CLINICAL—ALIMENTARY TRACT

Budesonide Orodispersible Tablets Maintain Remission in a Randomized, Placebo-Controlled Trial of Patients With Eosinophilic Esophagitis

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Quiescent eosinophilic esophagitis

A 48-weeks twice daily treatment with Budesonide 0.5mg or 1mg orodispersible tablets (BOT) was safe and highly effective for achieving:
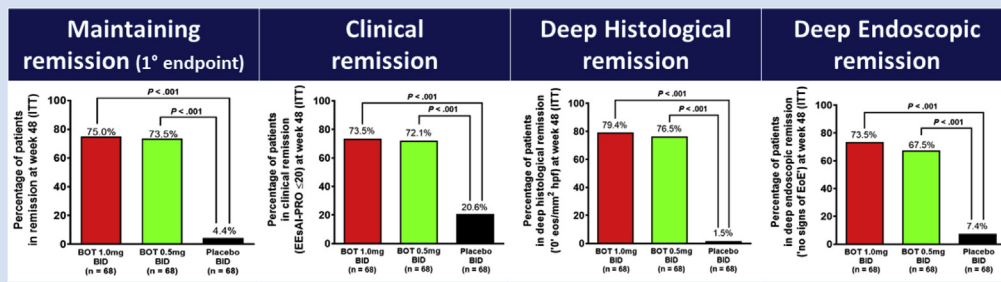
Gastroenterology

BACKGROUND & AIMS: Eosinophilic esophagitis (EoE) is a chronic inflammatory disorder. Swallowed topical-acting corticosteroids are effective in bringing active EoE into remission. However, it is not clear whether these drugs are effective for long-term maintenance of remission. **METHODS:** We performed a double-blind trial to compare the efficacy and safety of 2 dosages of a budesonide orodispersible tablet (BOT) vs placebo in maintaining remission of EoE. Maintenance of remission was defined as absence of clinical and histologic relapse and no premature withdrawal for any reason. Two hundred and four adults with EoE in clinical and histologic remission, from 29 European study sites, were randomly assigned to groups given BOT 0.5 mg twice daily (n = 68), BOT

1.0 mg twice daily (n = 68), or placebo twice daily (n = 68) for up to 48 weeks. **RESULTS:** At end of treatment, 73.5% of patients receiving BOT 0.5 mg twice daily and 75% receiving BOT 1.0 mg twice daily were in persistent remission compared with 4.4% of patients in the placebo group ($P <$ .001 for both comparisons of BOT with placebo). Median time to relapse in the placebo group was 87 days. The frequency of adverse events was similar in the BOT and placebo groups. Morning serum levels of cortisol were in the normal range at baseline and did not significantly change during treatment. Four patients receiving BOT developed asymptomatic, low serum levels of cortisol. Clinically manifested candidiasis was suspected in 16.2% of patients in the BOT 0.5 mg group and in 11.8% of patients in the BOT 1.0 mg group; all infections resolved with treatment. **CONCLUSIONS:** In a phase 3 trial, up to 48 weeks of treatment with BOT (0.5 mg or 1.0 mg twice daily) was superior to placebo in maintaining remission of EoE. Both dosages were equally effective and well tolerated. EudraCT number; 2014-001485-99; ClinicalTrials.gov number, NCT02434029.

Keywords: Topical Corticosteroids; Dysphagia; Remission; Patient-Reported Outcomes.

E osinophilic esophagitis (EoE) is a chronic, immune-mediated, esophageal-restricted disease, characterized clinically by symptoms of esophageal dysfunction and histologically by an eosinophil-predominant inflammation.[1,2] Dramatic increases in incidence and prevalence of EoE have been documented during the last 2 decades.[3–5] EoE is currently the most common cause of esophageal dysphagia and food bolus impaction.[6] Long-standing eosinophilic inflammation leads to esophageal remodeling in EoE, resulting in fibrosis with stricture formation and functional damage.[7–10] Consequently, EoE negatively impacts on the health-related quality of life (HRQoL) of patients by causing emotional distress and restricting social activities.[11] An active EoE is therefore a clear indication to treat these patients.[12]

The efficacy of swallowed topical corticosteroids (STC), such as budesonide or fluticasone, to improve symptoms and inflammation in patients with EoE has been confirmed in multiple trials,[13] placing STCs as a first-line medical therapy for active disease.[2] However, original formulations of these drugs developed for airway administration in asthma,[14,15] until now used off-label in EoE, resulted in suboptimal esophageal targeting and efficacy. Results from a phase 3 trial showed the effectiveness of a 6-week treatment with new budesonide orodispersible tablet (BOT) to induce clinicohistologic remission in 58% of adult patients with EoE, which increased to 85% when therapy was extended to 12 weeks in nonresponders.[16] Because EoE is a chronic condition[17] and the vast majority of patients experience a relapse rapidly after discontinuation of treatment,[18] long-term management is required. However, confirmatory maintenance trials with STCs are missing.

In this study, we evaluated the efficacy and safety of this BOT formulation for the maintenance of remission in adult patients with EoE.

Methods

Study Design

This phase 3, randomized, double-blind, placebo-controlled, multicenter, 48-week maintenance trial was conducted at 37 medical centers in 6 European countries (Supplementary Table 1) from January 2016 to November 2018. The protocol was approved by the national ethics committees in all participating countries. All patients provided written informed consent. The study was conducted and reported in accordance with the protocol.

Study Population

Eligible patients were 18–75 years of age with previously confirmed diagnosis of proton pump inhibitor (PPI)-refractory EoE according to established criteria[1,2] and in confirmed clinicohistologic remission at baseline after achieving study goals of a double-

blind controlled induction treatment study (EOS-1) with BOT 1.0 mg twice daily,[16] or by receiving open-label induction with BOT 1.0 mg twice daily for 6 weeks. Patients from either route of entry had to be enrolled via the same inclusion and exclusion criteria to enter the induction of clinicohistologic remission phase. Therefore, patients from both entry routes showed similar demographic and disease-specific characteristics. Clinical remission was defined as a severity of ≤2 points on 1- to 10-point numerical rating scale (NRS) for dysphagia and a severity of ≤2 points on a 0- to 10-point NRS for odynophagia on each day in the last week of induction treatment. Histologic remission was defined as peak eosinophil count <16 eosinophils (eos)/mm^2 high-power field (hpf; 400×; corresponding to <5 eos/hpf as reported previously[15,16,19]) at baseline endoscopy, measured in hpf derived from 6 biopsies, 2 of each esophageal third. Patients were ineligible if there was a clinical and endoscopic suspicion for gastroesophageal reflux disease; achalasia or scleroderma; evidence of reasons for esophageal eosinophilia other than EoE; pathologic eosinophilic infiltration in gastric and duodenal biopsies; history of esophageal surgery at any time or of esophageal dilation procedures within the last 8 weeks before induction treatment; or any relevant systemic disease.

Randomization and Study Intervention

Included patients were randomly assigned, in a 1:1:1 ratio, to receive BOT 0.5 mg twice daily (Jorveza 0.5 mg orodispersible tablets; Dr Falk Pharma GmbH, Freiburg, Germany), BOT 1.0 mg twice daily (Jorveza 1 mg orodispersible tablets; Dr Falk Pharma GmbH) or placebo, using an Interactive Web Response System and a computer-generated list of sequentially random numbers with randomly permuted block size of 6. Allocation concealment was ensured as patients, investigators and their study team, the sponsor, monitoring staff, central laboratory, and central pathologist, were all kept blinded to the randomization sequence, block size, and patient's treatment, until all patients had completed the study and the database was clean and locked. No individual unblinding was needed or performed.

At baseline and at each of the interim visits, patients received study medication for the next period. BOT 0.5 mg, 1.0 mg, and placebo tablets were identical in physical appearance and taste. BOT and placebo were administered twice daily. The orodispersible tablet was placed on the tip of the tongue and pressed gently against the hard palate until it had completely disintegrated by contact with saliva, the production of which was stimulated by the effervescence properties of the study medication. The components dissolved in saliva were then continuously swallowed (approximately 10 swallows within several minutes). Patients were instructed to avoid eating, drinking, or oral hygiene procedures for 30 minutes after study drug administration. Compliance was assessed at each study visit by pill count; patients who returned less than two-thirds of the distributed study medication or having an adherence to treatment of <70% were assessed as being noncompliant and were excluded from the per-protocol analysis. The use of other STCs, systemic glucocorticoids, immunosuppressants, biologic drugs, or onset of dietary restrictions was not permitted. Concomitant PPI treatment was to be kept stable.

Evaluation of Efficacy and Safety

Post-randomization interim visits took place at weeks 4, 12, 24, 36, and 48. In addition, telephone interviews were conducted at 4-week intervals in-between clinical visits.

Symptoms (dysphagia and odynophagia) and Patient's Global Assessment of EoE activity were assessed at each visit using 0–10 NRS (higher scores indicating more severe symptoms or disease activity). The use of a simple clinical readout instrument with an obvious face validity such as NRS was suggested by Scientific Protocol Advice from the European Medicines Agency. Validated Eosinophilic Esophagitis Activity Index–Patient Reported Outcome score (range, 0–100 points) was completed at every visit (higher scores indicating more severe disease activity).[20] Validated Eosinophilic Esophagitis Quality of Life Scale for Adults (EoE-QoL-A) questionnaire version 2.0 (licensed from Northwestern University, Evanston, IL) was completed at weeks 0, 24, and 48 (range 0–4 points; with higher scores indicating better HRQoL).[21,22]

Upper endoscopy was performed at baseline and end of treatment (EoT) or in case of patient's premature withdrawal. Esophageal findings were classified according to the validated modified Endoscopic Reference Score (EREFS) grading system (range, 0–9 points; with higher scores indicating more severe endoscopic findings).[23] In addition, a global assessment of endoscopic EoE activity was performed and classified as "none," "mild," "moderate," or "severe."

At each endoscopy, 2 biopsies of each esophageal third were obtained and analyzed blindly. Biopsy specimens were fixed in 4% neutral-buffered formalin and embedded in paraffin. On each H&E-stained esophageal biopsy specimen, all levels were surveyed and the eosinophils in the most densely infiltrated area were counted (hpf area of 0.345 mm^2) and reported as eos/mm^2 hpf. In patients with clinically, endoscopically, or histologically suspected local fungal infection. Grocott silver staining was performed on esophageal biopsy specimen for final confirmation.

Physical examinations were performed during screening and at EoT visits. During all interim visits, vital signs, concomitant medications, and adverse events were assessed and general laboratory tests were performed. Serum morning cortisol (8:00 AM to 9:00 AM) levels were measured at baseline and EoT visits. Tolerability was classified by the patient and the investigator independently at the EoT. Regular eye examinations were performed to check for cataract and glaucoma.

Outcomes

The primary outcome was remission at week 48, that is, rate of patients fulfilling none of the following criteria: clinical relapse (ie, dysphagia or odynophagia [7-day recall period] with severity ≥4 points, confirmed by ≥4 points on at least 1 day during the subsequent week on the respective 0–10 point NRS for dysphagia or odynophagia [24-hours recall period]); histologic relapse (ie, peak of ≥48 eos/mm^2 hpf [corresponding to ≥15 eos/hpf[15]] at EoT; food impaction requiring endoscopic intervention; need for dilation; or premature withdrawal for any reasons.

A priori–ordered secondary outcomes at week 48 included rate of histologic relapse (as defined above); change in the peak eos/mm^2 hpf from baseline to EoT; rate of clinical relapse (as defined above); food impaction that required endoscopic intervention or endoscopic dilation; rate of clinical remission (Eosinophilic Esophagitis Activity Index–Patient Reported Outcome score ≤20).

Exploratory outcomes were change from baseline in the Patient's Global Assessment of EoE activity; time to clinical

relapse; deep histologic remission (0 eos/mm^2 hpf); changes in endoscopic alterations; deep endoscopic remission (0 points total EREFS score); and HRQoL and patient's global satisfaction with treatment.

As a post-hoc analysis, the rate of patients in clinicohistologic remission, as defined at baseline, was assessed at week 48/EoT.

Study Oversight

The study was designed and implemented by members of the EOS-2 protocol review board (A. Straumann, A.J.L., S.M., A. Schoepfer) and researchers employed by Dr Falk Pharma (R.M., R.G.). Data were collected and analyzed by a contract research organization. The first draft manuscript was written by A. Straumann; all authors had access to the study data and reviewed and approved the final manuscript.

Statistical Analyses

Assuming relapse/treatment failure rates of 50%, 30%, and 25% with placebo, BOT 0.5 mg twice daily, and BOT 1.0 mg twice daily, respectively, simulations with ADDPLAN, version 6.0 (ICON Clinical Research, Dublin, Ireland) showed that a total of 192 intention-to-treat patients were needed using the normal approximation test for rates based on 1-sided $\alpha = .025$ with a statistical power of at least 80%. Sample size was increased for 5% of randomized patients who might not have taken at least 1 dose of the study drug, and in total 204 patients were to be randomized.

The primary efficacy variable and the dichotomous a priori–ordered secondary efficacy variables were confirmatory tested (1-sided, with the intent to show the superiority of active treatment over placebo) separately for both BOT arms vs placebo at Bonferroni adjusted significance levels of .0125, using the normal approximation tests for the comparison of rates. Two-sided 97.5% (Bonferroni correction) confidence intervals (CIs) for the difference of rates were provided. Efficacy significance testing continued in hierarchical fashion for the secondary end points. Once a 1-sided nonsignificant P value ($P > .0125$) occurred, subsequent significance tests were considered exploratory. Change in peak eos/mm^2 hpf was analyzed using the Wilcoxon rank sum test also at Bonferroni-adjusted significance level of .0125.

Analyses of exploratory end points between treatment groups or between baseline and EoT were performed using 2-sided t tests or Wilcoxon rank-sum tests, as appropriate. Two-sided Fisher exact test was applied to dichotomous data. Time-to-event variables were described using Kaplan-Meier methods. Descriptive statistics were used to summarize data.

Adverse events were classified using the *Medical Dictionary for Regulatory Activities*, version 19.[24]

Analyses were performed using SAS, version 9.3 (SAS Institute, Cary, NC) and according to the intention-to-treat principle. Missing data at week 48 were not replaced, in such case a treatment failure was assumed.

Results

Patient Flow and Baseline Characteristics

From a total of 269 patients treated with BOT 1.0 mg twice daily for 6–12 weeks for induction of remission, 204 came into clinicohistologic remission, fulfilling the inclusion criteria for the double-blind phase, and were randomized for 48-week maintenance treatment into 3 groups (BOT 0.5 mg twice daily, BOT 1.0 mg twice daily, and placebo twice daily) of identical size of 68 patients, each. In total, 141 patients completed the double-blind phase (69.1%), but all 204 patients were evaluable for the primary analysis (Supplementary Figure 1).

All 3 treatment groups had similar demographic and disease-specific characteristics at baseline of the maintenance phase, in particular the rate of concomitant PPI treatment in all of the treatment groups was the same (Table 1). Baseline characteristics before the initial acute therapy for induction of clinicohistologic remission were also similar between the treatment groups (see Supplementary Table 2).

Efficacy

The primary outcome—number of patients in remission after a 48-week maintenance treatment—was achieved in 50 of 68 (73.5%; $P < .001$), 51 of 68 (75.0%; $P < .001$), and 3 of 68 (4.4%) patients in the BOT 0.5 mg twice daily, BOT 1.0 mg twice daily, and placebo groups, respectively (Table 2, Figure 1A). The efficacy of BOT was generally consistent across subgroups and the results were not significantly influenced by baseline conditions (ie, history of allergic diseases, localization of inflammation at baseline of induction treatment, or concomitant PPI use; see Supplementary Table 3). However, remission rates under BOT 1.0 mg twice daily were clinically relevant higher compared with BOT 0.5 mg twice daily in patients with an extended inflammation (ie, all 3 esophageal segments were affected; 80% vs 68%) at baseline of their induction treatment and for patients with a longstanding disease history (ie, 9 years or longer; see Supplementary Table 3). The time to clinical relapses during the 48-week study period in the 3 treatment groups is illustrated in Figure 2.

All secondary efficacy outcomes proved superiority of BOT 0.5 mg twice daily and BOT 1.0 mg twice daily over placebo in a confirmatory manner: Rates of patients experiencing a histologic relapse were 9 of 68 (13.2%; $P < .001$), 7 of 68 (10.3%; $P < .001$), and 61 of 68 (89.7%) in the BOT 0.5 mg twice daily, BOT 1.0 mg twice daily, and placebo group, respectively. Clinical relapses occurred in 7 of 68 (10.3%, $P < .001$), 5 of 68 (7.4%; $P < .001$), and 41 of 68 (60.3%) in the 3 treatment groups (Table 2). In a post-hoc assessment, clinicohistologic remission, as defined at baseline, was in line with the primary end point and was achieved in 48 of 68 (70.6%; $P < .001$), 50 of 68 (73.5%; $P < .001$), and 1 of 68 (1.5%) patients in the BOT 0.5 mg twice daily, BOT 1.0 mg twice daily, and placebo group, respectively (Table 2). Histologic remission in the BOT 0.5 and 1.0 mg twice daily group was independently maintained in all esophageal segments (data not presented).

The rates of endoscopic remission decreased under BOT 0.5 mg twice daily slightly from 74% at baseline to 68% at week 48 ($P = .670$), increased with BOT 1.0 mg twice daily from 66% to 74% ($P = .127$), but dropped significantly with

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Table 1. Demographic, Clinical, and Disease-Specific Characteristics of Study Patients at Baseline of Maintenance Phase

Characteristics	BOT		Placebo BID (n = 68)	All patients (n = 204)
	0.5 mg BID (n = 68)	1.0 mg BID (n = 68)		
Age, *y*, mean ± SD	36 ± 10.9	37 ± 11.1	36 ± 9.9	36 ± 10.6
Male sex, n (%)	57 (83.8)	57 (83.8)	55 (80.9)	169 (82.8)
White race,[a] n (%)	68 (100.0)	68 (100)	68 (100.0)	204 (100.0)
Body weight, *kg*, mean ± SD (n)	76.0 ± 11.6 (67)	79.7 ± 14.2 (67)	76.8 ± 15.2 (67)	77.5 ± 13.8 (201)
Time since first EoE symptoms, *y*, mean ± SD	12.6 ± 8.5	11.8 ± 9.4	9.6 ± 8.2	11.4 ± 8.8
Time since EoE diagnosis, *y*, mean ± SD	4.3 ± 3.5	4.2 ± 4.0	3.3 ± 2.9	3.9 ± 3.5
History of esophageal dilation, n (%)	13 (19.1)	8 (11.8)	4 (5.9)	25 (12.3)
History of allergic disease, n (%)	54 (79.4)	55 (80.9)	50 (73.5)	159 (77.9)
History of having experienced, n (%)				
Dysphagia	68 (100.0)	66 (97.1)	68 (100.0)	202 (99.0)
Odynophagia	42 (61.8)	40 (58.8)	41 (60.3)	123 (60.3)
Food impaction (with or without endoscopic removal)	65 (95.6)	59 (86.8)	61 (89.7)	185 (90.7)
Concomitant treatment with PPI, n (%)	16 (23.5)	12 (17.6)	9 (13.2)	37 (18.1)
Daily dysphagia NRS last 7 d,[b] mean ± SD	1 ± 0.9	1 ± 0.9	1 ± 0.8	1 ± 0.9
Daily odynophagia NRS last 7 d,[b] mean ± SD	1 ± 0.9	1 ± 1.0	0 ± 0.8	1 ± 0.9
EEsAI-PRO,[c] mean ± SD	16 ± 14.1	16 ± 15.8	16 ± 15.8	18 ± 16.6
EEsAI-PRO ≤20 points,[c] n (%)	43 (63.2)	46 (67.6)	38 (55.9)	127 (62.3)
PatGA,[d] mean ± SD	1 ± 0.8	1 ± 0.8	1 ± 0.9	1 ± 0.8
EoE-QoL-A 30 items weighted questionnaire,[e] mean ± SD	3.2 ± 0.6	3.2 ± 0.6	3.0 ± 0.7	3.1 ± 0.6
Overall peak eos/mm^2 hpf,[f] mean ± SD	0 ± 1.4	0 ± 1.7	1 ± 3.6	0 ± 2.4
Deep histologic remission (0 eos/mm^2 hpf),[f] n (%)	65 (95.6)	68 (95.6)	64 (94.1)	194 (95.1)
Total modified EREFS score (0–9 points),[g] mean ± SD	1 ± 1.1	1 ± 1.1	1 ± 1.0	1 ± 1.0
Inflammatory signs subscore (0–4 points)	0 ± 0.6	0 ± 0.6	0 ± 0.6	0 ± 0.6
Fibrotic signs subscore (0–4 points)	1 ± 0.7	0 ± 0.6	0 ± 0.6	0 ± 0.6
Inflammatory remission, all inflammatory grades 0, n (%)	48 (70.6)	49 (72.1)	49 (72.1)	146 (71.6)
Complete remission, all grades 0, n (%)	34 (50.0)	34 (50.0)	35 (51.5)	103 (50.5)
Endoscopist Global Assessment				
No signs of EoE, n (%)	50 (73.5)	45 (66.2)	43 (63.2)	138 (67.6)
Moderate or severe signs of EoE, n (%)	1 (1.5)	2 (2.9)	1 (1.5)	4 (2.0)

BID, twice daily; EEsAI-PRO, Eosinophilic Esophagitis Activity Index Patient Reported Outcome; PatGA, Patient's Global Assessment of EoE activity.
[a]Race was self-reported.
[b]NRS for dysphagia and odynophagia, respectively, ranging from 0 to 10 points; higher scores indicating greater symptom severity.
[c]EEsAI-PRO score ranging from 0 to 100 points with higher scores indicating greater disease severity; clinical remission is defined as a score of ≤20 points.
[d]PatGA is an NRS ranging from 0 to 10 points; higher scores indicating greater disease activity.
[e]EoE-QoL-A questionnaire, version 2.0, is a validated 24-item scale with a 6-questions addendum for those on elimination diet therapies, to measure HRQoL for adult patients with EoE, in which every item is scored from 0 (very poor HRQoL) to 4 (very good HRQoL).
[f]Peak eosinophils count standardized to mm^2 hpf (400×). Peak of <16 eos/mm^2 hpf in all 6 biopsies, 2 each derived from the derived proximal, mid, and distal esophagus, was defined as histologic remission; 0 eos/mm^2 hpf in all biopsies was deep histologic remission.
[g]Modified EREFS grading system summing the scores of the 5 major features (edema [0–1], rings [0–3], exudates [0–2], furrows [0–1], strictures [0–1]) and 1 minor (crêpe paper esophagus [0–1]); total score ranged from 0 to 9 points, with higher score indicating more severe endoscopic findings. Inflammatory subscore (edema [0–1], exudates [0–2], furrows [0–1]), ranged from 0 to 4 points, with higher score indicating more severe inflammatory findings; Fibrotic subscore (rings [0–3], strictures [0–1]), ranged from 0 to 4 points, with higher score indicating more severe fibrotic findings.

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Table 2. Efficacy of Maintenance Treatment of Eosinophilic Esophagitis With Orodispersible Budesonide Tablets

Outcome variable	BOT 0.5 mg BID (n = 68)	BOT 1.0 mg BID (n = 68)	Placebo BID, n (%) (n = 68)	Between-group difference			
				BOT 0.5 mg vs placebo, % (97.5% CI)[a]	P value	BOT 1.0 mg vs placebo, % (97.5% CI)[a]	P value
Primary outcome							
Maintaining remission, n/N (%)	50/68 (73.5)	51/68 (75.0)	3/68 (4.4)	69.1 (55.9 to 82.3)	.001[b]	70.6 (57.6 to 83.6)	.001[b]
A priori–ordered secondary outcomes							
Histologic relapse (≥48 eos/mm² hpf at EoT),[c] n/N (%)	9/68 (13.2)	7/68 (10.3)	61/68 (89.7)	−76.5 (−88.8 to −64.1)	.001[b]	−79.4 (−91.1 to −67.7)	.001[b]
Change in peak eos/mm² hpf from baseline to EoT,[c] mean ± SD (n)	38 ± 112.6 (66)	21 ± 64.0 (65)	262 ± 216.3 (65)	ND	.001[d]	ND	.001[d]
Clinical relapse, food impaction needing endoscopic intervention, or need for dilation (multiple reasons possible), n/N (%)	7/68 (10.3)	5/68 (7.4)	41/68 (60.3)	−50.0 (−65.7 to −34.3)	.001[b]	−52.9 (−68.0 to −37.9)	.001[b]
Clinical relapse	7/68 (10.3)	5/68 (7.4)	41/68 (60.3)				
Food impaction needing endoscopic intervention	0/68 (0)	0/68 (0)	1/68 (1.5)				
Need for dilation	0/68 (0)	0/68 (0)	0/68 (0)				
Weekly EEsAI-PRO (0–100) score of ≤20 at EoT,[e] n/N (%)	49/68 (72.1)	50/68 (73.5)	14/68 (20.6)	51.5 (35.1 to 67.9)	.001[b]	52.9 (39.4 to 66.5)	.001[b]

Exploratory outcomes	BOT 0.5 mg BID (n = 68)	BOT 1.0 mg BID (n = 68)	Placebo BID, n (%) (n = 68)	Between-group difference			
				BOT 0.5 mg vs placebo, % (95% CI)	P value	BOT 1.0 mg vs placebo, % (95% CI)	P value
Post-hoc analysis							
Maintaining clinicohistologic remission at EoT (dysphagia NRS [0–10] and odynophagia NRS [0–10] both ≤2 points in the last week before EoT and <16 eos/mm² hpf at EoT), n/N (%)	48/68 (70.6)	50/68 (73.5)	1/68 (1.5)	69.1 (57.9 to 80.3)	.001	72.1 (61.2 to 82.9)	.001

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Table 2. Continued

Exploratory outcomes	BOT 0.5 mg BID (n = 68)	BOT 1.0 mg BID (n = 68)	Placebo BID, n (%) (n = 68)	Between-group difference BOT 0.5 mg vs placebo, % (95% CI)	P value	Between-group difference BOT 1.0 mg vs placebo, % (95% CI)	P value
Clinical							
PatGA (0–10) at EoT,[f] mean ± SD (n)	1 ± 1.8 (66)	1 ± 1.7 (67)	4 ± 2.6 (64)	ND	.001[g]	ND	.001[g]
Absolute change from baseline to EoT,[f] mean ± SD (n)	–0 ± 2.0 (66)	–0 ± 1.8 (67)	3 ± 2.7 (63)	ND	.001[g]	ND	.001[g]
PatGA ≤2 at EoT,[f] n/N (%)	60/68 (88.2)	58/69 (85.3)	22/68 (32.4)	55.9 (42.4 to 69.4)	.001[h]	52.9 (39.0 to 66.9)	.001[h]
Dysphagia NRS (0–10) change from baseline to EoT,[i] mean ± SD (n)	0 ± 2.0 (66)	0 ± 1.8 (67)	3 ± 2.9 (65)	ND	.001[g]	ND	.001[g]
Odynophagia NRS (0–10) change from baseline to EoT,[i] mean ± SD (n)	0 ± 1.8 (66)	–0 ± 1.6 (67)	2 ± 2.7 (65)	ND	.001[g]	ND	.001[g]
EEsAI-PRO at EoT,[e] mean ± SD (n)	14 ± 18.5 (65)	11 ± 18.0 (66)	39 ± 21.4 (65)	ND	.001[g]	ND	.001[g]
Absolute change from baseline to EoT in EEsAI-PRO, mean ± SD (n)[e]	–2 ± 19.2 (64)	–7 ± 18.1 (65)	22 ± 23.1 (65)	ND	.001[g]	ND	.001[g]
Histologic							
Histologic remission (<16 eos/mm² hpf at EoT),[c] n/N (%)	53/68 (77.9)	57/68 (83.8)	2/68 (2.9)	75.0 (64.4 to 85.6)	.001[h]	80.9 (71.3 to 90.5)	.001[h]
Deep histologic remission (0 eos/mm² hpf at EoT),[c] n/N (%)	52/68 (76.5)	54/68 (79.4)	1/68 (1.5)	75.0 (64.5 to 85.5)	.001[h]	77.9 (67.9 to 88.0)	.001[h]
Maintaining deep histologic remission (0 eos/mm² hpf) from baseline to EoT,[c] n/N (%)	50/65 (76.9)	51/65 (78.5)	1/64 (1.6)	75.4 (64.9 to 86.0)	.001[h]	76.9 (66.5 to 87.3)	.001[h]
Endoscopic							
Total modified EREFS score (0–9 points) at EoT,[j] mean ± SD (n)	1 ± 1.2 (65)	1 ± 1.1 (65)	4 ± 1.8 (65)	ND	.001[g]	ND	.001[g]
Absolute change from baseline to EoT in total modified EREFS score,[j] mean ± SD (n)	–0 ± 1.4 (65)	–0 ± 1.2 (65)	3 ± 1.9 (65)	ND	.001[g]	ND	.001[g]
Absolute change from baseline to EoT in inflammatory signs subscore,[j] mean ± SD (n)	0 ± 1.0 (65)	–0 ± 0.8 (65)	2 ± 1.2 (65)	ND	.001[g]	ND	.001[g]
Absolute change from baseline to EoT in fibrotic signs subscore,[j] mean ± SD (n)	–0 ± 0.7 (65)	–0 ± 0.5 (65)	1 ± 1.0 (65)	ND	.001[g]	ND	.001[g]
Complete remission (all grades 0) at EoT,[j] n/N (%)	36/68 (52.9)	39/68 (57.4)	4/68 (5.9)	47.1 (33.9 to 60.2)	.001[h]	51.5 (38.5 to 64.5)	.001[h]
Moderate or severe fixed rings present at EoT, n/N (%)	4/68 (5.9)	2/68 (2.9)	20/68 (29.4)	–23.5 (–35.7 to –11.3)	.001[h]	–26.5 (–38.0 to –14.9)	.001[h]
Endoscopist's assessment, no signs of EoE at EoT, n/N (%)	46/68 (67.5)	50/68 (73.5)	5/68 (7.4)	60.3 (47.6 to 73.0)	.001[h]	66.2 (54.0 to 78.4)	.001[h]
Endoscopist's assessment, moderate or severe signs of EoE at EoT, n/N (%)	2/68 (2.9)	2/68 (2.9)	41/68 (60.3)	–57.4 (–69.7 to –45.1)	.001[h]	–57.4 (–69.7 to –45.1)	.001[h]

Table 2. Continued

Exploratory outcomes	BOT 0.5 mg BID (n = 68)	BOT 1.0 mg BID (n = 68)	Placebo BID, n (%) (n = 68)	BOT 0.5 mg vs placebo, % (95% CI)	P value	BOT 1.0 mg vs placebo, % (95% CI)	P value
				Between-group difference			
HRQoL							
EoE-QoL-A 30 items questionnaire[k]							
Baseline, mean ± SD (n)	3.2 ± 0.56 (64)	3.2 ± 0.59 (64)	3.0 ± 0.70 (64)	ND	ND	ND	ND
EoT, mean ± SD (n)	3.3 ± 0.46 (66)	3.5 ± 0.48 (67)	2.8 ± 0.75 (65)	ND	.001[g]	ND	.001[g]
Absolute change from baseline to EoT, mean (95% CI); n	0.2 (0.12 to 0.34); 62	0.3 (0.14 to 0.39); 63	−0.2 (−0.39 to −0.08); 61	0.46 (0.27 to 0.66)	.001[g]	0.50 (0.30 to 0.70)	.001[g]
Patient's global satisfaction with treatment at EoT, extremely satisfied or satisfied,[l] n/N (%)	62/68 (91.2)	49/68 (94.1)	46/68 (67.6)	23.5 (10.5 to 36.5)	.001[h]	26.5 (14.0 to 38.9)	.001[h]

BID, twice daily; EEsAI-PRO, Eosinophilic Esophagitis Activity Index Patient Reported Outcome; ND, not determined; PatGA, Patient's Global Assessment of EoE activity.

[a]Bonferroni correction.

[b]Normal approximation test was used for testing 1-sided P value (α = .0125).

[c]Peak eosinophils count standardized to mm^2 hpf (400×). Peak of ≥48 eos/mm^2 hpf (corresponding to ≥15 eos/hpf) in at least 1 of 6 biopsies (2 each derived from the proximal, mid, and distal esophagus) was defined as histologic relapse; peak of <16 eos/mm^2 hpf (corresponding to <5 eos/hpf[15]) in all biopsies was histologic remission and 0 eos/mm^2 hpf in all biopsies was deep histologic remission.

[d]Wilcoxon rank-sum test was used for testing 1-sided P value (α = .0125).

[e]EEsAI-PRO score ranging from 0 to 100 points with higher scores indicating greater disease severity; clinical remission is defined as a score of ≤20 points.

[f]PatGA is an NRS ranging from 0 to 10 points; higher scores indicating greater disease activity.

[g]Wilcoxon rank-sum test was used for testing 2-sided P value (α = .025).

[h]Wilcoxon rank-sum test was used for testing 2-sided p-value (α = .025). Normal approximation test was used for testing 2-sided P value (α = .025).

[i]NRS for dysphagia and odynophagia, respectively, ranging from 0 to 10 points; higher scores indicating greater symptom severity.

[j]Modified EREFS grading system summing the scores of the 5 major features (edema [0–1], rings [0–3], exudates [0–2], furrows [0-1], strictures [0–1]) and 1 minor (crêpe paper esophagus [0–1]); total score ranged from 0 to 9 points, with higher score indicating more severe endoscopic findings. Inflammatory subscore (edema [0–1], exudates [0–2], furrows [0–1]), ranged from 0 to 4 points, with higher score indicating more severe inflammatory findings; Fibrotic subscore (rings [0–3], strictures [0–1]), ranged from 0 to 4 points, with higher score indicating more severe fibrotic findings.

[k]EoE-QoL-A questionnaire, version 2.0, a validated 24-item scale with a 6-questions addendum for those on elimination diet therapies, to measure HRQoL for adult patients with EoE, in which every item is scored from 0 (very poor HRQoL) to 4 (very good HRQoL).

[l]Patient's global satisfaction with treatment was assessed at EoT within the 5 categories: extremely satisfied, satisfied, neither satisfied nor dissatisfied, dissatisfied, or extremely dissatisfied.
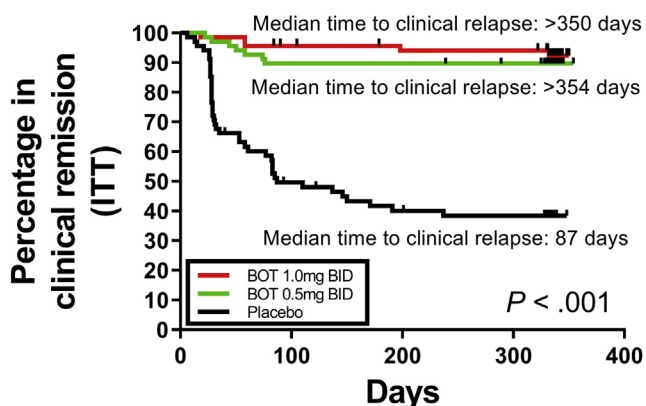
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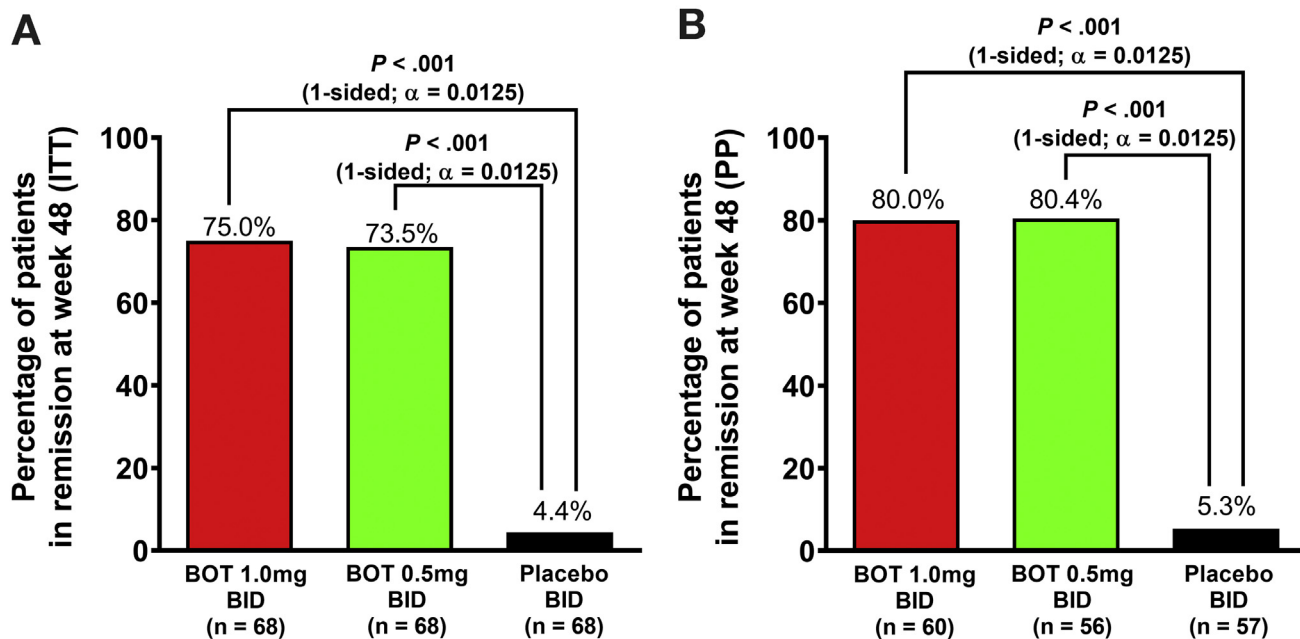
Figure 1. Primary end point: maintenance of remission. Percentage of patients in remission after 48-week treatment with budesonide 1.0 mg orodispersible tablet twice daily (BOT 1.0mg BID), BOT 0.5mg BID, or placebo BID. (*A*) Intention-to-treat (ITT) analysis. (*B*) Per-protocol (PP) analysis.

placebo during the study period from 63% to 7% (*P* < .001). Baseline total modified EREFS score was low in all treatment groups and comparable with a mean of 1 point at baseline (Table 2), as well as in later remitters or non-remitters (Supplementary Table 4). Interestingly, treatment failures with placebo also showed a substantial change in total modified EREFS score (mean change, 3; 95% CI, 2.7 to 3.6; *P* < .001), due mainly to an increase of the inflammatory subscore, whereas treatment failures with BOT 0.5 mg twice daily and BOT 1 mg twice daily had only a small and

Hazard ratio (HR):
BOT 1.0mg BID vs placebo: HR 0.086 (*P* < .001)
BOT 0.5mg BID vs placebo: HR 0.120 (*P* < .001)

Figure 2. Kaplan-Meier analysis of time to clinical relapse. Median time to clinical relapse during a 48-week treatment with either budesonide 1.0 mg orodispersible tablet twice daily (BOT 1.0mg BID), BOT 0.5mg BID, or placebo BID, in the intention-to-treat (ITT) analysis.

not significant increase in total modified EREFS score of 1 (95% CI, –0.2 to 1.6; *P* = .148) and 1 (95% CI, –0.1 to 1.6; *P* = .125) (Supplementary Table 4). In contrast, clinicohistologic remitters with BOT 1 mg twice daily treatment showed even further significant improvement in their total modified EREFS score (–0; 95% CI, –0.7 to –0.2; *P* < .001; Supplementary Table 4).

HRQoL overall and its subscores (eating and diet impact, social impact, emotional impact, disease anxiety, and swallowing anxiety) improved significantly from baseline to EoT in both BOT groups, whereas a significant deterioration in HRQoL was detected in the total EoE-QoL-A and most of its subscores after placebo treatment. The intragroup comparison (BOT vs placebo) of the mean changes from baseline to EoT was also significant for both BOT dosage groups (Table 2).

Safety

Overall, both BOT dosages were well tolerated and no serious drug-related adverse events (AEs) were reported. No significant differences were observed among the study groups in commonly reported AEs, most of them were unrelated to the investigational product. Food impaction requiring endoscopic intervention occurred in 2 patients receiving placebo, but in no patients in the 2 BOT groups. The AE "aggravated condition" was more frequent with placebo (64.7%) than with BOT 0.5 mg twice daily and BOT 1.0 mg twice daily (16.2%, *P* < .001 and 11.8%, *P* < .001, respectively). The most commonly reported drug-related AEs were mild to moderate symptoms of local candidiasis, which were treated easily with antimycotics, with no impact on daily life activities or need to stop study medication, recovering rapidly after medical treatment, and suspected in

Table 3. Safety of Maintenance Treatment of Eosinophilic Esophagitis With Orodispersible Budesonide Tablets

Variable	BOT 0.5 mg BID (n = 68)	BOT 1.0 mg BID (n = 68)	Placebo BID (n = 68)
Patients with at least 1, n (%)			
Treatment-emergent AE	57 (83.8)	59 (86.8)	61 (89.7)
Adverse drug reaction	22 (32.4)	22 (32.4)	3 (4.4)
Serious AE[a]	3 (4.4)	1 (1.5)	—
Cartilage injury	1 (1.5)	—	—
Upper limb fracture	1 (1.5)	—	—
Sinusitis	1 (1.5)[b]	—	—
Inguinal hernia	1 (1.5)[b]	—	—
Skull fracture	—	1 (1.5)	—
AE leading to withdrawal	7 (10.3)	8 (11.8)	42 (61.8)
Condition aggravated (clinical relapse)	7 (10.3)	5 (7.4)[c]	41 (60.3)[d]
Food impaction needing endoscopic intervention	—	—	2 (2.9)[d]
Chest pain	—	1 (1.5)[c]	—
Retinitis	—	1 (1.5)	—
Oropharyngeal pain	—	1 (1.5)	—
Dermatitis allergic	—	1 (1.5)	—
Esophageal dilation	—	—	1 (1.5)
Food impaction needing endoscopic intervention	—	—	2 (2.9)
Food impaction without need for endoscopic intervention	—	3 (4.4)	—
Patients with adverse drug reactions by system organ class and preferred term (if of special interest), n (%)			
Eye disorders	1 (1.5)	1 (1.5)	1 (1.5)
Cataract nuclear	—	—	1 (1.5)
Gastrointestinal disorders	5 (7.4)	5 (7.4)	—
General disorders and administration site conditions	2 (2.9)	2 (2.9)	—
Infections and infestations	12 (17.6)	10 (14.7)	1 (1.5)
Candidiasis overall:	12 (17.6)	9 (13.2)	—
Suspected symptomatic candidiasis	11 (16.2)	8 (11.8)	—
Histologic confirmed candidiasis	5 (7.4)	2 (2.9)	—
Histologic confirmed and symptomatic candidiasis	4 (5.9)	1 (1.5)	—
Investigations	3 (4.4)	2 (2.9)	—
Blood cortisol decreased	2 (2.9)[e]	2 (2.9)[f]	—
Neoplasms benign, malignant and unspecified	—	1 (1.5)	—
Lipoma	—	1 (1.5)	—
Nervous system disorders	3 (4.4)	3 (4.4)	—
Dysgeusia	—	1 (1.5)	—
Reproductive system and breast disorders	—	1 (1.5)	1 (1.5)
Respiratory, thoracic and mediastinal disorders	—	1 (1.5)	—
Skin and subcutaneous tissue disorders	1 (1.5)	3 (4.4)	—
Vascular disorders	—	1 (1.5)	—
Hypertension	—	1 (1.5)	—
Morning (8:00 AM to 9 AM) serum cortisol, $\mu g/dL$			
Baseline, mean ± SD (n)	12.1 ± 4.91 (45)	11.3 ± 4.81 (54)	10.1 ± 5.33 (50)
Week 48/EoT, mean ± SD (n)	12.8 ± 6.15 (54)	10.1 ± 4.53 (60)	11.9 ± 5.87 (55)
Absolute change from baseline to week 48/EoT, mean (95% CI); n	0.5 (–0.36 to 1.44); 45	–1.1 (–2.42 to 0.24); 54	1.7 (0.57 to 2.81); 50

[a]All serious AEs were assessed by the investigators as being not related to study drug intake.
[b]Sinusitis and inguinal hernia were reported in the same patient.
[c]Chest pain and clinical relapse were reported in the same patient.
[d]Food impaction needing endoscopic intervention and clinical relapse were reported in the same patient.
[e]Both without clinical symptoms of adrenal insufficiency, values normalized without change in the medication.
[f]Both without clinical symptoms of adrenal insufficiency; one value normalized and one was still ongoing without change in the medication.

16.1% and 11.8% of patients who received BOT 0.5 mg twice daily and BOT 1.0 mg twice daily, respectively. Mean morning cortisol levels at baseline were 12.1, 11.3, and 10.1 $\mu g/dL$ in the BOT 0.5 mg twice daily, BOT 1.0 mg twice daily, and placebo groups, respectively, and did not change at EoT (12.8, 10.1 and 11.9 $\mu g/dL$, respectively). However, a decrease in serum morning cortisol below the lower limit of normal (6.2 $\mu g/dL$) was observed in 4 patients allocated to

BOT (Table 3). Cataract was observed in only 1 patient receiving placebo.

Discussion

As EoE represents a chronic disease with a high relapse rate after cessation of therapy,[18] a long-term treatment is required. In contrast to the well-documented efficacy of STCs to induce remission of EoE,[2,12,13] data on maintenance treatment are scarce. Our study represents the first multi-center phase 3 trial analyzing efficacy and safety of long-term use of BOT, a newly developed, esophageal-targeted STC, to maintain EoE in clinicohistologic remission. In our study, BOT 0.5 mg twice daily and BOT 1.0 mg twice daily were effective and superior to placebo to keep adult patients with EoE in remission over 1 year with remission rates of up to 75%. This topic had been addressed so far by just a single-center controlled trial including a small number of adult patients that also used budesonide in a daily dosage of 0.5 mg as a watery solution.[25] In that study, only 35.7% of patients maintained histologic remission after 1 year, and three-quarters of them experienced symptom relapse despite budesonide.[25] Different dosages and formulations might explain differences in efficacy for the same compound.[26] With the newly developed BOT formulation, saliva is used as a vehicle, which most likely results in a prolonged deposition of the drug on the esophageal surface. In an additional prospective observational pediatric study that assessed long-term remission of EoE,[27] a daily dosage of 440 μg fluticasone propionate in an aerosolized formulation was used for a mean duration of 1.7 years. Despite a reported 30% relapse rate (13 of 43 patients), differences in study design, population, and compounds and formulations prevent comparison with our data.

As EoE is defined as a clinicohistologic syndrome[1,2,28] in which clinical manifestations and pathologic data should not be interpreted in isolation, a combined primary efficacy outcome was used in this trial. Our primary outcome consisted of both the absence of symptom recurrence and the lack of eosinophilic inflammation in the esophageal mucosa at EoT.

Our data demonstrate that 0.5 mg twice daily and 1.0 mg twice daily BOT were highly efficient in maintaining EoE in clinicohistologic remission. Overall, almost three-quarters of patients maintain EoE in remission in regard to symptoms and inflammatory activity during the whole 48-week study period, irrespective of the dose used (73.5% receiving BOT 0.5 mg twice daily and 75.0% receiving BOT 1.0 mg twice daily) and irrespective of the inflammatory activity (0 eos/mm^2 vs 1–15 eos/mm^2) at baseline. In contrast, patients in the placebo group relapsed in >95% during this period. Accordingly, "aggravation of disease" was the most common reported AE in 64.7% of patients receiving placebo. These findings illustrate, firstly, the effectiveness of BOT for the maintenance treatment of EoE and, secondly, that EoE requires a proper long-term anti-inflammatory therapy because, without active treatment, the vast majority of patients experience a relapse within the first 100 days after cessation of the medication. Relapse rates in patients treated with BOT did not increase throughout the whole study period, suggesting that, in contrast to a retrospective analysis performed in adult patients with EoE,[29] and clearly different from inflammatory bowel diseases, loss of efficacy over time is likely not a concern for budesonide used in EoE.

Histologic improvement of EoE is directly related to the mucosal contact time of the active component,[26] which highlights the importance of using appropriate drug formulations that optimize esophageal targeting, as demonstrated in the induction trials with BOT.[16,19] The same seems to happen for long-term maintenance treatment, as the active component reached all esophageal segments in sufficient concentrations to maintain long-term histologic remission. In addition, an esophageal longitudinal efficiency gradient for BOT was not observed, as the histologic relapse rates in the distal esophagus were not higher than in the proximal part.

As secondary outcomes, we assessed changes in endoscopic features of EoE during the study period, which mirrored the clinicohistologic evolution: endoscopic remission (no visible features of EoE activity) remained stable under BOT in around 70% of patients. In contrast, endoscopic signs of inflammation relapsed in the vast majority of the patients taking placebo, with only 7% of the patients showing no endoscopic features of EoE.

HRQoL (measured with EoE-QoL-A) significantly improved in all domains with BOT 0.5 mg and 1.0 mg twice daily, but deteriorated with placebo. Keeping in mind that all patients started with an already very good QoL, that is, a mean EoE-QoL-A total score of 3.0–3.2 of maximum 4.0, the relative 10% improvement and deterioration with active and placebo, respectively, are clinically relevant. No further decrease under placebo was to be expected, as patients were prematurely withdrawn from the double-blind phase as soon as a suspected clinical relapse was confirmed. Our findings are in line with previous research that identified symptom frequency and duration, severity of endoscopic features, and histologic disease activity as major determinants for HRQoL in adult patients with EoE.[11,30,31]

So far, no proper dosage-finding maintenance studies were performed in EoE,[12] thus we compared, in this study, the efficiency of 3 different dosages of BOT. Remission rates after 48-week treatment were not significantly different, so it is likely that a twice daily dosing of 0.5 mg might be sufficient to successfully maintain long-term remission for the average adult patient with EoE. Additional studies are needed to confirm this and to evaluate other treatment schedules, for example, an easier to adhere once per day regimen, or an intermittent or even on-demand treatment strategy.

AE rates were comparable among all 3 treatment groups, most of them were mild and not related to the investigational product. No serious drug-related AE occurred. Local fungal infections with *Candida* occurred in a higher frequency with budesonide. This well-known AE of STCs was searched systematically regarding localization and clinical relevance. In addition, clinically, endoscopically, or histologically suspected candidiasis was confirmed using Grocott staining in esophageal biopsies.

Overall, the rates of suspected symptomatic *Candida* infections appears not to be dose-dependent, with 16.1% and 11.8% in the 0.5 mg and 1.0 mg twice daily BOT dosages, respectively, and just in the range of previously published studies with STCs in EoE.[2,12,16,19,32] One explanation for this finding might be a dose-independent ceiling effect due to the assumed longstanding contact time of the active ingredient with this special esophagus-targeted formulation. The rate of confirmed and symptomatic esophageal candidiasis was as low as 5.9% and 1.5% with BOT 0.5 mg twice daily and 1.0 mg twice daily BOT, respectively, and did not increase throughout the study period. It was easy to treat and almost never interfered with the daily life activities of patients.

BOT is a mainly locally acting corticosteroid, and so far neither short-term trials performed in adult patients with EoE nor a study evaluating prolonged use of swallowed budesonide[33] have raised relevant systemic safety concerns. Despite a phase 1 study with BOT that showed that a small fraction of budesonide appeared in the systemic circulation in patients with EoE,[34] no clinically relevant reduction in morning cortisol levels was found among our patients, independent of the BOT dosage used. However, 4 patients developed low serum cortisol levels with BOT but without symptoms of adrenal insufficiency. Nevertheless, we recommend monitoring symptoms and signs of adrenal insufficiency when administrating topical-acting corticosteroids over prolonged time periods, in particular in children and when using higher dosages.

Our study also had some limitations. First, we did not identify a minimally effective dose regimen to maintain EoE in remission because the 2 BOT dosages assessed achieved similar remission rates under the end points evaluated, which does not preclude that a dosage even lower than 0.5 mg twice daily could still maintain long-term remission of EoE compared with placebo. However, an extensive subgroup analysis should be performed to assess potential prognostic factors for future guidance on which patients might benefit from a higher maintenance dosage of BOT 1.0 mg twice daily. Second, concomitant treatment with PPIs at stable dosages was allowed along the trial, which could have contributed to the lack of symptoms at EoT in a proportion of patients with placebo. Finally, we did not measure, systematically, squamous epithelium thickness at baseline and after long-term exposure to STCs, so the potential of developing STC-induced epithelial atrophy in the esophagus as already reported in the skin[35] was not excluded.

In conclusion, this trial confirmed that EoE requires therapeutic long-term management and demonstrated that BOT is effective and safe as maintenance therapy for adult patients with EoE who achieved disease remission with the same compound.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2020.07.039.

References

1. Dellon ES, Liacouras CA, Molina-Infante J, et al. Updated International Consensus Diagnostic Criteria for Eosinophilic Esophagitis: proceedings of the AGREE Conference. Gastroenterology 2018;155:1022–1233. e10.

2. Lucendo AJ, Molina-Infante J, Arias A, et al. Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. United European Gastroenterol J 2017;5:335–358.

3. Navarro P, Arias A, Arias-Gonzalez L, et al. Systematic review with meta-analysis: the growing incidence and prevalence of eosinophilic oesophagitis in children and adults in population-based studies. Aliment Pharmacol Ther 2019;49:1116–1125.

4. Prasad GA, Alexander JA, Schleck CD, et al. Epidemiology of eosinophilic esophagitis over three decades in Olmsted County, Minnesota. Clin Gastroenterol Hepatol 2009;7:1055–1061.

5. Warners MJ, de Rooij W, van Rhijn BD, et al. Incidence of eosinophilic esophagitis in the Netherlands continues to rise: 20-year results from a nationwide pathology database. Neurogastroenterol Motil 2018; 30:e13165.

6. Sperry SL, Crockett SD, Miller CB, et al. Esophageal foreign-body impactions: epidemiology, time trends, and the impact of the increasing prevalence of eosinophilic esophagitis. Gastrointest Endosc 2011;74:985–991.

7. Dellon ES, Kim HP, Sperry SL, et al. A phenotypic analysis shows that eosinophilic esophagitis is a progressive fibrostenotic disease. Gastrointest Endosc 2014;79:577–585.e4.

8. Lipka S, Kumar A, Richter JE. Impact of diagnostic delay and other risk factors on eosinophilic esophagitis phenotype and esophageal diameter. J Clin Gastroenterol 2016;50:134–140.

9. Schoepfer AM, Safroneeva E, Bussmann C, et al. Delay in diagnosis of eosinophilic esophagitis increases risk for stricture formation in a time-dependent manner. Gastroenterology 2013;145:1230–1236; e1–e2.

10. Warners MJ, Oude Nijhuis RAB, de Wijkerslooth LRH, et al. The natural course of eosinophilic esophagitis and long-term consequences of undiagnosed disease in a large cohort. Am J Gastroenterol 2018;113:836–844.

11. Lucendo AJ, Arias-Gonzalez L, Molina-Infante J, et al. Systematic review: health-related quality of life in children and adults with eosinophilic oesophagitis-instruments for measurement and determinant factors. Aliment Pharmacol Ther 2017;46:401–409.

12. Furuta GT, Katzka DA. Eosinophilic esophagitis. N Engl J Med 2015;373:1640–1648.

13. Murali AR, Gupta A, Attar BM, et al. Topical steroids in eosinophilic esophagitis: systematic review and meta-analysis of placebo-controlled randomized clinical trials. J Gastroenterol Hepatol 2016;31:1111–1119.

14. Faubion WA, Perrault J, Burgart LJ, et al. Treatment of eosinophilic esophagitis with inhaled corticosteroids. J Pediatr Gastroenterol Nutr 1998;27:90–93.

15. Straumann A, Conus S, Degen L, et al. Budesonide is effective in adolescent and adult patients with active eosinophilic esophagitis. Gastroenterology 2010; 139:1526–1537.

16. **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.

17. Straumann A, Spichtin HP, Grize L, et al. Natural history of primary eosinophilic esophagitis: a follow-up of 30 adult patients for up to 11.5 years. Gastroenterology 2003;125:1660–1669.

18. Greuter T, Bussmann C, Safroneeva E, et al. long-term treatment of eosinophilic esophagitis with swallowed topical corticosteroids: development and evaluation of a therapeutic concept. Am J Gastroenterol 2017; 112:1527–1535.

19. **Miehlke S, Hruz P**, Vieth M, et al. A randomised, double-blind trial comparing budesonide formulations and dosages for short-term treatment of eosinophilic oesophagitis. Gut 2016;65:390–399.

20. **Schoepfer AM, Straumann A**, Panczak R, et al. Development and validation of a symptom-based activity index for adults with eosinophilic esophagitis. Gastroenterology 2014;147:1255–1266.e21.

21. Bajaj S, Taft T, Keefer L, et al. Validity, usability, and acceptability of the eosinophilic esophagitis quality of life scale for adults (EoE-QOL-A). Gastroenterology 2012; 142:S–434.

22. Taft TH, Kern E, Kwiatek MA, et al. The adult eosinophilic oesophagitis quality of life questionnaire: a new measure of health-related quality of life. Aliment Pharmacol Ther 2011;34:790–798.

23. Hirano I, Moy N, Heckman MG, et al. Endoscopic assessment of the oesophageal features of eosinophilic oesophagitis: validation of a novel classification and grading system. Gut 2013;62:489–495.

24. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). Drug Saf 1999;20:109–117.

25. Straumann A, Conus S, Degen L, et al. Long-term budesonide maintenance treatment is partially effective for patients with eosinophilic esophagitis. Clin Gastroenterol Hepatol 2011;9:400–409.

26. Dellon ES, Sheikh A, Speck O, et al. Viscous topical is more effective than nebulized steroid therapy for patients with eosinophilic esophagitis. Gastroenterology 2012; 143:321–324.

27. Andreae DA, Hanna MG, Magid MS, et al. Swallowed fluticasone propionate is an effective long-term maintenance therapy for children with eosinophilic esophagitis. Am J Gastroenterol 2016;111:1187–1197.

28. Attwood SE, Smyrk TC, Demeester TR, et al. Esophageal eosinophilia with dysphagia. A distinct clinicopathologic syndrome. Dig Dis Sci 1993;38:109–116.

29. 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.

30. Lucendo AJ, Arias-Gonzalez L, Molina-Infante J, et al. Determinant factors of quality of life in adult patients with eosinophilic esophagitis. United European Gastroenterol J 2018;6:38–45.

31. **Safroneeva E, Coslovsky M**, Kuehni CE, et al. Eosinophilic oesophagitis: relationship of quality of life with clinical, endoscopic and histological activity. Aliment Pharmacol Ther 2015;42:1000–1010.

32. Dellon ES, Woosley JT, Arrington A, et al. Efficacy of budesonide vs fluticasone for initial treatment of eosinophilic esophagitis in a randomized controlled trial. Gastroenterology 2019;157:65–73.e5.

33. Dellon ES, Katzka DA, Collins MH, et al. Safety and efficacy of budesonide oral suspension maintenance therapy in patients with eosinophilic esophagitis. Clin Gastroenterol Hepatol 2018;17:6366–6373.e8.

34. Dilger K, Lopez-Lazaro L, Marx C, et al. Active eosinophilic esophagitis is associated with impaired elimination of budesonide by cytochrome P450 3A enzymes. Digestion 2013;87:110–117.

35. Brazzini B, Pimpinelli N. New and established topical corticosteroids in dermatology: clinical pharmacology and therapeutic use. Am J Clin Dermatol 2002;3:47–58.

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CRediT Authorship Contributions

Alex Straumann, MD (Conceptualization: Equal; Formal analysis: Equal; Investigation: Equal; Methodology: Lead; Writing – original draft: Lead; Patient Recruitment: Lead). Alfredo Lucendo, MD, PhD (Conceptualization: Equal; Formal analysis: Lead; Methodology: Equal; Writing – original draft: Equal; Patient Recruitment: Equal). Stephan Miehlke, MD (Conceptualization: Supporting; Formal analysis: Supporting; Methodology: Supporting; Writing – original draft: Supporting; Patient Recruitment: Equal). Michael Vieth, MD, PhD (Formal analysis: Lead; Methodology: Equal; Project administration: Equal). Christoph Schlag, MD (Patient Recruitment: Equal). Luc Biedermann, MD (Patient Recruitment: Equal). Cecilio Santander Vaquero, MD (Patient Recruitment: Equal). Constanza Ciriza De los Rios, MD, PhD (Patient Recruitment: Equal). Christoph Schmoecker, MD (Patient Recruitment: Equal). Ahmed Madisch, MD (Patient Recruitment: Equal). Petr Hruz, MD, PhD (Patient Recruitment: Equal). Jamal Hayat, MD (Patient Recruitment: Equal). Ulrike von Arnim, MD (Patient Recruitment: Equal). Albert Jan Bredenoord, MD (Patient Recruitment: Equal). Stephan Schubert, MD (Patient Recruitment: Equal). Ralph Mueller, PhD (Conceptualization: Equal; Data curation: Equal; Formal analysis: Lead; Methodology: Equal; Project administration: Lead; Validation: Equal; Writing – original draft: Supporting; Writing – review & editing: Equal). Roland Greinwald, PhD (Conceptualization: Equal; Funding acquisition: Lead; Investigation: Equal; Methodology: Equal; Writing – original draft: Supporting). Alain Schoepfer, MD (Conceptualization: Supporting; Formal analysis: Su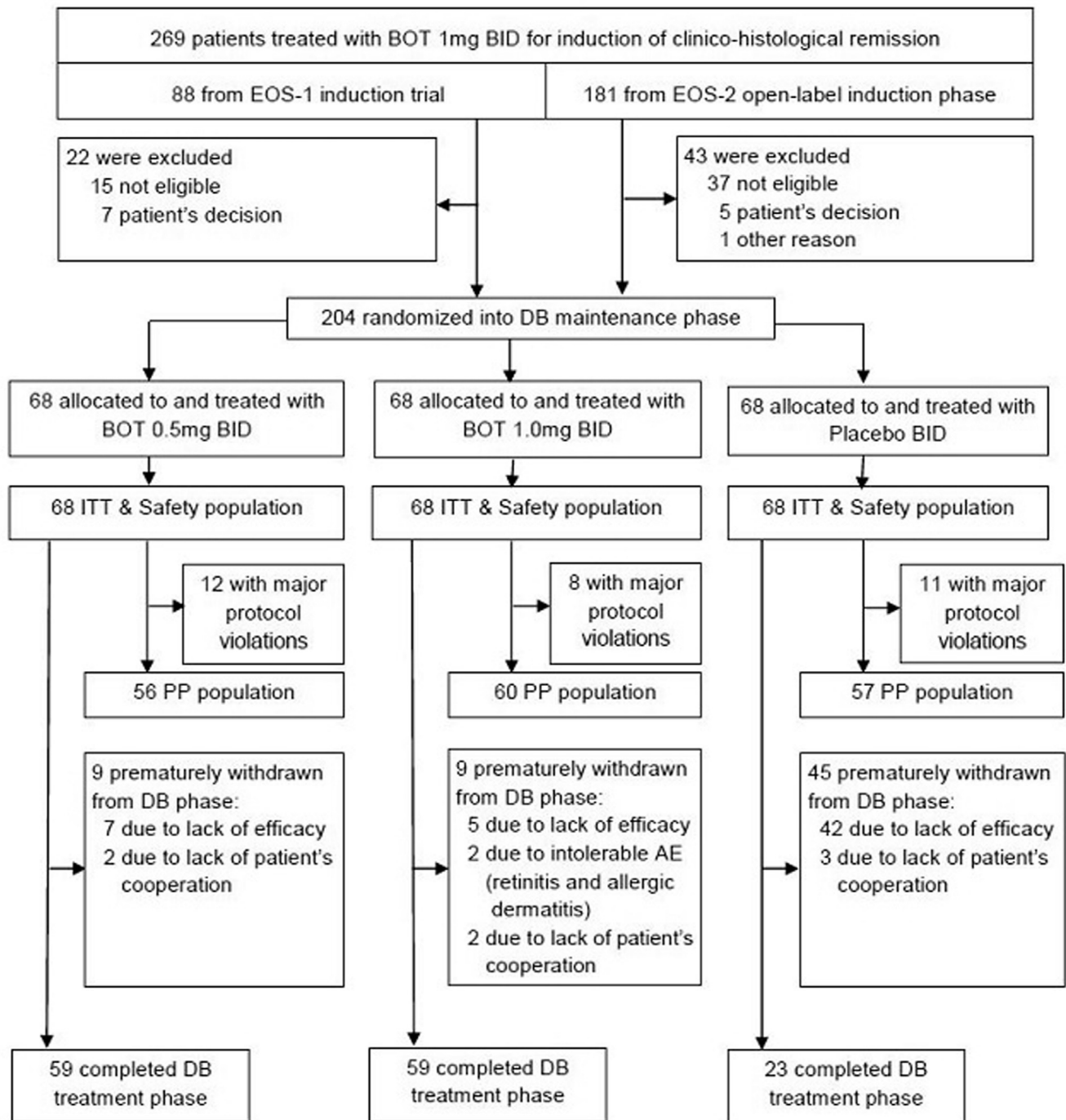pporting; Methodology: Equal; Validation: Equal; Patient Recruitment: Equal). Stephen Attwood, MD (Conceptualization: Equal; Formal analysis: Equal; Methodology: Equal; Supervision: Equal; Writing – original draft: Equal).

Conflicts of interest

Funding

Supplementary Figure 1. Consolidated Standards of Reporting Trials diagram showing the patient flow in the study. Patients with active EoE from 29 European medical centers were screened and brought into clinicohistologic remission either via controlled EOS-1 trial[16] or via a 6-week open-label induction treatment with budesonide 1.0 mg orodispersible tablet twice daily (BOT 1.0mg BID). After randomization, patients received double-blind (DB) treatment with either BOT 0.5 mg BID, BOT 1.0 mg BID, or placebo BID for 48 weeks. The intention-to-treat (ITT) population for efficacy and safety analyses included 204 patients and the per-protocol (PP) population for efficacy analyses consisted of 173 patients.

Supplementary Table 1. List of International EOS-2 Study Group Institutions

Country	Institution
Belgium	Universitaire Ziekenhuis Leuven, Leuven
Germany	Center for Digestive Diseases, Internal Medicine Center Eppendorf, Hamburg, and Center for Esophageal Disorders, University Hospital Hamburg-Eppendorf
	II. Medizinische Klinik, Klinikum rechts der Isar, Technische Universität München, Munich
	Universitätsklinikum Carl Gustav Carus Technische Universität Dresden, Dresden
	Israelitisches Krankenhaus in Hamburg, Hamburg
	Gastroenterologische Gemeinschaftspraxis, Wiesbaden
	Sana Klinikum Lichtenberg, Berlin
	Universitätsklinikum des Saarlandes, Homburg, Saar
	Clinical-Center Region Hannover Clinic Siloah, Hannover
	Städt. Klinikum Braunschweig GmbH, Braunschweig
	Praxis für Innere Medizin und Gastroenterologie, Berlin
	Otto-von-Guericke-Universitäts Klinikum Magdeburg, Magdeburg
	Gastroenterologische Gemeinschaftspraxis Mainz, Mainz
	Medizinisches Versorgungszentrum Dachau, Dachau
	Klinikum Ludwigsburg, Ludwigsburg
	Klinikum der Johann Wolfgang Goethe-Universität, Frankfurt am Main
	Allgemeines Krankenhaus Celle, Celle
	Klinikum Augsburg, Augsburg
The Netherlands	Academic Medical Center Amsterdam, Amsterdam
	St Antonius Ziekenhuis, Nieuwegein
	Albert Schweizer Ziekenhuis, Dordrecht
Spain	Hospital General de Tomelloso, Tomelloso, Ciudad Real, and Instituto de Investigación Sanitaria Princesa, Madrid
	Hospital Universitario de la Princesa, Madrid
	Hospital Universitario 12 de Octubre, Madrid
	Hospital de Viladecans, Barcelona
	Hospital Universitario Central de Asturias, Oviedo
	Hospital General du Ciudad Real, Ciudad Real
	Hospital Universitario Rio Hortega, Valladolid
	Agencia Sanitaria Costa del Sol, Marbella, Málaga
Switzerland	Swiss EoE Research Group, Olten and University Hospital Zurich, Zurich,
	University Hospital Basel, Basel
	Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne,
	University Hospital Zurich, Zurich
United Kingdom	St George's Hospital, London
	Darlington Memorial Hospital, Darlington

Supplementary Table 2. Disease-Specific Characteristics of Study Patients Before Initial Acute Therapy for Induction of Clinicohistologic Remission With Budesonide Orodispersible Tablets

Characteristics	BOT 0.5 mg BID (n = 68)	BOT 1.0 mg BID (n = 68)	Placebo BID (n = 68)	All patients (n = 204)
Weekly sum of daily dysphagia NRS (0–70 points),[a] mean ± SD	34 ± 14.8	33 ± 16.1	33 ± 15.0	33 ± 15.3
Weekly sum of daily odynophagia NRS (0–70 points),[a] mean ± SD	26 ± 16.1	24 ± 18.9	24 ± 16.7	25 ± 17.2
EEsAI-PRO,[b] mean ± SD	50 ± 16.3	52 ± 18.2	53 ± 15.3	52 ± 16.6
PatGA,[c] mean ± SD	6 ± 1.6	6 ± 1.7	6 ± 1.4	6 ± 1.6
Overall peak eos/mm^2 hpf,[d] mean ± SD	277 ± 214	295 ± 237	300 ± 273	291 ± 241
Peak eos/mm^2 hpf by esophageal location,[d] mean ± SD				
Proximal	146 ± 149	194 ± 231	191 ± 266	177 ± 221
Mid	188 ± 198	190 ± 174	198 ± 197	192 ± 189
Distal	201 ± 185	211 ± 177	220 ± 164	210 ± 175
Localization of inflammation, n (%)				
Proximal	57 (83.8)	56 (82.4)	61 (89.7)	174 (85.3)
Mid	57 (83.8)	60 (88.2)	64 (94.1)	181 (88.7)
Distal	65 (95.6)	62 (91.2)	66 (97.1)	193 (94.6)
Number of inflamed segments, n (%)				
1 segment	7 (10.3)	7 (10.3)	3 (4.4)	17 (8.3)
2 segments	11 (16.2)	12 (17.6)	7 (10.3)	30 (14.7)
3 segments	50 (73.5)	49 (72.1)	58 (85.3)	157 (77.0)

BID, twice daily; EEsAI-PRO, Eosinophilic Esophagitis Activity Index Patient Reported Outcome; PatGA, Patient's Global Assessment of EoE activity.

[a]Daily NRS for dysphagia and odynophagia, respectively, ranging from 0 to 10 points; higher scores indicating greater symptom severity.

[b]EEsAI-PRO score ranging from 0 to 100 points with higher scores indicating greater disease severity; clinical remission is defined as a score of ≤20 points.

[c]PatGA is an NRS ranging from 0 to 10 points; higher scores indicating greater disease activity.

[d]Peak eosinophils count standardized to mm^2 hpf (400×). Peak of <16 eos/mm^2 hpf in all 6 biopsies, 2 each derived from the derived proximal, mid, and distal esophagus, was defined as histologic remission; 0 eos/mm^2 hpf in all biopsies was deep histologic remission.

Supplementary Table 3. Protocol Prespecified Subgroup Analyses of the Primary Study End Point in Eosinophilic Esophagitis Patients Treated With Budesonide Orodispersible Tablets or Placebo in the Double-Blind Phase

Characteristic	Patients in clinicopathologic remission at wk 48 stratified by protocol prespecified criteria, n (%)		
	BOT 0.5 mg BID (n = 68)	BOT 1.0 mg BID (n = 68)	Placebo BID (n = 68)
Localization of inflammation at baseline of induction treatment			
Proximal esophagus			
No	11/11 (100.0)	9/12 (75.0)	1/7 (14.3)
Yes	39/57 (68.4)	42/56 (75.0)	2/61 (3.3)
Middle esophagus			
No	10/11 (90.9)	6/8 (75.0)	0/3 (0.0)
Yes	40/57 (70.2)	45/60 (75.0)	3/64 (4.7)
Distal esophagus			
Not evaluable	—	0/1 (0.0)	0/1 (0.0)
No	2/3 (66.7)	3/5 (60.0)	0/1 (0.0)
Yes	48/65 (73.8)	48/62 (77.4)	3/66 (4.5)
Extent of inflammation at baseline of induction treatment, no. of esophageal segments affected			
1	7/7 (100.0)	6/7 (85.7)	0/3 (0.0)
2	9/11 (81.8)	6/12 (50.0)	1/7 (14.3)
3	34/50 (68.0)	39/49 (79.6)	2/58 (3.4)
Concomitant use of PPIs during the double-blind phase			
No	37/52 (71.2)	42/56 (75.0)	2/59 (3.4)
Yes	13/16 (81.3)	9/12 (75.0)	1/9 (11.1)
History of allergic diseases			
No	9/14 (64.3)	10/13 (76.9)	1/18 (5.6)
Yes	41/54 (75.9)	41/55 (74.5)	2/50 (4.0)
Time since first symptoms			
Not evaluable	—	—	0/2 (0.0)
Less than median (9.8 y)	21/27 (77.8)	23/33 (69.7)	2/41 (4.9)
Median or longer (9.8 y)	29/41 (70.7)	28/35 (80.0)	1/25 (4.0)
Post-hoc analyses			
Baseline histology			
0 eos/mm^2 hpf	49/65 (75.4)	48/65 (73.8)	3/64 (4.7)
1 to 15 eos/mm^2 hpf	1/3 (33.3)	3/3 (100.0)	0/2 (0.0)

BID, twice daily.

Supplementary Table 4. Post-Hoc Analyses of Endoscopic Parameters for Remitters and Nonremitters of Maintenance Treatment of Eosinophilic Esophagitis with Orodispersible Budesonide Tablets

Outcome variable[a]	BOT 0.5 mg BID		BOT 1.0 mg BID		Placebo BID	
	Remitters (n = 50)	Nonremitters (n = 17)	Remitters (n = 51)	Nonremitters (n = 16)	Remitters (n = 3)	Nonremitters (n = 65)
Total modified EREFS score (0–9 points),[b] mean (95% CI); n						
Baseline	1 (0.6 to 1.3)	1 (0.4 to 1.1)	1 (0.6 to 1.2)	1 (0.1 to 1.3)	1 (–1.5 to 3.5)	1 (0.5 to 1.0)
EoT	1 (0.4 to 0.9)	1 (0.4 to 2.4); 15	0 (0.2 to 0.7)	2 (0.7 to 2.3); 14	1 (–1.5 to 4.2)	4 (3.5 to 4.4); 62
Absolute change from baseline to EoT	–0 (–0.7 to 0.1)	1 (–0.2 to 1.6); 15	–0 (–0.7 to –0.2)	1 (–0.1 to 1.7); 14	0 (–1.1 to 1.8)	3 (2.7 to 3.6); 62
P value	.117[a]	.148[a]	<001[a]	.125[a]	NA	<.001[a]
Inflammatory signs subscore (0–4 points),[b] mean (95% CI); n						
Baseline	0 (0.2 to 0.5)	0 (0.1 to 0.6)	0 (0.2 to 0.6)	0 (–0.1 to 0.3)	1 (–0.8 to 2.1)	0 (0.2 to 0.4)
EoT	0 (0.1 to 0.5)	1 (0.1 to 1.5); 15	0 (0.0 to 0.3)	1 (0.3 to 1.6); 14	1 (–1.5 to 3.5)	3 (2.3 to 2.9); 62
Absolute change from baseline to EoT	–0 (–0.3 to 0.2)	0 (–0.3 to 1.2); 15	–0 (–0.4 to –0.1)	1 (0.1 to 1.4); 14	0 (–1.5 to 1.8)	2 (2.0 to 2.6); 62
P value	.614[a]	P = .281[a]	.004[a]	.031[a]	NA	<.001[a]
Fibrotic signs subscore (0–4 points),[b] mean (95% CI); n						
Baseline	1 (0.4 to 0.8)	0 (0.1 to 0.6)	0 (0.3 to 0.6)	1 (0.1 to 1.1)	0 (–1.1 to 1.8)	0 (0.3 to 0.6)
EoT	0 (0.2 to 0.5)	1 (0.1 to 1.1); 15	0 (0.1 to 0.4)	1 (0.1 to 1.1); 14	0 (–1.1 to 1.8)	1 (0.8 to 1.4); 62
Absolute change from baseline to EoT	–0 (–0.4 to –0.0)	0 (–0.2 to 0.6); 15	–0 (–0.3 to –0.0)	0 (–0.4 to 0.5); 14	0 (–)	1 (0.4 to 0.9); 62
P value	.025[a]	.453[a]	.020[a]	1.000[a]	NA	<.001[a]

NOTE. Two patients with nonassessable remission status after 48 weeks of treatment were excluded from this analysis. BID, twice daily; NA, not applicable.

[a]Two-sided Wilcoxon signed rank test for absolute change from baseline to EoT within a treatment group.

[b]Modified EREFS grading system summing the scores of the 5 major features (edema [0–1], rings [0–3], exudates [0–2], furrows [0–1], strictures [0–1]) and 1 minor (crêpe paper esophagus [0–1]); total score ranged from 0 to 9 points, with higher score indicating more severe endoscopic findings. Inflammatory subscore (edema [0–1], exudates [0–2], furrows [0–1]), ranged from 0 to 4 points, with higher score indicating more severe inflammatory findings; fibrotic subscore (rings [0–3], strictures [0–1]), ranged from 0 to 4 points, with higher score indicating more severe fibrotic findings.