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Budesonide Oral Suspension Improves Symptomatic, Endoscopic, and Histologic Parameters Compared With Placebo in Patients With Eosinophilic Esophagitis

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See Covering the Cover synopsis on page 671.

BACKGROUND & AIMS: Pharmacologic treatment of eosinophilic esophagitis (EoE) is limited to off-label use of corticosteroids not optimized for esophageal delivery. We performed a randomized, controlled phase 2 trial to assess the ability of budesonide oral suspension (BOS), a novel muco-adherent topical steroid formulation, to reduce symptoms and esophageal eosinophilia in adolescents and adults with EoE. **METHODS:** In this multicenter, randomized, double-blind, placebo-controlled, parallel-group trial, 93 EoE patients between the ages of 11 and 40 years with dysphagia and active esophageal eosinophilia were randomized to receive either BOS 2 mg or placebo twice daily for 12 weeks. Co-primary outcomes were change in Dysphagia Symptom Questionnaire (DSQ) score from baseline, and proportion of patients with a histologic response (≤6 eosinophils/high-power field) after treatment. Endoscopic severity scores and safety parameters were assessed. **RESULTS:** At baseline, mean DSQ scores were 29.3 and 29.0, and mean peak eosinophil counts were 156 and 130 per hpf in the BOS and placebo groups, respectively. After treatment, DSQ scores were 15.0 and 21.5, and mean peak eosinophil counts were 39 and 113 per high-power field, respectively ($P < .05$ for all). For BOS vs placebo, change in DSQ score was −14.3 vs −7.5 ($P = .0096$), histologic response rates were 39% vs 3% ($P < .0001$), and change in endoscopic severity score was −3.8 vs 0.4 ($P < .0001$). Adverse events were similar between groups. **CONCLUSIONS:** Treatment with BOS was well tolerated in adolescent and young adult patients with EoE and resulted in improvement in symptomatic, endoscopic, and histologic parameters using validated outcome instruments. ClinicalTrials.gov ID NCT01642212.

Keywords: Corticosteroids; Dysphagia; Eosinophilic Esophagitis; Patient-Reported Outcomes.

Eosinophilic esophagitis (EoE) is an allergen/immune-mediated condition characterized clinically by symptoms of esophageal dysfunction and histologically by eosinophilic infiltration of the esophageal mucosa.[1–3] Typical symptoms include dysphagia and food impaction in adolescents and adults, and heartburn, regurgitation, vomiting, and feeding intolerance in children.[4] Over the past 2 decades, EoE has rapidly emerged as a major cause of upper gastrointestinal morbidity, and it is now the most common cause of food bolus impaction[5,6] and the second most common cause of esophagitis.[7–9] The incidence and prevalence of EoE are increasing,[8,10,11] and health care expenditure related to EoE in the United States approaches $1 billion annually.[12]

Corticosteroids are the first-line pharmacologic therapy for patients diagnosed with EoE.[1,2,13,14] These medications are used topically: asthma preparations are swallowed rather than inhaled to coat the esophagus, but are suboptimal for use in EoE. For example, inadequate esophageal delivery and undesired pulmonary deposition can result from medication administered into the mouth using metered-dose inhalers, and variable drug concentrations are possible when patients mix aqueous forms into viscous slurries.[13,15] Although data support the use of both fluticasone[16–24] and budesonide,[15,25–30] neither are approved by the Food and Drug Administration for this indication. In addition, although these agents can decrease or resolve esophageal eosinophilia, symptom response has been inconsistent.[13,15,20,21,29–31] In addition, published trials have not evaluated EoE symptoms using a validated patient-reported outcome (PRO) measure.[32,33]

Budesonide oral suspension (BOS) is a novel muco-adherent medication formulated specifically for use in EoE, with standardized viscosity and concentration. It has

Abbreviations used in this paper: ANCOVA, analysis of covariance; BOS, budesonide oral suspension; CI, confidence interval; DSQ, Dysphagia Symptom Questionnaire; EoE, eosinophilic esophagitis; eos/hpf, eosinophils per high-power field; EREFS, Endoscopic Reference Score; OR, odds ratio; PPI, proton pump inhibitor; PRO, patient-reported outcome; SD, standard deviation.

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previously been shown to induce a dose-dependent histologic response in children with EoE,[29] but has not been assessed in adults. The aim of this phase 2 study was to determine whether BOS was superior to placebo in decreasing symptoms of dysphagia, as measured by a validated instrument, and decreasing esophageal eosinophil counts in adolescents and adults with EoE.

Materials and Methods

Study Design and Participants

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group phase 2 trial conducted from July 2012 to October 2014 at 25 centers throughout the United States (see Supplementary Material). The study was approved by the Institutional Review Board at each center, registered at ClinicalTrials.gov (NCT01642212), performed in accordance with the provisions of the Declaration of Helsinki, and reported per the CONSORT (Consolidated Standards of Reporting Trials) statement. Participants or parents/legal guardians provided written informed consent before taking part in the study. Participants did not receive a stipend from the study sponsor.

Potential study participants were aged 11−40 years. The lower bound of the age range was selected as this was considered to be the minimum age at which patients would be able to self-assess dysphagia, understand the Dysphagia Symptom Questionnaire (DSQ) and complete the daily DSQ entries. The upper bound of the age range was chosen as, at the time of the study design, it was felt to be the most appropriate cutoff to exclude older patients who are more likely to have fibrostenotic disease and typically are not amenable to anti-inflammatory treatment alone.[31,34] Patients aged younger than 18 years were also included in this study, as the previous pediatric study did not measure symptom response using a validated instrument.[29] Study participants were also required to have a confirmed diagnosis of EoE using 2011 consensus guidelines:[1] specifically, symptoms of esophageal dysfunction and at least 15 intra-epithelial eosinophils per high-power field (eos/hpf) (hpf area: 0.3 mm^2) after an 8-week, high-dose (refers to a total daily dose, which could be administered as a once or twice daily dosing regimen), proton pump inhibitor (PPI) trial using any approved PPI. The PPI trial was either historical or could have been performed during the screening period of this study; PPI-responsive EoE was defined as $<$15 eos/hpf, as recommended by the current guidelines.[1] Other potential causes of esophageal eosinophilia had also been excluded. For inclusion, patients with EoE were required to have at least 15 eos/hpf from at least 2 esophageal levels on screening endoscopy, at least 4 days with symptoms of dysphagia over the last 2 weeks of a 4-week blinded placebo run-in period, and at least 70% compliance with a daily symptom diary. The purpose of these criteria was to include patients with active EoE who were highly symptomatic and whose symptoms persisted during the placebo run-in period. The exclusion criteria included presence of any of the following: non-EoE gastrointestinal diseases, including eosinophilic gastroenteritis/colitis, inflammatory bowel disease, celiac disease, *Helicobacter pylori* infection, esophageal candidiasis (defined based on investigator discretion), or esophageal varices; diseases causing systemic eosinophilia; or esophageal stricture on screening endoscopy that precluded passage of an adult upper endoscope. Gastroesophageal reflux disease and erosive esophagitis were not formal exclusion criteria, but patients with esophageal eosinophilia related to gastroesophageal reflux disease were excluded, as based on PPI-responsive eosinophilia. Other exclusion criteria were: use of corticosteroids (topical or systemic) in the 4 weeks preceding the screening endoscopy; use of immunomodulatory therapy in the 8 weeks preceding the screening endoscopy; change in dosing regimen of PPIs, allergy medications, or inhaled corticosteroids; pregnancy; and medical instability.

Randomization, Interventions, and Outcomes

After a screening upper endoscopy and biopsy, symptoms were assessed during a 4-week placebo-run-in period, during which all patients received single-blind placebo. If patients met histology and symptom eligibility criteria, they were randomized 1:1 to either BOS 2 mg twice daily (given as 10 mL, once in the morning after breakfast and once in the evening before bedtime to provide a total daily dose of 4 mg), or a placebo suspension twice daily, for 12 weeks. BOS is formulated in a viscous suspension designed to increase the time the drug is in contact with the surface of the esophagus after swallowing. The pre-mixed suspension uses a combination of 2 viscosity-modifying agents to give the suspension a syrup-like consistency (as opposed to a slurry), along with buffers, preservatives, and flavoring agents. Patients were instructed not to eat, drink, brush their teeth or rinse their mouth for 30 minutes after taking BOS. After 30 minutes, patients were instructed to rinse their mouth with water.

The randomization schedule was generated by SynteractHCR, Inc. and was verified for accuracy using strict quality-control procedures. Randomization was stratified by site with a block size of 4. Participants eligible for randomization received sequentially generated randomization numbers issued by Clinical Supplies Management, Inc., which were matched to the number on their study drug kit. The randomization number was not used to identify a patient's study data. Instead, all patients were assigned a unique 6-digit patient identification number at screening. Participants, investigators, the sponsor, study site personnel, and the central pathologist were blinded to patients' treatment, until after all patients had completed the treatment period and the database was locked. Treatment assignment was only to be unblinded in a situation where unblinding was absolutely necessary for the management of patient safety or for regulatory reporting purposes to the Food and Drug Administration. However, no patients required treatment assignment unblinding before the database lock in this study. Active study medication and placebo were dispensed in identical amber glass bottles to maintain the blind.

Compliance was measured by residual volume in the medication bottles. At the end of the treatment period, repeat endoscopy and biopsy were performed. The co-primary outcomes were the change in DSQ score from baseline; and the proportion of patients with a histologic response, defined as $\leq$6 eos/hpf. This cutoff of $\leq$6 eos/hpf was used in the previous pediatric study of BOS,[29] and is supported by a number of studies in the literature.[35,36] Secondary end points included endoscopic findings and safety.

The DSQ is a 3-question daily diary that has been validated for the measurement of dysphagia frequency and severity in patients with EoE.[37,38] The questions ask whether solid food

has been eaten; whether food has gone down slowly or become stuck; and what, if any, measures have been taken to achieve relief. DSQ scores are calculated on the basis of the responses to these questions over a 2-week period. The scores for questions 2 and 3 are summed, then divided by the number of days for which the diary has been completed and multiplied by 14. Scores can range from 0 to 84, with higher values indicating more frequent and severe dysphagia. A DSQ score of 0 represents an absence of dysphagia symptoms. DSQ scores over the last 14 days of the 12-week treatment period were used for the symptom outcome measure using the algorithm above. Two prespecified secondary end points were also examined: the proportion of patients with a $\geq$30% or a $\geq$50% reduction in DSQ score from baseline; and 2) patients who had this symptom response combined with a histologic response ($\leq$6 eos/hpf).

For histology assessment, 2 to 4 esophageal biopsies were obtained from each level of the esophagus (proximal, mid, and distal). Biopsies were reviewed centrally by the study pathologist (M.H.C., who was blinded to treatment allocation). All biopsies from each site in the esophagus were examined, and intraepithelial eosinophils were counted in the areas of greatest eosinophil density.[39] Counts were reported as the number of eos/hpf (hpf area = 0.3 mm^2) and multiple hpfs were analyzed until the peak count was clearly identified. In addition, gastric and duodenal biopsies were obtained and reviewed centrally during the screening period to exclude patients with concomitant eosinophilic gastroenteritis.

Upper endoscopy was performed using standard techniques. Endoscopic findings (esophageal rings, white plaques or exudates, linear furrows, decreased vascularity or edema, and strictures) were recorded and quantified using the validated EoE Endoscopic Reference Score (EREFS);[40] esophageal biopsies were obtained at the same time. The total EREFS was calculated by summing the severity scores of the individual components of the EREFS (edema 0−2, rings 0−3, exudates 0−2, furrows 0−2, strictures 0−1) assessed for both the proximal and distal esophagus, and ranged from 0 to 20, with higher scores indicating more severe endoscopic findings.

Safety was assessed at each study visit by carrying out a physical examination and recording height, weight, and vital signs. Clinical laboratory tests were also performed, including assessment of a morning cortisol level to monitor the adrenal axis. Patients received a follow-up telephone call 4 weeks after receiving their last dose of the study drug. All clinical laboratory tests were performed by a centralized clinical laboratory (LabConnect, LLC).

Statistical Analyses

Data were collected by investigators at each site and the database was managed by the study sponsor. All authors had access to the study data and reviewed and approved the final manuscript. There were 2 analysis sets. The safety analysis set included all patients who received any study drug. The modified intention-to-treat analysis set included all randomized patients who received at least 1 dose of study drug and had both an evaluable post-treatment DSQ score and a post-treatment biopsy. Characteristics of the treatment and placebo arms were summarized with descriptive statistics. The change in DSQ score and change in EREFS were each compared using analysis of covariance, and the proportion of patients with a histologic response was compared using Fisher's exact test. We also compared levels of symptom, histologic, and endoscopic response using Fisher's exact test. For exploratory analyses based on histologic response, odds ratios (for categorical variables) and differences (for continuous variables) with 95% confidence intervals were calculated.

The planned sample size was to have at least 40 patients in each arm complete the study. This would yield >90% power to detect an 88% difference in histologic response,[29] and 89% power to detect a 35% difference in symptom response. Assuming a 20% dropout rate, the goal was to enroll 50 patients in each arm.

Role of the Funding Source

Meritage Pharma, Inc, now part of the Shire group of companies, contributed to the design and conduct of the study; collection and management of the data; and reviewed the manuscript for medical accuracy. Approval of the manuscript, and the decision to submit the manuscript for publication was the responsibility of the authors.

Results

Patient Flow and Baseline Characteristics

Of the 203 patients screened, 119 met eligibility criteria and entered the blinded placebo run-in period. Of these, 26 were excluded, primarily for experiencing dysphagia on too few days, and 93 were randomized, 51 to BOS and 42 to placebo. This group comprised the safety analysis set. Of the randomized patients, 5 dropped out, 2 in the BOS arm (1 because of an adverse event and 1 owing to lack of compliance) and 3 in the placebo arm (1 because of lack of efficacy, 1 because of lack of compliance, and 1 owing to pregnancy); 1 additional patient in the placebo arm did not have an evaluable post-treatment biopsy. Therefore, 87 were included in the outcome analysis set (49 on BOS and 38 on placebo) (Supplementary Figure 1).

The BOS and placebo groups had similar baseline characteristics (Table 1). The BOS and placebo groups also had a similarly high prevalence of endoscopic findings, such as esophageal rings (61% and 64%), white plaques (73% and 69%), linear furrows (94% and 86%), and edema (80% and 76%, respectively). Compliance with study medication was high in both the BOS and the placebo groups, with 86% and 88% receiving the intended dose.

Symptomatic, Histologic, and Endoscopic Outcomes

The baseline mean DSQ scores were 29.3 in the BOS group and 29.0 in the placebo group. After treatment, these decreased to 15.0 and 21.5, respectively. There was a significantly larger decrease in the BOS group (−14.3) than the placebo group (−7.5; $P = .0096$) (Table 2; Figure 1*A*). The first of the co-primary end points was therefore met. When examining symptom thresholds (prespecified secondary end point), 34 patients (69%) in the BOS group had a $\geq$30% reduction in DSQ score compared with 17 patients (45%) in the placebo group ($P = .021$). Similarly, 31

Table 1. Demographics and Baseline Measures in Patients With Eosinophilic Esophagitis Receiving Budesonide Oral Suspension or Placebo

Characteristic	BOS (n = 51)	Placebo (n = 42)
Age, *y*, mean ± SD	22.3 ± 7.9	20.8 ± 7.5
Younger than 18 y, n (%)	18 (35)	17 (41)
Age of those younger than 18 y, mean ± SD	14.6 ± 2.2	13.6 ± 1.6
Male, n (%)	35 (69)	29 (69)
White, n (%)	48 (94)	40 (95)
Months since EoE diagnosis, mean ± SD	38.5 ± 34.3	36.5 ± 42.6
Height, *cm,* mean ± SD	173.6 ± 9.9	170.7 ± 13.0
Weight, *kg*, mean ± SD	72.0 ± 16.9	67.8 ± 17.3
Previous medication, n (%)		
Corticosteroids	14 (28)	13 (31)
Systemic, oral	2 (4)	2 (5)
Systemic, intravenous	5 (10)	5 (12)
Inhaled	2 (4)	4 (10)
Intranasal	7 (14)	6 (14)
Antihistamines	8 (16)	3 (7)
Leukotriene antagonists	6 (12)	6 (14)
Proton pump inhibitors		
Past	35 (69)	29 (69)
Current	36 (71)	28 (67)
Endoscopic findings, n (%)		
Normal	1 (2)	2 (5)
Esophageal rings	31 (61)	27 (64)
White plaques or exudates	37 (73)	29 (69)
Linear furrows	48 (94)	36 (86)
Edema or decreased vascularity	41 (80)	32 (76)
Esophageal stricture	7 (14)	4 (10)
Total EREFS, mean ± SD[a]	7.7 ± 3.5	7.0 ± 3.3
DSQ score, mean ± SD[b]	30.4 ± 15.9	29.0 ± 13.5
Peak eosinophil counts, *eos/hpf*, mean ± SD		
Overall	157.8 ± 96.1	133.0 ± 81.6
By esophageal location		
Proximal	100.9 ± 99.6	53.4 ± 58.5
Mid	103.8 ± 67.5	94.4 ± 80.5
Distal	107.4 ± 79.5	95.6 ± 74.8

[a]The total EREFS was calculated by summing the scores for the 5 major individual findings (grade 0–3 for esophageal rings; grade 0–2 for white plaques or exudates, edema or decreased vascularity, and linear furrows; and grade 0–1 for esophageal stricture) from both the proximal and distal esophagus.
[b]DSQ score calculated based on patient responses to questions 2 and 3 of the questionnaire (frequency and intensity of dysphagia) over a 2-week period. Scores from these questions were summed, divided by number of days for which the diary was completed, and multiplied by 14 (days). Scores could range from 0 to 84.

patients (63%) in the BOS group had a ≥50% reduction in DSQ score compared with 15 patients (40%) in the placebo group ($P = .028$). The number of patients who experienced complete symptom resolution (DSQ score 0) at week 12 was reported as an exploratory outcome, and was higher in the BOS group (20% [10 of 49]) than in the placebo group (13% [5 of 38]).

Table 2. Baseline and Post-Treatment Measures in Patients With Eosinophilic Esophagitis Receiving Budesonide Oral Suspension or Placebo

Variable	BOS (n = 49)	Placebo (n = 38)	*P* value
DSQ score, mean ± SD[a]			
Baseline	29.3 ± 15.1	29.0 ± 13.9	
Post-treatment	15.0 ± 16.9	21.5 ± 16.0	
Difference	−14.3 ± 13.0	−7.5 ± 10.7	.0096
Proportion of histologic responders, n (%)[b]	19 (39)	1 (3)	<.0001
Peak eosinophil count, *eos/hpf*, mean ± SD			
Baseline	156.3 ± 97.6	130.2 ± 81.8	
Post-treatment	39.3 ± 48.1	112.9 ± 84.3	
Difference	−117.0 ± 111.6	−17.3 ± 83.8	<.0001
EREFS, mean ± SD[c]			
Baseline	7.7 ± 3.6	6.9 ± 3.4	
Post-treatment	3.9 ± 3.3	7.3 ± 4.0	
Difference	−3.8 ± 3.9	0.4 ± 6.7	<.0001

[a]DSQ score calculated based on patient responses to questions 2 and 3 of the questionnaire (frequency and intensity of dysphagia) over a 2-week period. Scores from these questions were summed, divided by number of days for which the diary was completed, and multiplied by 14 (days). Scores could range from 0 to 84.
[b]Proportion of histologic responders post-treatment; histologic response defined as ≤6 eos/hpf.
[c]The total EREFS was calculated by summing the scores for the 5 major individual parameters (grade 0–3 for esophageal rings; grade 0–2 for white plaques or exudates, edema or decreased vascularity, and linear furrows; and grade 0–1 for esophageal stricture) from both the proximal and distal esophagus.

At baseline, the means of the peak eosinophil counts were 156 eos/hpf in the BOS group and 130 eos/hpf in the placebo group. Post-treatment, these were 39 and 113, respectively ($P < .0001$; Table 2). The distribution of peak eosinophil counts for patients in the BOS and placebo groups at baseline (safety analysis set) by esophageal region is shown in Supplementary Figure 2. A total of 19 patients (39%) in the BOS group achieved the histologic response end point of ≤6 eos/hpf, compared with 1 patient (3%) in the placebo group ($P < .0001$) (Table 2; Figure 1*B*), thus meeting the second of the co-primary end points. Illustrative pre- and post-treatment biopsies are shown in Figure 2. When examining additional histologic response thresholds, a total of 23 patients (47%) in the BOS group had ≤15 eos/hpf vs 3 (8%) in the placebo group ($P = .0001$), and 15 (31%) patients in the BOS group had ≤1 eos/hpf vs none in the placebo group ($P < .0001$).

An additional secondary efficacy end point showed that a higher proportion of patients in the BOS group had both a histologic response and a ≥30% reduction in DSQ score compared with patients in the placebo group (27% vs 3%; $P = .0026$); a higher proportion of patients receiving BOS also experienced both a histologic response and a ≥50% reduction in DSQ score compared with placebo (20% vs 3%; $P = .0199$).

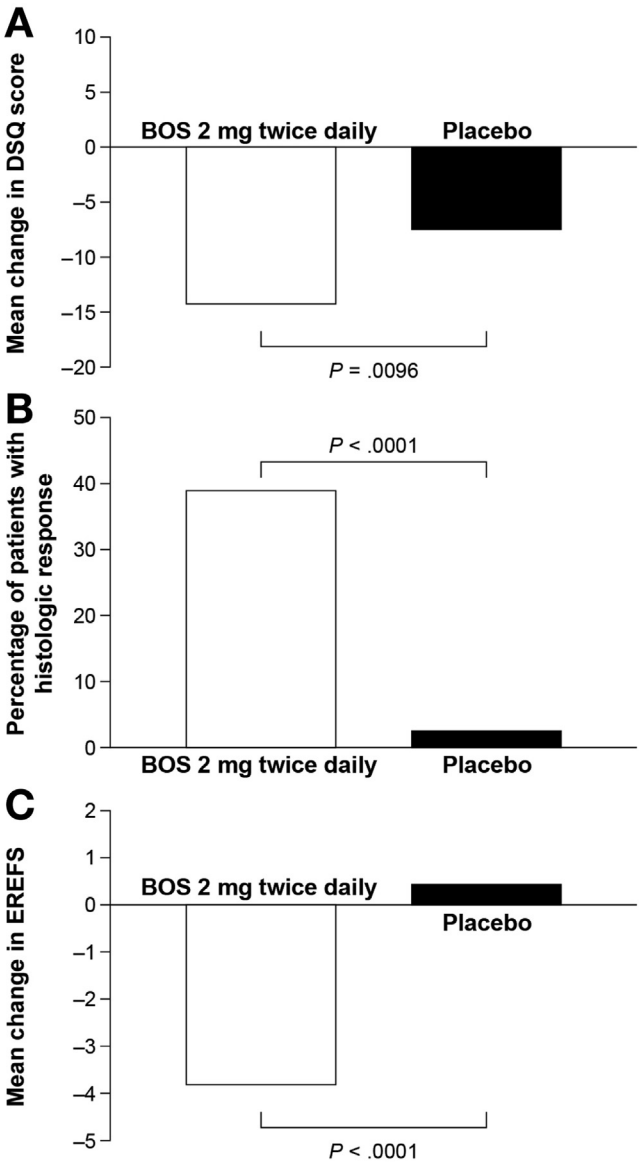

Figure 1. Study outcomes in patients with eosinophilic esophagitis receiving budesonide oral suspension vs placebo. (*A*) Change in DSQ score; (*B*) histologic outcomes; and (*C*) endoscopic outcomes from baseline.

The baseline mean EREFSs were 7.7 in the BOS group and 6.9 in the placebo group. After treatment, these were 3.9 and 7.3, respectively. There was a significantly larger decrease in the BOS group (−3.8) than in the placebo group (0.4; $P < .0001$) (Table 2; Figure 1*C*). In addition to the improvement in total EREFS, significant improvements within each EREFS component (with the exception of strictures) from baseline were also observed for patients receiving BOS compared with those receiving placebo (Figure 3). The severity score for esophageal rings in the BOS group decreased (improved) from 1.7 to 1.0, but was unchanged in the placebo group (1.4 to 1.7) (change from baseline: −0.7 vs +0.3; $P = .006$). Similarly, the severity score for esophageal exudates in the BOS group decreased from 1.6 to 0.4, but was unchanged in the placebo group (1.4 to 1.3) (change from baseline: −1.2 vs −0.1; $P < .001$). Severity scores for furrows in the BOS group decreased from 2.3 to 1.2 without a change in the placebo group (2.0 to 2.1) (change from baseline: −1.1 vs +0.1; $P < .0001$. Severity scores for edema in the BOS group decreased from 1.9 to 1.1, again without any change in the placebo group (1.9 to 2.1) (change from baseline: −0.8 vs +0.2; $P = .004$) (Figure 3). These scores were calculated from 2 levels of the esophagus (proximal and distal); and the data are presented by location in Supplementary Table 1. These results show an improvement in endoscopic features in the BOS group from baseline in both the proximal and distal regions of the esophagus. Furthermore, a total of 7 patients (14%) in the BOS group and 1 patient (3%) in the placebo group had normal endoscopic findings (EREFS 0) after treatment. Illustrative pre- and post-treatment endoscopic images are shown in Figure 2.

Given that symptoms, histology, and endoscopic severity all improved with BOS compared with placebo, we investigated correlations between these responses. In the BOS group, there was a weak correlation between change in peak eosinophil count and change in DSQ score ($R = 0.04$) and between change in DSQ score and change in EREFS ($R = 0.05$), but a moderate correlation between change in peak eosinophil count and change in EREFS ($R = 0.33$).

Overall, clinical, endoscopic, and histologic baseline characteristics were similar in patients treated with BOS who did and did not have a histologic response (Table 3). However, compared with histologic responders, nonresponders had been diagnosed with the disease for almost twice as long (46 vs 25 months) and were more than 10 kg heavier (76 vs 65 kg). Symptoms and endoscopic findings improved more in histologic responders than in nonresponders. The mean change in the DSQ score was −16.2 in histologic responders and −9.9 in nonresponders ($P < .001$). Similarly, the mean change in total EREFS was −5.1 in histologic responders and −2.9 in nonresponders ($P = .06$).

Safety and Adverse Events

Reports of treatment-emergent adverse events were similar in the BOS (47%) and placebo (50%) groups (Supplementary Table 2). There was 1 severe adverse event in the BOS group related to an episode of food poisoning and deemed unrelated to the study drug, and a second adverse event in the BOS group that led to withdrawal because of chest pain, dyspnea, nausea, and vomiting, which was deemed related to the study drug. Nasopharyngitis, upper respiratory infection, and oropharyngeal pain were the most commonly reported adverse events in both groups. There was 1 case each of esophageal candidiasis and oral candidiasis in the BOS group. There were no laboratory-related treatment-emergent adverse events. Additionally, there were no notable differences between groups in cortisol levels (Supplementary Table 3) or growth characteristics (for those aged younger than 18 years; Supplementary Table 4), and vital signs remained stable for all participants.

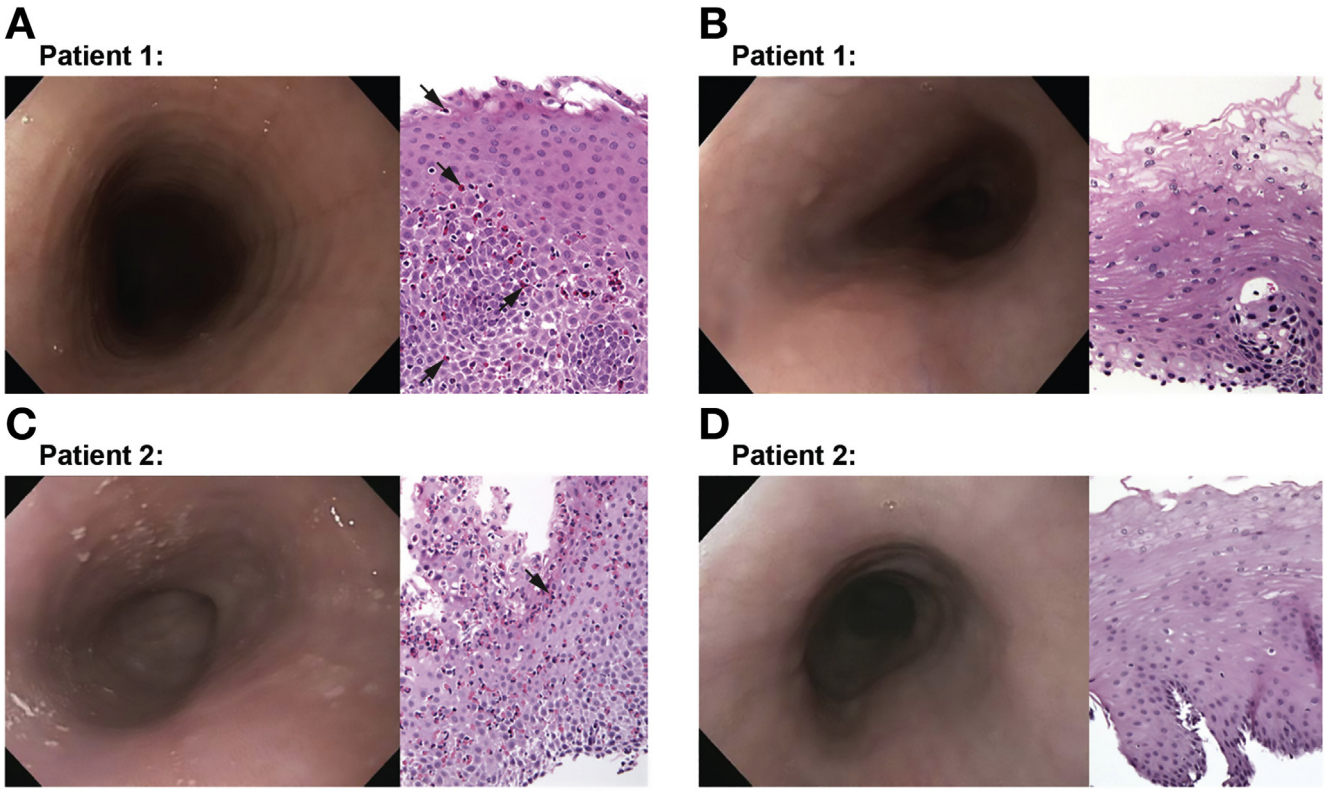

Figure 2. Baseline and post-treatment endoscopies with corresponding esophageal biopsies for 2 patients with eosinophilic esophagitis receiving budesonide oral suspension. Pretreatment images show esophageal rings, linear furrows, and edema (patient 1 [*A*]), and white plaques and edema (patient 2, [*C*]). Both biopsy specimens have elevated mucosal eosinophilia, indicated by *arrows* (*A, C*). Post-treatment images show normalization of the esophageal mucosa and the epithelium (*B, D*). Histology images: stained with H&E; 200× original magnification.

Discussion

Topical corticosteroids are the first-line pharmacologic treatment option for patients with EoE, but none are Food and Drug Administration–approved or designed for EoE and none have previously been assessed using a validated PRO instrument.[1,2,4,13,32,33] This multicenter, randomized, double-blind, placebo-controlled, parallel-group phase 2 trial aimed to determine whether BOS was superior to placebo in decreasing symptoms of dysphagia and esophageal eosinophil counts. Not only did BOS induce a histologic response in a significantly higher proportion of patients than placebo, we show for the first time that it also significantly decreased symptoms of dysphagia as assessed by a validated PRO instrument. Importantly, the decrease in symptom score was clinically meaningful with dysphagia being experienced on approximately 3 fewer days over 2 weeks in the BOS group than in the placebo group. Furthermore, the study is the first to demonstrate improvement in endoscopic severity scores, assessed using the validated EREFS instrument. In addition, patients with a histologic response experienced greater improvements in dysphagia symptoms and endoscopic severity compared with nonresponders. No safety issues related to BOS were identified during the 12-week treatment period, and patients were highly compliant. There were only 2 cases of esophageal candidiasis in patients receiving BOS; this is lower than the reported rates in the literature for other swallowed corticosteroids;[28,30] however, this finding is consistent with a previous study of this budesonide formulation.[29]

Several formulations of budesonide have previously been used in clinical trials, including a slurry created by mixing an aqueous form with sucralose,[15,27] a nebulized form (allowing aerosolized droplets to be swallowed),[15,28] a pre-mixed viscous solution,[29,30] and an effervescent dissolvable tablet.[30] Doses in these studies were 1–4 mg/d, with treatment periods of 2–12 weeks. Histologic responses were variable (27%–100% depending on the age group, formulation, and histologic response threshold studied) and symptom response rates were equally variable. None of these studies used a validated symptom instrument, and in 3 of the 5 trials there were discordant symptomatic and histologic responses.[15,29,30] In addition to these individual studies, a number of systematic reviews/meta-analyses have been performed to examine the efficacy of current pharmacologic treatments for EoE. These reviews have shown that patients treated with topical corticosteroids typically experience improvements in histologic outcomes compared with placebo (or therapy control); however, a clear symptom response is often less evident,[41–44] in part due to the absence of a validated clinical outcome assessment for EoE.

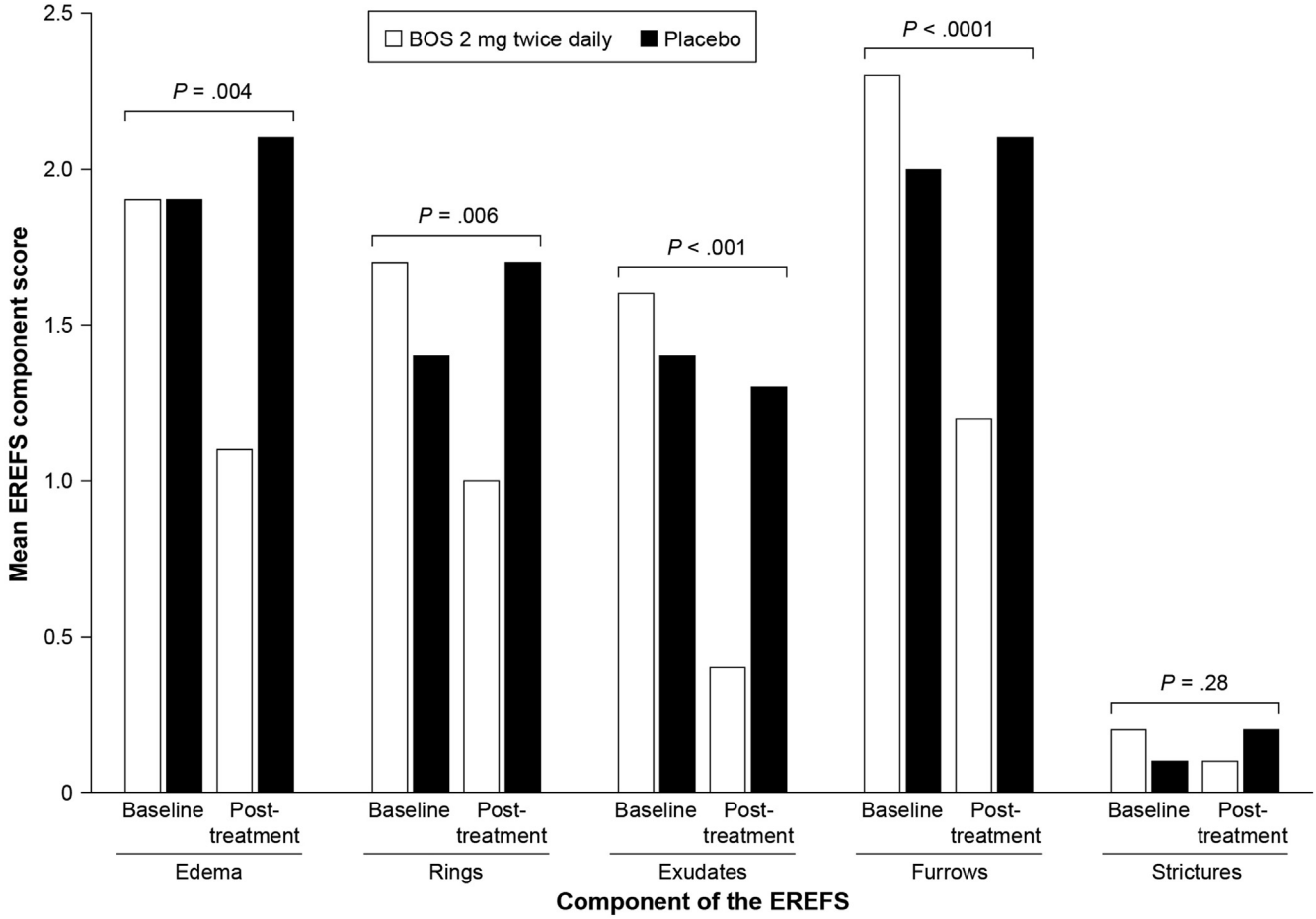

Figure 3. Baseline and post-treatment changes in endoscopic severity for individual components of the EREFS for patients with eosinophilic esophagitis receiving budesonide oral suspension vs placebo. Findings for esophageal edema, rings, exudates, furrows, and strictures are presented at baseline and post-treatment for the BOS and placebo groups. *P* values compare change in scores from baseline between treatment arms.

In the previous study of BOS,[29] children were treated with age-based dosing, and of those receiving the highest dose (2 mg twice daily), 94% had a histologic response compared with 6% in the placebo group. The present study had a lower histologic response rate than this. However, our observed response rate is consistent with the range of responses that have been reported for topical steroids overall in the literature.[15,18,19,21,27–30,45] The reasons for the difference in histologic response observed in this study and the previous study of BOS[29] are not known, but earlier studies of pediatric EoE have shown that age, body mass, and height are predictors of steroid response.[18] The lower histologic response observed in the present study may also be a result of the study design, in particular the inclusion criteria. For enrollment in the current study, patients were required to have active inflammation and also to be highly symptomatic, with at least 4 days of dysphagia in the 2 weeks before study entry. In addition, patients had to maintain this high level of symptomatology during a blinded placebo run-in period in order to be randomized. They also had to have eosinophilic inflammation at 2 levels in the esophagus, a stringent inclusion criterion used only in the previous BOS study.[29] This probably resulted in a more severe disease phenotype than seen in other studies,[28–30] which might also have been more treatment resistant. For example, the peak baseline eosinophil count in this study, 156.3 eos/0.3 mm^2 hpf (or 521 eos/mm^2) in the BOS arm, is among the highest reported in the literature; in other studies of budesonide using this as an outcome measure, peak baseline eosinophil densities were 320−421 eos/mm^2 (after conversion of counts based on hpf area).[15,29,30] To our knowledge, no other published study has been designed to enroll a comparably symptomatic and histologically severe population of patients with EoE. Indeed, Eluri and colleagues have recently identified disease severity as a significant predictor of response to steroids.[46] Finally, although a number of studies have reported high (>90%) histologic response rates in patients receiving topical corticosteroids,[29,30] no statistically significant difference in symptom response compared with placebo was observed in these earlier studies.

We found few predictors of histologic response; only shorter disease duration and lower body weight were associated with response. However, these results may have

Table 3. Comparison of Baseline Characteristics in Patients With Eosinophilic Esophagitis Receiving Budesonide Oral Suspension According to Histologic Response (≤6 eos/hpf)

Characteristic	Patients with histologic response[a]		
	Responders (n = 19)	Nonresponders (n = 30)	OR or difference (95% CI)
Age, *y*, mean ± SD	22.5 ± 7.7	21.7 ± 7.6	0.9 (−3.7 to 5.4)
Younger than 18 y, n (%)	8 (42)	10 (33)	0.69 (0.21 to 2.25)
Male, n (%)	11 (58)	24 (80)	2.91 (0.81 to 10.4)
White, n (%)	16 (84)	30 (100)	—
Time since EoE diagnosis, *mo*, mean ± SD	25.2 ± 22.3	45.5 ± 36.8	−20.3 (−39.9 to −0.8)
Height, *cm*, mean ± SD	172.5 ± 8.3	174.8 ± 11.0	−2.4 (−8.3 to 3.5)
Weight, *kg*, mean ± SD	64.6 ± 10.5	76.4 ± 18.4	−11.7 (−21.0 to −2.3)
Previous medication, n (%)			
Corticosteroids (any)	5 (26)	9 (30)	1.20 (0.33 to 4.34)
Antihistamines	5 (16)	4 (13)	0.82 (0.16 to 4.15)
Leukotriene antagonists	1 (5)	5 (17)	3.60 (0.39 to 33.5)
Current proton pump inhibitors	15 (79)	20 (67)	0.53 (0.14 to 2.03)
Endoscopic findings, n (%)			
Esophageal rings	10 (53)	20 (67)	1.80 (0.55 to 5.84)
White plaques or exudates	15 (79)	20 (67)	0.53 (0.14 to 2.03)
Linear furrows	18 (95)	28 (93)	0.78 (0.07 to 9.22)
Edema or decreased vascularity	14 (74)	25 (83)	1.79 (0.44 to 7.25)
Esophageal stricture	2 (11)	5 (17)	1.70 (0.29 to 9.80)
Total EREFS, mean ± SD[b]	7.4 ± 3.7	7.8 ± 3.6	−0.4 (−2.5 to 1.8)
DSQ score, mean ± SD[c]	30.9 ± 15.1	28.2 ± 15.3	2.6 (−6.3 to 11.6)
Peak eosinophil counts, *eos/hpf*, mean ± SD			
Overall	154.2 ± 98.0	157.7 ± 99.0	−3.5 (−61.7 to 54.6)
By esophageal location			
Proximal	86.7 ± 78.8	104.1 ± 113.0	−17.4 (−78.0 to 43.2)
Mid	102.9 ± 50.3	106.1 ± 78.6	−3.2 (−45.2 to 38.9)
Distal	113.1 ± 96.2	105.2 ± 71.2	7.8 (−40.3 to 56.0)
By baseline eosinophil count, n (%)			
>50 eos/hpf	19 (100)	27 (90)	—
>100 eos/hpf	11 (58)	21 (70)	1.70 (0.51 to 5.63)

[a]Histologic responders defined as ≤6 eos/hpf; nonresponders defined as >6 eos/hpf.
[b]The total EREFS was calculated by summing the scores for the 5 major individual findings (grade 0−3 for esophageal rings; grade 0−2 for white plaques or exudates, edema or decreased vascularity, and linear furrows; and grade 0−1 for esophageal stricture) from both the proximal and distal esophagus.
[c]DSQ score calculated based on patient responses to questions 2 and 3 of the questionnaire (frequency and intensity of dysphagia) over a 2-week period. Scores from these questions were summed, divided by number of days for which the diary was completed, and multiplied by 14 (days). Scores could range from 0 to 84.

been found by chance, and as such, may not reflect a true difference between responders and nonresponders. As mentioned previously, lower body weight, shorter stature, and younger age were identified as predictors in a pediatric study using topical fluticasone.[18] There are few published data on predictors of response to topical budesonide. In 1 large retrospective study,[45] esophageal dilation was associated with nonresponse, and other studies have shown that the prevalence of esophageal strictures (and hence the need for dilation) increased with increasing disease duration.[47,48] Additionally, we observed no statistically significant difference in EREFS between responders and nonresponders at baseline, which is consistent with the study by van Rhijn and colleagues,[49] which identified limitations in the correlation between EREFS and histologic remission.

Limitations of this study include a restricted age range (11−40 years), so results may not be applicable to young children or older adults. There was also an imbalance with regards to patient numbers after randomization (BOS, n = 51; placebo, n = 42), which was due to the site stratification method used (block size of 4), a site randomization error that occurred at 2 of the sites (these 2 sites skipped random numbers in error), and a number of sites only enrolling 1 patient per site. Specifically, there were 5 sites where only 1 patient was enrolled and 3 sites where there was an imbalance (of 1−3 patients per site). Patients with severe strictures were excluded at screening to avoid esophageal dilation as a confounder to symptom response; although patients with mild strictures were included, none of these patients developed severe strictures during the 12-week treatment period. It should also be noted that patients were allowed to remain on a stable dose of PPI during the trial, which could have impacted the treatment effect size. However, this would have been unlikely to introduce bias, as patients in the BOS and placebo groups

had similar levels of PPI use. Finally, although the 12-week treatment period is longer than some previous trials,[28,30] long-term efficacy data are needed. This study was not powered to assess treatment effect by age (ie, adolescents vs adults); however, this would be useful to examine in future studies of BOS.

A key strength of the study is that this was a rigorously conducted, multicenter, randomized, blinded, placebo-controlled, parallel-group trial that is the largest study of topical corticosteroids to date in patients with EoE. The strict inclusion criteria yielded a histologically severe and symptomatic population of patients with EoE. Safety monitoring was comprehensive. Finally, this is the first trial to use validated symptom and endoscopy outcome measures specifically developed for EoE,[37,40] as well as the first to show improvement in symptomatic, endoscopic, and histologic outcomes. Recent clinical trials of topical steroids in EoE have failed to show this relationship with non-validated symptom measures.[29,30] These design elements, including the blinded placebo run-in period, should help to inform future therapeutic trials in EoE.

In conclusion, compared with placebo, 12 weeks of BOS treatment significantly improved both esophageal eosinophilia and symptoms of dysphagia in adolescents and adults with active EoE. There were no unexpected safety signals, and compliance with medication was high, suggesting that this formulation can be reliably used. In addition, this is the first prospective study to use a validated PRO instrument and a validated endoscopy classification to demonstrate improvement in dysphagia symptoms and endoscopic severity scores. BOS is therefore a promising formulation for treatment of EoE.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2016.11.021.

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Conflicts of interest

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Supplementary Material

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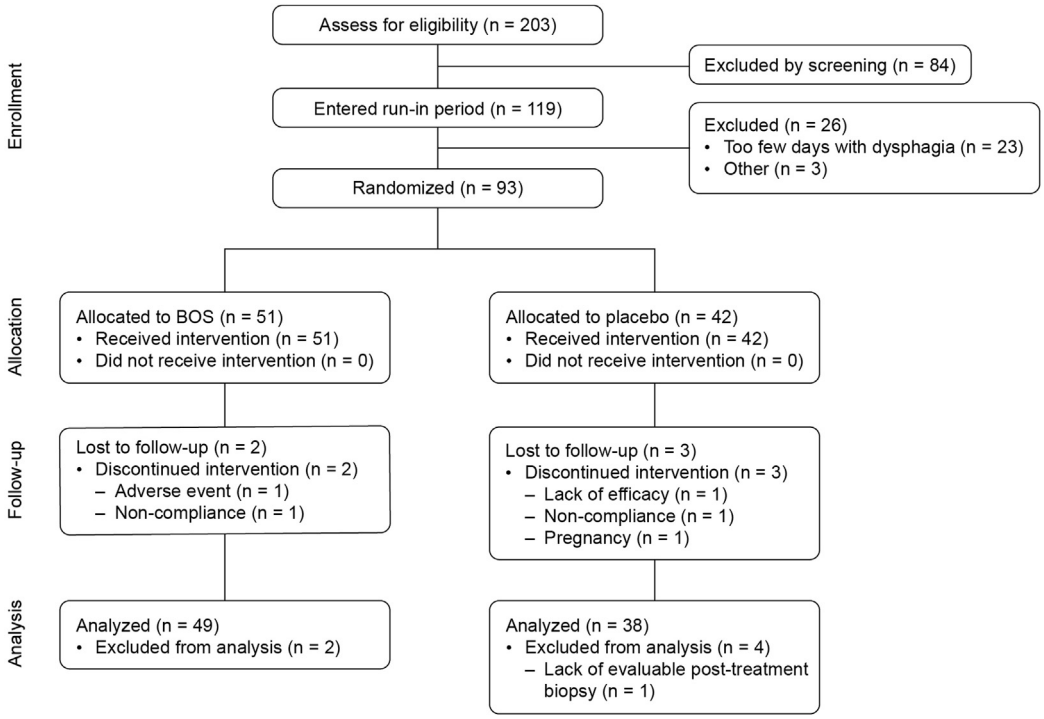
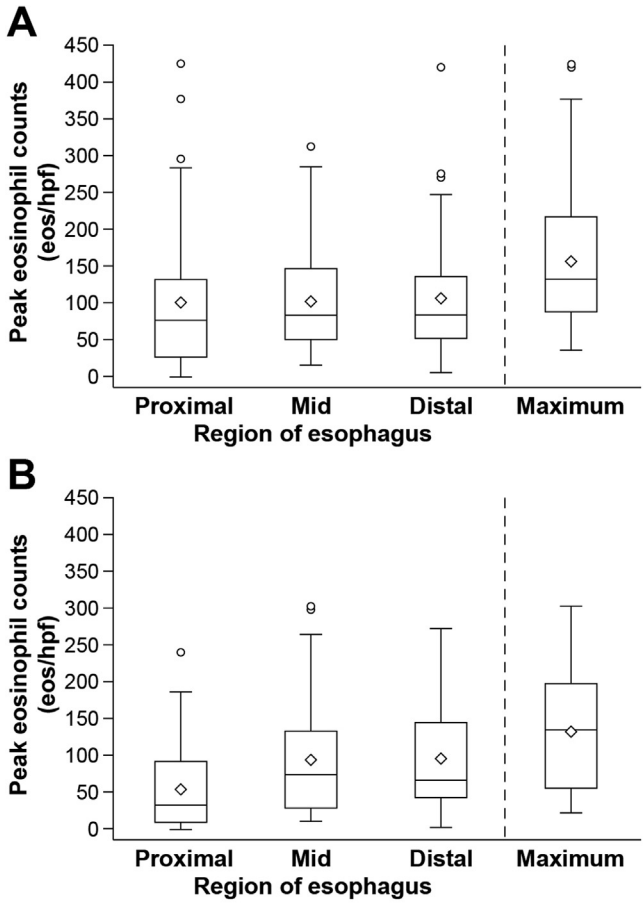


Supplementary Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram showing patient flow. Of 203 screened, 119 met initial eligibility criteria. The majority of those who were ineligible did not meet histologic or symptom thresholds. Of the 119 eligible, 26 were excluded, primarily for experiencing dysphagia on too few days. In total, 93 participants were randomized and comprised the safety analysis set. Of these, 87 patients were included in the outcome analysis set.



Supplementary Figure 2. Distribution of mean peak eosinophil counts by esophageal region and their mean maximum counts for patients receiving budesonide oral suspension (*A*) or placebo (*B*) (safety analysis set). *Boxplots* show mean (*diamond*), median (*middle line*), interquartile ranges ([IQR]; *top and bottom edges of box*), minimum and maximum values (*error bars*, within 1.5 × IQR), and values considered to be outliers (*circles*, values < or >1.5 × IQR).

Supplementary Table 1. Baseline and Post-Treatment Total Endoscopic Reference Score and Individual Component Scores From Proximal and Distal Regions of the Esophagus in Patients With Eosinophilic Esophagitis Receiving Budesonide Oral Suspension or Placebo[a]

	Proximal			Distal		
	BOS (n = 49)	Placebo (n = 38)	*P* value	BOS (n = 49)	Placebo (n = 38)	*P* value
EREFS[b]						
Baseline	3.4 ± 2.2	3.3 ± 2.0		4.3 ± 1.9	3.6 ± 1.6	
Post-treatment	1.5 ± 1.8	3.4 ± 2.2		2.4 ± 1.8	3.9 ± 2.2	
Difference	−1.8 ± 2.2	0.1 ± 2.2	.0001	−1.9 ± 2.1	0.3 ± 2.0	<.0001
Fixed rings						
Baseline	0.8 ± 0.8	0.7 ± 0.7		0.8 ± 0.8	0.7 ± 0.7	
Post-treatment	0.4 ± 0.7	0.9 ± 0.9		0.6 ± 0.8	0.8 ± 0.8	
Difference	−0.4 ± 0.7	0.2 ± 0.8	.0046	−0.2 ± 0.8	0.1 ± 0.9	.1394
Exudates						
Baseline	0.7 ± 0.7	0.7 ± 0.7		0.9 ± 0.7	0.8 ± 0.7	
Post-treatment	0.2 ± 0.5	0.6 ± 0.8		0.2 ± 0.5	0.8 ± 0.8	
Difference	−0.6 ± 0.8	−0.1 ± 0.9	.0142	−0.6 ± 0.8	0.0 ± 0.8	.0006
Furrows						
Baseline	1.0 ± 0.7	1.0 ± 0.6		1.4 ± 0.6	1.1 ± 0.6	
Post-treatment	0.4 ± 0.7	0.9 ± 0.7		0.8 ± 0.7	1.2 ± 0.7	
Difference	−0.6 ± 0.7	0.0 ± 0.7	.0007	−0.6 ± 0.7	0.2 ± 0.7	<.0001
Edema						
Baseline	0.8 ± 0.7	0.9 ± 0.8		1.1 ± 0.7	1.0 ± 0.7	
Post-treatment	0.4 ± 0.7	0.9 ± 0.7		0.7 ± 0.7	1.2 ± 0.7	
Difference	−0.3 ± 0.8	0.0 ± 0.7	.0281	−0.4 ± 0.8	0.2 ± 0.7	.0012
Strictures						
Baseline	0.0 ± 0.2	0.1 ± 0.2		0.1 ± 0.4	0.1 ± 0.3	
Post-treatment	0.0 ± 0.2	0.1 ± 0.3		0.1 ± 0.3	0.1 ± 0.3	
Difference	0.0 ± 0.3	0.0 ± 0.3	.6698	0.0 ± 0.3	0.0 ± 0.2	.4470

NOTE. Values are expressed as mean ± SD unless otherwise indicated.
ANCOVA, analysis of covariance.
[a]Estimates were determined using an ANCOVA model including treatment group and baseline value as a covariate.
[b]The total EREFS was calculated by summing the scores for the 5 major individual parameters (grade 0−3 for esophageal rings; grade 0−2 for white plaques or exudates, edema or decreased vascularity, and linear furrows; and grade 0−1 for esophageal stricture).

Supplementary Table 2. Treatment-Emergent Adverse Events in Patients Receiving Budesonide Oral Suspension or Placebo

TEAE	BOS (n = 51)	Placebo (n = 42)
All TEAEs	24 (47)	21 (50)
TEAEs related to study drug	5 (10)	4 (10)
Severe TEAEs	1 (2)[a]	0 (0)
Serious adverse events	1 (2)	0 (0)
TEAEs leading to withdrawal from study	1 (2)	0 (0)
TEAEs related to study drug and leading to withdrawal from study	1 (2)[b]	0 (0)
Infections and infestations	13 (25)	7 (17)
Nasopharyngitis	3 (6)	4 (10)
Upper respiratory tract infection	3 (6)	2 (5)
Sinusitis	2 (4)	1 (2)
Clostridium difficile infection	1 (2)	0 (0)
Oral candidiasis	1 (2)	0 (0)
Esophageal candidiasis	1 (2)	0 (0)
Gastrointestinal disorders	3 (6)	9 (21)
Diarrhea	0 (0)	1 (2)
Food poisoning	2 (4)	0 (0)
Vomiting	1 (2)	1 (2)
Abdominal pain/discomfort	0 (0)	3 (7)
Respiratory disorders	6 (12)	3 (7)
Oropharyngeal pain	2 (4)	2 (5)
Cough	1 (2)	0 (0)
Dyspnea	1 (2)	0 (0)
Allergic rhinitis	1 (2)	0 (0)
Skin disorders	3 (6)	3 (7)
Acne	1 (2)	0 (0)
Contact dermatitis	1 (2)	0 (0)
Eczema	0 (0)	1 (2)
General	3 (6)	2 (5)
Fever	1 (2)	1 (2)
Fatigue	1 (2)	0 (0)

NOTE. Values are expressed as n (%).
TEAE, treatment-emergent adverse event.
[a]Episode of food poisoning, deemed not related to the study drug.
[b]Due to chest pain, dyspnea, nausea, and vomiting, deemed related to the study drug.

Supplementary Table 3. Morning Serum Cortisol Results in Patients With Eosinophilic Esophagitis Receiving Budesonide Oral Suspension and Placebo

	BOS[a]	Placebo[a]
Absolute value, *μg/dL*, mean ± SD		
Baseline visit	10.4 ± 3.9	10.9 ± 4.3
After 4 wks of study drug	10.1 ± 4.3	12.0 ± 11.1
End of treatment	9.6 ± 4.2	11.3 ± 4.6
Change from baseline, *μg/dL*, mean ± SD		
After 4 wks of study drug	−0.3 ± 5.0	1.2 ± 3.0
End of treatment	−0.7 ± 4.4	0.4 ± 4.2
Below the lower limit of normal, n (%)		
Baseline visit	0 (0)	0 (0)
After 4 wks of study drug	3 (6)	1 (2)
End of treatment	3 (6)	2 (5)

[a]Baseline, 4-wk, and end-of-treatment data were available for 49, 50, and 51 patients in the BOS group, and 42, 41, and 42 patients in the placebo group.

Supplementary Table 4. Growth Characteristics in Patients With Eosinophilic Esophagitis Aged Younger Than 18 Years Receiving Budesonide Oral Suspension and Placebo

Variable	BOS	Placebo
Growth velocity, *cm/y*		
Total number	17	14
Mean ± SD	4.0 ± 4.8	5.8 ± 3.4
Median (range)	4.1 (−5.8 to 12.0)	5.1 (0.7 to 13.7)
Sex-matched height-for-age *Z* score		
Baseline		
Total number	18	15
Mean ± SD	0.15 ± 0.52	0.03 ± 0.60
Median (range)	0.17 (−0.70 to 1.00)	0.12 (−1.16 to 0.86)
End of treatment		
Total number	17	14
Mean ± SD	0.31 ± 0.60	0.16 ± 0.57
Median (range)	0.23 (−0.55 to 1.64)	0.35 (−0.99 to 1.02)