

# ALIMENTARY TRACT

## Long-term Efficacy and Tolerability of RPC4046 in an Open-Label Extension Trial of Patients With Eosinophilic Esophagitis



Evan S. Dellon,<sup>\*</sup> Margaret H. Collins,<sup>†</sup> Marc E. Rothenberg,<sup>§</sup> Yehudith Assouline-Dayan,<sup>||</sup> Larry Evans,<sup>¶</sup> Sandeep Gupta,<sup>#</sup> Alain Schoepfer,<sup>\*\*</sup> Alex Straumann,<sup>‡‡</sup> Ekaterina Safroneeva,<sup>§§</sup> Cristian Rodriguez,<sup>||||</sup> Neil Minton,<sup>##</sup> Steven Y. Hua,<sup>\*\*\*</sup> and Ikuo Hirano<sup>¶¶</sup>

<sup>\*</sup>Department of Medicine, Division of Gastroenterology and Hepatology, University of North Carolina School of Medicine, Chapel Hill, North Carolina; <sup>†</sup>Division of Pathology and Laboratory Medicine, <sup>§</sup>Division of Allergy and Immunology, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, Ohio; <sup>||</sup>Department of Gastroenterology, Carver College of Medicine, University of Iowa, Iowa City, Iowa; <sup>¶</sup>Department of Gastroenterology, Grand Teton Research Group, Idaho Falls, Idaho; <sup>#</sup>Department of Pediatrics, University of Illinois College of Medicine, Children's Hospital of Illinois, Peoria, Illinois; <sup>\*\*</sup>Division of Gastroenterology and Hepatology, Centre Hospitalier Universitaire Vaudois, University of Lausanne, Lausanne, Switzerland; <sup>‡‡</sup>Division of Gastroenterology and Hepatology, Swiss EoE Clinic, Olten, Switzerland; <sup>§§</sup>Institute of Social and Preventative Medicine, University of Bern, Bern, Switzerland; <sup>||||</sup>Inflammation & Fibrosis, <sup>##</sup>Drug Safety, <sup>\*\*\*</sup>Department of Biostatistics, Celgene Corporation, Summit, New Jersey; <sup>¶¶</sup>Division of Medicine, Gastroenterology, Feinberg School of Medicine, Chicago, Illinois

**BACKGROUND & AIMS:** The short-term efficacy of RPC4046, a monoclonal antibody against interleukin-13, has been shown in patients with eosinophilic esophagitis (EoE). We investigated the long-term efficacy and safety of RPC4046 in an open-label, long-term extension (LTE) study in adults with EoE.

**METHODS:** We analyzed data from 66 patients who completed the 16-week, double-blind, induction portion of a phase 2 study of RPC4046 (180 mg or 360 mg/wk) vs placebo and then completed a 52-week LTE, receiving open-label RPC4046 360 mg/wk. The study was conducted at 28 centers in 3 countries; patients were enrolled between September 2014 and January 2017. Outcomes were stratified by double-blind dose group and included esophageal eosinophil counts, EoE endoscopic reference score, EoE histologic scoring system score, symptom-based EoE activity index score, and safety.

**RESULTS:** By week 12 of the LTE, esophageal eosinophil mean and peak counts, total EoE endoscopic reference scores, and EoE histologic scoring system grade and stage scores did not differ considerably between patients who originally received placebo vs RPC4046. Most patients maintained responses through week 52. Symptom remission (symptom-based EoE activity index score,  $\leq 20$ ) increased from 14% at LTE entry to 67% at LTE week 52 in placebo–RPC4046 patients and from 30% to 54% in RPC4046–RPC4046 (either dose) patients. Of the 28 patients who did not have a histologic response to RPC4046 during the double-blind induction phase, 10 patients (36%) achieved response during the LTE. The most common adverse events were upper respiratory tract infection (21%) and nasopharyngitis (14%).

**CONCLUSIONS:** One year of treatment with RPC4046 is generally well tolerated and results in continued improvement and/or maintenance of endoscopic, histologic, and clinical measures of EoE disease activity relative to baseline. Trial registration: NCT02098473.

**Keywords:** EREFS; EoEHSS; EEsAI; Inflammation.

**Abbreviations used in this paper:** ADA, anti-drug antibody; AE, adverse event; DB, double-blind; DSD, daily symptom diary; EoE, eosinophilic esophagitis; EEsAI, Symptom-based Eosinophilic Esophagitis Activity Index; EoEHSS, Eosinophilic Esophagitis Histologic Scoring System Score; EREFS, Eosinophilic Esophagitis Endoscopic Reference Score; hpf, high-power field; IL, interleukin; LTE, long-term extension; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Most current article

© 2021 by the AGA Institute. Published by Elsevier, Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1542-3565

<https://doi.org/10.1016/j.cgh.2020.03.036>

Eosinophilic 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> Complications of EoE, including strictures and food impaction, are related mostly to esophageal remodeling and fibrostenosis and associated with a longer duration of untreated disease.<sup>3,4</sup> Although a topical steroid in orodispersible tablet form<sup>5</sup> is approved for EoE treatment in Europe, there are no approved EoE treatments in the United States. Off-label orally/topically administered corticosteroids are a mainstay of therapy,<sup>6-12</sup> but their use is limited by side effects, including candidal esophagitis, oral candidiasis, and atrophy of the esophageal mucosa, and long-term safety data are limited.<sup>13</sup> Moreover, evidence suggests prolonged topical corticosteroid use may be only partially effective in maintaining disease remission<sup>14-19</sup> and associated with resistance.<sup>20</sup>

Interleukin 13 (IL13), a pleotropic cytokine involved in T-helper cell 2-type inflammation, plays an important role in the pathogenesis of EoE.<sup>21</sup> IL13 is overexpressed in the esophageal mucosa of EoE subjects; it has been shown to induce a gene transcript profile that overlaps with the EoE-specific esophageal transcriptome<sup>22</sup> and to modulate cellular and molecular pathways involved in eosinophil recruitment,<sup>23</sup> esophageal barrier function,<sup>24</sup> and tissue remodeling and fibrosis.<sup>25</sup> Simulated altered expression/blockade of IL13 in animal models produces fluctuations in EoE disease status and esophageal function.<sup>25-28</sup> Given the prominent role of IL13 in EoE pathogenesis, blockade of this cascade is a potential treatment target.

RPC4046 is a recombinant, humanized, highly selective, monoclonal (IgG1k) antibody that recognizes the wild-type and variant human IL13 and inhibits binding to both IL13-receptor subtypes: IL13R $\alpha$ 1 and IL13R $\alpha$ 2.<sup>29</sup> The safety and efficacy of RPC4046 vs placebo were shown in the induction period of a phase 2, 16-week, randomized, controlled study in adults with symptomatic EoE (RPC02-201; [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02098473) study ID: NCT02098473).<sup>30</sup> Subjects completing the induction period then had the option to enroll in a subsequent 52-week, open-label, long-term extension (LTE) period; these findings are reported herein.

## Methods

### *Trial Design*

We conducted an open-label LTE of the phase 2 RPC02-201 study (NCT02098473) after completion of the 16-week double-blind (DB) period in subjects with symptomatic EoE. The study was conducted at 28 centers in 3 countries ([Supplementary Table 1](#)), with enrollment between September 2014 and January 2017

## What You Need to Know

### Background

The safety and efficacy of RPC4046 was shown in the 16-week induction period of a phase 2, randomized, controlled study of adults with symptomatic eosinophilic esophagitis (EoE). This study reports results from the 52-week, open-label, long-term extension period.

### Findings

Over 52 weeks, RPC4046 resulted in continued improvement and/or maintenance of endoscopic, histologic, and clinical measures of EoE activity, relative to baseline, and was generally well tolerated.

### Implications for patient care

Encouraging findings from a study of 1 year or longer of RPC4046 treatment of patients with symptomatic EoE support confirmatory studies.

and study completion in October 2017. The study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice Guidelines established by the International Conference on Harmonization. Protocols, amendments, and informed consent documentation were reviewed and approved by the Institutional Review Boards and/or Independent Ethics Committee of each study center. All subjects provided informed consent.

Key inclusion/exclusion criteria have been reported previously<sup>30</sup> and are detailed in the [Supplementary Material](#). During the initial DB period (16 weeks), subjects received placebo (n = 34), RPC4046 180 mg (n = 31), or RPC4046 360 mg (n = 34) subcutaneously once weekly; 90 subjects completed the DB induction portion (through week 16). Subjects entering the LTE period were required to have 80% or greater study drug compliance and no clinically significant adverse events (AEs), as deemed by the investigator, that would preclude further dosing. During the LTE, all subjects received RPC4046 360 mg for 52 additional weeks; the higher dose was chosen for LTE because at the time of the study design, the dose-response and efficacy profile of RPC4046 were not known.

Prior treatment with corticosteroids for EoE was recorded at the DB baseline. Steroid-refractory status was defined as an adequate trial of systemic or topical steroids failing to result in improvements in inflammation and patient symptoms, as judged by the investigator.

### *Outcome Measures*

Primary efficacy outcome measures included esophageal eosinophil counts (mean counts [eosinophils per high-power field (hpf); hpf size, 0.3 mm<sup>2</sup>] calculated from the 5 most inflamed hpfs from

**Table 1.** Patient Demographics and Disease Characteristics: LTE Population

	Placebo (n = 29)	RPC4046 180 mg (n = 28)	RPC4046 360 mg (n = 29)	Total (n = 86)
Age, y				
Mean	39.8 (11.02)	38.8 (9.79)	32.8 (9.74)	37.1 (10.56)
Minimum, maximum	21, 64	19, 59	18, 60	18, 64
Sex, n (%)				
Male	19 (65.5)	18 (64.3)	19 (65.5)	56 (65.1)
Female	10 (34.5)	10 (35.7)	10 (34.5)	30 (34.9)
Race, n (%)				
White	29 (100)	27 (96.4)	29 (100)	85 (98.8)
Black or African American	0	1 (3.6)	0	1 (1.2)
Years since EoE diagnosis				
Mean	4.331 (3.003)	4.220 (3.900)	3.711 (2.864)	4.086 (3.253)
Minimum, maximum	0.14, 10.89	0.12, 15.52	0.04, 9.53	0.04, 15.52
Steroid stratification factor, n (%)				
Steroid-refractory	14 (48.3)	12 (42.9)	15 (51.7)	41 (47.7)
Not steroid-refractory	15 (51.7)	16 (57.1)	14 (48.3)	45 (52.3)
Baseline eosinophil count/hpf				
Mean (SD)	96.93 (54.45)	119.60 (80.80)	125.61 (74.53)	113.98 (70.96)
Minimum, maximum	23.6, 189.8	21.4, 273.0	22.2, 369.2	21.4, 369.2
Baseline peak eosinophil count/hpf				
Mean (SD)	111.0 (60.72)	135.4 (88.18)	143.0 (83.67)	129.8 (78.62)
Minimum, maximum	31, 212	24, 304	26, 389	24, 389
LTE baseline eosinophil count/hpf <sup>a</sup>				
Mean (SD)	88.39 (55.87)	27.12 (36.86)	25.61 (30.51)	47.27 (51.35)
Minimum, maximum	12.0, 265.4	0.0, 133.6	0.0, 123.4	0.0, 265.4
LTE baseline peak eosinophil count/hpf <sup>a</sup>				
Mean (SD)	102.6 (63.05)	31.2 (41.55)	31.3 (38.35)	55.3 (59.11)
Minimum, maximum	16, 302	0, 159	0, 157	0, 302
LTE baseline EREFS total score				
Mean (SD)	8.1 (5.14)	5.5 (3.83)	6.5 (4.43)	6.7 (4.59)
Minimum, maximum	0, 18	0, 14	0, 18	0, 18
LTE baseline EoEHSS grade score				
Mean (SD)	40.9 (13.55)	21.5 (12.41)	20.0 (6.47)	27.5 (14.67)
Minimum, maximum	16.27, 63.49	4.76, 66.87	10.32, 33.33	4.76, 66.87
LTE baseline EoEHSS stage score				
Mean (SD)	40.9 (12.69)	21.7 (12.64)	19.4 (6.98)	27.4 (14.66)
Minimum, maximum	17.46, 58.73	1.59, 59.33	9.33, 34.92	1.59, 59.33
LTE baseline EEsAI mean score				
Mean (SD)	40.3 (23.36)	37.8 (22.69)	30.1 (25.12)	36.0 (23.88)
Minimum, maximum	0, 78	0, 76	0, 76	0, 78
LTE baseline DSD composite score				
Mean (SD)	21.0 (18.55)	20.0 (17.63)	13.8 (16.77)	18.2 (17.66)
Minimum, maximum	0.0, 51.7	0.0, 46.7	0.0, 45.5	0.0, 51.7

DSD, daily symptom diary; EEsAI, Eosinophilic Esophagitis Activity Index; EoE, eosinophilic esophagitis; EoEHSS, Eosinophilic Esophagitis Histologic Scoring System Score; EREFS, Eosinophilic Esophagitis Endoscopic Reference Score; LTE, long-term extension.

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

among all esophageal biopsy specimens [proximal, mid, and distal], peak counts, and peak response threshold of <15/hpf). Secondary outcome measures included daily symptom diary (DSD) scores, EoE Endoscopic Reference Score (EREFS), EoE Histologic Scoring System (EoEHSS) score, and symptom-based EoE Symptom Activity Index (EEsAI) score.<sup>31–34</sup> Eosinophil counts were quantified centrally by the study pathologist, who was blinded to treatment allocation. Endoscopic and histologic outcomes were measured at DB week 16 and at LTE weeks 12, 24, and 52 (additional information can be found in the [Supplementary Methods](#)).

### Statistical Analysis: Efficacy

Efficacy analyses were conducted in the LTE analysis population, defined as all subjects receiving at least 1 dose of study drug during the LTE. Results were analyzed by the original dose group assigned to subjects during the DB induction period (placebo, RPC4046 180 mg, or RPC4046 360 mg) and presented descriptively. The LTE baseline was defined as the last observed value scheduled, before the first dose date during the LTE. Continuous data were summarized using mean, SD or SEM, median, minimum, and maximum values. Categorical data were summarized as the proportions of subjects.

Safety Analyses

No statistical hypothesis testing was performed on safety results. AEs were described as the raw number of treatment-emergent AEs (TEAEs), percentages of subjects, and as exposure-adjusted incidence rates per 100 patient-years of exposure. TEAEs were defined as AEs with onset on or after the first dose of study drug during the LTE, or AEs that started before the first dose of study drug during the LTE but worsened on or after the first dose of study drug during the LTE. Serious AEs (SAEs) also were assessed.

n = 29; RPC4046 180 mg, n = 28; and RPC4046 360 mg, n = 29) (Supplementary Figure 1). Twenty of the 86 subjects (23%) did not complete the full 52-week duration as part of the LTE. Five of these patients had higher mean esophageal eosinophil counts before study drug discontinuation relative to baseline LTE; however, study discontinuations were not associated with the long-term efficacy of RPC4046. Reasons for study drug discontinuation during the LTE included withdrawal of consent (n = 7), AE (n = 6), noncompliance (n = 3), other (n = 2), investigator decision (n = 1), and pregnancy (n = 1).

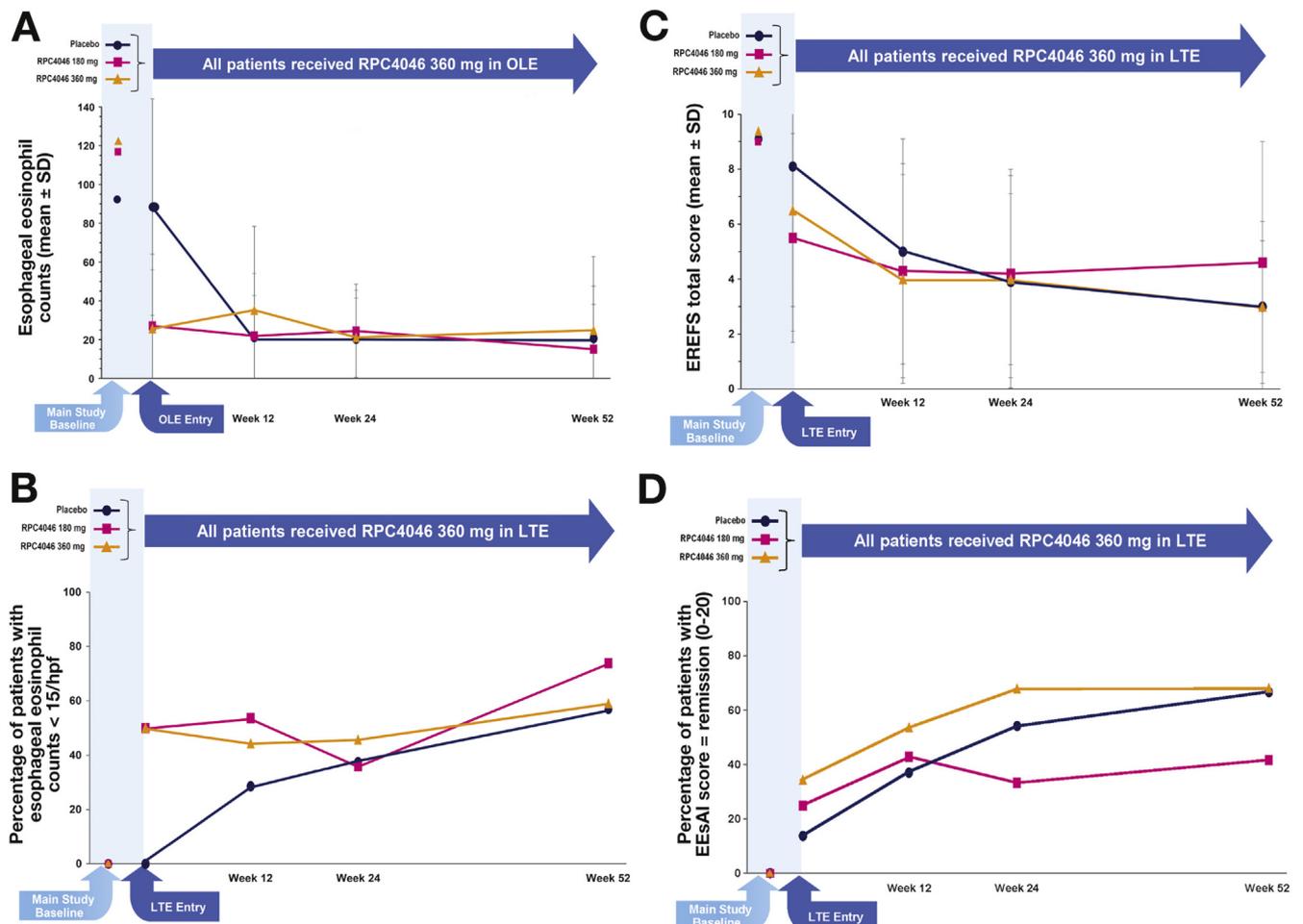
Results

Disposition

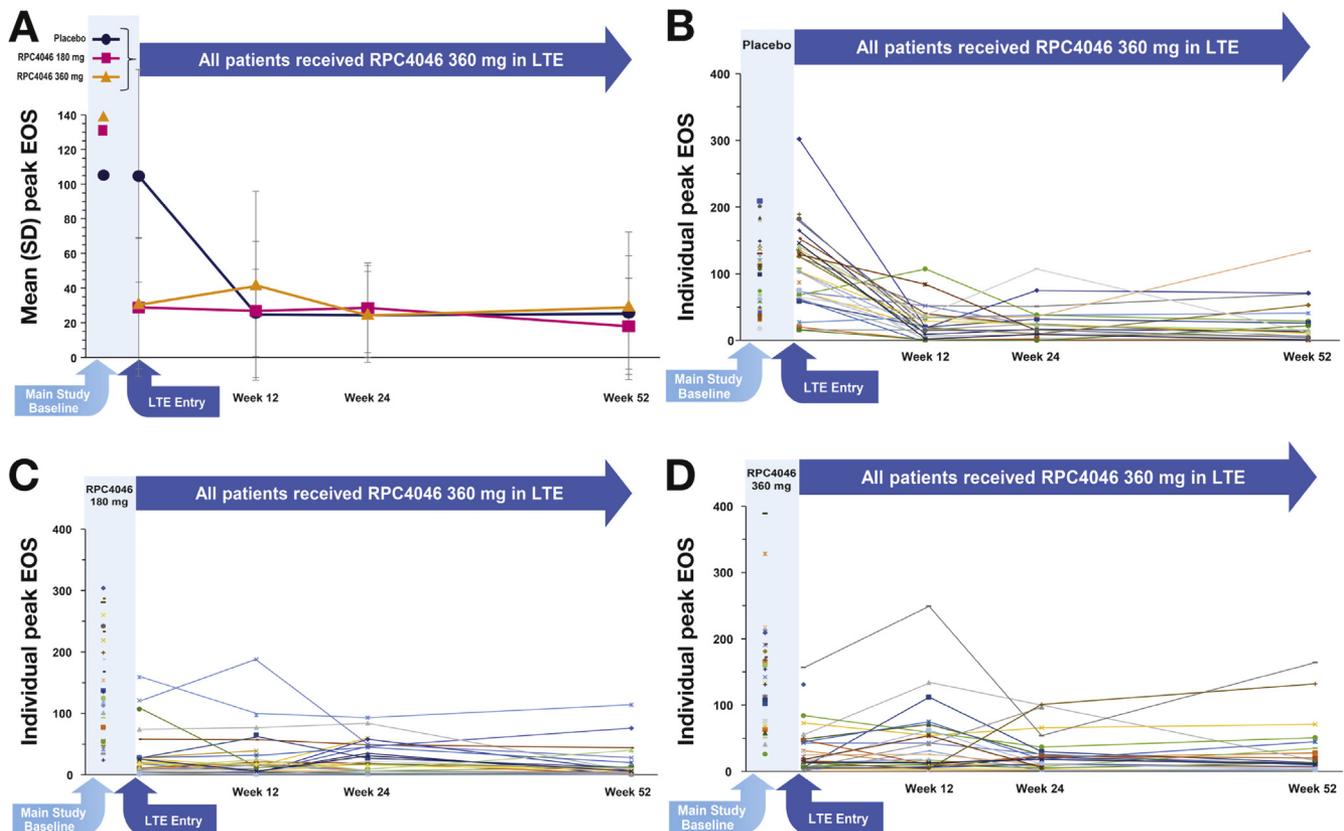
Among the 90 subjects who completed the DB treatment period, 86 were enrolled in the LTE (placebo,

Demographic and Disease Characteristics

Demographic and disease characteristics of subjects entering the LTE were consistent with the population characteristics of the initial DB induction phase of the trial. Subjects enrolled in the LTE had a mean age of 37.1 years, with a mean of 4.1 years since their EoE



**Figure 1.** Clinical efficacy outcomes. Clinical results for the long-term extension (LTE) patient group at main study baseline, LTE study entry, week 12, week 24, and week 52. (A) The mean esophageal eosinophil count per high-power field. (B) The proportion of subjects achieving a peak esophageal eosinophil count less than 15 eosinophils per high-power field. (C) The mean total eosinophilic esophagitis endoscopic reference score (EREFS) (endoscopic findings analyzed according to the modified scoring system described by Hirano et al<sup>31</sup>). (D) The proportion of subjects achieving symptomatic remission as determined by an Eosinophilic Esophagitis Activity Index (EEsAI) score of 20 or less (LTE population). OLE, open-label extension.



**Figure 2.** Peak eosinophils (EOS) over time (baseline double-blind week 16, long-term extension [LTE] weeks 12, 24, and 52) by treatment group. (A) Average of individuals within each treatment group: placebo, RPC4046 180 mg, and RPC4046 360 mg. (B) Individual data from the placebo group. (C) Individual data from the RPC4046 180 mg group. (D) Individual data from the RPC4046 360 mg group (LTE population). OLE, open-label extension.

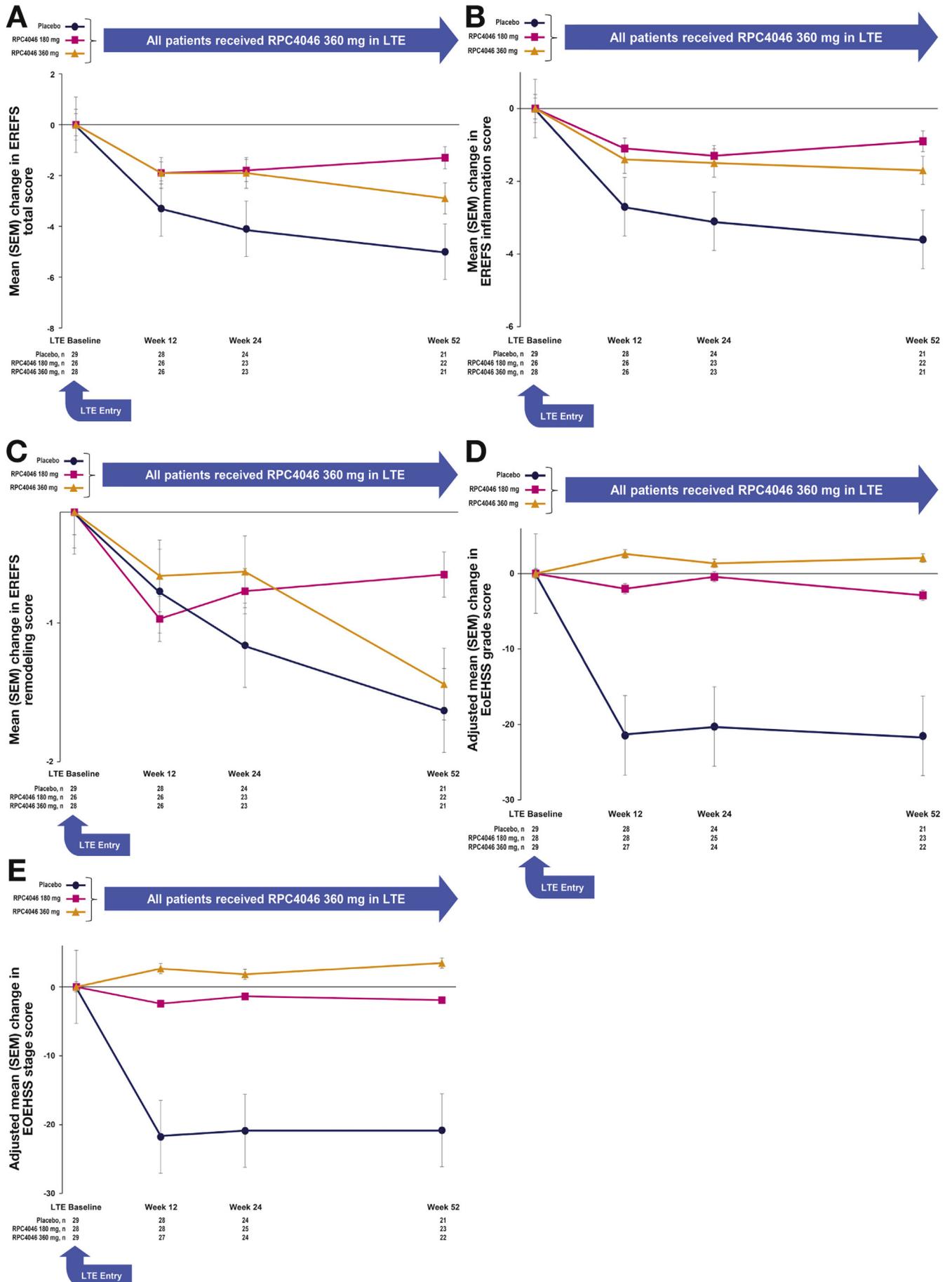
diagnosis; approximately 48% were steroid-refractory (Table 1).

### Clinical Efficacy

At LTE entry, the mean esophageal eosinophil counts for subjects previously treated with placebo were substantially higher than for subjects previously receiving active treatment (Table 1; Figure 1A); by LTE week 12, counts had decreased to the levels observed in both RPC4046 groups, which was maintained through LTE week 52 (Figure 1A). Similarly, at LTE entry, peak esophageal eosinophil counts in subjects previously treated with placebo were 3-fold greater than in subjects previously receiving active treatment (Table 1); these counts had decreased to levels observed in both RPC4046 groups by LTE week 12, which was maintained through LTE week 52 (Figure 2A). No effect of RPC4046 on the mean absolute blood eosinophil levels was observed at LTE week 52 (Supplementary Table 2). The proportion of responders (peak esophageal eosinophil count, <15 hpf) increased from LTE week 12 to LTE week 52 in all 3 groups (placebo, 28.6% [week 12] to 57.1% [week 52]; RPC4046 180 mg, 53.6% to 73.9%; RPC4046 360 mg, 44.4% to 59.1%) (Figure 1B).

The EREFS total and composite (inflammation and remodeling) scores over all locations decreased from LTE baseline through LTE week 52 in subjects previously randomized to placebo; in those previously receiving active treatment during the DB induction phase, further improvement beyond the LTE baseline was seen at both week 12 and week 52 (Figures 1C and 3A–C). At LTE week 52, decreases in EREFS scores were numerically greater in subjects previously treated with placebo vs RPC4046 (mean change from LTE baseline to week 52 for placebo, -5.0; for RPC4046 180 mg, -1.3; and for RPC4046 360 mg, -2.9). EREFS individual components scores over all locations (Supplementary Table 3) and EREFS components by location (data not shown) were similar across groups throughout the LTE period. EREFS total scores over time in individual subjects are shown in Supplementary Figure 2.

EoEHSS grade scores for subjects previously treated with placebo were 2-fold greater than for subjects previously treated with RPC4046 (either dose) at LTE entry (Table 1). By LTE week 52, EoEHSS grade scores had decreased substantially for subjects previously treated with placebo (mean change from LTE baseline to week 52 for placebo, -21.5; for RPC4046 180 mg, -2.9; and for RPC4046 360 mg, 2.1) (Figure 3D). The mean absolute EoEHSS grade scores were similar across the treatment



**Table 2.** Peak EOS Count Responder Analysis: Observed Cases in the LTE Population

	Randomized treatment assignment at DB baseline			
	Placebo (N = 29)	RPC4046 180 mg (n = 28)	RPC4046 360 mg (n = 29)	RPC4046 total (N = 57)
Proportion of patients with response at DB week 16, n/N (%)				
Peak EOS <15 at DB week 16	0/29 (0)	14/28 (50.0)	15/29 (51.7)	29/57 (50.9)
Peak EOS ≥15 at DB week 16	29/29 (100)	14/28 (50.0)	14/29 (49.3)	28/57 (49.1)
Proportion of patients with response at DB week 16 and LTE week 52, n/N (%)				
Peak EOS <15 at DB week 16 and peak EOS <15 at LTE week 52 <sup>a</sup>	0/0 (0)	10/14 (71.4)	10/15 (66.7)	20/29 (69.0)
Peak EOS <15 at DB week 16 and peak EOS ≥15 at LTE week 52 <sup>a</sup>	0/0 (0)	1/14 (7.1)	2/15 (13.3)	3/29 (10.3)
Peak EOS ≥15 at DB week 16 and peak EOS <15 at LTE week 52 <sup>b</sup>	12/29 (41.4)	7/14 (50.0)	3/14 (21.4)	10/28 (35.7)
Peak EOS ≥15 at DB week 16 and peak EOS ≥15 at LTE week 52 <sup>b</sup>	9/29 (31.0)	5/14 (35.7)	7/14 (50.0)	12/28 (42.9)

DB, double blind; EOS, eosinophilic esophagitis; LTE, long-term extension.

<sup>a</sup>Denominator is the number of subjects with a peak EOS less than 15 at DB week 16.

<sup>b</sup>Denominator is the number of subjects with a peak EOS of 15 or higher at DB week 16.

groups at LTE week 52 (19.9, 19.5, and 21.9, respectively). At LTE entry, the EoEHSS stage scores for subjects previously treated with placebo were 2-fold greater than for subjects previously receiving active treatment. By LTE week 52, scores for subjects previously treated with placebo had decreased (mean change from LTE baseline to week 52 for placebo, -20.8; for RPC4046 180 mg, -1.9; and for RPC4046 360 mg, 3.5) (Figure 3E), and the mean absolute values generally were similar to those in both RPC4046 groups (20.4, 21.4, and 22.2, respectively).

The EEsAI mean (SD) scores for the placebo, RPC4046 180 mg, and RPC4046 360 mg groups improved from LTE baseline through LTE week 12 (mean change: placebo, -9.1; RPC4046 180 mg, -9.1; and RPC4046 360 mg, -8.7) and from LTE baseline through LTE week 52 (mean change: placebo, -21.1; RPC4046 180 mg, -10.6; and RPC4046 360 mg, -14.6). The proportion of subjects achieving symptomatic remission (EEsAI score, ≤20) showed a similar trend of increase in all treatment groups from LTE baseline through LTE week 52 (Figure 1D). The proportion of subjects achieving EEsAI remission increased in the placebo (13.8% [LTE baseline] to 66.7% [LTE week 52]), RPC4046 180 mg (25.0% to 41.7%), and RPC4046 360 mg (34.5% to 68.2%) groups (Supplementary Table 4). EEsAI scores over time in individual subjects are shown in Supplementary Figure 3. At LTE entry, the mean DSD composite score in subjects previously treated with RPC4046 360 mg were lower than in subjects previously treated with placebo or RPC4046 180 mg. By LTE week

52, scores for all groups had decreased (mean change: placebo, -8.61; RPC4046 180 mg, -11.31; and RPC4046 360 mg, -8.46) (Supplementary Table 5).

Further post hoc analysis assessed whether peak esophageal eosinophil count response achieved with randomized treatment by week 16 of the DB induction period was maintained at week 52 with RPC4046 360-mg treatment (Table 2). A majority of the subjects (69.0%) who had a histologic response at DB week 16 with active treatment (RPC4046 180 mg or 360 mg) maintained it at LTE week 52 (20 of 29); 10.3% (3 of 29) lost prior response. Among subjects entering LTE who were not histologic responders (peak eosinophil counts, ≥15 hpf) after 16 weeks of active study drug treatment during the DB induction phase (n = 28), 10 (35.7%) subjects (RPC4046 180 mg, n = 7; RPC4046 360 mg, n = 3) were able to achieve histologic response with RPC4046 360 mg at LTE week 52 (Table 2; Figure 2C and D).

### Steroid-Refractory Vs Non-Steroid-Refractory Subjects

Forty-one of 86 subjects enrolled in the LTE study were considered steroid-refractory. No notable differences were observed between the steroid-refractory and non-steroid-refractory groups for mean changes from LTE entry over the LTE period in mean esophageal eosinophil counts (Supplementary Figure 4A and B), DSD composite scores and components (Supplementary Figure 4C and D), EREFS total score (Supplementary

**Figure 3.** Mean (SEM) changes from long-term extension (LTE) baseline to LTE weeks 12, 24, and 52 for Eosinophilic Esophagitis Endoscopic Reference Score (EREFs) (total, inflammation, and remodeling), and Eosinophilic Esophagitis Histologic Scoring System Score (EoEHSS) grade and stage scores. (A) EREFs total score. (B) EREFs inflammation composite score. (C) EREFs remodeling composite score. (D) EoEHSS grade score. (E) EoEHSS stage score (LTE population).

**Table 3.** Summary of Safety Findings by Study Group During the LTE Period: LTE Population

	Randomized treatment assignment at DB baseline			Total (n = 86)
	Placebo (n = 29)	RPC4046 180 mg (n = 28)	RPC4046 360 mg (n = 29)	
Subject with $\geq 1$ TEAE, n (%)	21 (72.4)	26 (92.9)	24 (82.8)	71 (82.6)
Subject with $\geq 1$ possible, probable, or related TEAE, <sup>a</sup> n (%)	8 (27.6)	13 (46.4)	14 (48.3)	35 (40.7)
Subject with TEAE by maximum severity, <sup>b</sup> n (%)				
Mild	12 (41.4)	11 (39.3)	10 (34.5)	33 (38.4)
Moderate	6 (20.7)	11 (39.3)	9 (31.0)	26 (30.2)
Severe	3 (10.3)	4 (14.3)	5 (17.2)	12 (14.0)
Subject with $\geq 1$ serious TEAE, <sup>c</sup> n (%)	0	2 (7.1)	4 (13.8)	6 (7.0)
Subject with TEAE leading to study drug discontinuation, <sup>d</sup> n (%)	3 (10.3)	1 (3.6)	2 (6.9)	6 (7.0)
Subject with TEAE leading to withdrawal from study, <sup>d</sup> n (%)	0	0	1 (3.4)	1 (1.2)
Most frequent TEAE ( $\geq 10\%$ of subjects), n (%) [EAIR/100 PYE]				
Upper respiratory tract infection	9 (31.0) [38.8]	6 (21.4) [23.3]	3 (10.3) [12.5]	18 (20.9) [24.7]
Nasopharyngitis	1 (3.4) [4.3]	3 (10.7) [11.6]	8 (27.6) [33.3]	12 (14.0) [16.4]
Oropharyngeal pain	1 (3.4) [4.3]	7 (25.0) [27.2]	2 (6.9) [8.3]	10 (11.6) [13.7]
Sinusitis	2 (6.9) [8.6]	2 (7.1) [7.8]	6 (20.7) [24.9]	10 (11.6) [13.7]
Headache	3 (10.3) [12.9]	4 (14.3) [15.5]	2 (6.9) [8.3]	9 (10.5) [12.3]
Injection site reactions, n (%) [EAIR/100 PYE]				
Any injection site reaction	3 (10.3)	6 (21.4)	7 (24.1)	16 (18.6)
Injection site erythema	1 (3.4) [4.3]	1 (3.6) [3.9]	2 (6.9) [8.3]	4 (4.7) [5.5]
Injection site hematoma	1 (3.4) [4.3]	1 (3.6) [3.9]	2 (6.9) [8.3]	4 (4.7) [5.5]

DB, double-blind; EAIR, exposure-adjusted incidence rate; LTE, long-term extension; PYE, patient-years of exposure; TEAE, treatment-emergent adverse event.

<sup>a</sup>Subjects reporting more than 1 TEAE were counted only once using the closest relationship to study drug.

<sup>b</sup>Subjects reporting more than 1 TEAE were counted only once using the highest severity.

<sup>c</sup>Serious adverse events included unlikely or not related to study drug (acute asthma exacerbation, schizophrenia, diverticulitis with microperforation, right femur fracture [motorcycle accident]) and possibly related (acute cholecystitis, spontaneous abortion).

<sup>d</sup>Because of how data were captured on the disposition electronic case report form, only 1 subject was reported to have TEAEs leading to withdrawal from the study. However, the 6 subjects who discontinued study drug because of TEAEs also withdrew from the study.

Table 3), or EEsAI scores (see [Supplementary Materials Results: Steroid-Refractory and Non-Steroid Refractory Subjects](#) for detailed results).

### Atopic Subjects

Sixty-one of 90 (67.8 %) subjects who completed the DB induction period had a history of atopy/allergies at baseline, of whom 45 received active study drug. Forty-three of 60 atopic subjects from the DB period completed 52 weeks of LTE treatment. Overall, no marked differences in histologic response ([Supplementary Table 6](#)), endoscopic (EREFS; [Supplementary Table 7](#)), or symptom scores (EEsAI remission score,  $\leq 20$ ) ([Supplementary Table 4](#)) were observed in atopic subjects vs the overall study population after long-term treatment with RPC4046 360 mg. No significant impact on IgE levels was observed in atopic patients or the overall study population.

### Safety Assessments

Generally, RPC4046 was well tolerated; the majority of AEs reported in the LTE period were consistent with those in the induction period, with no new clinically

significant AEs identified with longer-term treatment. Overall, the majority of subjects with TEAEs had TEAEs of mild or moderate severity (83.1%). Seventy-one subjects (82.6%) reported 1 or more TEAEs; 6 subjects (7%) reported 1 or more SAEs ([Table 3](#); [Supplementary Table 8](#)). All SAEs with the exception of the case of schizophrenia were resolved by the end of the study. The most commonly reported TEAEs ( $\geq 10\%$ ) were an upper respiratory tract infection in 18 subjects, nasopharyngitis in 12 subjects, sinusitis and oropharyngeal pain in 10 subjects each, and headache in 9 subjects ([Table 3](#)). Injection site reaction was reported in 18.6% of subjects in the LTE period, with injection-site erythema and hematoma occurring in 4 subjects (4.7%) (5.5 exposure-adjusted incidence rate/100 patient-years of exposure) each ([Supplementary Table 9](#)). Of note, there were no significant changes in blood eosinophils from baseline to week 52 in the LTE population ([Supplementary Table 2](#)). Increased blood eosinophil levels ( $\geq 1000$  cells/ $\mu\text{L}$ ) were observed in 11 subjects during LTE, including baseline, that were mostly transitory or observed at single time points; none were greater than 2100 cells/ $\mu\text{L}$ . No TEAEs were attributed to increases in blood eosinophil counts.

The incidence of immunogenicity was low; only 4 subjects tested positive for antidrug antibody (ADA) across the DB and LTE periods. Two subjects, both in the

RPC4046 180 mg group, tested positive for ADA during the DB period, 1 of whom was only ADA (+) at DB day 1 (predose) and DB week 12; the other subject was ADA (+) at DB weeks 12 and 16 and LTE weeks 2, 4, and 12, but ADA (-) at subsequent LTE visits. Two additional subjects in the DB randomized placebo group were ADA (+) during LTE, 1 at LTE week 24 only and the other at LTE weeks 12, 24, and 52 (additional details are provided in the [Supplementary Materials](#) Immunogenicity Assessment). The potential impact of immunogenicity on RPC4046 cannot be characterized because only a few subjects had ADAs during the trial period.

## Discussion

Targeted EoE immunotherapies present a potential treatment option for the significant numbers of patients who are refractory to current therapies.<sup>35</sup> Several biologic monoclonal antibodies have been evaluated,<sup>36</sup> but long-term data are limited.<sup>37</sup> In the DB randomized, placebo-controlled portion of this phase 2 trial, the novel anti-IL13 monoclonal antibody RPC4046 showed efficacy as a targeted therapeutic option in EoE patients.<sup>30</sup> We report several notable findings in the open-label LTE portion of this trial. Overall, subjects initially treated with RPC4046 (180 mg and 360 mg) in the DB phase had continued endoscopic, histologic, and clinical improvement of EoE disease activity for an additional 52 weeks. Improvements were shown by continued reductions in the mean and peak esophageal eosinophil count, stable histologic scores as determined by EoEHSS, and continued improvement in mucosal appearance by EREFS. Moreover, subjects who initially received placebo experienced improvements as early as the LTE week 12 visit, despite not having received an intravenous RPC4046 loading dose; these improvements were maintained for the remaining LTE period. Subjects who received RPC4046 180 mg during the DB period did not show significant differences in improvement when given an increased dose of 360 mg RPC4046 during LTE, indicating a consistent long-term effect of RPC4046. Importantly, similar responses were seen in the non-steroid-refractory subgroup and the difficult-to-treat steroid-refractory subgroup (a group with no current pharmacologic options who would be well-suited to biologic therapy). Although not all patients reached pre-defined peak esophageal eosinophil values defining treatment response, most patients showed notable decreases in peak eosinophil counts throughout the long-term treatment period relative to baseline.

RPC4046 was well tolerated with little immunogenicity elicited in the LTE period. Overall, the majority of TEAEs were mild or moderate in severity. No deaths occurred during the LTE, and only 2 SAEs were assessed as possibly related to the study drug (cholecystitis and spontaneous abortion), which resolved by study end.

The current open-label LTE portion of this phase 2 study includes long prospective LTE follow-up studies in

EoE patients, providing long-term data on biologic treatment in EoE using validated outcome measures. A potential limitation is that approximately 25% (20 of 86) of subjects were not able to complete the full 52-week LTE duration. The LTE portion of the study was open-label in design and thus not blinded, which limited the ability to conduct statistical comparisons. Symptom data, in particular, should be interpreted with caution because patients knew they were receiving an active medication; however, changes in symptom data were similar in the DB and LTE periods. Evaluation of only RPC4046 360 mg in the LTE period is another potential limitation; however, the safety and immunogenicity data suggest that this dose was well tolerated, with no new safety signals identified with longer-term treatment. Finally, the current study was not stratified by EoE endotype; therefore, evaluation of RPC4046 in patients with distinct EoE endotypes<sup>38</sup> remains an area for further exploration.

The current study showed no significant safety concerns in subjects receiving RPC4046 for 52 weeks and beyond. Subjects in the LTE period had clinical, endoscopic, and histologic improvement of EoE relative to baseline; those who switched from placebo to RPC4046 showed clinical disease improvement as early as 12 weeks. Subgroup analyses further suggest efficacy in both the steroid-refractory and non-steroid-refractory populations. These data support further confirmatory studies of RPC4046.

## Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at [www.cghjournal.org](http://www.cghjournal.org), and at <https://doi.org/10.1016/j.cgh.2020.03.036>.

## References

1. Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol* 2011;128:3–20.e6, quiz 21–22.
2. Furuta GT, Katzka DA. Eosinophilic esophagitis. *N Engl J Med* 2015;373:1640–1648.
3. Schoepfer AM, Safroneeva E, Bussmann C, et al. Delay in diagnosis of eosinophilic esophagitis increases risk for stricture formation in a time-dependent manner. *Gastroenterology* 2013;145:1230–1236.e1–2.
4. Dellon ES, Kim HP, Sperry SL, et al. A phenotypic analysis shows that eosinophilic esophagitis is a progressive fibrostenotic disease. *Gastrointest Endosc* 2014;79:577–585.e4.
5. Lucendo AJ, Miehke S, Schlag C, et al. Efficacy of budesonide orodispersible tablets as induction therapy for eosinophilic esophagitis in a randomized placebo-controlled trial. *Gastroenterology* 2019;157:74–86.e15.
6. Schaefer ET, Fitzgerald JF, Molleston JP, et al. Comparison of oral prednisone and topical fluticasone in the treatment of eosinophilic esophagitis: a randomized trial in children. *Clin Gastroenterol Hepatol* 2008;6:165–173.
7. Dohil R, Newbury R, Fox L, et al. Oral viscous budesonide is effective in children with eosinophilic esophagitis in a

- randomized, placebo-controlled trial. *Gastroenterology* 2010;139:418–429.
8. Straumann A, Conus S, Degen L, et al. Budesonide is effective in adolescent and adult patients with active eosinophilic esophagitis. *Gastroenterology* 2010;139:1526–1537, 1537.e1.
  9. Alexander JA, Jung KW, Arora AS, et al. Swallowed fluticasone improves histologic but not symptomatic response of adults with eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2012;10:742–749.e1.
  10. Dellon ES, Gonsalves N, Hirano I, et al. ACG clinical guideline: evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). *Am J Gastroenterol* 2013;108:679–692; quiz 693.
  11. Miehlke S, Hruz P, Vieth M, et al. A randomised, double-blind trial comparing budesonide formulations and dosages for short-term treatment of eosinophilic oesophagitis. *Gut* 2016;65:390–399.
  12. Konikoff MR, Noel RJ, Blanchard C, et al. A randomized, double-blind, placebo-controlled trial of fluticasone propionate for pediatric eosinophilic esophagitis. *Gastroenterology* 2006;131:1381–1391.
  13. von Arnim U, Malfertheiner P. Eosinophilic esophagitis—treatment of eosinophilic esophagitis with drugs: corticosteroids. *Dig Dis* 2014;32:126–129.
  14. Brazzini B, Pimpinelli N. New and established topical corticosteroids in dermatology: clinical pharmacology and therapeutic use. *Am J Clin Dermatol* 2002;3:47–58.
  15. Lebrun-Vignes B, Chosidow O. [Topical corticosteroids]. *Ann Dermatol Venereol* 2004;131:39–48.
  16. Straumann A, Conus S, Degen L, et al. Long-term budesonide maintenance treatment is partially effective for patients with eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2011;9:400–409.e1.
  17. Wolf WA, Cotton CC, Green DJ, et al. Predictors of response to steroid therapy for eosinophilic esophagitis and treatment of steroid-refractory patients. *Clin Gastroenterol Hepatol* 2015;13:452–458.
  18. Dellon ES. Management of refractory eosinophilic oesophagitis. *Nat Rev Gastroenterol Hepatol* 2017;14:479–490.
  19. Eluri S, Runge TM, Hansen J, et al. Diminishing effectiveness of long-term maintenance topical steroid therapy in PPI non-responsive eosinophilic esophagitis. *Clin Transl Gastroenterol* 2017;8:e97.
  20. Butz BK, Wen T, Gleich GJ, et al. Efficacy, dose reduction, and resistance to high-dose fluticasone in patients with eosinophilic esophagitis. *Gastroenterology* 2014;147:324–333.e5.
  21. Wechsler JB, Bryce PJ. Allergic mechanisms in eosinophilic esophagitis. *Gastroenterol Clin North Am* 2014;43:281–296.
  22. Blanchard C, Mingler MK, Vicario M, et al. IL-13 involvement in eosinophilic esophagitis: transcriptome analysis and reversibility with glucocorticoids. *J Allergy Clin Immunol* 2007;120:1292–1300.
  23. Brightling CE, Saha S, Hollins F. Interleukin-13: prospects for new treatments. *Clin Exp Allergy* 2010;40:42–49.
  24. Sherrill JD, Kc K, Wu D, et al. Desmoglein-1 regulates esophageal epithelial barrier function and immune responses in eosinophilic esophagitis. *Mucosal Immunol* 2014;7:718–729.
  25. Zuo L, Fulkerson PC, Finkelman FD, et al. IL-13 induces esophageal remodeling and gene expression by an eosinophil-independent, IL-13R alpha 2-inhibited pathway. *J Immunol* 2010;185:660–669.
  26. Kottyan LC, Davis BP, Sherrill JD, et al. Genome-wide association analysis of eosinophilic esophagitis provides insight into the tissue specificity of this allergic disease. *Nat Genet* 2014;46:895–900.
  27. Rothenberg ME, Wen T, Greenberg A, et al. Intravenous anti-IL-13 mAb QAX576 for the treatment of eosinophilic esophagitis. *J Allergy Clin Immunol* 2015;135:500–507.
  28. Davis BP, Stucke EM, Khorki ME, et al. Eosinophilic esophagitis-linked calpain 14 is an IL-13-induced protease that mediates esophageal epithelial barrier impairment. *JCI Insight* 2016;1:e86355.
  29. Tripp CS, Cuff C, Campbell AL, et al. RPC4046, a novel anti-interleukin-13 antibody, blocks IL-13 binding to IL-13 alpha1 and alpha2 receptors: a randomized, double-blind, placebo-controlled, dose-escalation first-in-human study. *Adv Ther* 2017;34:1364–1381.
  30. Hirano I, Collins MH, Assouline-Dayana Y, et al. RPC4046, a monoclonal antibody against IL13, reduces histologic and endoscopic activity in patients with eosinophilic esophagitis. *Gastroenterology* 2019;156:592–603.
  31. Hirano I, Moy N, Heckman MG, et al. Endoscopic assessment of the oesophageal features of eosinophilic oesophagitis: validation of a novel classification and grading system. *Gut* 2013;62:489–495.
  32. 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.
  33. Warners MJ, Ambarus CA, Bredenoord AJ, et al. Reliability of histologic assessment in patients with eosinophilic oesophagitis. *Aliment Pharmacol Ther* 2018;47:940–950.
  34. Schoepfer AM, Straumann A, Panczak R, et al. Development and validation of a symptom-based activity index for adults with eosinophilic esophagitis. *Gastroenterology* 2014;147:1255–1266.e21.
  35. Nhu QM, Moawad FJ. New developments in the diagnosis and treatment of eosinophilic esophagitis. *Curr Treat Options Gastroenterol* 2019;17:48–62.
  36. Wechsler JB, Hirano I. Biological therapies for eosinophilic gastrointestinal diseases. *J Allergy Clin Immunol* 2018;142:24–31.e2.
  37. Markowitz JE, Jobe L, Miller M, et al. Safety and efficacy of reslizumab for children and adolescents with eosinophilic esophagitis treated for 9 years. *J Pediatr Gastroenterol Nutr* 2018;66:893–897.
  38. Shoda T, Wen T, Aceves SS, et al. Eosinophilic oesophagitis endotype classification by molecular, clinical, and histopathological analyses: a cross-sectional study. *Lancet Gastroenterol Hepatol* 2018;3:477–488.

---

#### Reprint requests

Address requests for reprints to: Evan S. Dellon, MD, MPH, Division of Gastroenterology and Hepatology, University of North Carolina—Chapel Hill, School of Medicine, 130 Mason Farm Road, 4140 Bioinformatics Building, Campus Box 7080, Chapel Hill, North Carolina 27599-7080. e-mail: [evan\\_dellon@med.unc.edu](mailto:evan_dellon@med.unc.edu); fax: (919) 843-2508.

#### Acknowledgments

The authors thank Keith Usiskin for his critical review of the manuscript. Samom Biosciences and Peloton Advantage, LLC, an OPEN Health company, provided editorial support in the development of this manuscript, funded by Celgene Corporation. The data that support the findings of this study are not available in an online or public repository. However, data are available from the

authors upon reasonable request and with the permission of Celgene Corporation. 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>.

A complete list of investigators in the phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group open-label, extension study evaluating the clinical efficacy and safety of RPC4046 in adult subjects with eosinophilic esophagitis (A Phase 2, Multi-Center, Multi-national, Randomized, Double-blind, Placebo-controlled Parallel-group Clinical Trial to Evaluate the Efficacy and Safety of RPC4046 in Adult Subjects With Eosinophilic Esophagitis LTE) is provided in the [Supplementary Appendix](#).

#### CRedit Authorship Contributions

Evan S. Dellon, MD, MPH (Conceptualization: Equal; Data curation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal; data interpretation: Equal)

Margaret Collins, MD (Conceptualization: Equal; Data curation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal; data interpretation: Equal)

Marc E. Rothenburg, MD; PhD (Conceptualization: Equal; Data curation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal; data interpretation: Equal)

Yehudith Assouline Dayan, MD (Conceptualization: Equal; Data curation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal; data interpretation: Equal)

Larry Evans, DO (Conceptualization: Equal; Data curation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal; data interpretation: Equal)

Sandeep Gupta, PhD (Conceptualization: Equal; Data curation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal; data interpretation: Equal)

Alain Schoepfer, PD+MER1 (Conceptualization: Equal; Data curation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal; data interpretation: Equal)

Alex Straumann, MD (Conceptualization: Equal; Data curation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal; data interpretation: Equal)

Ekaterina Safroneeva, PhD (Conceptualization: Equal; Data curation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal; data interpretation: Equal)

Cristian Rodriguez, MD (Formal analysis: Equal; Writing – review & editing: Equal; data interpretation: Equal)

Neil Minton, MD (Formal analysis: Equal; Writing – review & editing: Equal; data interpretation: Equal)

Steven Y. Hua, PhD (Formal analysis: Equal; Writing – review & editing: Equal; data interpretation: Equal)

Ikuo Hirano, MD (Conceptualization: Equal; Data curation: Equal; Writing – original draft: Equal; Writing – review & editing: Equal; data interpretation: Equal).

#### Conflicts of interest

These authors disclose the following: Evan S. Dellon has served as a consultant for Adare, Aimmune, Alivio, Allakos, AstraZeneca, Banner, Biorasi, Calypso, Celgene Corporation, Enumeral, Esocap, Gossamer Bio, GSK, Regeneron, Robarts, Salix, and Shire, has received grant/research support from Adare, Allakos, Celgene Corporation, GSK, Meritage, Miraca, Nutricia, Regeneron, and Shire, and has received educational grants from Allakos, Banner, and Holoclara; Ikuo Hirano has served as a consultant for Adare, Allakos, Celgene Corporation, Esocap, Gossamer Bio, Regeneron, and Shire, and has received grant/research support from Adare, Allakos, Celgene Corporation, Regeneron, and Shire; Margaret H. Collins has served as a consultant for Allakos, Celgene Corporation, Esocap, Regeneron, and Shire, and has received grant/research support from Celgene Corporation, Regeneron, and Shire; Marc E. Rothenberg has served as a consultant for Pulm One, Spoon Guru, ClostraBio, Celgene, and AstraZeneca, has an equity interest in Pulm One, Spoon Guru, and ClostraBio, has received royalties from Teva Pharmaceuticals (reslizumab), Mapi Research Trust (PEESSv2), and UpToDate, and is an inventor of patents owned by Cincinnati Children's; Hospital Sandeep Gupta has received grant/research support from Shire and served as a consultant for Abbott, Adare, Allakos, Gossamer, 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; and Cristian Rodriguez, Neil Minton, and Steven Y. Hua are employees and shareholders of Celgene Corporation. The remaining authors disclose no conflicts.

#### Funding

This study was sponsored by Celgene Corporation.

## Supplementary Appendix

### Study Investigators

The study investigators at the initiated sites were as follows: Canada: Fergal Donnellan, Gastrointestinal Research Unit, The Gordon and Leslie Diamond Centre, Vancouver Hospital; Marietta Iacucci, Gastrointestinal Research Group, University of Calgary Health; and William Paterson, Hotel Dieu Hospital; Switzerland: Alain Schoepfer, Centre Hospitalier Universitaire Vaudois, and Alex Straumann, Swiss EoE Clinic; United States: Pablo Abonia, Cincinnati Children's Hospital Medical Center; Yehudith Assouline-Dayana, University of Iowa Hospitals and Clinics; Kamran Ayub, Southwest Gastroenterology; Allan Coates, West Michigan Clinical Research Center, Gastroenterology Associates of Western Michigan; Sidney Cohen, Thomas Jefferson University; Evan Dellon, University of North Carolina; Taddese Desta, Precision Research Institute, LLC; Larry Evans, Grand Teton Research Group; Gary Falk, The University of Pennsylvania; Steven Fein, Digestive Health Center; Nielsen Fernandez-Becker, Stanford University; David Fleischer, Children's Hospital Colorado; Keith Friedenberga, Great Lakes Gastroenterology Research; Fayez Ghishan, The University of Arizona Clinical and Translational Science; Sarah Glover, University of Florida; Gary Goldstein, Visions Clinical Research; Vikram Gopal, Borland-Groover Clinic; Craig Gross, Desert Sun Clinical Research, LLC; Robert Hardi, Metropolitan Gastroenterology Group Chevy Chase Clinical Research; Ikuo Hirano, Northwestern University; Subra Kugathasan, Emory University; Brian Lacy, Dartmouth-Hitchcock Medical Center; Jeffery Lewis, Children's Center for Digestive Healthcare; Paul Menard-Katcher, University of Colorado Anschutz Medical Center; Benjamin Mitlyng, Minnesota Gastroenterology; Fouad Moawad, Walter Reed Army Medical Center; Rodney Perez, Asheville Gastroenterology Associates; Kathryn Peterson, University of Utah; Francisco Ramirez, Clinical Studies Unit, Mayo Clinic Arizona; Vonda Reeves-Darby, Gastrointestinal Associates; Ron Schey, Temple University Hospital; Javaid Shad, Alliance Clinical Research; Michael Vaezi, Vanderbilt University Medical Center; John Wo, Indiana University; and Salam Zakko, Connecticut Clinical Research Foundation.

Note that the 40 listed sites were initiated for participation in this study; of these sites, 30 enrolled at least 1 subject.

### Study Administration

The study administration was as follows: the members of the Phase 2, Multi-Center, Multi-national, Randomized, Double-blind, Placebo-controlled Parallel-group Clinical Trial to Evaluate the Efficacy and Safety of RPC4046 in Adult Subjects With Eosinophilic Esophagitis protocol committee designed the trial in collaboration

with Celgene. Study data were collected by a contract research organization (Agility Clinical, Inc, Carlsbad, CA) and analyzed by Celgene. Celgene and the Phase 2, Multi-Center, Multi-national, Randomized, Double-blind, Placebo-controlled Parallel-group Clinical Trial to Evaluate the Efficacy and Safety of RPC4046 in Adult Subjects With Eosinophilic Esophagitis 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.

The Protocol Committee included the following: Evan S. Dellon, MD, MPH (University of North Carolina School of Medicine, Chapel Hill, NC); Ikuo Hirano, MD (Division of Gastroenterology, Northwestern University Feinberg School of Medicine, Chicago, IL); Alex Straumann, MD (Swiss EoE Clinic, Olten, Switzerland); and Alain M. Schoepfer, MD (Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland).

The Safety Review Committee included the following: Sandeep Gupta, MD (Pediatrics and Internal Medicine, University of Illinois College of Medicine, Peoria, IL); and Paul Frohna, MD, PhD, PharmD, and Michael Grimm, MD (formerly with Receptos, a wholly owned subsidiary of Celgene, Inc, San Diego, CA).

### Inclusion Criteria

As part of the initial phase 2 study, subjects were required to be 18 to 65 years of age with a confirmed diagnosis of EoE. Subjects were required to have 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 15 or more eosinophils per hpf (microscope hpf, 0.3 mm<sup>2</sup>) at any 2 of 3 levels of the esophagus (proximal, mid, distal) when off anti-inflammatory therapy for EoE. Subjects must have previously received an adequate trial of a proton pump inhibitor and been confirmed to not have proton pump inhibitor-responsive EoE. Subjects with a partial response to a proton pump inhibitor who met all other eligibility criteria could be enrolled; prospective subjects who discontinued use of a proton pump inhibitor had to wait at least 4 weeks before their screening endoscopy; if a prospective subject was receiving a proton pump inhibitor at screening, they 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; males and females 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; and all females 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.

Patients who completed the double-blind treatment period of the phase 2 study, who showed 80% or better study drug compliance, and who had no clinically significant adverse events during initial therapy the were eligible to be enrolled in the LTE period.

### *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 end points for this trial (eg, erosive esophagitis grade 2 or higher, Barrett's esophagus, upper gastrointestinal bleed, eosinophilic gastritis or gastroenteritis, active *Helicobacter pylori* infection, 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 the esophagus (eg, high-grade stenosis in which 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 IgE, and so forth) within 5 drug half-lives before screening; were receiving systemic or swallowed topical corticosteroid medication; prospective subjects with EoE treated with a corticosteroid must not have 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, and so forth); liver function impairment or persisting increases of aspartate aminotransferase or alanine aminotransferase greater than 2 times the upper limit of normal, or direct bilirubin level greater than 1.5 times the upper limit of normal; systemic or diarrheal illness after travel or residence in endemic areas of parasitic/helminthic infections, history of clinical schistosomiasis, history of travel to endemic areas within the 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 of less than 40 kg (88.2 pounds) or more 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 IgG-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; or esophageal dilation for symptom relief during the screening period and within 4 weeks before the 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.

**Protocol amendment 1: May 16, 2014.** The following amendments were made to the protocol. The LTE was removed 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 LTE after completion of a then ongoing longer-term toxicology study. The duration of double-blind dosing was extended 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. The time point for efficacy end points was changed from week 12 to week 16 to be consistent with the increased duration of double-blind treatment. A week 2 visit was added to assess ADA and pharmacokinetic data to provide an earlier time point for these assessments. The lower limit of the eligible age range was increased from 12 years to 18 years to address concerns about adolescents potentially receiving placebo and being exposed to more than minimal risk. The lower weight limit was increased to 40 kg in alignment with removal of adolescents from the trial. An exclusion criterion was added 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 therefore would confound efficacy assessment in this trial. The number of biomarkers to be assessed was reduced. The restriction for concurrent medication to treat asthma or allergies during the trial was modified to enable the investigator to contact the Medical Monitor to discuss treatment options if changes to treatments were required, providing more

flexibility for the physician to treat without withdrawal of the subject.

**Protocol amendment 2: October 17, 2014.** The following amendments were made to the protocol. Data from nonclinical toxicology studies were updated 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 subcutaneous injections of 20, 60, or 300 mg/kg RPC4046 or intravenous administration of 300 mg/kg RPC4046 for 26 consecutive weeks (26 total doses) to cynomolgus monkeys was well tolerated at all dose levels. Treatment was extended by an optional 24-week LTE. The esophageal string test was removed because of the limited availability of the test. A requirement was specified for collection of DSD for the last 2 consecutive weeks ( $\pm 3$  days) before day 1. Text was added regarding the day 1 intravenous loading dose + the subcutaneous dose, and subcutaneous doses once weekly for 15 additional weeks to avoid confusion regarding the number of weekly subcutaneous doses to be administered in the double-blind treatment period. Modified inclusion criteria were as follows: criterion 1: clarification that diagnosis of EoE must be confirmed before randomization; criterion 3: clarification that histologic evidence of EoE can come from any 2 levels of the esophagus; criterion 5: requirement for birth control use for 5 months after the 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). Additional modified exclusion criteria were as follows: criterion 10: specification that ongoing infections include active tuberculosis; and criterion 15: no history of cancer within 10 years of screening. The following changes also were made: changed the intravenous stability dose to 8 hours at 2°C to 8°C; clarified the food restriction diet and added instruction regarding environmental therapy; clarified the requirement not to 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 AE collection to 30 days after the last dose or last visit; and added text to clearly define the intention-to-treat and per-protocol populations.

**Protocol amendment 3: June 22, 2015.** The following amendments were made to the protocol: extended the LTE from 24 weeks to 52 weeks, and removed the interim analysis from the protocol.

## Supplementary Methods

### *Weekly Study Dose*

After day 1, dosing with two 1.2-mL subcutaneous injections of study drug continued weekly through week

15. During the LTE period, all subjects were treated with RPC4046 360 mg subcutaneously.

### *Immunogenicity Assessment*

**Double-blind treatment period and long-term extension period.** A validated electrochemiluminescence-based assay was used to measure the ADA response. A preliminary assessment was performed of the presence of neutralizing ADA through comparison of RPC4046 pharmacokinetics in ADA-positive and ADA-negative subjects.

The majority of subjects were ADA-negative at all visits. Two subjects, both in the RPC4046 180-mg group, tested positive for ADA during the study.

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

One subject was ADA-negative at all visits from day 1 through week 8 and was ADA-positive 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 the 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 the study drug (days 25–36); a mild TEAE of gastroenteritis that was unlikely related to the study drug (day 32); and a mild TEAE of nasopharyngitis that was unlikely related to the study drug (days 99–108). After enrollment into the LTE, this subject was ADA-positive at LTE weeks 2, 4, and 12. The subject subsequently was ADA-negative at LTE weeks 24 and 52, and at the LTE week 60 safety follow-up visit. The subject had the following TEAEs, all assessed as unlikely related to the study drug, during the LTE: mild gastroenteritis (LTE days 83–85); mild depression (LTE day 110–ongoing); 2 TEAEs of upper respiratory tract infection, 1 moderate (LTE days 236–270) and 1 mild (days 301–308); and moderate sinusitis (LTE days 253–270).

**Long-term extension period only.** One subject was ADA-negative at all visits during the double-blind treatment period from day 1 (predose) through week 16 and during the LTE at weeks 2, 4, and 12. The subject tested positive for ADA at LTE week 24 and subsequently was ADA-negative at LTE week 52 and at the LTE week 60 safety follow-up visit. The subject had the following TEAEs during the LTE: severe viral gastroenteritis (LTE days 10–13) assessed as possibly related to the study drug; moderate upper respiratory tract infection (LTE days 82–87) assessed as possibly related to the study drug; moderate influenza (LTE days 84–87) assessed as unrelated to the study drug; moderate arthralgia (LTE 147–162) assessed as possibly related to the study drug; 2 TEAEs of mild nausea (LTE days 179 and 366)

assessed as unrelated to the study drug; 2 TEAEs of mild vomiting (LTE days 179 and 366) assessed as unrelated to the study drug; and mild discolored feces (LTE days 189–200) assessed as unrelated to the study drug.

One subject was ADA-negative at all visits during the double-blind treatment period from day 1 (predose) through week 16 and during the LTE at weeks 2 and 4. The subject tested positive for ADA at LTE weeks 12, 24, and 52. The only TEAE reported for this subject during the LTE was a mild event of a headache (LTE day 71) assessed as unrelated to the study drug.

No subjects in the RPC4046 360-mg group were ADA-positive at any time during the trial.

### *Antidrug Antibody Assessments*

Serum samples to assess blood levels of antibodies to RPC4046 were obtained predose: on day 1; at weeks 4, 8 and 12 during double-blind treatment; at week 20 (for subjects who do not continue dosing in the LTE); at LTE weeks 4, 12, 24, and 32 (for subjects participating in the LTE); and at early termination.

If ADAs were detected, they were characterized further as to whether the ADAs were neutralizing or not in nature. Subjects testing positive for neutralizing antibodies were monitored until the antibody levels return to baseline.

### *Eosinophilic Esophagitis Activity Index*

The EEsAI is a paper-based, patient-reported outcome symptom instrument that assesses 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 the 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 end point.

### *Composite Daily Symptom Diary Score*

The DSD was completed daily for 2 weeks before LTE baseline (ie, 2 weeks before the week-16 visit of the double-blind treatment period); 2 weeks before LTE weeks 12, 24, and 52; and 2 weeks before the LTE week-60 safety follow-up visit.

### *Daily Symptom Diary Questions*

An interactive web-based or telephone response system was used by subjects to complete a DSD. Subjects were able to access the diary by telephone and/or by internet.

The following questions were included in the daily symptom diary:

- 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 3 is yes:

- 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 a daily symptom diary 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 a daily symptom diary for the 2 weeks before the safety follow-up visit at week 24 (if applicable).

### *Eosinophilic Esophagitis Endoscopic Reference Score*

The esophageal mucosal endoscopic features of EoE were assessed by each investigator using the EoE Endoscopic Reference Score<sup>1</sup> in 5 classification categories at screening, week 16, or if applicable at end of treatment. 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); and 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*

Esophageal eosinophil counts and other parameters were assessed using the EoEHSS, a validated measure for evaluating eosinophil density, basal zone hyperplasia, eosinophil abscesses, eosinophil surface layering, dilated intercellular spaces, surface epithelial alteration, dyskeratotic epithelial cells, and lamina propria fibrosis.<sup>2</sup>

The esophageal histologic changes characteristic of EoE were assessed by examining the following 8 parameters<sup>2</sup>: eosinophil inflammation was graded using the peak eosinophil count, which was obtained by counting eosinophils in the most densely inflamed hpf; basal zone hyperplasia: more than 15% of the total epithelial thickness; eosinophil abscess: solid mass of intra-epithelial eosinophils; eosinophil surface layering: linear alignment of eosinophils parallel to the epithelial surface; dilated intracellular spaces: spaces around squamous epithelial cells that show intercellular bridges; surface epithelial alteration: surface epithelial cells that show altered tinctorial properties, manifest as dark staining, with or without intraepithelial eosinophils; dyskeratotic epithelial cells: individual cells with deeply eosinophilic cytoplasm and hyperchromatic nuclei; and 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).

## Supplementary Results

### *Steroid-Refractory and Non-Steroid-Refractory Subjects*

**Eosinophil counts.** Forty-one of 86 subjects enrolled in the LTE study were considered steroid-refractory; results in the steroid-refractory subgroup were similar to those in the overall study population. In both steroid-status groups, reductions in the mean esophageal eosinophil count from LTE baseline to LTE weeks

12, 24, and 52 were observed for subjects who had been randomized to placebo during the DB induction portion of the study ([Supplementary Figure 4A and B](#)). At LTE week 52, steroid-refractory subjects in the placebo group showed a mean change in eosinophil counts of -86.4; the RPC4046 180-mg and RPC4046 360-mg groups showed mean changes of -25.5 and -4.0, respectively. The mean esophageal eosinophil counts generally were similar across all 3 randomized groups irrespective of steroid status starting at LTE week 12 and continuing through LTE week 52. The proportion of steroid-refractory subjects with a peak eosinophil count less than 15/hpf decreased from LTE week 12 (28.6% in the placebo, 41.7% in the RPC4046 180 mg, and 50.0% in the RPC4046 360 mg groups) to LTE week 52 (21.4% in the placebo, 33.3% in the RPC4046 180 mg, and 35.7% in the RPC4046 360 mg groups); whereas, the proportion of non-steroid-refractory subjects with a peak eosinophil count less than 15/hpf increased overall from LTE week 12 (33.3% in the placebo, 62.5% in the RPC4046 180 mg, and 38.5% in the RPC4046 360 mg groups) to LTE week 52 (46.7% in the placebo, 43.8% in the RPC4046 180 mg, and 53.8% in the RPC4046 360 mg groups).

**Daily symptom diary composite score and components.** The mean DSD composite scores among non-steroid-refractory subjects were similar across all 3 groups at LTE baseline (placebo, 11.9; RPC4046 180 mg, 16.3; and RPC4046 360 mg, 14.7), and at each visit starting at LTE week 12 through LTE week 52, with the exception of the RPC4046 180-mg dose group at LTE week 24, which was slightly higher. By LTE week 52, all 3 groups showed a decrease in mean DSD composite scores ([Supplementary Figure 4D](#)). The mean DSD composite scores among steroid-refractory subjects for the placebo, RPC4046 180-mg, and RPC4046 360-mg groups were 31.0, 24.3, and 12.6, respectively. Scores for all 3 groups decreased from LTE baseline to LTE week 52 ([Supplementary Figure 4C](#)).

**Eosinophilic esophagitis endoscopic reference total scores.** Among steroid-refractory subjects, the mean EREFS total score over all locations was higher at LTE baseline in the placebo group vs the RPC4046 180-mg and 360-mg groups ([Supplementary Table 3](#)). Decreases in the mean EREFS total score over all locations were observed from LTE baseline to each LTE visit across all 3 treatment groups. By LTE week 52, the mean EREFS total scores over all locations were similar in all 3 groups. Similarly, reductions for steroid-refractory subjects from LTE baseline to similar mean values at LTE week 52 also were noted across all 3 groups for the inflammation composite score and for the exudates score over all locations. For other EREFS scores of remodeling composite score, fixed rings, furrows, edema, and stricture over all locations, decreases from LTE baseline to most post-LTE baseline visits were observed, but the absolute mean values at week 52 varied across DB randomized treatment groups ([Supplementary Table 3](#)).

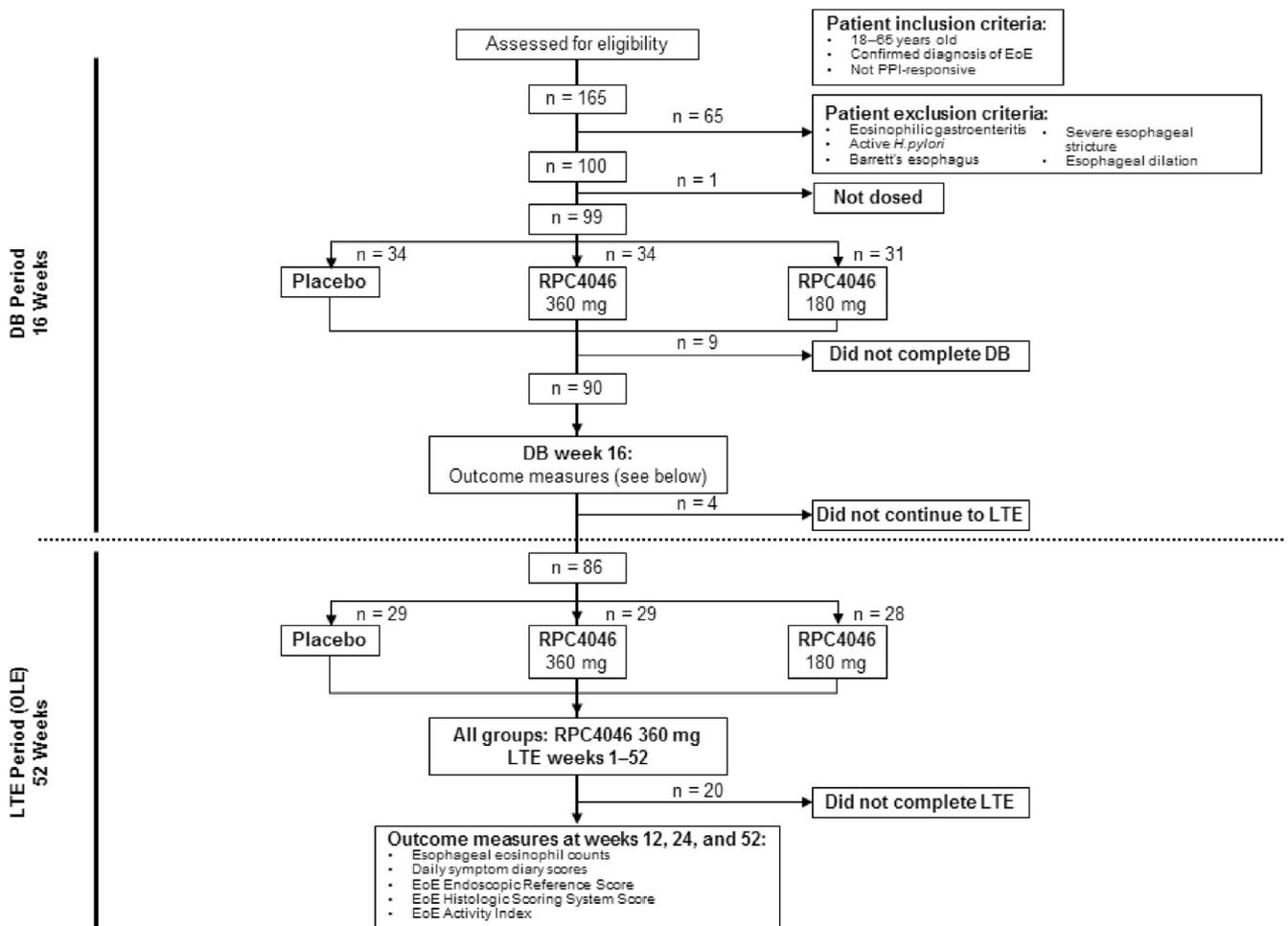
Among non-steroid-refractory subjects, mean decreases from LTE baseline to LTE week 52 in EREFS total score and the majority of the component scores also were observed across all 3 randomized treatment groups. For the total score and component scores of the inflammation composite score, remodeling composite score, fixed rings, exudates, and edema, there were no consistent trends.

**Other efficacy end points.** EEsAI scores were similar between the steroid-refractory and non-steroid-refractory subjects at week 52 LTE, with the exception of the placebo group. Steroid-refractory and non-steroid-

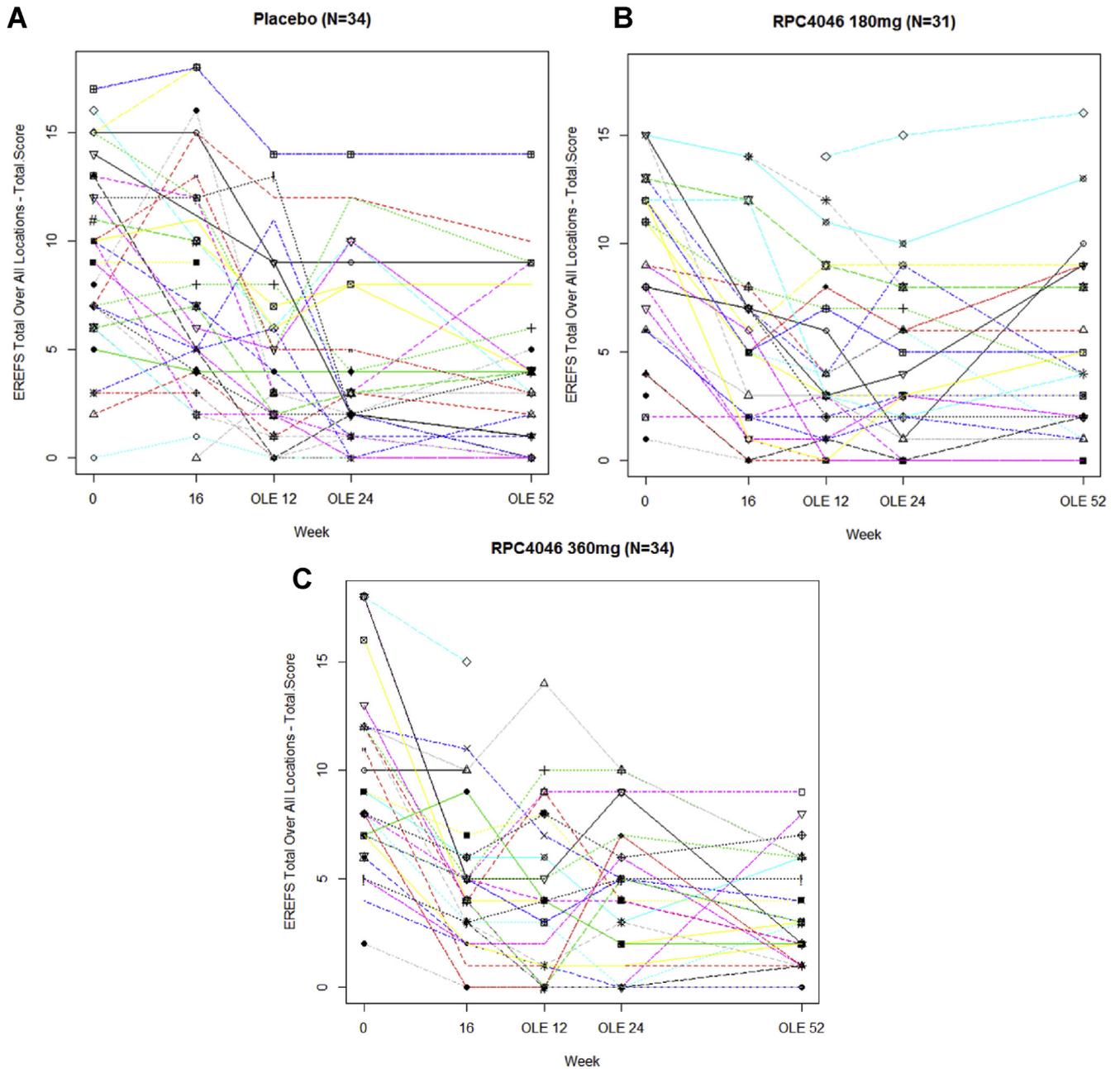
refractory subjects continued to show improvement in EEsAI patient-reported outcome scores during the DB treatment period through week 52 of LTE.

**Supplementary References**

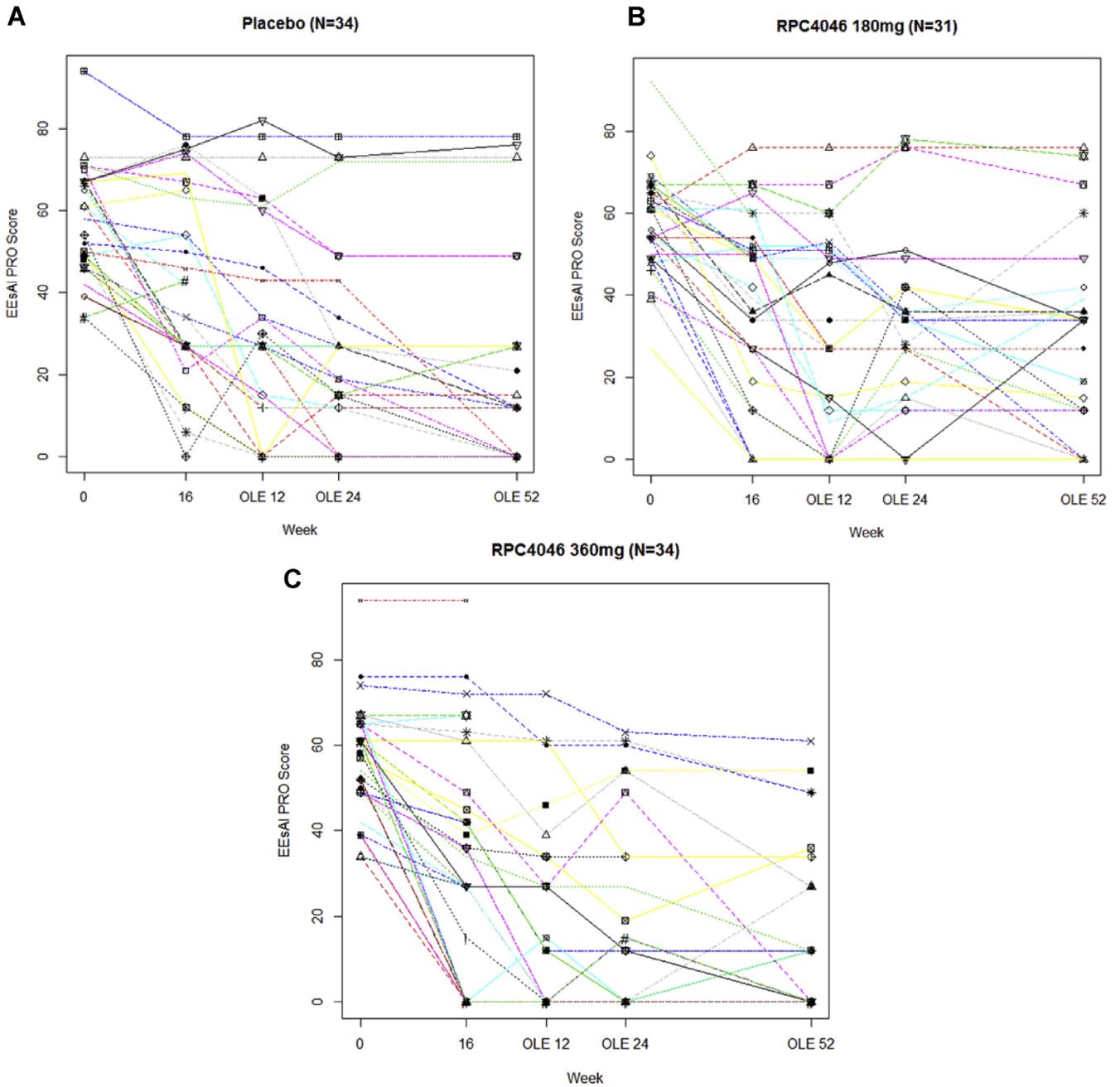
1. Hirano I, Moy N, Heckman MG, et al. Endoscopic assessment of the esophageal features of eosinophilic esophagitis: validation of a novel classification and grading system. *Gut* 2013;62:489–495.
2. Collins MH, Martin LJ, Alexander ES, et al. Newly developed and validated eosinophilic esophagitis histology scoring system and evidence that it outperforms peak eosinophil count for disease diagnosis and monitoring. *Dis Esophagus* 2017;30:1–8.



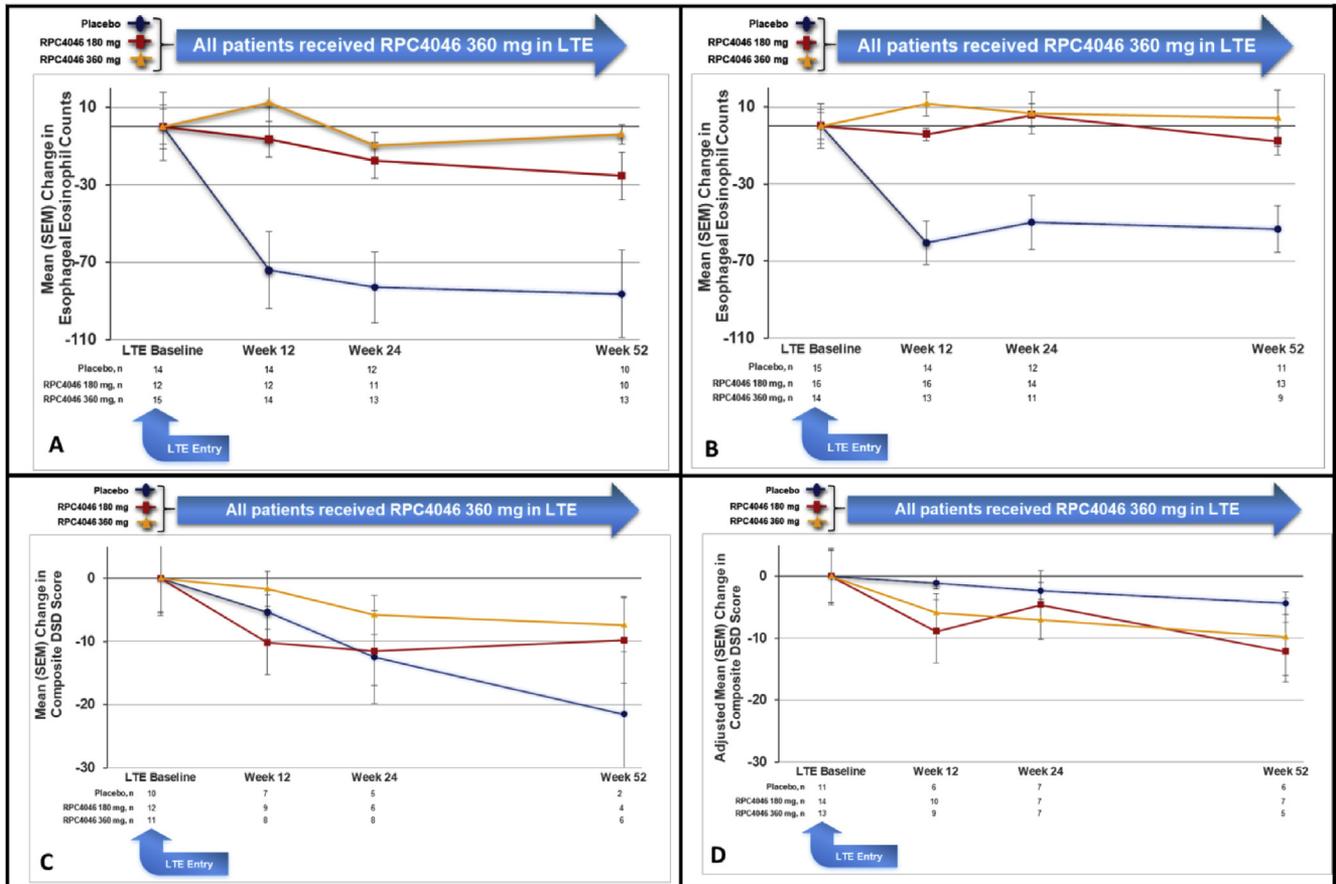
**Supplementary Figure 1.** Patient flow chart. DB, double-blind; EoE, eosinophilic esophagitis; LTE, long-term extension; OLE, open-label extension; PPI, proton pump inhibitor.



**Supplementary Figure 2.** Eosinophilic esophagitis endoscopic reference score (EREFs) total over all locations - total score over time for each subject by treatment group (intention-to-treat population). EREFs total over all locations at double-blind weeks 0 and 16 and long-term extension weeks 12, 24, and 52. Individual data from the (A) placebo group (n = 34), (B) RPC4046 180-mg group (n = 31), and (C) RPC4046 360-mg group (n = 34). OLE, open-label extension.



**Supplementary Figure 3.** Symptom-based eosinophilic esophagitis activity index (EEsAI) over time for each subject by treatment group (intention-to-treat population). EEsAI over all locations at double-blind weeks 0 and 16 and long-term extension weeks 12, 24, and 52. Individual data from the (A) placebo group (n = 34), (B) RPC4046 180-mg group (n = 31), and (C) RPC4046 360-mg group (n = 34). OLE, open-label extension; PRO, patient-reported outcome.



**Supplementary Figure 4.** Mean change (SEM) from long-term extension baseline in esophageal eosinophil counts and composite diary scores by steroid-refractory status at long-term extension (LTE) weeks 12, 24, and 52. (A) Esophageal eosinophil counts in the steroid-refractory group (eosinophils/high-power field [eos/hpf]), (B) Esophageal eosinophil counts in the non-steroid-refractory group (eos/hpf). (C) Composite daily symptom diary (DSD) score in the steroid-refractory group. (D) Composite DSD score in the non-steroid-refractory group (LTE population).

**Supplementary Table 1.** Participants Across Study Sites by Country in the LTE Period in the LTE Population

		Double-Blind Randomized Treatment Group							
		Placebo (n = 29), n (%)		RPC4046 180 mg (n = 28), n (%)		RPC4046 360 mg (n = 29), n (%)		Total (N = 86), n (%)	
Country	Site	Dosed, n (%)	Completed, n (%)	Dosed, n (%)	Completed, n (%)	Dosed, n (%)	Completed, n (%)	Dosed, n (%)	Completed, n (%)
United States	102	4 (13.8)	3 (10.3)	4 (14.3)	3 (10.7)	3 (10.3)	2 (6.9)	11 (12.8)	8 (9.3)
	104	1 (3.4)	1 (3.4)	2 (7.1)	2 (7.1)	4 (13.8)	2 (6.9)	7 (8.1)	5 (5.8)
	106	2 (6.9)	2 (6.9)	3 (10.7)	2 (7.1)	2 (6.9)	2 (6.9)	7 (8.1)	6 (7.0)
	107	4 (13.8)	4 (13.8)	0	0	0	0	4 (4.7)	4 (4.7)
	112	1 (3.4)	0	3 (10.7)	3 (10.7)	0	0	4 (4.7)	3 (3.5)
	115	1 (3.4)	0	1 (3.6)	1 (3.6)	0	0	2 (2.3)	1 (1.2)
	116	0	0	2 (7.1)	2 (7.1)	3 (10.3)	3 (10.3)	5 (5.8)	5 (5.8)
	118	0	0	1 (3.6)	1 (3.6)	1 (3.4)	0	2 (2.3)	1 (1.2)
	121	0	0	0	0	1 (3.4)	1 (3.4)	1 (1.2)	1 (1.2)
	122	1 (3.4)	1 (3.4)	0	0	0	0	1 (1.2)	1 (1.2)
	124	0	0	0	0	1 (3.4)	1 (3.4)	1 (1.2)	1 (1.2)
	125	1 (3.4)	1 (3.4)	0	0	3 (10.3)	3 (10.3)	4 (4.7)	4 (4.7)
	130	1 (3.4)	0	2 (7.1)	2 (7.1)	0	0	3 (3.5)	2 (2.3)
	132	0	0	1 (3.6)	1 (3.6)	0	0	1 (1.2)	1 (1.2)
	133	1 (3.4)	1 (3.4)	0	0	0	0	1 (1.2)	1 (1.2)
	135	1 (3.4)	0	0	0	0	0	1 (1.2)	0
	136	1 (3.4)	1 (3.4)	1 (3.6)	0	1 (3.4)	1 (3.4)	3 (3.5)	2 (2.3)
	139	0	0	0	0	2 (6.9)	1 (3.4)	2 (2.3)	1 (1.2)
	141	0	0	1 (3.6)	1 (3.6)	0	0	1 (1.2)	1 (1.2)
	143	4 (13.8)	3 (10.3)	1 (3.6)	1 (3.6)	1 (3.4)	1 (3.4)	6 (7.0)	5 (5.8)
144	2 (6.9)	1 (3.4)	1 (3.6)	1 (3.6)	4 (13.8)	2 (6.9)	7 (8.1)	4 (4.7)	
145	1 (3.4)	1 (3.4)	1 (3.6)	1 (3.6)	4 (13.8)	2 (6.9)	7 (8.1)	4 (4.7)	
146	0	0	1 (3.6)	0	1 (3.4)	1 (3.4)	2 (2.3)	1 (1.2)	
147	1 (3.4)	1 (3.4)	0	0	0	0	1 (1.2)	1 (1.2)	
148	0	0	0	0	1 (3.4)	0	1 (1.2)	0	
Canada	202	1 (3.4)	0	0	0	0	0	1 (1.2)	0
Switzerland	301	1 (3.4)	1 (3.4)	2 (7.1)	2 (7.1)	0	0	3 (3.5)	3 (3.5)
	302	0	0	0	0	1 (3.4)	1 (3.4)	1 (1.2)	1 (1.2)

NOTE. Dosed refers to the number of subjects receiving the study drug in the LTE period. Completed refers to the number of subjects completing the LTE period. Percentages are used on the number of subjects dosed. LTE, long-term extension.

**Supplementary Table 2.** Change From Baseline in the Blood EOS: Observed Cases in the ITT and LTE Populations

Week 16			
Visit	Placebo (n = 34)	RPC4046 180 mg (n = 31)	RPC4046 360 mg (n = 34)
ITT population			
Baseline			
N	34	31	34
Mean (SD)	.44 (.232)	.51 (.282)	.39 (.191)
Median	.4	.5	.35
Min, Max	.1, 1.0	.1, 1.4	.1, .8
DB week 16			
N	32	28	31
Mean (SD)	.37 (.219)	.45 (.291)	.34 (.158)
Median	.3	.45	.3
Min, Max	0, .9	0, 1.3	.1, .8
Change to DB week 16			
N	32	28	31
Mean (SD)	-.07 (.237)	-.07 (.294)	-.05 (.161)
Median	0	-.1	0
Min, Max	-.8, .3	-.9, .8	-.5, .2
LSMD (RPC4046 - placebo) (SE)		.045 (.051)	-.01 (.050)
95% CI of LSMD		-.06, .15	-.11, .09
P value <sup>a</sup>		.3864	.8341
	Placebo (n = 17)	RPC4046 180 mg (n = 26)	RPC4046 360 mg (n = 22)
ITT atopic subgroup <sup>b</sup>			
Baseline			
N	17	26	22
Mean (SD)	.42 (.222)	.53 (.280)	.38 (.185)
Median	.4	.5	.35
Min, Max	.1, 1.0	.2, 1.4	.1, .8
DB week 16			
N	15	24	21
Mean (SD)	.41 (.222)	.45 (.284)	.32 (.137)
Median	.4	.45	.3
Min, Max	.1, .9	.1, 1.3	.1, .6
Change to DB week 16			
N	15	24	21
Mean (SD)	-.02 (.132)	-.09 (.311)	-.06 (.175)
Median	0	-.15	0
Min, Max	-.2, .3	-.9, .8	-.5, .2
LSMD (RPC4046 - placebo) (SE)		0 (.063)	-.05 (.064)
95% CI of LSMD		-.12, .13	-.18, .08
P value <sup>a</sup>		.9480	.4600

continued on next page

Supplementary Table 2. continued

Week 52			
	Placebo (n = 29)	RPC4046 180 mg (n = 28)	RPC4046 360 mg (n = 29)
LTE population			
Baseline			
N	29	28	29
Mean (SD)	.45 (.223)	.52 (.283)	.38 (.201)
Median	.40	.50	.3
Min, Max	.1, 1.0	.1, 1.4	.1, .8
LTE week 52			
N	21	24	22
Mean (SD)	.36 (.234)	.48 (.446)	.39 (.301)
Median	.3	.4	.4
Min, Max	.1, 1.1	.0, 2.1	.1, 1.4
Change to LTE week 52			
N	21	24	22
Mean (SD)	-.1 (.192)	-.05 (.373)	.03 (.307)
Median	-.1	-.05	0
Min, Max	-.5, .3	-.7, 1.2	-.3, 1.1
	Placebo (n = 14)	RPC4046 180 mg (n = 24)	RPC4046 360 mg (n = 20)
LTE atopic subgroup			
Baseline			
N	14	24	20
Mean (SD)	.44 (.238)	.53 (.278)	.38 (.194)
Median	.4	.5	.35
Min, Max	.1, 1.0	.2, 1.4	.1, .8
LTE week 52			
N	11	20	13
Mean (SD)	.37 (.276)	.42 (.292)	.43 (.357)
Median	.3	.4	.4
Min, Max	.1, 1.1	.0, 1.4	.1, 1.4
Change to LTE week 52			
N	11	20	13
Mean (SD)	-.06 (.157)	-.13 (.268)	.08 (.377)
Median	-.1	-.15	0
Min, Max	11	20	13

DB, double-blind; EOS, eosinophils; ITT, intent-to-treat; LSMD, least-squares mean difference; LTE, long-term extension; Max, maximum; Min, minimum.

<sup>a</sup>P values comparing RPC4046 with placebo are based on an analysis of covariance model with treatment group and actual steroid-refractory status as factors and the baseline blood EOS as a covariate.

<sup>b</sup>The atopic subgroup includes a medical history of atopic dermatitis, allergy, asthma, anaphylaxis, eczema, or nasal polyp.

**Supplementary Table 3.** Inflammatory Component (Edema, Exudate, Furrows) and Stenosis (Fixed Rings, Stricture) Component of EREFS for the Total Population and Steroid-Refractory Group in the LTE Period in the LTE Population

	Total population			Steroid-refractory subjects		
	Placebo (n = 29)	RPC4046 180 mg (n = 28)	RPC4046 360 mg (n = 29)	Placebo (n = 14)	RPC4046 180 mg (n = 12)	RPC4046 360 mg (n = 15)
<b>Total score</b>						
Baseline <sup>a</sup>	n = 29	n = 26	n = 28	n = 14	n = 12	n = 14
Mean (SD)	8.1 (5.1)	5.5 (3.8)	6.5 (4.4)	11.1 (4.7)	6.2 (4.7)	5.9 (4.0)
Week 52	n = 21	n = 24	n = 22	n = 10	n = 10	n = 13
Mean (SD)	3.0 (3.1)	4.6 (4.4)	3.0 (2.4)	4.1 (2.9)	4.6 (4.2)	3.1 (2.6)
<b>Edema</b>						
Baseline <sup>a</sup>	n = 29	n = 27	n = 28	n = 14	n = 12	n = 14
Mean (SD)	1.7 (1.4)	1.1 (1.3)	1.6 (1.3)	2.6 (0.9)	1.1 (1.4)	1.4 (1.2)
Week 52	n = 21	n = 24	n = 22	n = 10	n = 10	n = 13
Mean (SD)	0.9 (1.2)	0.8 (1.2)	0.8 (1.1)	1.5 (1.4)	0.4 (1.0)	0.8 (1.2)
<b>Exudates</b>						
Baseline <sup>a</sup>	n = 29	n = 26	n = 28	n = 14	n = 12	n = 14
Mean (SD)	1.3 (1.6)	0.7 (1.3)	1.0 (1.7)	2.0 (1.8)	0.7 (1.1)	1.1 (1.6)
Week 52	n = 21	n = 24	n = 22	n = 10	n = 10	n = 13
Mean (SD)	0.3 (0.9)	0.7 (1.3)	0.5 (0.9)	0.5 (1.1)	0.3 (1.0)	0.4 (0.9)
<b>Furrows</b>						
Baseline <sup>a</sup>	n = 29	n = 26	n = 28	n = 14	n = 12	n = 14
Mean (SD)	1.9 (1.1)	1.0 (1.2)	1.3 (1.2)	1.0 (1.3)	0.8 (0.1)	1.2 (1.3)
Week 52	n = 21	n = 24	n = 22	n = 10	n = 10	n = 13
Mean (SD)	0.4 (1.0)	0.6 (1.2)	0.8 (1.0)	0.2 (0.6)	0.8 (1.3)	0.8 (1.0)
<b>Fixed rings</b>						
Baseline <sup>a</sup>	n = 29	n = 27	n = 28	n = 14	n = 12	n = 14
Mean (SD)	2.6 (2.1)	2.4 (1.7)	2.3 (1.9)	1.5 (0.9)	2.3 (1.6)	1.1 (1.0)
Week 52	n = 21	n = 24	n = 22	n = 10	n = 10	n = 13
Mean (SD)	1.2 (1.5)	2.0 (1.7)	1.0 (1.0)	1.5 (0.9)	2.3 (1.6)	1.1 (1.0)
<b>Stricture</b>						
Baseline <sup>a</sup>	n = 29	n = 26	n = 28	n = 14	n = 12	n = 14
Mean (SD)	0.6 (0.9)	0.4 (0.9)	0.3 (0.5)	0.9 (1.1)	0.7 (1.2)	0.3 (0.5)
Week 52	n = 21	n = 24	n = 22	n = 10	n = 10	n = 13
Mean (SD)	0.2 (0.4)	0.5 (0.9)	0.0 (0.2)	0.4 (0.5)	0.8 (1.2)	0.1 (0.3)

EREFs, eosinophilic esophagitis endoscopic reference score; LTE, long-term extension.

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

**Supplementary Table 4.** Remission in ITT Population: EEsAI PRO Score of 20 or Less

Visit	Placebo (n = 34), n/N (%)	180 mg (n = 31), n/N (%); <i>P</i> value	360 mg, (n = 34), n/N (%); <i>P</i> value
ITT population			
Baseline	0/34 (0)	0/30 (0)	0/34 (0)
Week 16	4/34 (11.8)	7/31 (22.6); .2466	10/34 (29.4); .0767
LTE week 12	10/29 (34.5)	12/28 (42.9); .5038	15/27 (55.6); .1240
LTE week 24	14/29 (48.3)	10/28 (35.7); .3299	18/27 (66.7); .1651
LTE week 52	16/29 (55.2)	13/28 (46.4); .4921	18/27 (66.7); .3755
ITT atopic subgroup			
Baseline	0/17 (0)	0/25 (0)	0/22 (0)
Week 16	2/17 (11.8)	7/26 (26.9); .2102	6/22 (27.3); .2850
LTE week 12	6/14 (42.9)	11/25 (44.0); .6931	10/18 (55.6); .4386
LTE week 24	7/14 (50.0)	9/24 (37.5); .5419	11/18 (61.1); .5867
LTE week 52	7/14 (50.0)	12/24 (50.0); .9436	11/18 (61.1); .4946

EEsAI, Eosinophilic Esophagitis Activity Index; ITT, intent to treat; LTE, long-term extension; PRO, patient-reported outcome.

**Supplementary Table 5.** Mean Daily Symptom Diary Composite Score by Visit in the Open-Label Extension: Observed Cases in the LTE Population

Visit	Placebo (n = 29)		RPC4046 180 mg (n = 28)		RPC4046 360 mg (n = 29)		Total (N = 86)	
	Actual value	Change from baseline	Actual value	Change from baseline	Actual value	Change from baseline	Actual value	Change from baseline
LTE baseline, <sup>a</sup> n, mean (SD)	21, 21.00 (18.554)		26, 20.01 (17.626)		24, 13.76 (16.767)		71, 18.19 (17.664)	
LTE week 12, n, mean (SD)	15, 14.94 (17.171)	13, -3.35 (5.750)	19, 9.60 (14.897)	19, -9.50 (15.286)	17, 9.03 (14.031)	17, -3.90 (8.596)	51, 10.98 (15.236)	49, -5.93 (11.349)
LTE week 24, n, mean (SD)	14, 9.25 (14.137)	12, -6.54 (11.511)	13, 9.91 (16.169)	13, -7.82 (13.911)	15, 7.73 (12.751)	15, -6.35 (8.351)	42, 8.91 (14.010)	40, -6.89 (11.063)
LTE week 52, n, mean (SD)	9, 7.11 (10.952)	8, -8.61 (10.732)	12, 6.67 (11.785)	11, -11.31 (12.481)	11, 4.35 (6.936)	11, -8.46 (11.569)	32, 5.99 (9.862)	30, -9.54 (11.382)
LTE week 60, n, mean (SD)	6, 20.72 (13.924)	6, 2.76 (20.348)	5, 7.38 (16.506)	5, -10.68 (21.484)	10, 5.64 (7.463)	10, -6.95 (12.303)	21, 10.36 (13.175)	21, -5.06 (17.086)

LTE, long-term extension.

<sup>a</sup>Baseline was defined as the composite diary score in the last 14 days before double-blind week 16.

**Supplementary Table 6.** Histologic Response Responder Analysis: Observed Cases in ITT and LTE Populations

	Placebo	RPC4046 180 mg	RPC4046 360 mg	Total RPC4046	Total
Atopic subgroup					
Histologic response at week 16 (ITT population)	0/16	12/24 (50.0)	9/20 (45.0)	21/44 (47.7)	21/60 (35.0)
Histologic response at LTE week 52 (LTE population)	7/11 (63.6)	14/19 (73.7)	5/13 (38.5)	19/32 (59.4)	26/43 (60.5)
All subjects					
Histologic response at week 16 (ITT population)	0/29	14/28 (50.0)	15/29 (51.7)	29/57 (50.9)	29/86 (33.7)
Histologic response at LTE week 52 (LTE population)	12/21 (57.1)	17/23 (73.9)	13/22 (59.1)	30/45 (66.7)	42/66 (63.6)

ITT, intent-to-treat; LTE, long-term extension.

**Supplementary Table 7.** EREFS Total Over All Locations in the ITT Population

Visit	Placebo (n = 17, DB period; = 14, LTE period)		RPC4046 180 mg (n = 26, DB period; = 24, LTE period)		RPC4046 360 mg (n = 22, DB period; = 20, LTE period)	
	Actual value	Change from baseline	Actual value	Change from baseline	Actual value	Change from baseline
ITT population						
Baseline, n, mean (SD)	32, 9.13 (4.301)		27, 8.96 (4.345)		31, 9.39 (4.287)	
Week 16, n, mean (SD)	32, 7.94 (5.136)	30, -0.9 (3.863)	27, 5.30 (4.168)	24, -4.17 (3.306)	30, 4.80 (3.388)	27, -4.81 (4.086)
LTE week 12, n, mean (SD)	29, 4.93 (4.053)	27, -4.11 (4.492)	28, 4.29 (3.943)	24, -5.71 (3.495)	27, 4.04 (3.777)	24, -5.13 (4.730)
LTE week 24, n, mean (SD)	29, 4.28 (4.157)	27, -4.85 (3.949)	28, 4.14 (3.808)	24, -5.75 (2.938)	27, 4.00 (3.258)	24, -5.38 (4.604)
LTE week 52, n, mean (SD)	29, 3.66 (3.754)	27, -5.37 (4.208)	28, 4.57 (4.246)	24, -5.21 (3.134)	27, 3.26 (2.551)	24, -6.17 (4.584)
ITT atopic subgroup						
Baseline, n, mean (SD)	16, 9.75 (4.313)		24, 9.63 (4.052)		21, 8.67 (3.706)	
Week 16, n, mean (SD)	15, 10.13 (5.579)	14, 0.5 (4.274)	24, 5.71 (4.175)	22, -4.23 (3.366)	21, 4.86 (3.623)	20, -3.9 (3.210)
LTE week 12, n, mean (SD)	14, 6.64 (3.973)	13, -3.23 (4.475)	24, 4.04 (3.495)	22, -5.91 (3.504)	18, 4.44 (4.232)	17, -3.76 (4.191)
LTE week 24, n, mean (SD)	14, 5.43 (4.669)	13, -4.62 (3.948)	24, 3.83 (3.293)	22, -6.05 (2.853)	18, 4.06 (3.455)	17, -4.47 (4.170)
LTE week 52, n, mean (SD)	14, 4.5 (4.274)	13, -5.31 (4.644)	24, 4.21 (3.647)	22, -5.41 (3.142)	18, 3.67 (2.808)	17, -4.76 (3.456)

DB, double-blind; EREFS, eosinophilic esophagitis endoscopic reference score; ITT, intent-to-treat; LTE, long-term extension.

**Supplementary Table 8.** Treatment-Emergent Serious Adverse Events by Preferred Term for the LTE Period in the LTE Population

Preferred term	RPC4046			Total (N = 86)
	Placebo (n = 29)	180 mg (n = 28)	360 mg (n = 29)	
Total serious adverse events, <sup>a</sup> n (%)				
Patients with a serious adverse event	0	2 (7.1)	4 (13.8)	6 (7.0)
Acute cholecystitis	0	1	0	1
Spontaneous abortion	0	0	1	1
Asthma	0	1	0	1
Diverticulitis	0	0	1	1
Schizophrenia <sup>b</sup>	0	0	1	1
Femur fracture	0	0	1	1

NOTE. Data shown are number or number (%).

LTE, long-term extension.

<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 an existing hospitalization, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect.

<sup>b</sup>This treatment-emergent adverse event led to discontinuation of the study drug and withdrawal from the study.

**Supplementary Table 9.** Injection Site Treatment-Emergent Adverse Events in LTE in the LTE Population

	RPC4046			
	Placebo (n = 29)	180 mg (n = 28)	360 mg (n = 29)	Total (N = 86)
Number of subjects experiencing $\geq 1$ TEAE	3 (10.3)	6 (21.4)	7 (24.1)	16 (18.6)
Injection site erythema	1 (3.4)	1 (3.6)	2 (6.9)	4 (4.7)
Injection site hematoma	1 (3.4)	1 (3.6)	2 (6.9)	4 (4.7)

NOTE. Data are shown as number (%).

LTE, long-term extension; TEAE, treatment-emergent adverse event.