 15 101.6 (64.7)	n = 12 27.5 (35.4)	n = 15 28.3 (34.8)
P value <sup>b</sup>		.0001	<.0001

SD, standard deviation.

<sup>a</sup>Baseline is defined as the last observed mean esophageal eosinophil count before the first dose of study drug.

<sup>b</sup>P values comparing RPC4046 180 mg with placebo and RPC4046 360 mg with placebo are based on an analysis of covariance model with treatment group as a factor and the baseline mean esophageal eosinophil count as a covariate.

**Supplementary Table 7.** Mean Composite Diary Score in the Steroid-refractory Subgroup

	Steroid-refractory subjects		
	Placebo (n = 16)	RPC4046 180 mg (n = 14)	RPC4046 360 mg (n = 17)
Baseline <sup>a</sup>	n = 14	n = 14	n = 12
Mean (SD)	32.7 (12.0)	26.9 (14.6)	29.3 (9.4)
Week 16	n = 16	n = 14	n = 15
Mean (SD)	31.0 (18.1)	25.6 (17.8)	16.9 (19.0)
P value <sup>b</sup>		.8284	.0547

SD, standard deviation.

<sup>a</sup>Baseline is defined as the composite diary scores in the past 11–14 days during the screening period.

<sup>b</sup>P values comparing RPC4046 180 mg with placebo and RPC4046 360 mg with placebo are based on an analysis of covariance model with treatment group as a factor and the baseline composite diary score as a covariate.

**Supplementary Table 8.** Eosinophilic Esophagitis Histology Grade and Stage Scores (EoEHSS) in the Steroid-refractory Subgroup

	Steroid-refractory subjects		
	Placebo (n = 16)	RPC4046 180 mg (n = 14)	RPC4046 360 mg (n = 17)
Mean adjusted grade score			
Baseline <sup>a</sup>	n = 16	n = 14	n = 17
Mean (SD)	42.4 (15.3)	52.1 (14.0)	51.0 (14.1)
Week 16	n = 15	n = 12	n = 15
Mean (SD)	44.0 (14.0)	20.8 (6.7)	21.4 (6.4)
P value <sup>b</sup>		<.0001	<.0001
Mean adjusted stage score			
Baseline <sup>a</sup>	n = 16	n = 14	n = 17
Mean (SD)	41.2 (11.2)	47.1 (10.9)	46.9 (10.7)
Week 16	n = 15	n = 12	n = 15
Mean (SD)	42.2 (13.4)	22.1 (10.8)	20.0 (12.7)
P value <sup>b</sup>		<.0001	<.0001

SD, standard deviation.

<sup>a</sup>Baseline is defined as the last observed score before the first dose of study drug.

<sup>b</sup>P values comparing RPC4046 180 mg with placebo and RPC4046 360 mg with placebo are based on an analysis of covariance model with treatment group as the factor and the baseline mean adjusted score as a covariate.

**Supplementary Table 9.** Eosinophilic Esophagitis Activity Index (EEsAI) in the Steroid-refractory Subgroup

	Steroid-refractory subjects		
	Placebo (n = 16)	RPC4046 180 mg (n = 14)	RPC4046 360 mg (n = 17)
Baseline <sup>a</sup>	n = 16	n = 14	n = 17
Mean (SD)	56.8 (16.3)	57.7 (15.1)	59.9 (14.8)
Week 16	n = 16	n = 14	n = 17
Mean (SD)	51.1 (23.2)	38.6 (27.0)	39.1 (31.0)
P value <sup>b</sup>		.0852	.0393

SD, standard deviation.

<sup>a</sup>Baseline is defined as the last observed score before the first dose of study drug.

<sup>b</sup>P values comparing RPC4046 180 mg with placebo and RPC4046 360 mg with placebo are based on an analysis of covariance model with treatment group as a factor and the baseline EEsAI patient-reported outcomes score as a covariate.

**Supplementary Table 10.** Treatment-emergent Serious Adverse Events by Preferred Term for the Double-blind Treatment Period

Preferred term	Placebo (n = 34)	RPC4046	
		180 mg (n = 31)	360 mg (n = 34)
Total serious adverse events <sup>a</sup>	2	0	1
Patients with a serious adverse event	2 (5.9)	0	1 (2.9)
Umbilical hernia	1 (2.9)	0	0
Appendicitis	1 (2.9)	0	1 (2.9)

Data are number or number (%).

<sup>a</sup>The definition of a serious adverse event is any untoward medical occurrence that results in death, is life-threatening (has an immediate risk of death), requires admission to a hospital or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect.

**Supplementary Table 11.** Injection Site TEAEs

	RPC4046		
	Placebo (n = 34)	180 mg (n = 31)	360 mg (n = 34)
Number of subjects experiencing $\geq 1$ TEAE	6 (17.6)	4 (12.9)	9 (26.5)
Injection site erythema	2 (5.9)	0	3 (8.8)
Injection site hematoma	0	0	2 (5.9)
Injection site pain	3 (8.8)	1 (3.2)	1 (2.9)
Injection site pruritus	1 (2.9)	0	2 (5.9)
Injection site reaction	1 (2.9)	1 (3.2)	1 (2.9)
Injection site bruising	0	0	1 (2.9)
Injection site inflammation	0	1 (3.2)	0
Injection site irritation	0	1 (3.2)	0
Injection site mass	0	1 (3.2)	0
Injection site edema	0	1 (3.2)	0
Injection site swelling	0	0	1 (2.9)
Injection site urticaria	0	0	1 (2.9)

Data are number (%).

TEAE, treatment-emergent adverse event.