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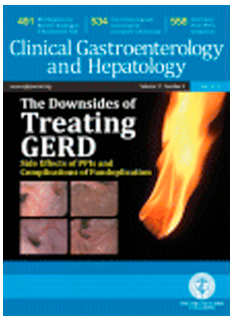

Long-term Efficacy and Tolerability of RPC4046 in an Open-Label Extension Trial of Patients With Eosinophilic Esophagitis

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SHORT TITLE

Anti-IL-13 RPC4046 EoE Trial LTE

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ABBREVIATIONS

IL, interleukin; EoE, eosinophilic esophagitis; AE, adverse event; EREFS, Eosinophilic Esophagitis Endoscopic Reference Score; EoEHSS, Eosinophilic Esophagitis Histologic Scoring System Score; EEsAI, Symptom-based Eosinophilic Esophagitis Activity Index; LTE, long-term extension; SD, standard deviation; CI, confidence interval; EAIR, exposure-adjusted incidence rate; PYE, patient-years of exposure; DB, double-blind; TEAE, treatment-emergent adverse event; eos/hpf, eosinophils per high power field; DSD, daily symptom diary; SAE, serious adverse event; QW, once per week; ADA, anti-drug antibody

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of RPC4046 in adult subjects with eosinophilic esophagitis (HEROES LTE) is provided in the Supplementary Materials.

Author Disclosures (Financial, Conflicts of Interests)

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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, Allkos, Celgene Corporation, GSK, Meritage, Miraca, Nutricia, Regeneron, and Shire, and has received educational grants from Allakos, Banner and Holoclara.

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Cristian Rodriguez, Neil Minton, and Steven Y. Hua participated in the data analysis, data interpretation, and editing of the manuscript.

All authors had full access to the data and approved the final manuscript for submission.

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Data Sharing Statement

The data that support the findings of this study are not available in an online or public repository. Data are, however, 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, healthcare 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/

Abstract:

Background & Aims: The short-term efficacy of RPC4046, a monoclonal antibody against interleukin-13, has been demonstrated 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/weekly) vs placebo and then completed a 52-week LTE, receiving open-label RPC4046 360 mg/weekly. 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 of 20 or less) increased from 14% at LTE entry to 67% at LTE week 52 in placebo–RPC4046 patients and from 30% to 54% in RPC4046 (either dose)–RPC4046 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%).

Conclusion: One year 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.

KEYWORDS: EREFS, EoEHSS, EEsAI, inflammation

TRIAL REGISTRATION NUMBERS

NCT02098473

Clinical trial registry website:

https://clinicaltrials.gov/ct2/show/NCT02098473?term=RPC4046&rank=1

WHAT YOU NEED TO KNOW

Background: The safety and efficacy of RPC4046 were demonstrated 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 more of RPC4046 treatment of patients with symptomatic EoE support confirmatory studies.

INTRODUCTION

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.[1, 2] Complications of EoE, including strictures and food impaction, are mostly related to esophageal remodeling and fibrostenosis and associated with longer duration of untreated disease.[3, 4] Although a topical steroid in orodispersible tablet form[5] 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,[6-12] but their use is limited by side effects, including candida esophagitis, oral candidiasis, and atropy of the esophageal mucosa, and long-term safety data are limited.[13] Moreover, evidence suggests prolonged topical corticosteroid use may only be partially effective in maintaining disease remission[14-19] and associated with resistance.[20]

Interleukin-13 (IL-13), a pleotropic cytokine involved in Th2 type inflammation, plays an important role in the pathogenesis of EoE.[21] IL-13 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[22] and to modulate cellular and molecular pathways involved in eosinophil recruitment,[23] esophageal barrier function,[24] and tissue remodeling and fibrosis.[25] Simulated altered expression/blockade of IL-13 in animal models produces fluctuations in EoE disease status and esophageal function.[25-28] Given the prominent role of IL-13 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 IL-13 and inhibits binding to both IL-13 receptor subtypes—IL-13Rα1 and IL-13Rα2.[29] The safety and efficacy of RPC4046 versus placebo were demonstrated in the induction period of a Phase 2, 16-week, randomized, controlled study in adults with symptomatic EoE (RPC02-201; ClinicalTrials.gov Study ID: NCT02098473).[30] Subjects completing the induction period then had the option to enroll into 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) following 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 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[30] 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 (QW); 90 subjects completed the DB induction portion (through Week 16). Subjects entering the LTE period were required to have ≥80% 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 study design, the dose-response and efficacy profile of RPC4046 were not known.

Prior treatment with corticosteroids for EoE was recorded at 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 [eos/hpf; hpf size=0.3 mm^2] calculated from the 5 most inflamed hpf from among all esophageal biopsies [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 Activity Index (EEsAI) score.[31-34] 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 Supplementary Materials).

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. LTE baseline was defined as the last observed value scheduled, before the first dose date during the LTE. Continuous data were summarized using mean, standard deviation (SD) or standard error of the mean, 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 (EAIR/100 PYE). 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.

RESULTS

Disposition

Among the 90 subjects who completed the DB treatment period, 86 were enrolled in the LTE (placebo, n=29; RPC4046 180 mg, n=28; RPC4046 360 mg, n=29; **Supplementary Figure 1**). Twenty of the 86 subjects (23%) did not complete the full 52 weeks 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 LTE included withdrawal of consent (n=7), AE (n=6), non-compliance (n=3), other (n=2), investigator decision (n=1), and pregnancy (n=1).

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

Clinical Efficacy

At LTE entry, the mean esophageal esoinophil 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 three-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 mean absolute blood eosinophil levels was observed at LTE Week 52 (**Supplementary Table 2**). The proportion of responders (peak esophageal eosinophil count <15hpf) 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 versus RPC4046 (mean change from LTE baseline to Week 52 for placebo: -5.0; RPC4046 180 mg: -1.3; 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 two-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; RPC4046 180 mg: -2.9; RPC4046 360 mg: 2.1; **Figure 3D**); mean absolute EoEHSS Grade scores were similar across the treatment 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 two-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; RPC4046 180 mg: -1.9; RPC4046 360 mg: 3.5; **Figure 3E**), and mean absolute values were generally similar to those in both RPC4046 groups (20.4, 21.4, and 22.2, respectively).

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: -21.1, -10.6, and -14.6, respectively). 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: -8.61, -11.31, and -8.46, respectively) (**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 (69.0%) of the subjects who had a histological response at DB Week 16 with active treatment (RPC4046 180 mg or 360 mg) maintained it at LTE Week 52 (20/29); 10.3% (3/29) lost prior response. Among subjects entering LTE who were not histological 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 histological response with RPC4046 360 mg at LTE Week 52 (**Table 2**; **Figure 2C, 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 Figures 4A, B**), DSD composite scores and components (**Supplementary Figures 4C, D**), EREFS total score (**Supplementary Table 3**), or EEsAI scores (see Supplementary Materials 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 histological response (**Supplementary Table 6**), endoscopic (EREFS; **Supplementary Table 7**) or symptoms scores (EEsAI remission score ≤20; **Supplementary Table 4**) were observed in atopic subjects versus 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 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 TEAE; 6 subjects (7%) reported 1 or more SAE (**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 (≥10%) were 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 EAIR/100 PYE] 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**). Elevated blood eosinophil levels (≥1000 cells/µL) were observed in 11 subjects during LTE, including baseline, that were mostly transitory or observed at single time points; none were >2100 cells/µL. No TEAEs were attributed to increases in blood eosinophil counts.

The incidence of immunogenicity was low; only 4 subjects tested positive for anti-drug 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 (pre-dose) 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 provided in Supplementary Materials). 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.[35] Several biologic monoclonal antibodies have been evaluated,[36] but long-term data are limited.[37] In the DB randomized, placebo-controlled portion of this Phase 2 trial, the novel anti-IL-13 monoclonal antibody RPC4046 demonstrated efficacy as a targeted therapeutic option in EoE patients.[30] 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 demonstrated by continued reductions in 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 study drug (cholecystitis and spontaneous abortion), which resolved by study end.

The current open-label LTE portion of this Phase 2 study is one of the longest 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% (20/86) of subjects were not able to complete the full 52 weeks 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[38] remains an area for further exploration.

The current study demonstrated 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.

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 21-2.
2. Furuta GT, Katzka DA. Eosinophilic Esophagitis. N. Engl. J. Med. 2015;373:1640-8.
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;145:1230-6.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;79:577-85.e4.
5. Lucendo AJ, Miehlke 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;6:165-73.
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;139:418-29.

8. Straumann A, Conus S, Degen L, et al. Budesonide is effective in adolescent and adult patients with active eosinophilic esophagitis. Gastroenterology 2010;139:1526-37, 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;108:679-92; 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;65:390-9.

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;131:1381-91.

13. von Arnim U, Malfertheiner P. Eosinophilic esophagitis--treatment of eosinophilic esophagitis with drugs: corticosteroids. Dig Dis 2014;32:126-9.

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;9:400-9.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;13:452-8.

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;147:324-33.e5.

21. Wechsler JB, Bryce PJ. Allergic mechanisms in eosinophilic esophagitis. Gastroenterol Clin North Am 2014;43:281-96.

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;120:1292-300.

23. Brightling CE, Saha S, Hollins F. Interleukin-13: prospects for new treatments. Clin. Exp. Allergy 2010;40:42-9.

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;7:718-29.

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;185:660-9.

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;135:500-7.

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-Dayan 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;62:489-95.

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;147:1255-66.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.

TABLES

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[a]				
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[a]				
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

EoE, eosinophilic esophagitis; LTE, long-term extension, SD, standard deviation
[a]Baseline was defined as the last observed score prior to the first dose of study drug during the LTE.

Table 2. Peak EOS Count-Responder Analysis–Observed Case (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[a]	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[a]	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[b]	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[b]	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.
[a]Denominator is the number of subjects with peak EOS <15 at DB Week 16.
[b]Denominator is the number of subjects with peak EOS ≥15 at DB Week 16.

Table 3. Summary of Safety Findings by Study Group During the LTE Period (LTE Population)

	Randomized Treatment Assignment at DB Baseline			
	Placebo (n=29)	RPC4046 180 mg (n=28)	RPC4046 360 mg (n=29)	Total (n=86)
Subject with ≥ 1 TEAE, n (%)	21 (72.4)	26 (92.9)	24 (82.8)	71 (82.6)
Subject with ≥ 1 Possible, Probable, or Related TEAE[a], n (%)	8 (27.6)	13 (46.4)	14 (48.3)	35 (40.7)
Subject with TEAE by Maximum Severity[b], 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 ≥ 1 Serious TEAE[c], n (%)	0	2 (7.1)	4 (13.8)	6 (7.0)
Subject with TEAE Leading to Study Drug Discontinuation[d], n (%)	3 (10.3)	1 (3.6)	2 (6.9)	6 (7.0)
Subject with TEAE Leading to Withdrawal from Study[d], n (%)	0	0	1 (3.4)	1 (1.2)
Most Frequent TEAE (≥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]
Nasophyringitis	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 haematoma	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.

[a]Subjects reporting >1 TEAE were counted only once using the closest relationship to study drug.
[b]Subjects reporting >1 TEAE were counted only once using the highest severity.

[c]Serious AEs 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).
[d]Due to how data were captured on the disposition eCRF, only 1 subject was reported to have TEAEs leading to withdrawal from the study. However, the 6 subjects who discontinued study drug due to TEAEs also withdrew from the study.

FIGURES

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 include: (A) the mean esophageal eosinophil count (eos/hpf); (B) proportion of subjects achieving peak esophageal eosinophil count <15 eos/hpf; (C) mean total eosinophilic esophagitis endoscopic reference score (EREFS) (endoscopic findings analyzed according to modified scoring system described by Hirano 2013); and (D) proportion of subjects achieving symptomatic remission as determined by an Eosinophilic Esophagitis Activity Index (EEsAI) score ≤20 (LTE population).

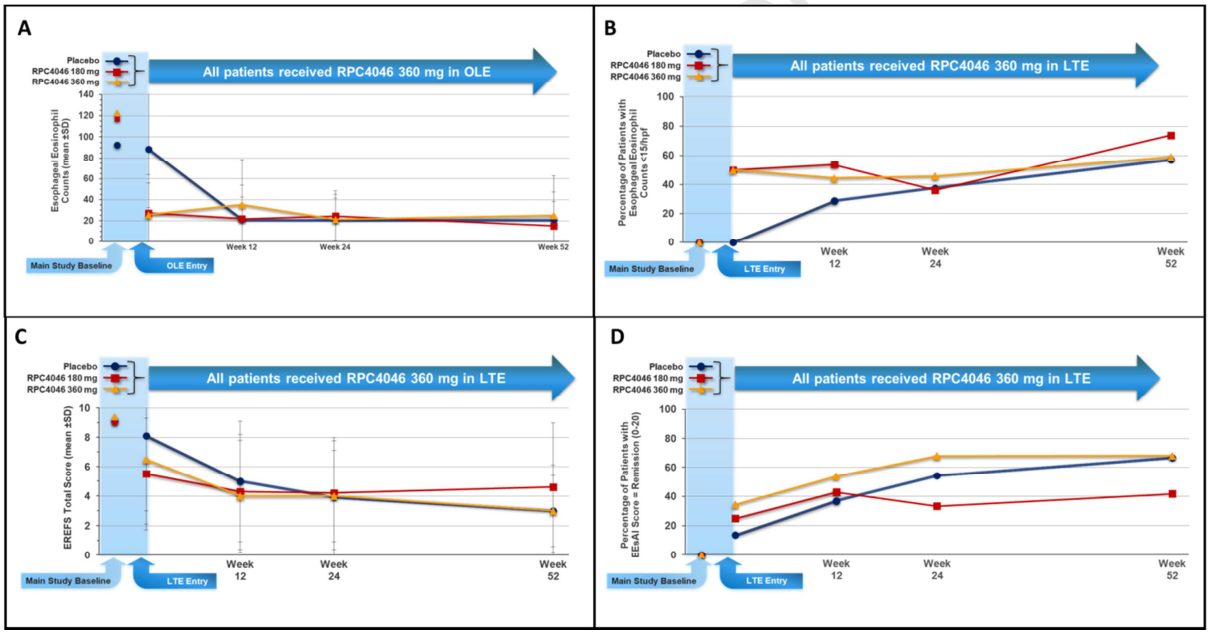


Figure 2. Peak EOS over time (baseline DB Week 16, LTE Week 12, 24, and 52) by treatment group. (A) Average of individuals within each treatment group: placebo, RPC4046 180 mg, and RPC4046 360 mg; (B) Individual data from placebo group; (C) Individual data from RPC4046 180 mg group; (D) Individual data from RPC4046 360 mg group (LTE population).

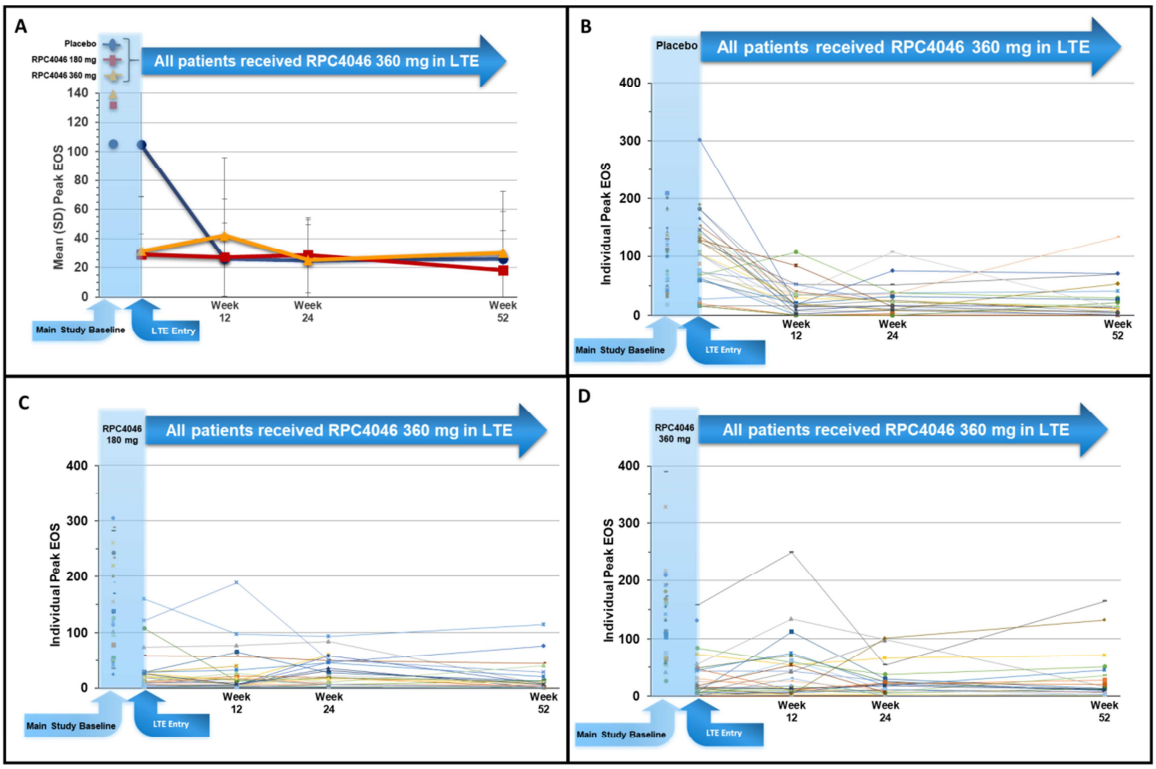
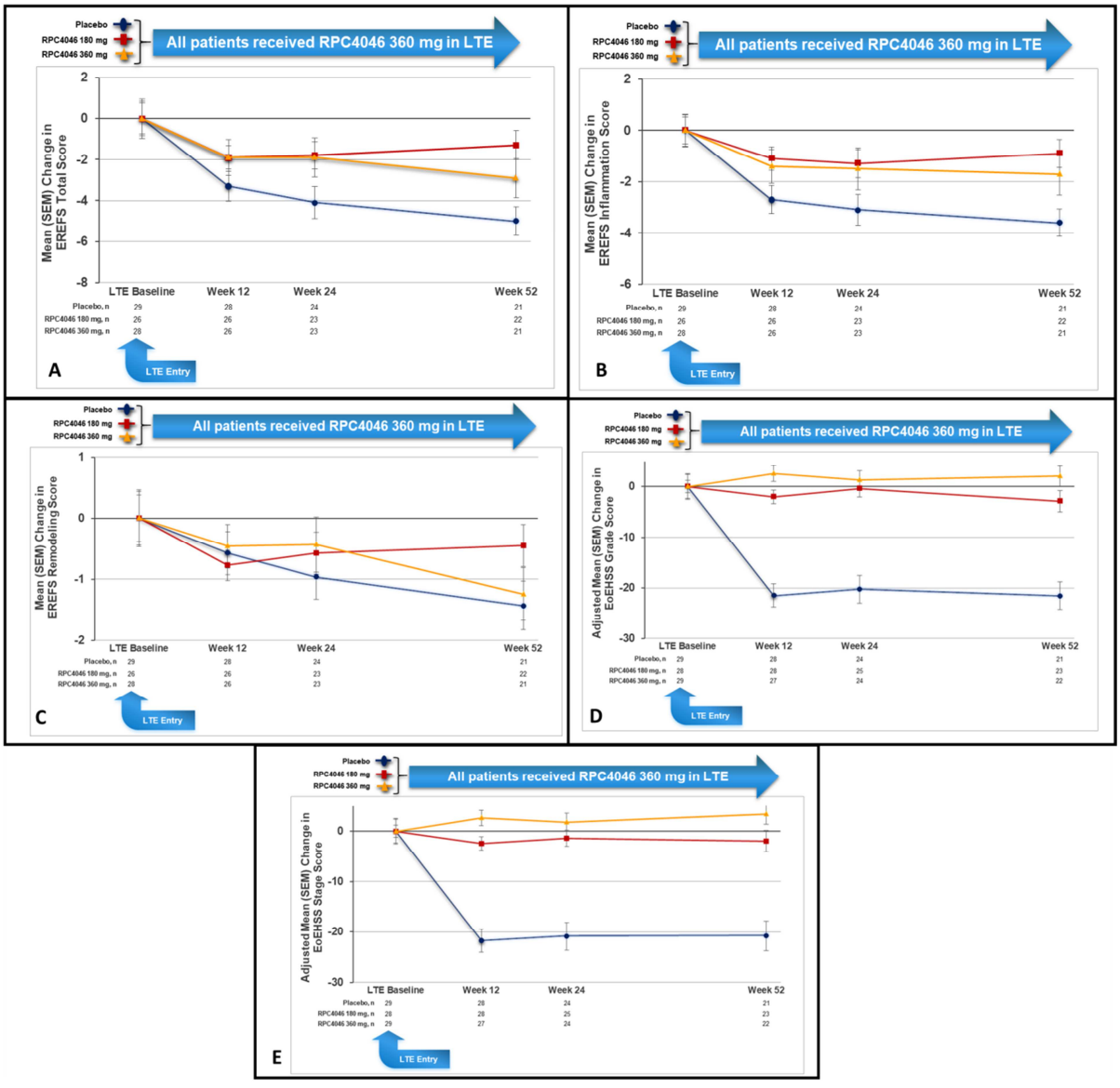


Figure 3. Mean (SEM) changes from LTE baseline to LTE Weeks 12, 24, and 52 for EREFS (total, inflammation, and remodeling), and EoEHSS grade and stage scores: (A) EREFS total score; (B) EREFS inflammation composite score; (C) EREFS remodeling composite score; (D) EoEHSS grade score; (E) EoEHSS stage score (LTE population).



Supplementary Material

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

Supplement to: Dellon ES, Collins MH, Rothenberg ME, et al. Long-term Efficacy and Tolerability of RPC4046 in an Open-Label Extension Trial of Patients With Eosinophilic Esophagitis

TABLE OF CONTENTS

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*Note: The 40 listed sites were initiated for participation in this study; of these sites, 30 enrolled at least one 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. Editorial support was provided by Celgene. Confidentiality agreements were in place between Celgene and all authors.

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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 eosinophils per high-power field (eos/hpf; microscope hpf = 0.3 mm^2) 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 (PPI) and been confirmed to not have PPI-responsive EoE. 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, they must have been receiving a stable dose for at least 4 weeks prior to the screening endoscopy and agreed to continue on a 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; all females of childbearing potential must have had a negative serum pregnancy test at screening and a negative urine (or serum) pregnancy test prior to dosing on Day 1.

Patients who completed the Double Blind Treatment Period of the Phase 2 study, demonstrated ≥80% study drug compliance, and had no clinically significant adverse events during initial therapy were eligible to be enrolled into 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 endpoints for this trial (e.g., erosive esophagitis Grade 2 or above, 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 esophagus (e.g., high-grade stenosis where an 8-10 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 (e.g., methotrexate, cyclosporine, interferon alpha, tumor necrosis factor alpha inhibitors, antibodies to IgE, etc) within 5 drug half-lives prior to 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 (e.g., 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, etc); liver function impairment or persisting elevations of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >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 (e.g., hepatitis B or C, human immunodeficiency virus [HIV], 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 prior to 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 non metastatic 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 prior to baseline assessment of dysphagia or anticipated to be performed during the trial.

Protocol Amendments

The original protocol (dated 13 March 2014) was amended 3 times. The first amendment (dated 16 May 2014) was implemented prior to enrolment of the first patient in the study (03 September 2014). Summaries of the major changes included in each amendment are provided below.

Protocol Amendment 1 (dated 16 May 2014):

- Removed the LTE 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

- 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 ADA and PK 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 prior to 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 17 October 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 LTE

- Removed the Esophageal String Test due to limited availability of the test

- Specified the requirement for collection of DSD for the last 2 consecutive weeks (± 3 days) prior to 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 prior to 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 AE collection to 30 days after last dose or last visit
- Added text to clearly define the ITT and PP populations

Protocol Amendment 3 (dated 22 June 2015):

- Extended the LTE from 24 weeks to 52 weeks
- Removed the interim analysis from the protocol

Methods

Weekly Study Dose

After Day 1, dosing with two 1.2 mL SC injections of study drug continued weekly through Week 15. During the LTE period, all subjects were treated with RPC4046 360mg SC.

Immunogenicity Assessment

Double-Blind Treatment Period and LTE Period

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

The majority of 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 adverse event (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, one mild and unrelated (Days 3-8) and one 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). After enrollment into the LTE, this subject was ADA (+) at LTE Weeks 2, 4, and 12. The subject was subsequently ADA (-) at LTE Weeks 24, 52, and at the LTE Week 60 Safety Follow-up visit. The subject had the following TEAEs, all assessed as unlikely related to study drug, during the LTE; mild gastroenteritis (LTE Days 83-85); mild depression (LTE Day 110 – ongoing); 2 TEAEs of upper respiratory tract infection, one moderate (LTE Days 236-270) and one mild (Days 301-308); and moderate sinusitis (LTE Days 253-270).

LTE Period Only

One subject was ADA (-) at all visits during the Double-Blind Treatment Period from Day 1 (pre-dose) through Week 16 and during the LTE at Weeks 2, 4, and 12. The subject tested positive for ADA at LTE Week 24 and was subsequently ADA (-) at LTE Week 52 and at the LTE Week 60 Safety Follow-up Visit. The subject had the following TEAEs during the LTE: severe gastroenteritis viral (LTE Days 10-13) assessed as possibly related to study drug; moderate upper respiratory tract infection (LTE Days 82-87) assessed as possibly related to study drug; moderate influenza (LTE Days 84-87) assessed as unrelated to study drug; moderate arthralgia (LTE 147-162) assessed as possibly related to study drug; 2 TEAEs of mild nausea (LTE Days 179 and 366) assessed as unrelated to study drug; 2 TEAEs of mild vomiting (LTE Days 179 and 366) assessed as unrelated to study drug; and mild feces discolored (LTE Days 189-200) assessed as unrelated to study drug.

One subject was ADA (-) at all visits during the Double-Blind Treatment Period from Day 1 (pre-dose) through Week 16 and during the LTE at LTE 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 headache (LTE Day 71) assessed as unrelated to study drug.

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

Anti-drug Antibody Assessments

Serum samples to assess blood levels of antibodies to RPC4046 will be obtained pre-dose: 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); at early termination.

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

Eosinophilic Esophagitis Activity Index (EEsAI)

The EEsAI is another paper-based patient-reported outcome (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 utilizes 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.

Composite Daily Symptom Diary (DSD) Score

The DSD was completed daily for 2 weeks prior to LTE baseline (i.e., 2 weeks prior to Week 16 visit of the Double-Blind Treatment Period), 2 weeks prior to LTE Weeks 12, 24, 52, and 2 weeks prior to LTE Week 60 safety follow-up visit.

DSD Questions

An interactive web-based or phone response system was used by subjects to complete a daily symptom diary. Subjects were able to access the diary by phone 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 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 a daily symptom diary for at least the last 2 weeks ± 3 days during the screening period prior to Day 1 and daily from Day 1 through Week 16. In addition, subjects completed a daily symptom diary for the 2 weeks prior to 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 EoE Endoscopic Reference Score[1] in 5 classification categories at screening, Week 16, or if applicable at ET. 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

Esophageal eosinophil counts and other parameters were assessed using the EoE Histologic Scoring System (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.[2]

The esophageal histologic changes characteristic of EoE were assessed by examining 8 parameters[2]:

- Eosinophil inflammation (EI) was graded using peak eosinophil count (PEC) obtained by counting eosinophils in the most densely inflamed high-power field (HPF);
- Basal zone hyperplasia (BZH): >15% of the total epithelial thickness;
- Eosinophil abscess (EA): solid mass of intraepithelial eosinophils;
- Eosinophil surface layering (SL): linear alignment of eosinophils parallel to the epithelial surface;
- Dilated intracellular spaces (DIS): spaces around squamous epithelial cells that exhibit intercellular bridges;

- Surface epithelial alteration (SEA): surface epithelial cells that exhibit altered tinctorial properties, manifest as dark staining, with or without intraepithelial eosinophils;
- Dyskeratotic epithelial cells (DEC): individual cells with deeply eosinophilic cytoplasm and hyperchromatic nuclei;
- Lamina propria fibers (LPF): 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).

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 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 4 A, 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. Mean esophageal eosinophil counts were generally similar across all three randomized groups irrespective of steroid status starting at LTE Week 12 and continuing through LTE Week 52. The proportion of steroid-refractory subjects with peak eosinophil count <15/hpf decreased from LTE Week 12 (28.6% placebo, 41.7% RPC4046 180 mg, 50.0% RPC4046 360 mg) to LTE Week 52 (21.4% placebo, 33.3% RPC4046 180 mg, 35.7% RPC4046 360 mg); whereas, the proportion of non-steroid refractory subjects with peak eosinophil count <15/hpf increased overall from LTE Week 12 (33.3% placebo, 62.5% RPC4046 180 mg, 38.5% RPC4046 360 mg) to LTE Week 52 (46.7% placebo, 43.8% RPC4046 180 mg, 53.8% RPC4046 360 mg).

DSD Composite Score and Components

Mean DSD composite scores among non-steroid refractory subjects were similar across all three 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 three groups displayed a decrease in mean DSD composite scores (**Supplementary Figure 4D**). 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 three groups decreased from LTE baseline to LTE Week 52 (**Supplementary Figure 4C**).

EREFS Total Scores

Among steroid-refractory subjects, mean EREFS total score over all locations was higher at LTE baseline in the placebo group versus the RPC4046 180 mg and 360 mg groups (**Supplementary Table 3**). Decreases in mean EREFS total score over all locations were observed from LTE baseline to each LTE visit across all three treatment groups. By LTE Week 52, mean EREFS total scores over all locations value were similar in all three groups. Similarly, reductions for steroid-refractory subjects from LTE baseline to similar mean values at LTE Week 52 were also noted across all three 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 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 were also observed across all three randomized treatment groups. For total score and component scores of inflammation composite score, remodeling composite score, fixed rings, exudates, and edema, there were no consistent trends.

Other Efficacy Endpoints

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 PRO scores during the DB treatment period through Week 52 of LTE.

References

1. Hirano I, Moy N, Heckman MG, Thomas CS, Gonsalves N, Achem SR. Endoscopic assessment of the esophageal features of eosinophilic esophagitis: validation of a novel classification and grading system. Gut 2013; 62: 489–95.
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 in the LTE Period (LTE Population)

Country	Site	Double-Blind Randomized Treatment Group						Total (N=86) n (%)	
		Placebo (n=29) n (%)		RPC4046 180 mg (n=28) n (%)		RPC4046 360 mg (n=29) n (%)			
		Dosed[a] n (%)	Completed[a] n (%)	Dosed[a] n (%)	Completed[a] n (%)	Dosed[a] n (%)	Completed[a] n (%)	Dosed[a] n (%)	Completed[a] 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)

LTE, long-term extension.

[a]Dosed refers to the number of subjects receiving 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.

Supplementary Table 2. Change from Baseline in the Blood EOS - Observed Cases (ITT and LTE Populations)

Week 16				
ITT Population				
Visit		**Placebo (n=34)**	**RPC4046 180 mg (n=31)**	**RPC4046 360 mg (n=34)**
Baseline	N	34	31	34
	Mean (SD)	0.44 (0.232)	0.51 (0.282)	0.39 (0.191)
	Median	0.4	0.5	0.35
	Min, Max	0.1, 1.0	0.1, 1.4	0.1, 0.8
DB Week 16	N	32	28	31
	Mean (SD)	0.37 (0.219)	0.45 (0.291)	0.34 (0.158)
	Median	0.3	0.45	0.3
	Min, Max	0.0, 0.9	0.0, 1.3	0.1, 0.8
Change to DB Week 16	N	32	28	31
	Mean (SD)	-0.07 (0.237)	-0.07 (0.294)	-0.05 (0.161)
	Median	0	-0.1	0
	Min, Max	-0.8, 0.3	-0.9, 0.8	-0.5, 0.2
	LSMD (RPC4046 - Placebo) (SE)		0.045 (0.051)	-0.01 (0.050)
	95% CI of LSMD		-0.06, 0.15	-0.11, 0.09
	p-value[a]		0.3864	0.8341
Visit		**Placebo (n=17)**	**RPC4046 180 mg (n=26)**	**RPC4046 360 mg (n=22)**
ITT Atopic Subgroup				
Baseline	N	17	26	22
	Mean (SD)	0.42 (0.222)	0.53 (0.280)	0.38 (0.185)
	Median	0.4	0.5	0.35
	Min, Max	0.1, 1.0	0.2, 1.4	0.1, 0.8
DB Week 16	N	15	24	21
	Mean (SD)	0.41 (0.222)	0.45 (0.284)	0.32 (0.137)
	Median	0.4	0.45	0.3
	Min, Max	0.1, 0.9	0.1, 1.3	0.1, 0.6
Change to DB Week 16	N	15	24	21
	Mean (SD)	-0.02 (0.132)	-0.09 (0.311)	-0.06 (0.175)
	Median	0	-0.15	0
	Min, Max	-0.2, 0.3	-0.9, 0.8	-0.5, 0.2
	LSMD (RPC4046 - Placebo) (SE)		0.00 (0.063)	-0.05 (0.064)
	95% CI of LSMD		-0.12, 0.13	-0.18, 0.08
	p-value[a]		0.9480	0.4600
Week 52				
LTE Population				
Visit		**Placebo (n=29)**	**RPC4046 180 mg (n=28)**	**RPC4046 360 mg (n=29)**
Baseline	N	29	28	29
	Mean (SD)	0.45 (0.223)	0.52 (0.283)	0.38 (0.201)
	Median	0.40	0.50	0.3
	Min, Max	0.1, 1.0	0.1, 1.4	0.1, 0.8
LTE Week 52	N	21	24	22
	Mean (SD)	0.36 (0.234)	0.48 (0.446)	0.39 (0.301)
	Median	0.3	0.4	0.4
	Min, Max	0.1, 1.1	0.0, 2.1	0.1, 1.4

Change to LTE Week 52	N	21	24	22
	Mean (SD)	-0.1 (0.192)	-0.05 (0.373)	0.03 (0.307)
	Median	-0.1	-0.05	0
	Min, Max	-0.5, 0.3	-0.7, 1.2	-0.3, 1.1
LTE Atopic Subgroup				
Visit		**Placebo (n=14)**	**RPC4046 180 mg (n=24)**	**RPC4046 360 mg (n=20)**
Baseline	N	14	24	20
	Mean (SD)	0.44 (0.238)	0.53 (0.278)	0.38 (0.194)
	Median	0.4	0.5	0.35
	Min, Max	0.1, 1.0	0.2, 1.4	0.1, 0.8
LTE Week 52	N	11	20	13
	Mean (SD)	0.37 (0.276)	0.42 (0.292)	0.43 (0.357)
	Median	0.3	0.4	0.4
	Min, Max	0.1, 1.1	0.0, 1.4	0.1, 1.4
Change to LTE Week 52	N	11	20	13
	Mean (SD)	-0.06 (0.157)	-0.13 (0.268)	0.08 (0.377)
	Median	-0.1	-0.15	0
	Min, Max	11	20	13

ANCOVA, analysis of covariance; CI, confidence interval; EOS, eosinophils; ITT, intent to treat; LSMD, least squares mean difference; LTE, long-term extension; SD, standard deviation; SE, standard error.

[a]p-values comparing RPC4046 to placebo are based on an ANCOVA model with treatment group and actual steroid-refractory status as factors and the baseline blood EOS as a covariate.

Atopic includes medical history of atopic dermatitis, allergy, asthma, anaphylaxis, eczema, nasal polyp.

Supplementary Table 3. Inflammatory Component (Edema, Exudate, Furrows) and Stenosis (Fixed Rings, Stricture) Component of EREFS for Total Population and Steroid-Refractory Group in the LTE Period (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)
Total Score						
Baseline[a]	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)
Edema						
Baseline[a]	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)
Exudates						
Baseline[a]	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)
Furrows						
Baseline[a]	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)
Fixed Rings						
Baseline[a]	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)
Stricture						
Baseline[a]	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; SD, standard deviation; LTE, long-term extension.
[a]Baseline is defined as the last observed score prior to the first dose of study drug during the LTE.

Supplementary Table 4. Remission: EEsAI PRO score ≤ 20 (ITT Population)

Visit	Placebo (n=34) n/N (%)	180 mg (n=31) n/N (%), p-val	360 mg (n=34) n/N (%), p-val
ITT Population			
Baseline	0/34 (0)	0/30 (0)	0/34 (0)
Week 16	4/34 (11.8)	7/31 (22.6), 0.2466	10/34 (29.4), 0.0767
LTE Week 12	10/29 (34.5)	12/28 (42.9), 0.5038	15/27 (55.6), 0.1240
LTE Week 24	14/29 (48.3)	10/28 (35.7), 0.3299	18/27 (66.7), 0.1651
LTE Week 52	16/29 (55.2)	13/28 (46.4), 0.4921	18/27 (66.7), 0.3755
ITT Atopic Subgroup			
Baseline	0/17 (0)	0/25 (0)	0/22 (0)
Week 16	2/17 (11.8)	7/26 (26.9), 0.2102	6/22 (27.3), 0.2850
LTE Week 12	6/14 (42.9)	11/25 (44.0), 0.6931	10/18 (55.6), 0.4386
LTE Week 24	7/14 (50.0)	9/24 (37.5), 0.5419	11/18 (61.1), 0.5867
LTE Week 52	7/14 (50.0)	12/24 (50.0), 0.9436	11/18 (61.1), 0.4946

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 (LTE Population)

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

LTE, long-term extension; SD, standard deviation.
[a]Baseline was defined as the composite diary score in the last 14 days prior to double-blind Week 16.

Supplementary Table 6. Histologic Response-Responder Analysis – Observed Case (ITT and LTE Populations)

	Placebo	RPC4046 180mg	RPC4046 360mg	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 (ITT Population)

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

DB, double-blind; EREFS, Eosinophilic Esophagitis Endoscopic Reference Score; ITT, intent-to-treat; LTE, long-term extension; SD, standard deviation.

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

Preferred Term	Placebo (n=29)	RPC4046		Total (N=86)
		180 mg (n=28)	360 mg (n=29)	
Total serious adverse events[a], n (%)				
Patients with a serious adverse event	0	2 (7.1)	4 (13.8)	6 (7.0)
Cholecystitis acute	0	1	0	1
Spontaneous abortion	0	0	1	1
Asthma	0	1	0	1
Diverticulitis	0	0	1	1
Schizophrenia[b]	0	0	1	1
Femur fracture	0	0	1	1

LTE, long-term extension; TEAE, treatment-emergent adverse event.
Data are number or number (%).
[a]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.
[b]This TEAE led to discontinuation of study drug and withdrawal from the study.

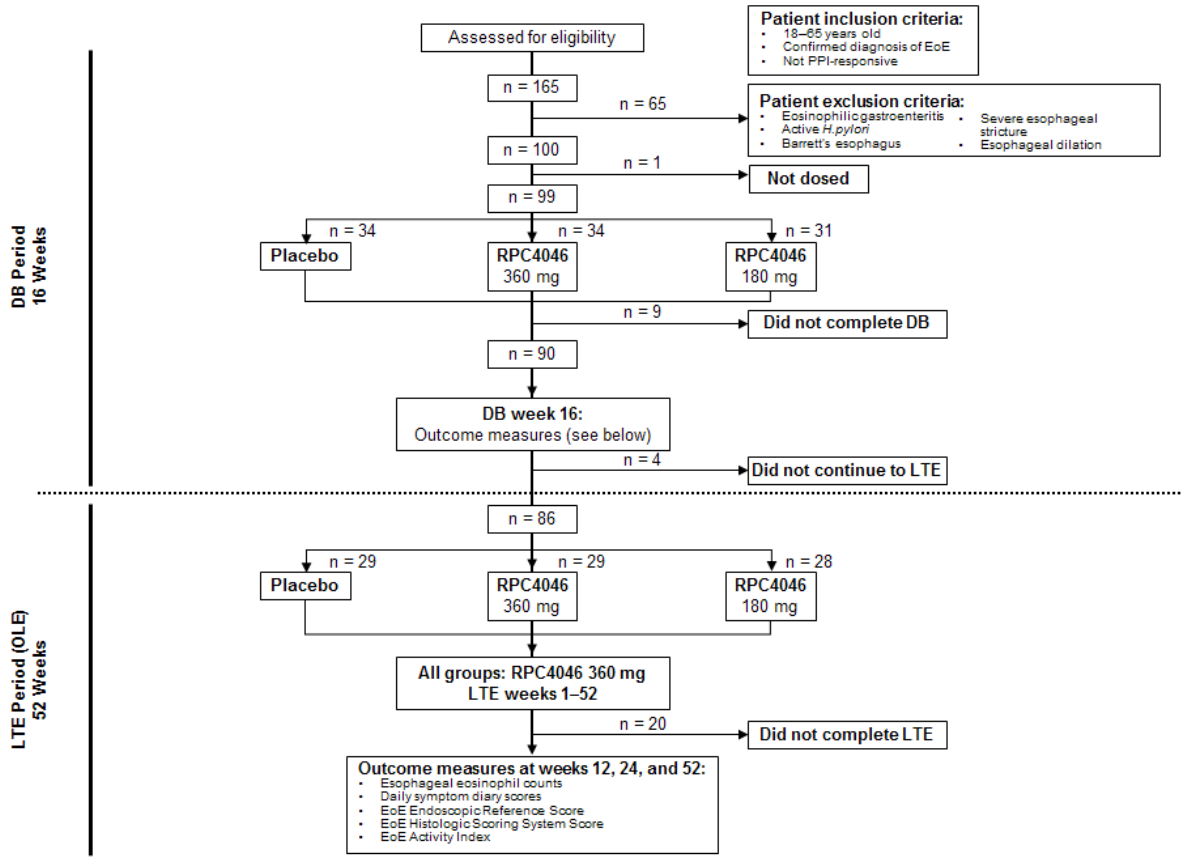
Supplementary Table 9. Injection Site Treatment-Emergent Adverse Events in LTE (LTE Population)

	Placebo (n=29)	RPC4046		Total (N=86)
		180 mg (n=28)	360 mg (n=29)	
Number of subjects experiencing ≥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)

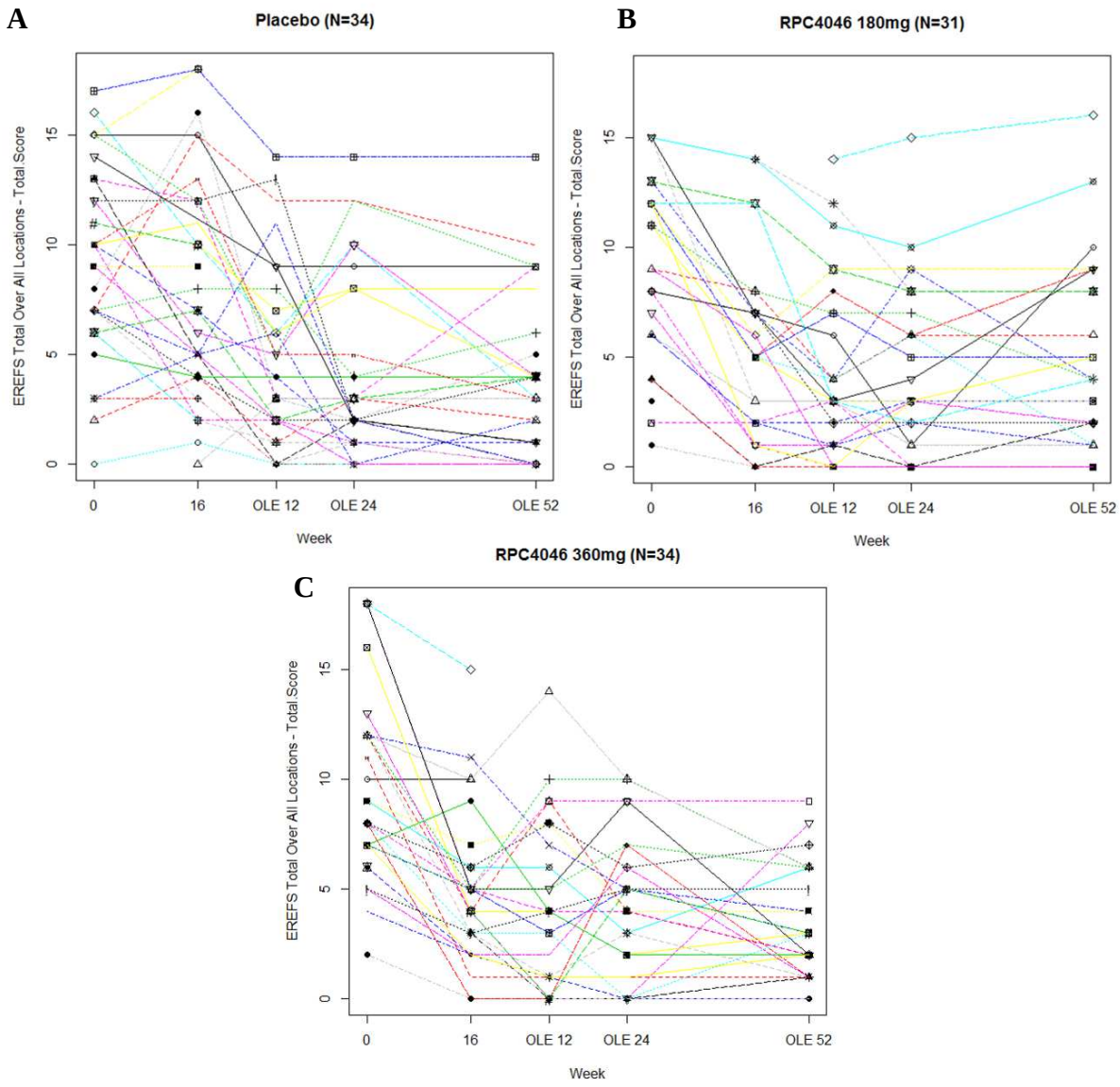
Data are number (%).

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

Supplementary Figure 1. Patient Flow Chart

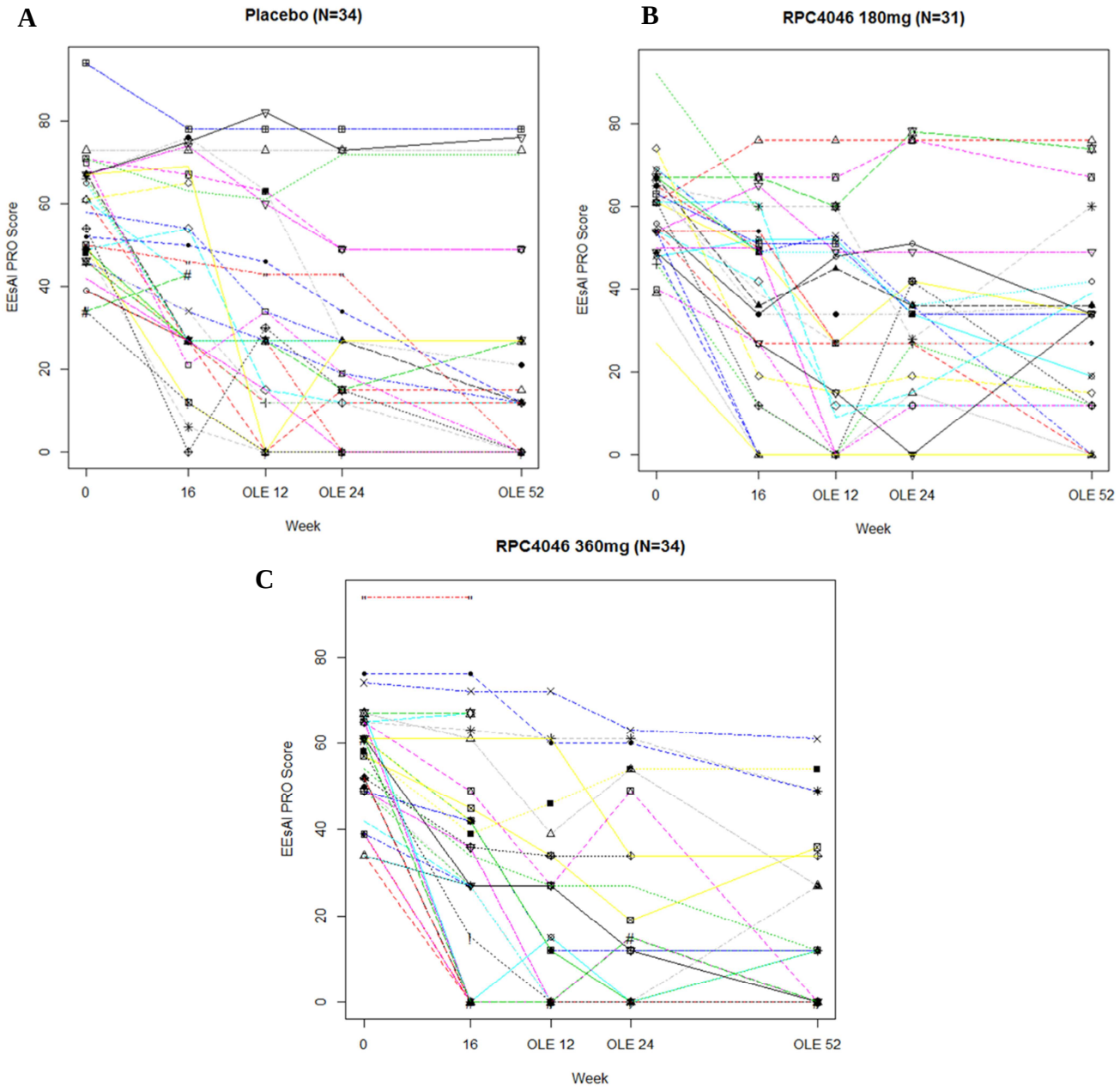


Supplementary Figure 2. EREFS Total Over All Locations - Total Score over time for each subject by treatment group (ITT population)



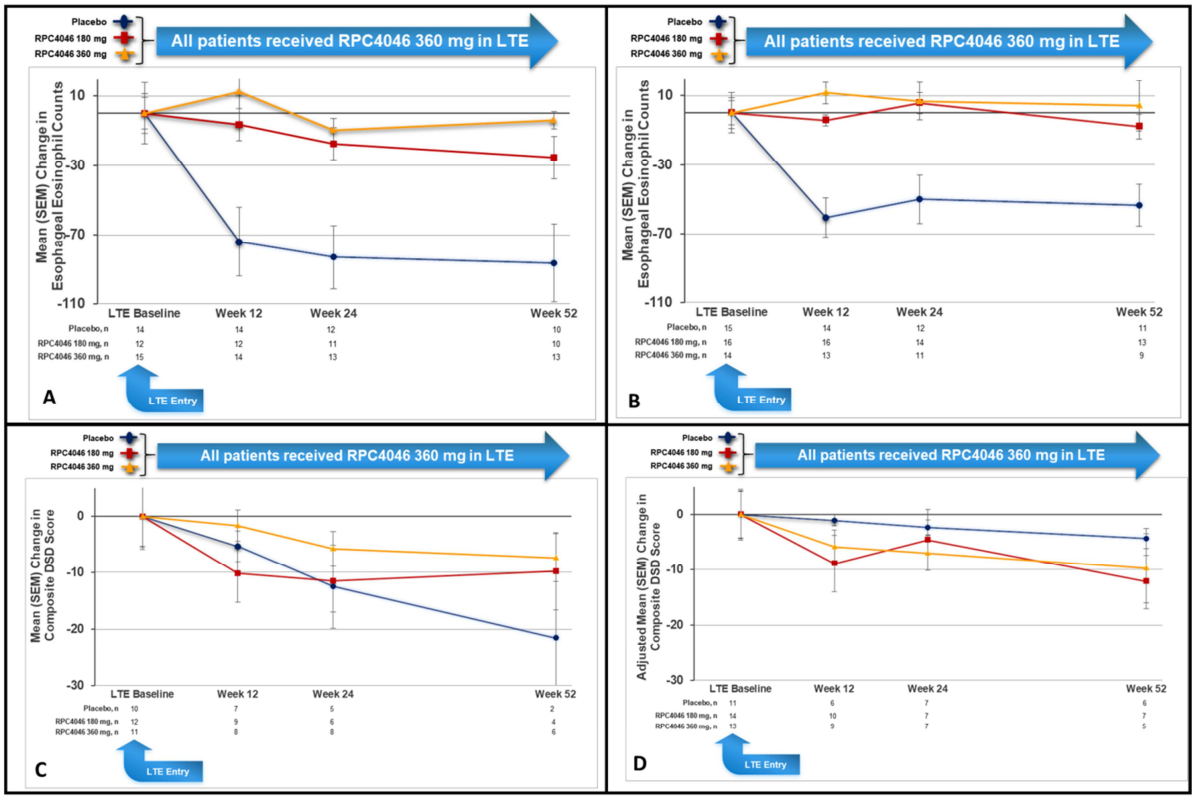
EREFS total over all locations at DB Weeks 0 and 16 and LTE Weeks 12, 24, and 52. (A) Individual data from placebo group (n=34); (B) RPC4046 180 mg (n=31); and (C) RPC4046 360 mg (n=34).

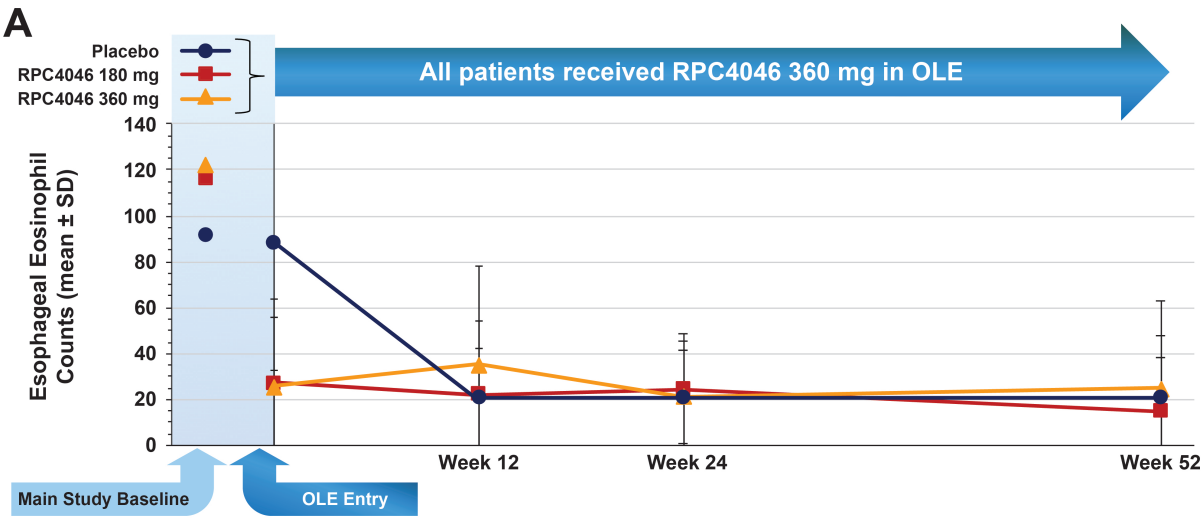
Supplementary Figure 3. EEsAI over time for each subject by treatment group (ITT population)

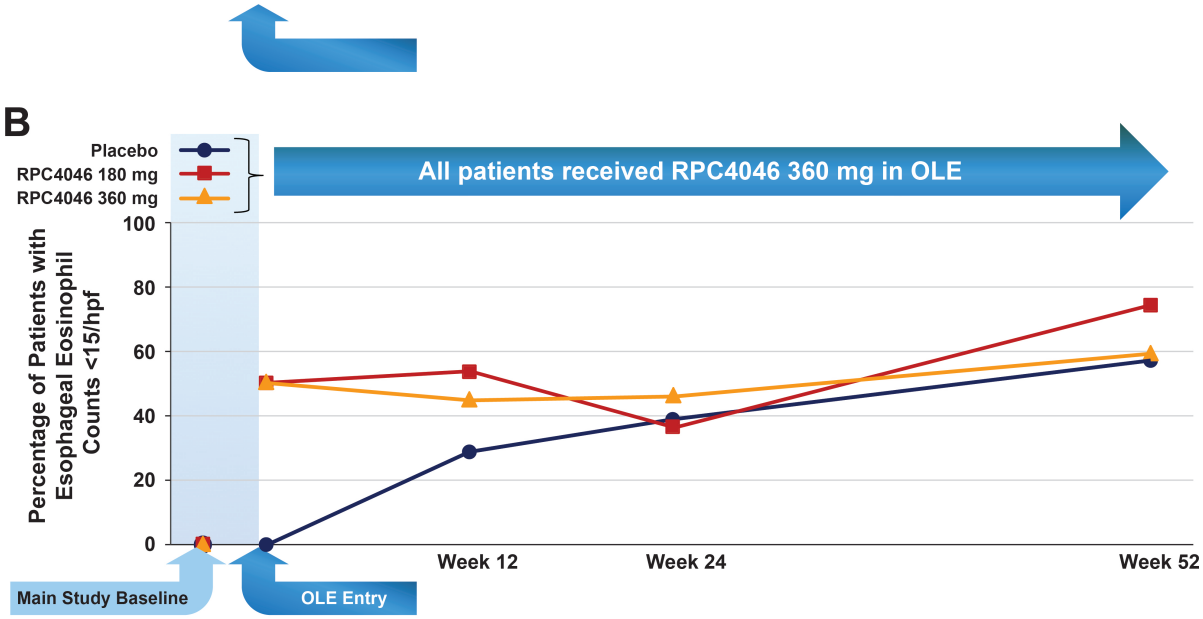


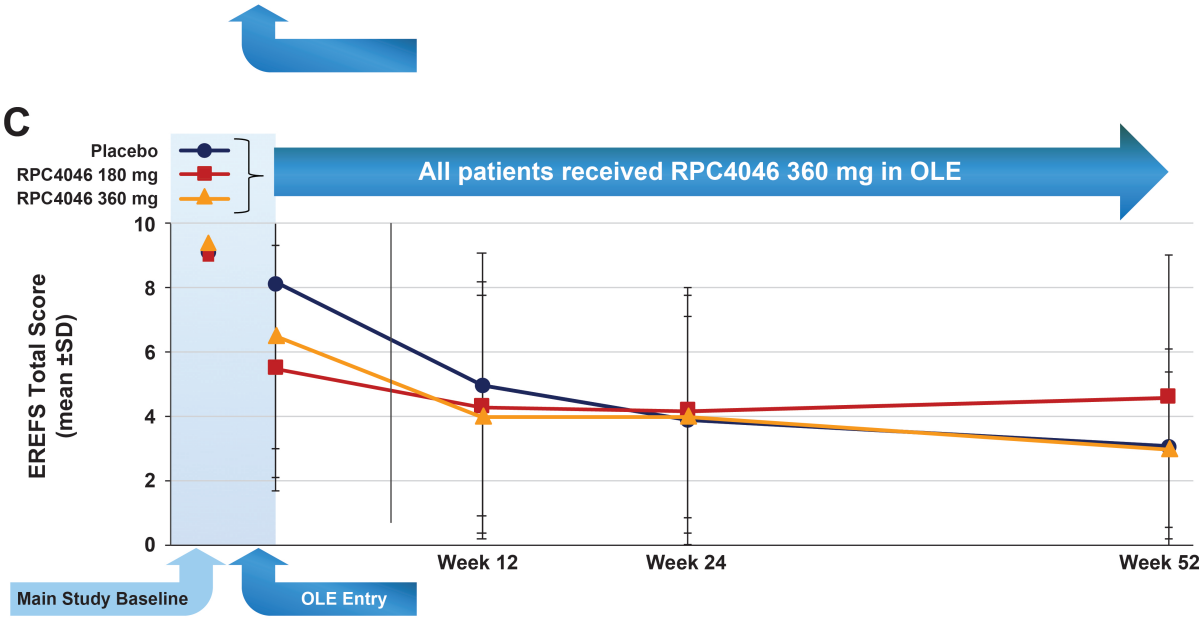
EEsAI over all locations at DB Weeks 0 and 16 and LTE Weeks 12, 24, and 52. (A) Individual data from placebo group (n=34); (B) RPC4046 180 mg (n=31); and (C) RPC4046 360 mg (n=34).

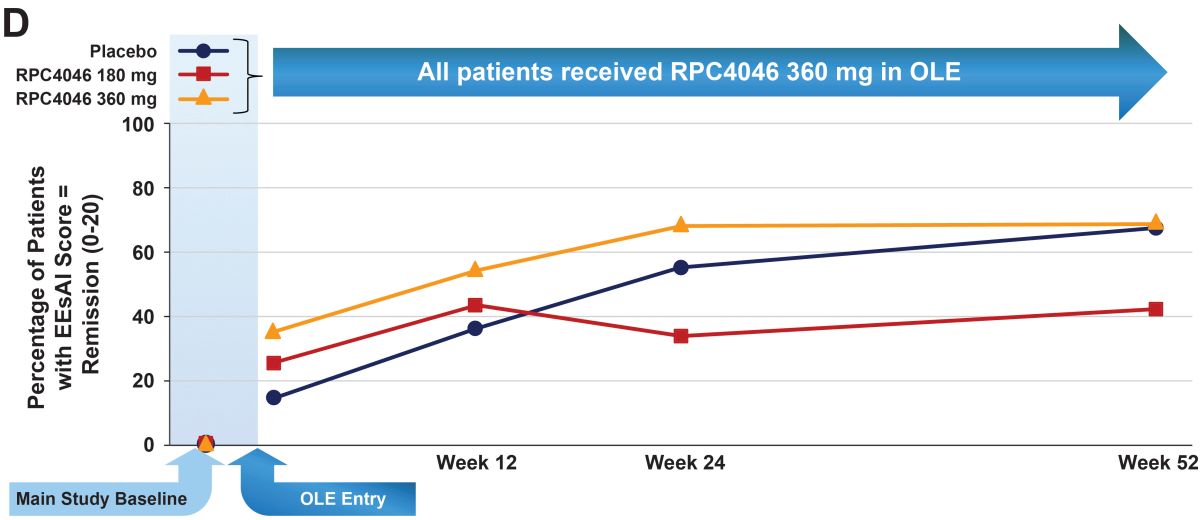
Supplementary Figure 4. Mean change (SEM) from LTE baseline in esophageal eosinophil counts and composite diary scores by steroid-refractory status at LTE Weeks 12, 24, and 52.
(A) Esophageal eosinophil counts in steroid-refractory group (eos/hpf); (B) Esophageal eosinophil counts in non-steroid refractory group (eos/hpf); (C) Composite DSD score in steroid-refractory group; (D) Composite DSD score in non-steroid refractory group (LTE population)

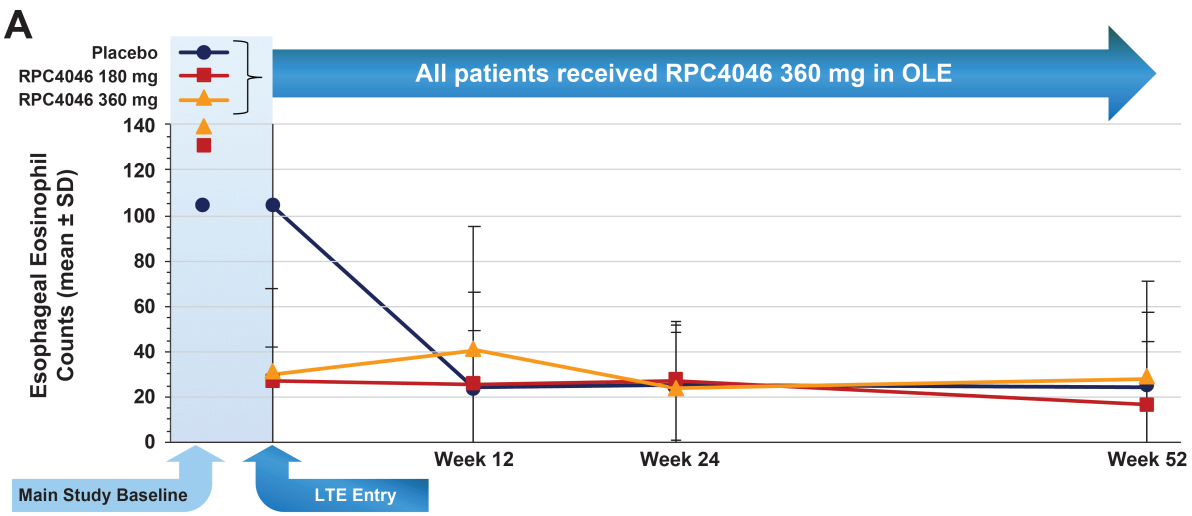


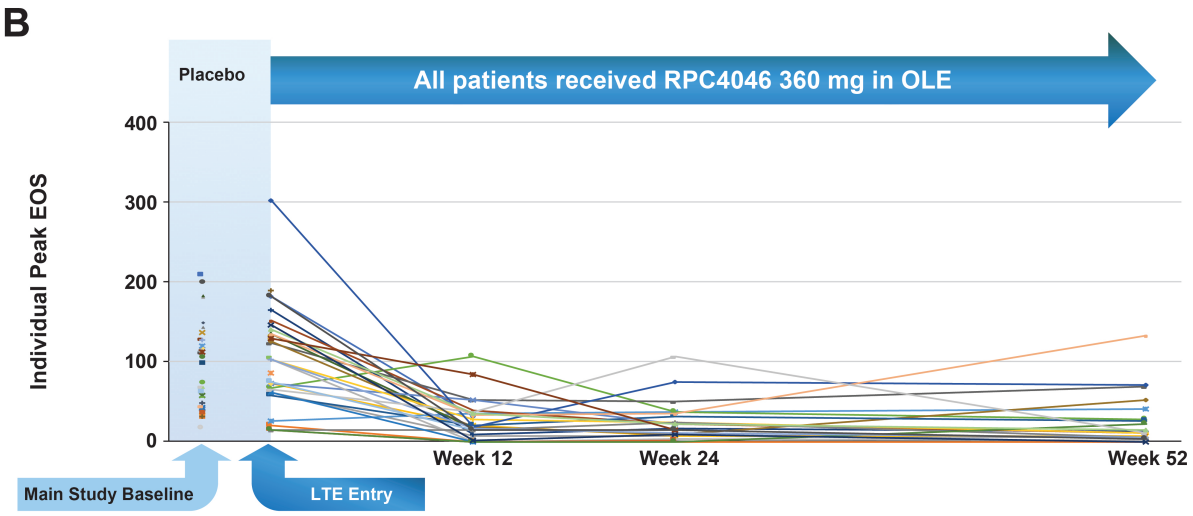



B
Placebo
RPC4046 180 mg
RPC4046 360 mg
All patients received RPC4046 360 mg in OLE
Percentage of Patients with Esophageal Eosinophil Counts <15/hpf
100
80
60
40
20
0
Week 12
Week 24
Week 52
Main Study Baseline
OLE Entry


C
Placebo
RPC4046 180 mg
RPC4046 360 mg
All patients received RPC4046 360 mg in OLE
EREFS Total Score
(mean ±SD)
10
8
6
4
2
0
Week 12
Week 24
Week 52
Main Study Baseline
OLE Entry







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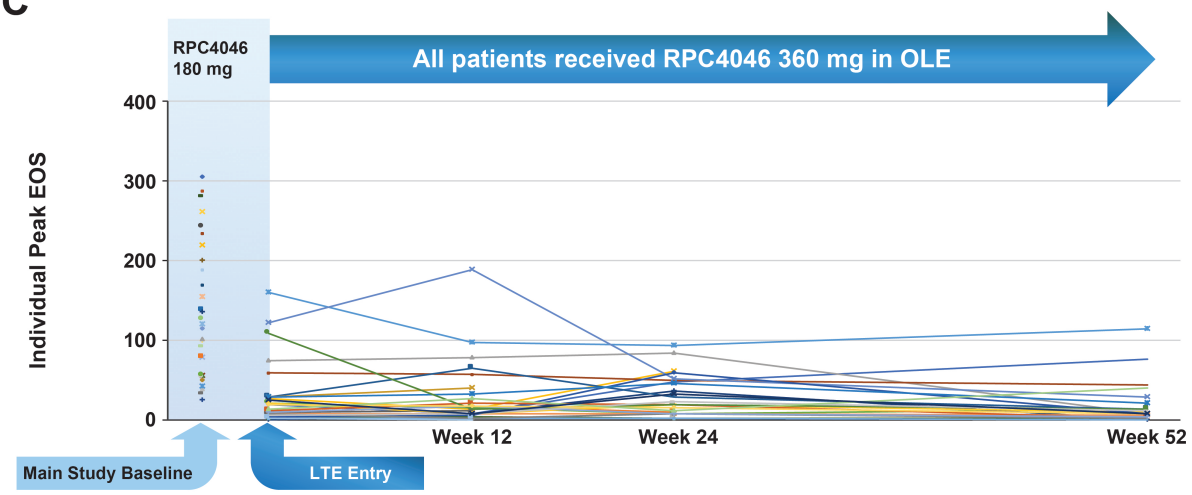

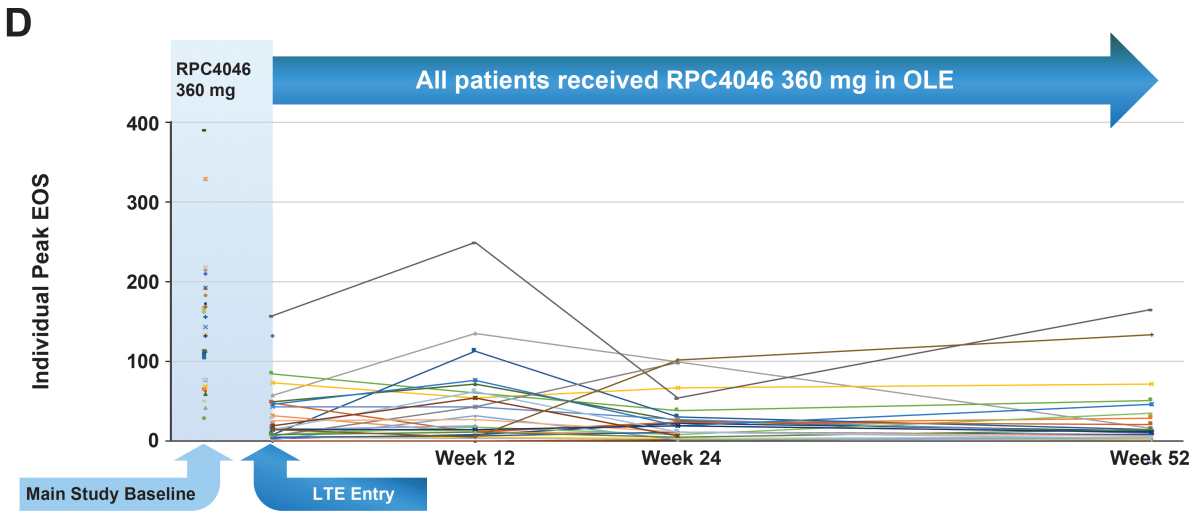

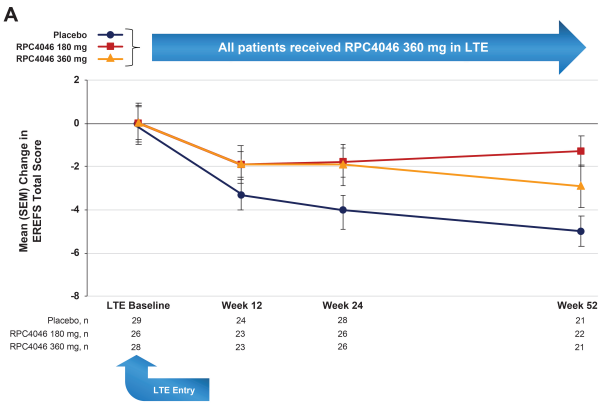

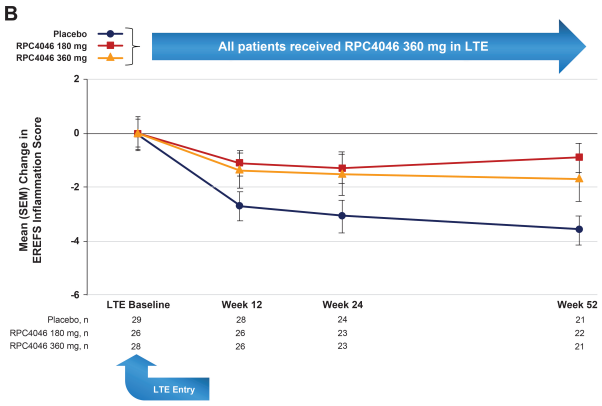

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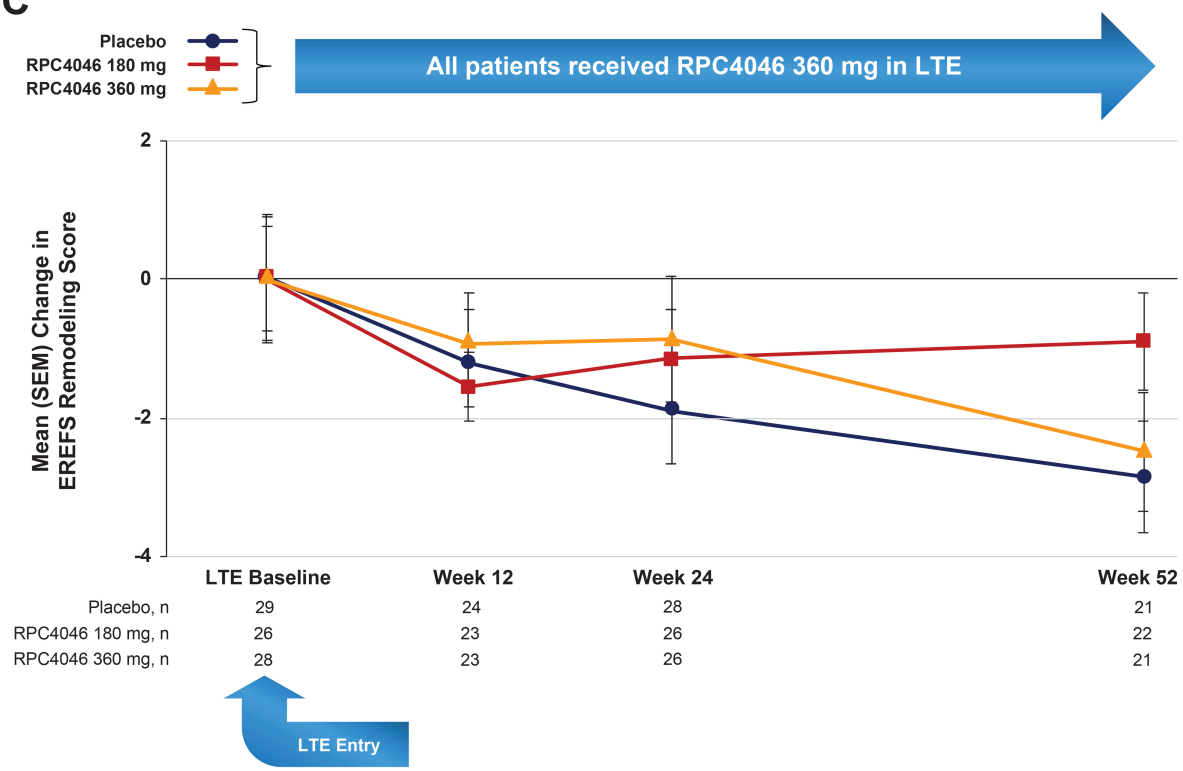

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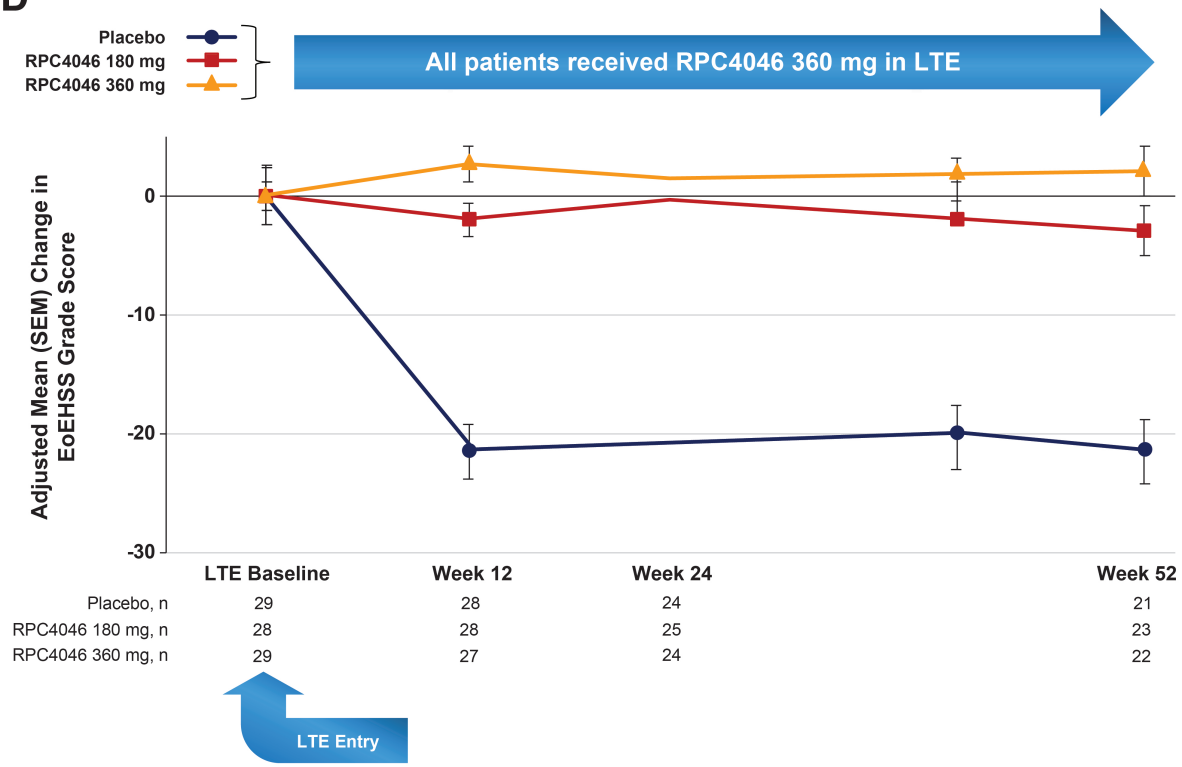

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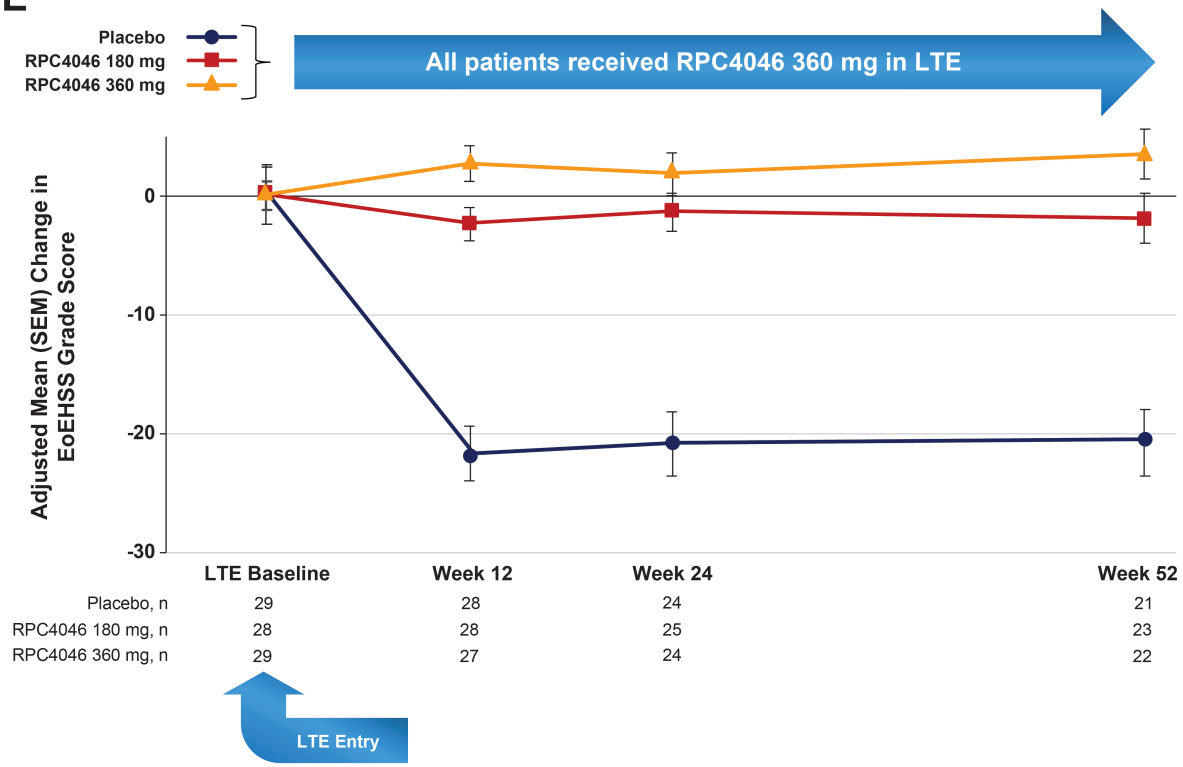

Supplementary Material

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

Supplement to: Dellon ES, Collins MH, Rothenberg ME, et al. Long-term Efficacy and Tolerability of RPC4046 in an Open-Label Extension Trial of Patients With Eosinophilic Esophagitis

TABLE OF CONTENTS

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USA	Assouline-Dayan, Yehudith	University of Iowa Hospitals and Clinics
USA	Ayub, Kamran	Southwest Gastroenterology
USA	Coates, Allan	West Michigan Clinical Research Center Gastroenterology Associates of Western Michigan
USA	Cohen, Sidney	Thomas Jefferson University
USA	Dellon, Evan	University of North Carolina
USA	Desta, Taddese	Precision Research Institute, LLC
USA	Evans, Larry	Grand Teton Research Group
USA	Falk, Gary	The University of Pennsylvania
USA	Fein, Steven	Digestive Health Center
USA	Fernandez-Becker, Nielsen	Stanford University
USA	Fleischer, David	Children's Hospital Colorado
USA	Friedenberg, Keith	Great Lakes Gastroenterology Research
USA	Ghishan, Fayez	The University of Arizona Clinical and Translational Science
USA	Glover, Sarah	University of Florida
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USA	Gross, Craig	Desert Sun Clinical Research, LLC
USA	Hardi, Robert	Metropolitan Gastroenterology Group Chevy Chase Clinical Research
USA	Hirano, Ikuo	Northwestern University
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USA	Schey, Ron	Temple University Hospital
USA	Shad, Javaid	Alliance Clinical Research
USA	Vaezi, Michael	Vanderbilt University Medical Center
USA	Wo, John	Indiana University
USA	Zakko, Salam	Connecticut Clinical Research Foundation

*Note: The 40 listed sites were initiated for participation in this study; of these sites, 30 enrolled at least one 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. Editorial support was provided by Celgene. Confidentiality agreements were in place between Celgene and all authors.

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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 eosinophils per high-power field (eos/hpf; microscope hpf = 0.3 mm^2) 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 (PPI) and been confirmed to not have PPI-responsive EoE. 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, they must have been receiving a stable dose for at least 4 weeks prior to the screening endoscopy and agreed to continue on a 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; all females of childbearing potential must have had a negative serum pregnancy test at screening and a negative urine (or serum) pregnancy test prior to dosing on Day 1.

Patients who completed the Double Blind Treatment Period of the Phase 2 study, demonstrated ≥80% study drug compliance, and had no clinically significant adverse events during initial therapy were eligible to be enrolled into 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 endpoints for this trial (e.g., erosive esophagitis Grade 2 or above, 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 esophagus (e.g., high-grade stenosis where an 8-10 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 (e.g., methotrexate, cyclosporine, interferon alpha, tumor necrosis factor alpha inhibitors, antibodies to IgE, etc) within 5 drug half-lives prior to 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 (e.g., 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, etc); liver function impairment or persisting elevations of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >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 (e.g., hepatitis B or C, human immunodeficiency virus [HIV], 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 prior to 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 non metastatic 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 prior to baseline assessment of dysphagia or anticipated to be performed during the trial.

Protocol Amendments

The original protocol (dated 13 March 2014) was amended 3 times. The first amendment (dated 16 May 2014) was implemented prior to enrolment of the first patient in the study (03 September 2014). Summaries of the major changes included in each amendment are provided below.

Protocol Amendment 1 (dated 16 May 2014):

- Removed the LTE 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

- 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 ADA and PK 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 prior to 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 17 October 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 LTE

- Removed the Esophageal String Test due to limited availability of the test

- Specified the requirement for collection of DSD for the last 2 consecutive weeks (± 3 days) prior to 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 prior to 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 AE collection to 30 days after last dose or last visit

- Added text to clearly define the ITT and PP populations

Protocol Amendment 3 (dated 22 June 2015):

- Extended the LTE from 24 weeks to 52 weeks

- Removed the interim analysis from the protocol

Methods

Weekly Study Dose

After Day 1, dosing with two 1.2 mL SC injections of study drug continued weekly through Week 15. During the LTE period, all subjects were treated with RPC4046 360mg SC.

Immunogenicity Assessment

Double-Blind Treatment Period and LTE Period

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

The majority of 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 adverse event (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, one mild and unrelated (Days 3-8) and one 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). After enrollment into the LTE, this subject was ADA (+) at LTE Weeks 2, 4, and 12. The subject was subsequently ADA (-) at LTE Weeks 24, 52, and at the LTE Week 60 Safety Follow-up visit. The subject had the following TEAEs, all assessed as unlikely related to study drug, during the LTE; mild gastroenteritis (LTE Days 83-85); mild depression (LTE Day 110 – ongoing); 2 TEAEs of upper respiratory tract infection, one moderate (LTE Days 236-270) and one mild (Days 301-308); and moderate sinusitis (LTE Days 253-270).

LTE Period Only

One subject was ADA (-) at all visits during the Double-Blind Treatment Period from Day 1 (pre-dose) through Week 16 and during the LTE at Weeks 2, 4, and 12. The subject tested positive for ADA at LTE Week 24 and was subsequently ADA (-) at LTE Week 52 and at the LTE Week 60 Safety Follow-up Visit. The subject had the following TEAEs during the LTE: severe gastroenteritis viral (LTE Days 10-13) assessed as possibly related to study drug; moderate upper respiratory tract infection (LTE Days 82-87) assessed as possibly related to study drug; moderate influenza (LTE Days 84-87) assessed as unrelated to study drug; moderate arthralgia (LTE 147-162) assessed as possibly related to study drug; 2 TEAEs of mild nausea (LTE Days 179 and 366) assessed as unrelated to study drug; 2 TEAEs of mild vomiting (LTE Days 179 and 366) assessed as unrelated to study drug; and mild feces discolored (LTE Days 189-200) assessed as unrelated to study drug.

One subject was ADA (-) at all visits during the Double-Blind Treatment Period from Day 1 (pre-dose) through Week 16 and during the LTE at LTE 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 headache (LTE Day 71) assessed as unrelated to study drug.

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

Anti-drug Antibody Assessments

Serum samples to assess blood levels of antibodies to RPC4046 will be obtained pre-dose: 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); at early termination.

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

Eosinophilic Esophagitis Activity Index (EEsAI)

The EEsAI is another paper-based patient-reported outcome (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 utilizes 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.

Composite Daily Symptom Diary (DSD) Score

The DSD was completed daily for 2 weeks prior to LTE baseline (i.e., 2 weeks prior to Week 16 visit of the Double-Blind Treatment Period), 2 weeks prior to LTE Weeks 12, 24, 52, and 2 weeks prior to LTE Week 60 safety follow-up visit.

DSD Questions

An interactive web-based or phone response system was used by subjects to complete a daily symptom diary. Subjects were able to access the diary by phone 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 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 a daily symptom diary for at least the last 2 weeks ± 3 days during the screening period prior to Day 1 and daily from Day 1 through Week 16. In addition, subjects completed a daily symptom diary for the 2 weeks prior to 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 EoE Endoscopic Reference Score[1] in 5 classification categories at screening, Week 16, or if applicable at ET. 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

Esophageal eosinophil counts and other parameters were assessed using the EoE Histologic Scoring System (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.[2]

The esophageal histologic changes characteristic of EoE were assessed by examining 8 parameters[2]:

- Eosinophil inflammation (EI) was graded using peak eosinophil count (PEC) obtained by counting eosinophils in the most densely inflamed high-power field (HPF);
- Basal zone hyperplasia (BZH): >15% of the total epithelial thickness;
- Eosinophil abscess (EA): solid mass of intraepithelial eosinophils;
- Eosinophil surface layering (SL): linear alignment of eosinophils parallel to the epithelial surface;
- Dilated intracellular spaces (DIS): spaces around squamous epithelial cells that exhibit intercellular bridges;
- Surface epithelial alteration (SEA): surface epithelial cells that exhibit altered tinctorial properties, manifest as dark staining, with or without intraepithelial eosinophils;
- Dyskeratotic epithelial cells (DEC): individual cells with deeply eosinophilic cytoplasm and hyperchromatic nuclei;
- Lamina propria fibers (LPF): 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).

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 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 4 A, 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. Mean esophageal eosinophil counts were generally similar across all three randomized groups irrespective of steroid status starting at LTE Week 12 and continuing through LTE Week 52. The proportion of steroid-refractory subjects with peak eosinophil count <15/hpf decreased from LTE Week 12 (28.6% placebo, 41.7% RPC4046 180 mg, 50.0% RPC4046 360 mg) to LTE Week 52 (21.4% placebo, 33.3% RPC4046 180 mg, 35.7% RPC4046 360 mg); whereas, the proportion of non-steroid refractory subjects with peak eosinophil count <15/hpf increased overall from LTE Week 12 (33.3% placebo, 62.5% RPC4046 180 mg, 38.5% RPC4046 360 mg) to LTE Week 52 (46.7% placebo, 43.8% RPC4046 180 mg, 53.8% RPC4046 360 mg).

DSD Composite Score and Components

Mean DSD composite scores among non-steroid refractory subjects were similar across all three 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 three groups displayed a decrease in mean DSD composite scores (**Supplementary Figure 4D**). 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 three groups decreased from LTE baseline to LTE Week 52 (**Supplementary Figure 4C**).

EREFS Total Scores

Among steroid-refractory subjects, mean EREFS total score over all locations was higher at LTE baseline in the placebo group versus the RPC4046 180 mg and 360 mg groups (**Supplementary Table 3**). Decreases in mean EREFS total score over all locations were observed from LTE baseline to each LTE visit across all three treatment groups. By LTE Week 52, mean EREFS total scores over all locations value were similar in all three groups. Similarly, reductions for steroid-refractory subjects from LTE baseline to similar mean values at LTE Week 52 were also noted across all three 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 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 were also observed across all three randomized treatment groups. For total score and component scores of inflammation composite score, remodeling composite score, fixed rings, exudates, and edema, there were no consistent trends.

Other Efficacy Endpoints

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 PRO scores during the DB treatment period through Week 52 of LTE.

References

1. Hirano I, Moy N, Heckman MG, Thomas CS, Gonsalves N, Achem SR. Endoscopic assessment of the esophageal features of eosinophilic esophagitis: validation of a novel classification and grading system. Gut 2013; 62: 489–95.
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 in the LTE Period (LTE Population)

Country	Site	Double-Blind Randomized Treatment Group						Total (N=86) n (%)	
		Placebo (n=29) n (%)		RPC4046 180 mg (n=28) n (%)		RPC4046 360 mg (n=29) n (%)			
		Dosed[a] n (%)	Completed[a] n (%)	Dosed[a] n (%)	Completed[a] n (%)	Dosed[a] n (%)	Completed[a] n (%)	Dosed[a] n (%)	Completed[a] 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)

LTE, long-term extension.

[a]Dosed refers to the number of subjects receiving 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.

Supplementary Table 2. Change from Baseline in the Blood EOS - Observed Cases (ITT and LTE Populations)

Week 16				
ITT Population				
Visit		**Placebo (n=34)**	**RPC4046 180 mg (n=31)**	**RPC4046 360 mg (n=34)**
Baseline	N	34	31	34
	Mean (SD)	0.44 (0.232)	0.51 (0.282)	0.39 (0.191)
	Median	0.4	0.5	0.35
	Min, Max	0.1, 1.0	0.1, 1.4	0.1, 0.8
DB Week 16	N	32	28	31
	Mean (SD)	0.37 (0.219)	0.45 (0.291)	0.34 (0.158)
	Median	0.3	0.45	0.3
	Min, Max	0.0, 0.9	0.0, 1.3	0.1, 0.8
Change to DB Week 16	N	32	28	31
	Mean (SD)	-0.07 (0.237)	-0.07 (0.294)	-0.05 (0.161)
	Median	0	-0.1	0
	Min, Max	-0.8, 0.3	-0.9, 0.8	-0.5, 0.2
	LSMD (RPC4046 - Placebo) (SE)		0.045 (0.051)	-0.01 (0.050)
	95% CI of LSMD		-0.06, 0.15	-0.11, 0.09
	p-value[a]		0.3864	0.8341
Visit		**Placebo (n=17)**	**RPC4046 180 mg (n=26)**	**RPC4046 360 mg (n=22)**
ITT Atopic Subgroup				
Baseline	N	17	26	22
	Mean (SD)	0.42 (0.222)	0.53 (0.280)	0.38 (0.185)
	Median	0.4	0.5	0.35
	Min, Max	0.1, 1.0	0.2, 1.4	0.1, 0.8
DB Week 16	N	15	24	21
	Mean (SD)	0.41 (0.222)	0.45 (0.284)	0.32 (0.137)
	Median	0.4	0.45	0.3
	Min, Max	0.1, 0.9	0.1, 1.3	0.1, 0.6
Change to DB Week 16	N	15	24	21
	Mean (SD)	-0.02 (0.132)	-0.09 (0.311)	-0.06 (0.175)
	Median	0	-0.15	0
	Min, Max	-0.2, 0.3	-0.9, 0.8	-0.5, 0.2
	LSMD (RPC4046 - Placebo) (SE)		0.00 (0.063)	-0.05 (0.064)
	95% CI of LSMD		-0.12, 0.13	-0.18, 0.08
	p-value[a]		0.9480	0.4600
Week 52				
LTE Population				
Visit		**Placebo (n=29)**	**RPC4046 180 mg (n=28)**	**RPC4046 360 mg (n=29)**
Baseline	N	29	28	29
	Mean (SD)	0.45 (0.223)	0.52 (0.283)	0.38 (0.201)
	Median	0.40	0.50	0.3
	Min, Max	0.1, 1.0	0.1, 1.4	0.1, 0.8
LTE Week 52	N	21	24	22
	Mean (SD)	0.36 (0.234)	0.48 (0.446)	0.39 (0.301)
	Median	0.3	0.4	0.4
	Min, Max	0.1, 1.1	0.0, 2.1	0.1, 1.4

Change to LTE Week 52	N	21	24	22
	Mean (SD)	-0.1 (0.192)	-0.05 (0.373)	0.03 (0.307)
	Median	-0.1	-0.05	0
	Min, Max	-0.5, 0.3	-0.7, 1.2	-0.3, 1.1
LTE Atopic Subgroup				
Visit		**Placebo (n=14)**	**RPC4046 180 mg (n=24)**	**RPC4046 360 mg (n=20)**
Baseline	N	14	24	20
	Mean (SD)	0.44 (0.238)	0.53 (0.278)	0.38 (0.194)
	Median	0.4	0.5	0.35
	Min, Max	0.1, 1.0	0.2, 1.4	0.1, 0.8
LTE Week 52	N	11	20	13
	Mean (SD)	0.37 (0.276)	0.42 (0.292)	0.43 (0.357)
	Median	0.3	0.4	0.4
	Min, Max	0.1, 1.1	0.0, 1.4	0.1, 1.4
Change to LTE Week 52	N	11	20	13
	Mean (SD)	-0.06 (0.157)	-0.13 (0.268)	0.08 (0.377)
	Median	-0.1	-0.15	0
	Min, Max	11	20	13

ANCOVA, analysis of covariance; CI, confidence interval; EOS, eosinophils; ITT, intent to treat; LSMD, least squares mean difference; LTE, long-term extension; SD, standard deviation; SE, standard error.

[a]p-values comparing RPC4046 to placebo are based on an ANCOVA model with treatment group and actual steroid-refractory status as factors and the baseline blood EOS as a covariate.

Atopic includes medical history of atopic dermatitis, allergy, asthma, anaphylaxis, eczema, nasal polyp.

Supplementary Table 3. Inflammatory Component (Edema, Exudate, Furrows) and Stenosis (Fixed Rings, Stricture) Component of EREFS for Total Population and Steroid-Refractory Group in the LTE Period (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)
Total Score						
Baseline[a]	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)
Edema						
Baseline[a]	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)
Exudates						
Baseline[a]	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)
Furrows						
Baseline[a]	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)
Fixed Rings						
Baseline[a]	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)
Stricture						
Baseline[a]	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; SD, standard deviation; LTE, long-term extension.
[a]Baseline is defined as the last observed score prior to the first dose of study drug during the LTE.

Supplementary Table 4. Remission: EEsAI PRO score ≤ 20 (ITT Population)

Visit	Placebo (n=34) n/N (%)	180 mg (n=31) n/N (%), p-val	360 mg (n=34) n/N (%), p-val
ITT Population			
Baseline	0/34 (0)	0/30 (0)	0/34 (0)
Week 16	4/34 (11.8)	7/31 (22.6), 0.2466	10/34 (29.4), 0.0767
LTE Week 12	10/29 (34.5)	12/28 (42.9), 0.5038	15/27 (55.6), 0.1240
LTE Week 24	14/29 (48.3)	10/28 (35.7), 0.3299	18/27 (66.7), 0.1651
LTE Week 52	16/29 (55.2)	13/28 (46.4), 0.4921	18/27 (66.7), 0.3755
ITT Atopic Subgroup			
Baseline	0/17 (0)	0/25 (0)	0/22 (0)
Week 16	2/17 (11.8)	7/26 (26.9), 0.2102	6/22 (27.3), 0.2850
LTE Week 12	6/14 (42.9)	11/25 (44.0), 0.6931	10/18 (55.6), 0.4386
LTE Week 24	7/14 (50.0)	9/24 (37.5), 0.5419	11/18 (61.1), 0.5867
LTE Week 52	7/14 (50.0)	12/24 (50.0), 0.9436	11/18 (61.1), 0.4946

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 (LTE Population)

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

LTE, long-term extension; SD, standard deviation.
[a]Baseline was defined as the composite diary score in the last 14 days prior to double-blind Week 16.

Supplementary Table 6. Histologic Response-Responder Analysis – Observed Case (ITT and LTE Populations)

	Placebo	RPC4046 180mg	RPC4046 360mg	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 (ITT Population)

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

DB, double-blind; EREFS, Eosinophilic Esophagitis Endoscopic Reference Score; ITT, intent-to-treat; LTE, long-term extension; SD, standard deviation.

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

Preferred Term	Placebo (n=29)	RPC4046		Total (N=86)
		180 mg (n=28)	360 mg (n=29)	
Total serious adverse events[a], n (%)				
Patients with a serious adverse event	0	2 (7.1)	4 (13.8)	6 (7.0)
Cholecystitis acute	0	1	0	1
Spontaneous abortion	0	0	1	1
Asthma	0	1	0	1
Diverticulitis	0	0	1	1
Schizophrenia[b]	0	0	1	1
Femur fracture	0	0	1	1

LTE, long-term extension; TEAE, treatment-emergent adverse event.
Data are number or number (%).
[a]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.
[b]This TEAE led to discontinuation of study drug and withdrawal from the study.

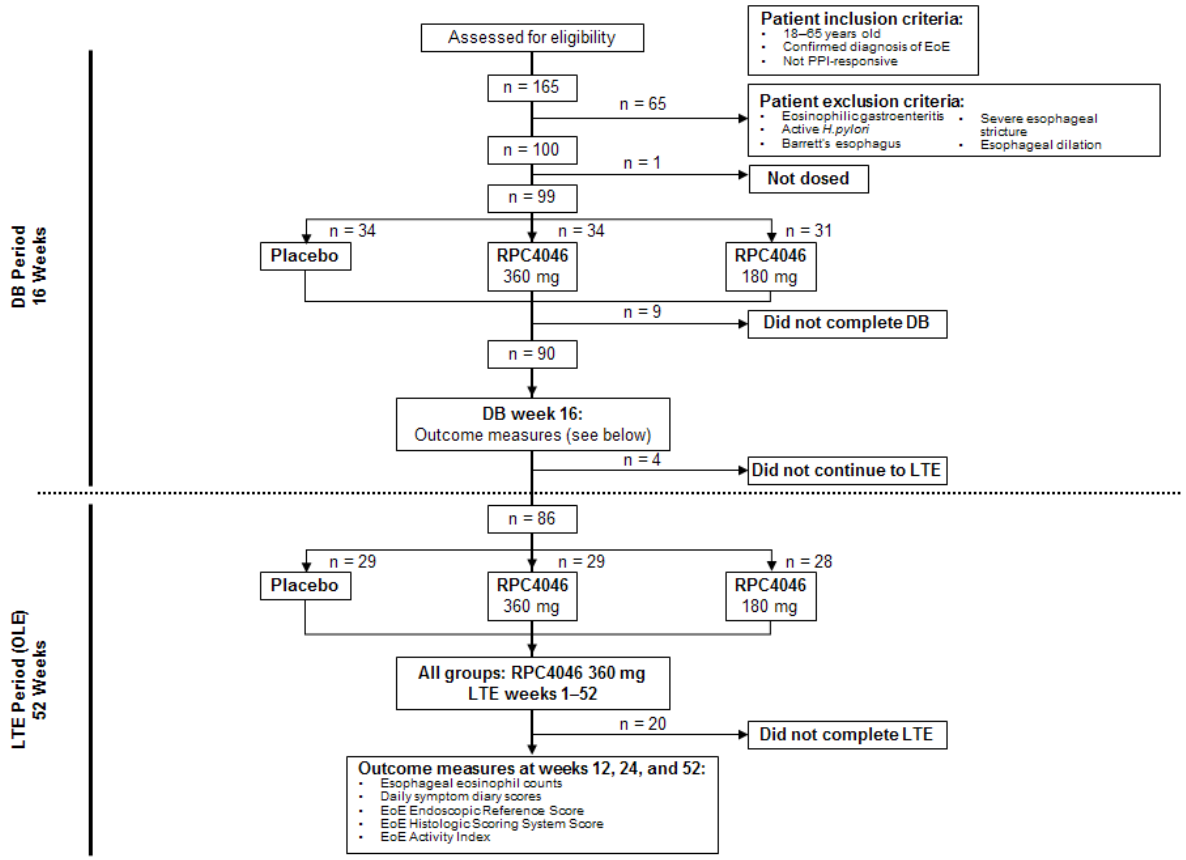
Supplementary Table 9. Injection Site Treatment-Emergent Adverse Events in LTE (LTE Population)

	Placebo (n=29)	RPC4046		Total (N=86)
		180 mg (n=28)	360 mg (n=29)	
Number of subjects experiencing ≥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)

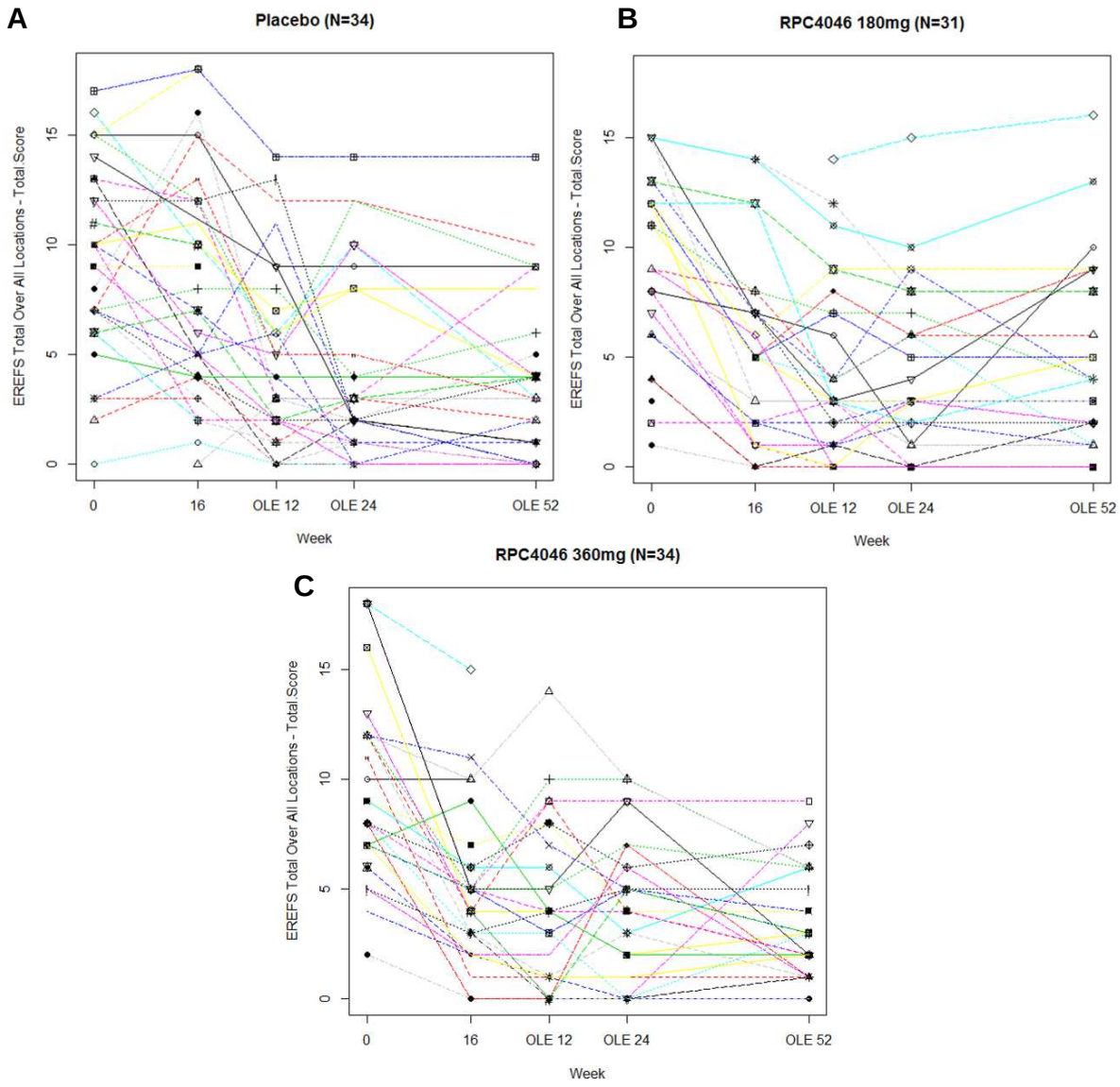
Data are number (%).

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

Supplementary Figure 1. Patient Flow Chart

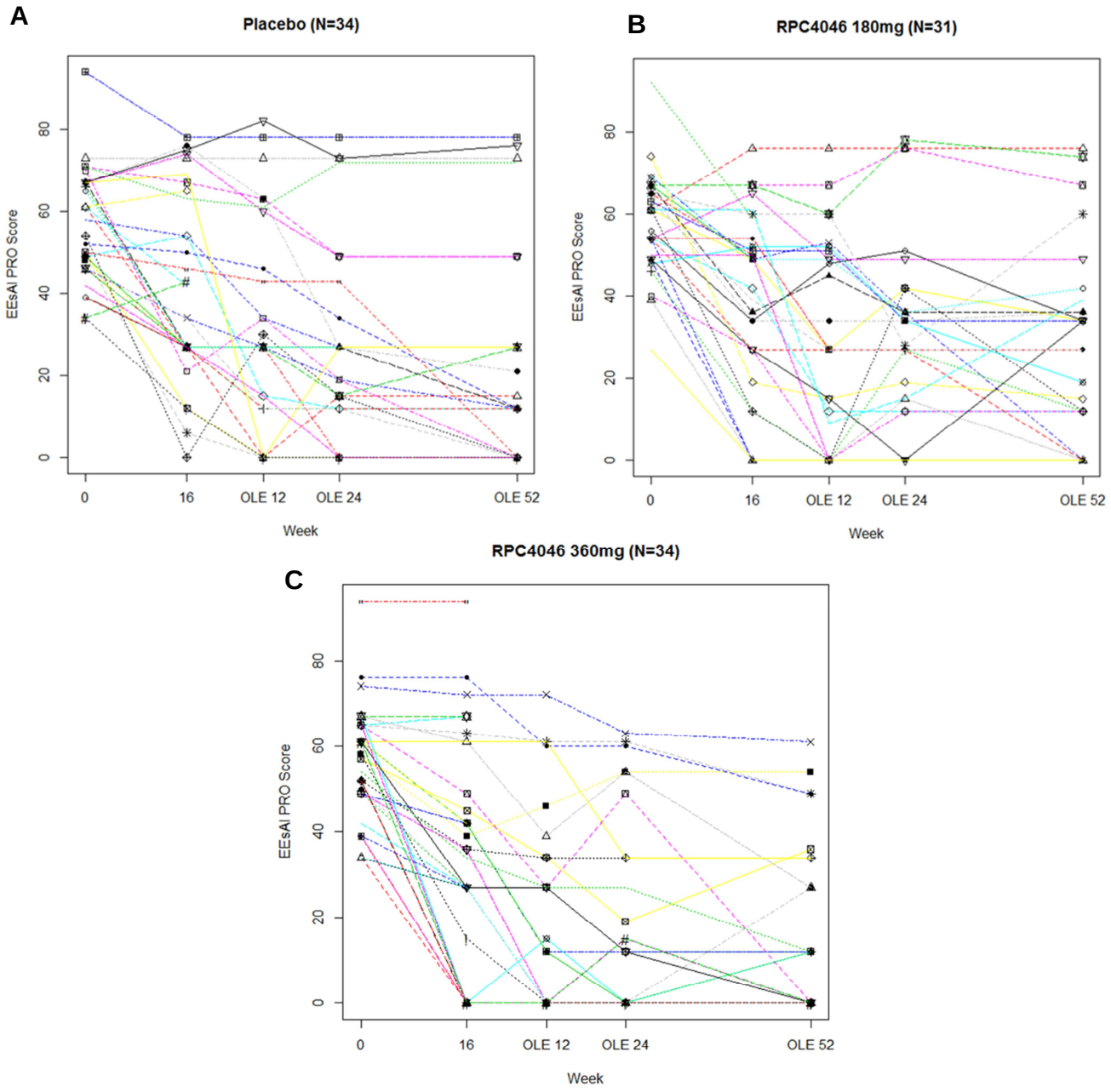


Supplementary Figure 2. EREFS Total Over All Locations - Total Score over time for each subject by treatment group (ITT population)



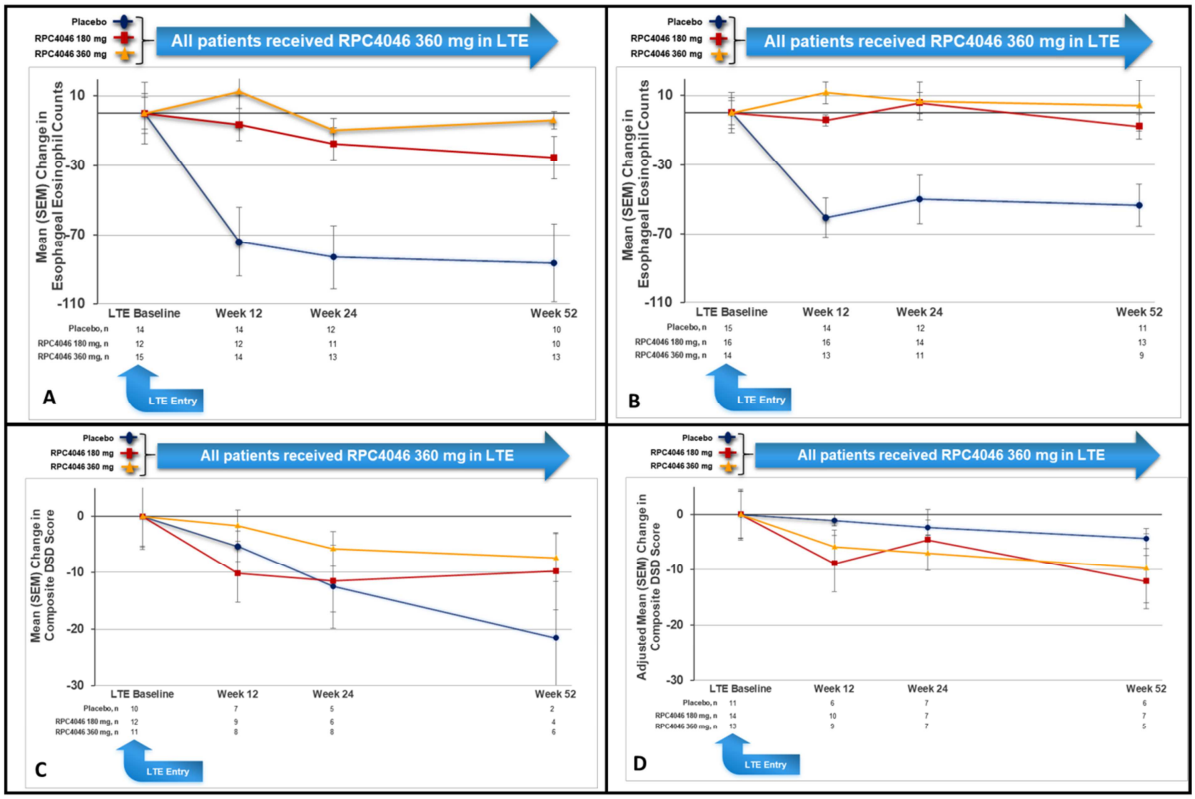
EREFS total over all locations at DB Weeks 0 and 16 and LTE Weeks 12, 24, and 52. (A) Individual data from placebo group (n=34); (B) RPC4046 180 mg (n=31); and (C) RPC4046 360 mg (n=34).

Supplementary Figure 3. EEsAI over time for each subject by treatment group (ITT population)



EEsAI over all locations at DB Weeks 0 and 16 and LTE Weeks 12, 24, and 52. (A) Individual data from placebo group (n=34); (B) RPC4046 180 mg (n=31); and (C) RPC4046 360 mg (n=34).

Supplementary Figure 4. Mean change (SEM) from LTE baseline in esophageal eosinophil counts and composite diary scores by steroid-refractory status at LTE Weeks 12, 24, and 52.
(A) Esophageal eosinophil counts in steroid-refractory group (eos/hpf); (B) Esophageal eosinophil counts in non-steroid refractory group (eos/hpf); (C) Composite DSD score in steroid-refractory group; (D) Composite DSD score in non-steroid refractory group (LTE population)



WHAT YOU NEED TO KNOW

Background

RPC4046 safety and efficacy were demonstrated in the 16-week induction period of a Phase 2, randomized, controlled study in adults with symptomatic eosinophilic esophagitis; here we report results from the 52-week, open-label long-term extension period.

Findings

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

Implications for patient care

The encouraging results observed with 1 year or more of RPC4046 treatment in patients with symptomatic eosinophilic esophagitis support conducting further confirmatory studies.