CLINICAL AT

Efficacy of Budesonide Orodispersible Tablets as Induction Therapy for Eosinophilic Esophagitis in a Randomized Placebo-Controlled Trial

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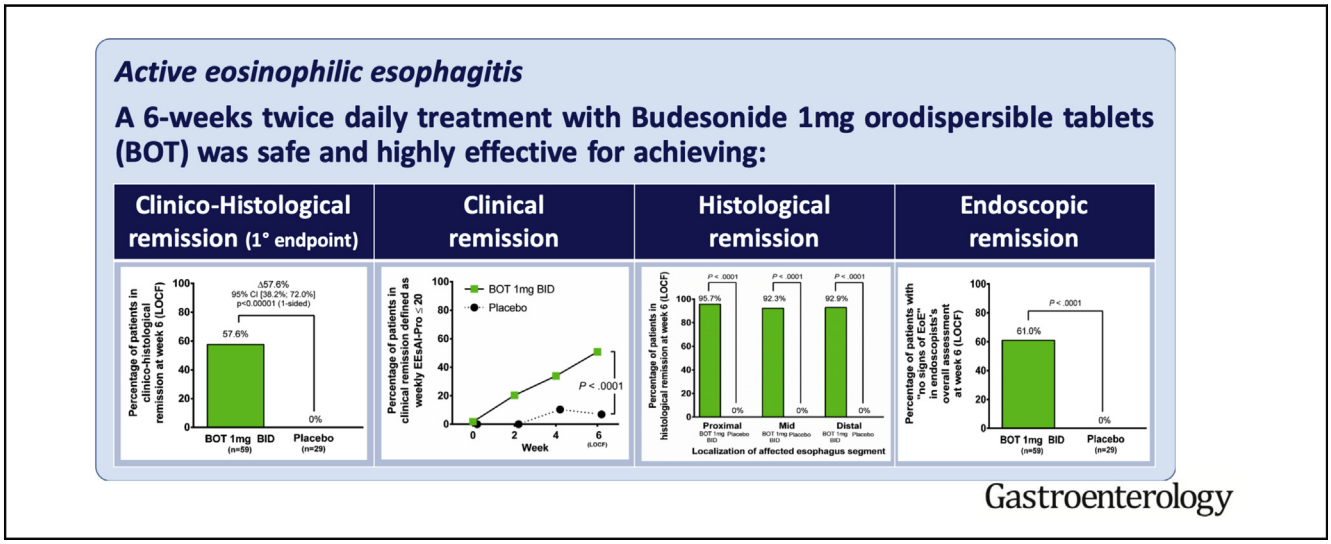

BACKGROUND & AIMS: Swallowed topical-acting corticosteroids are recommended as first-line therapy for eosinophilic esophagitis (EoE). Asthma medications not optimized for esophageal delivery are sometimes effective, although given off-label. We performed a randomized, placebo-controlled trial to assess the effectiveness and tolerability of a budesonide orodispersible tablet (BOT), which allows the drug to be delivered to the esophagus in adults with active EoE. **METHODS:** We performed a double-blind, parallel study of 88 adults with active EoE in Europe. Patients were randomly assigned to groups that received BOT (1 mg twice daily; n = 59) or placebo (n = 29) for 6 weeks. The primary end point was complete remission, based on clinical and histologic factors, including dysphagia and odynophagia severity ≤2 on a scale of 0–10 on each of the 7 days before the end of the double-blind phase and a peak eosinophil count <5 eosinophils/high power field. Patients who did not achieve complete remission at the end of the 6-week double-blind phase were offered 6 weeks of open-label

treatment with BOT (1 mg twice daily). **RESULTS:** At 6 weeks, 58% of patients given BOT were in complete remission compared with no patients given placebo ($P < .0001$). The secondary end point of histologic remission was achieved by 93% of patients given BOT vs no patients given placebo ($P < .0001$). After 12 weeks, 85% of patients had achieved remission. Six-week and 12-week BOT administration were safe and well tolerated; 5% of patients who received BOT developed symptomatic, mild candida, which was easily treated with an oral antifungal agent. **CONCLUSIONS:** In a randomized trial of adults with active EoE, we found that budesonide oral tablets were significantly more effective than placebo in inducing clinical and histologic remission. Eudra-CT number 2014-001485-99; ClinicalTrials.gov ID NCT02434029.

Keywords: Phase 3 Trial; Immune Response; Esophagus; Patient-Reported Outcomes.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Eosinophilic Esophagitis (EoE) is a newly identified disease that is rapidly rising in frequency and is now the second most common disease in the esophagus. Until now there has been no licenced therapy; treatment using drugs adapted from other conditions has been limited and not standardized.

NEW FINDINGS

A newly created, specific formulation, of topical steroid was shown in a randomized, placebo controlled, double blind clinical trial, to resolve both the symptoms and the underlying inflammation in EoE in most patients.

LIMITATIONS

Patients selected for this study were all PPI-resistant. Long-term outcomes of this therapy need to be assessed and maintenance regimes, doses and duration need to be identified.

IMPACT

This study demonstrates the effectiveness of a new therapy that is specifically licenced for EoE. The majority of patients are likely to respond fully and it provides a licensed standard to which other therapies may be compared.

Eosinophilic esophagitis (EoE) is a chronic, immune-mediated, esophageal-restricted disease characterized clinically by symptoms related to esophageal dysfunction and histologically by an eosinophil-predominant inflammation.[1] A dramatic increase in incidence and prevalence of EoE has been documented over the last 2 decades,[2] especially in Western countries.[3,4] EoE is currently the most common cause of dysphagia and bolus impaction,[5] and the second leading cause of chronic esophagitis after gastroesophageal reflux disease.[6]

Predominant symptoms of EoE in adult patients are chronic dysphagia, food impaction, and chest pain.[1] EoE is a chronic-progressive disease and, if left untreated, is usually associated with persistence of symptoms and inflammation.[7] Furthermore, it is well established that the ongoing eosinophilic inflammation leads to esophageal remodeling, resulting in fibrosis with possible stricture formation and functional damage.[8,9] Consequently, EoE has a substantial negative impact on the health-related quality of life (HRQoL) of patients and their families by causing emotional distress and restricting social activities.[10] There is, therefore, a clear indication to treat patients suffering from active EoE.

Today, swallowed topical-acting corticosteroids (STCs) are an established first-line pharmacologic treatment for patients with EoE.[1] Proton pump inhibitors (PPIs)[11] and dietary modifications[12] are alternatives. From the first positive attempt to treat EoE with STCs, drugs that were originally developed for airway administration in patients with asthma,[13] multiple trials have confirmed the efficacy of these compounds in improving symptoms as well as inflammation in patients with EoE.[14] Fluticasone or budesonide have shown comparable potencies, but the vehicle depositing the compound on the esophageal surface seems to be critical.[15] However, variability regarding inclusion criteria, daily dosages, length of treatment (from 2 to 12 weeks), delivery systems, and the definition of histologic remission (from <1 to <20 eosinophils per high power field [eos/hpf]) hampers comparative analyses among these studies. In contrast to histologic remission, several trials could not demonstrate a clear superiority of STCs over placebo in symptom improvement.[16–18]

A previous phase 2 trial with a new budesonide orodispersible tablet formulation (BOT, originally defined as an "effervescent tablet for orodispersible use [BET]"[18]) in adult patients with active EoE demonstrated high effectiveness and safety for short-term treatment, achieving up to 100% histologic remission rate. Doses of 1 mg or 2 mg BOT twice daily were equally effective, with 100% and 94.7% remission rates, respectively.[18] The purpose of this multicenter trial was to evaluate efficacy and safety of this BOT formulation and to assess the superiority of BOT 1 mg twice daily over placebo for inducing symptomatic and histologic remission in adults with active EoE.

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Abbreviations used in this paper: **BOT, budesonide orodispersible tablet; DB, double-blind; EEsAI-PRO, Eosinophilic Esophagitis Activity Index–Patient Reported Outcome; EoE, eosinophilic esophagitis; EoE-QoL-A, Eosinophilic Esophagitis Quality of Life Scale for Adults; eos/hpf, eosinophils per high power field; EoT, end of treatment; EREFS, Endoscopic Reference Score; HRQoL, health-related quality of life; NRS, numerical rating scale; OLI, open-label induction; PatGA, Patient's Global Assessment; PGA, Physician's Global Assessment; PP, per-protocol; PPI, proton pump inhibitor; SHS, Short Health Scale; STC, swallowed topical-acting corticosteroid.**

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Methods

Study Design and Conduct

This was a randomized, double-blind (DB), placebo-controlled, parallel group, phase 3 study comparing the efficacy and tolerability of 6 weeks of treatment with budesonide (BOT 1 mg twice daily) vs placebo in adult patients with active EoE (see Supplementary Figure 1). Patients not achieving clinico-histologic remission at the end of the 6-week DB phase, or who dropped out after at least 4 weeks of DB treatment due to lack of efficacy, were offered an additional 6 weeks of open-label induction (OLI) treatment with BOT 1 mg twice daily. Patients achieving clinico-histologic remission either at end of treatment (EoT) of DB or OLI phase could enter the maintenance of remission study EOS-2 (EudraCT number 2014-001485-99). The study was conducted at 26 centers in 6 countries from November 2015 to October 2016 (see Supplementary Material).

The study protocol (see Supplementary Material) was approved by the national ethics committees in all participating countries and registered at www.clinicaltrialsregister.eu (EudraCT 2014-001485-99) and at www.ClinicalTrials.gov (NCT02434029). All patients provided written informed consent. The study was conducted in accordance with the protocol, Good Clinical Practice, and within the provisions of the Declaration of Helsinki. The first draft of the manuscript was written by the first author; all authors had access to the study data and reviewed and approved the final manuscript.

Patients

Key inclusion criteria were the following: patients aged 18–75 years with clinico-histologic active EoE and being refractory to treatment with a PPI used at least standard dosages (eg, omeprazole 20 mg/d, pantoprazole 40 mg/d, esomeprazole 40 mg/d, lansoprazole 30 mg/d, or rabeprazole 20 mg/d) for a 4-week period.[19] Patients had to have a severity of $\geq$4 points on a 0–10 numerical rating scale (NRS) for either dysphagia or odynophagia for $\geq$1 day in the week before randomization. Additionally, Patient's Global Assessment (PatGA) of EoE activity was to be $\geq$4 points on a 0–10 NRS. Histologic activity with peak eos $\geq$65/mm^2 hpf in at least 1 hpf (corresponding to $\geq$20 eos/hpf), as measured in a total of 6 hpfs derived from 6 biopsies, 2 each from the proximal, mid, and distal segments of the esophagus.

Key exclusion criteria were the following: clinical and endoscopic suspicion for gastroesophageal reflux disease (at least Los Angeles Classification of Esophagitis Grade A); achalasia or scleroderma; evidence of causes other than EoE for esophageal eosinophilia; 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 screening; any relevant systemic disease; systemic glucocorticosteroids, immunosuppressants, biologic drugs within 4 weeks before screening, or topical glucocorticosteroids within 2 weeks before screening; and onset of dietary restrictions within 4 weeks before screening.

Randomization and Interventions

At baseline, eligible patients were centrally randomized in a 2:1 ratio (verum to 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, the 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 2-weekly interim visits, patients received study medication for the next period. BOT and corresponding placebo were identical in physical appearance and 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 slight effervescence of the study medication, which uniquely differentiates against conventional orodispersible tablet formulations. The components dissolved in saliva were then to be swallowed (approximately 5–10 swallows within a few minutes). Patients were instructed to avoid eating, drinking, or oral hygiene procedures for 30 minutes after study drug administration. Compliance was assessed by pill count. The use of other concomitant anti-inflammatory drugs (ie, systemic or topical glucocorticosteroids immunosuppressants, biologic drugs) or onset of dietary restrictions was not permitted. Concomitant PPI treatment was to be kept stable.

Procedures

Post-randomization visits took place every 2 weeks during the DB and the optional OLI phase, and at the 4-week follow-up visit if the patient did not switch to the EOS-2 maintenance of remission study (see Supplementary Figure 1).

Clinical symptoms were assessed daily during the 7 days before baseline and throughout the study using 0–10 points NRS with obvious face validity for dysphagia and odynophagia, respectively. Patients completed, at all visits, the PatGA of EoE activity (0–10 NRS) and the validated Eosinophilic Esophagitis Activity Index Patient Reported Outcome (EEsAI-PRO) score (0–100 points).[20] Physician's Global Assessment (PGA) of EoE activity (0–10 NRS) was assessed at baseline and EoT. Patients completed the Eosinophilic Esophagitis Quality of Life Scale for Adults (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 good HRQoL) to 4 (very poor HRQoL)[21,22] licensed from Northwestern University, Evanston, IL. A modified Short Health Scale (SHS), a visual analogue scales questionnaire (range 0–100 with lower values indicating better quality of life) representing each of 4 health dimensions: Symptom Burden, Social function, Disease-Related Worry, and General Well-Being, was completed.[23] To be used in this trial with EoE patients, the SHS was modified by replacing the terms with respect to the underlying disease in questions 1–3, that is, *bowel* with the *esophageal*.

Upper endoscopy was performed during screening and at EoT and the worst findings from the total esophagus were classified according to the modified Endoscopic Reference Score (EREFS) grading system, summing the scores of the 5 major (edema [0–1], rings [0–3], exudates [0–2], furrows [0–1], strictures [0–1]) and 1 minor (crêpe paper esophagus [0–1]) features; total score ranged from 0 to 9, with higher score

indicating more severe endoscopic findings.[24] In addition, a global assessment of endoscopic EoE activity was performed and classified as none, mild, moderate, or severe.

At each endoscopy, 2 biopsies each from the distal, mid, and proximal esophagus were obtained and analyzed in a blinded manner by the central pathologist (MV). In addition, biopsies from the stomach and duodenum were obtained at screening to exclude concomitant diseases, such as eosinophilic gastroenteritis. Biopsy specimen 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. The cutoff level for histologic remission of <16 eos/mm^2 hpf was chosen, as the same microscope was used in the previous trial by Straumann et al[25] and in the recent phase 2 trial with BOT,[18] and which corresponds to <5 eos/hpf as reported by Straumann et al.

In patients with suspected local fungal infection (ie, based on clinical symptoms, endoscopic appearance, or even from suspicious H&E-stained histologic slides), sensitive Grocott silver staining was performed on esophageal biopsy specimen for final confirmation.

Safety and Tolerability

Physical examinations were performed during screening and at EoT visits. Vital signs, concomitant medications, and adverse events were recorded, and general laboratory tests and urinalysis were performed. Serum morning cortisol (8:00–9:00 AM) levels were measured at Baseline and EoT visits. Tolerability was classified independently by the patient and the investigator at the EoT.

Study End Points

The primary efficacy end point was the rate of patients with clinico-histologic remission at week 6, that is, achieving both, histologic remission at EoT (peak eosinophil count <16 eos/mm^2 hpf) and clinical remission (symptoms severity of ≤ 2 points on each 0–10 NRS for dysphagia and odynophagia, respectively on each day in the week before EoT). Occurrence of food impaction, needing for endoscopic intervention or dilation, or prematurely withdrawal was assessed as treatment failure.

Secondary a priori–ordered end points, which could be tested in a confirmatory manner, included histologic remission, change in peak eosinophil count, resolution of symptoms on each day in the week before the EoT, and rate of clinical remission defined as EEsAI-PRO ≤ 20 at EoT. A full list of all clinical, endoscopic, histologic, and HRQoL end points used is shown in Supplementary Table 1.

Statistical Analyses

Assuming remission rates of 10% and 50% under placebo and BOT, respectively, simulations with ADDPLAN 6 (licensed by ADDPLAN, Inc, an ICON Clinical Research, LLC company) showed that a total of 81 full analysis set (FAS) patients (2:1 randomization) were needed to detect this difference of 40% in true remission rates using Fisher's exact test (1-sided $\alpha = .025$) with a statistical power of at least 90%. This sample size was increased to account for 10% of randomized patients who did not take at least 1 dose of the study drug.

For the primary end point, proportions of patients with clinico-histologic remission at week 6 with last observation carried forward were compared between treatment groups using 1-sided Fisher's exact test. Efficacy significance testing continued in hierarchical fashion for the a priori–ordered key secondary end points. Once a 1-sided non-significant P value ($> .025$) occurred, subsequent significance tests were considered exploratory. Dichotomous key secondary end points were analyzed using Fisher's exact test. Change in the peak eos/mm^2 hpf was analyzed by fitting a linear least squares model with treatment effect and baseline value as covariate.

Exploratory comparisons of further end points between treatment groups or between baseline and end of treatment were performed using 2-sided t tests or Wilcoxon rank sum tests, as appropriate, in case of continuous data. Two-sided Fisher's exact test was applied to dichotomous data. Descriptive statistics were used to summarize data, including incidences of adverse events.

Analyses were performed using SAS, version 9.3 (SAS Institute, Cary, NC) and ADDPLAN, version 6.1.1 and according to the intention-to-treat principle. Missing data at week 6 were replaced using the last observation carried forward method.

Results

Patient Flow and Baseline Characteristics

In total, 126 patients were screened, 88 met inclusion criteria and were randomized and treated. In total, 82 patients completed the DB phase (92.0%), but all 88 patients were evaluable for the primary analysis (Supplementary Figure 2).

Both treatment groups had similar baseline characteristics (Table 1), being typical for an adult patient population with EoE. Both study arms had a similar peak eosinophil count and moderate to severe esophageal symptom scores as assessed by NRS for dysphagia, odynophagia; NRS for PatGA and PGA, EEsAI-PRO, and dysphagia-free days. HRQoL, as measured by modified SHS and EoE-QoL-A scores, was moderately impaired in both treatment groups at baseline (Table 1).

Clinical Efficacy

The primary end point of clinico-histologic remission at week 6 was achieved in 34 of 59 (57.6%) patients receiving budesonide, but in none of the 29 (0%) patients receiving placebo ($P < .0001$) (Figure 1). This finding was extremely robust, as the per-protocol analysis (data not shown) as well as further protocol specified subgroup analyses were all in complete alignment. For example, the rates of clinico-histologic remission were not significantly influenced by the peak eosinophil count at baseline conditions, presence or absence of concomitant allergic diseases, blood eosinophil density, concomitant PPI use, or disease duration (Supplementary Table 2).

A further 6-week OLI therapy with BOT 1 mg twice daily was offered to clinical or histological non-responders at EoT of DB phase and was chosen by 23 patients from the BOT

Table 1. Demographic, Anamnestic, and Baseline Disease Characteristics of Study Patients

Characteristic	BOT 1 mg bid (n = 59)	Placebo (n = 29)
Male, n (%)	48 (81)	25 (86)
White, n (%)	59 (100)	29 (100)
Age, *y*, mean (SD)	37 (11.5)	37 (9.2)
Body mass index , kg/m^2, mean (SD)	24.4 (2.9)	25.6 (4.1)
Time since first EoE symptoms, *mo*, mean (SD)	134 (104.6)	139 (98.8)
Time since EoE diagnosis, *mo*, mean (SD)	49 (44.3)	58 (49.3)
History of allergic disease, n (%)	47 (80)	23 (79)
History of having experienced, n (%)		
Dysphagia	58 (98)	29 (100)
Odynophagia	35 (59)	14 (48)
Food impaction	56 (95)	26 (90)
Frequency of dysphagia in the last week, n (%)		
Never	2 (3)	0 (0)
1–3×/wk	21 (36)	12 (41)
4–6×/wk	10 (17)	2 (7)
Daily	24 (41)	13 (45)
Missing	2 (3)	2 (7)
Daily dysphagia (NRS 0–10) in the last week, mean (SD)	5.8 (2.0)	5.9 (1.7)
Weekly sum of daily dysphagia NRS (0–70), mean (95% CI)	35 (30–39)	36 (32–41)
Daily odynophagia (NRS 0–10) in the last week, mean (SD)	3.5 (2.8)	3.4 (3.2)
Weekly sum of daily odynophagia NRS (0–70), mean (95% CI)	27 (23–32)	26 (19–32)
Total weekly EEsAI-PRO (0–100), mean (SD)	54 (16)	55 (16)
Modified SHS (VAS 0–100), mean (SD)		
Symptom burden	58 (24)	55 (18)
Social function	55 (29)	46 (24)
Disease-related worry	57 (26)	52 (27)
General well-being	40 (23)	35 (29)
EoE-QoL-A questionnaire (0–4), mean (SD)		
Overall (24 items, weighted average)	2.23 (0.800)	2.30 (0.763)
Eating/diet impact (10 items, weighted average)	2.19 (1.023)	2.30 (0.848)
PatGA of EoE activity (NRS 0–10), mean (SD)	5.9 (1.5)	6.0 (1.5)
PGA of EoE activity (NRS 0–10), mean (SD)	6.1 (1.3)	6.2 (1.3)
Overall peak eos/mm^2 hpf, median (range)	205 (56–611)	197 (99–620)
Peak eos/mm^2 hpf by esophageal location, median (range)		
Proximal	83 (0–568)	153 (0–603)
Mid	142 (0–504)	136 (0–620)
Distal	176 (0–611)	139 (0–527)
Localization of inflammation, n (%)		
Proximal	47 (80)	25 (86)
Mid	52 (88)	26 (90)
Distal	56 (95)	28 (97)
No. of inflamed segments, n (%)		
1 segment	6 (10)	2 (7)
2 segments	10 (17)	4 (14)
3 segments	43 (73)	23 (79)
Total modified EREFS score (0–9), mean (SD)	3.8 (1.5)	4.6 (1.3)
Subscore inflammatory signs (0–4), mean (SD)	2.7 (1.0)	3.0 (1.0)
Subscore fibrotic signs (0–4), mean (SD)	1.0 (1.0)	1.4 (0.9)
Endoscopic findings, n (%)		
Normal	0 (0)	0 (0)
Exudates	47 (80)	23 (79)
Rings	33 (56)	24 (83)
Edema	44 (75)	24 (83)
Furrows	50 (85)	29 (100)
Strictures	9 (15)	4 (14)
Crêpe paper	10 (17)	3 (10)
Endoscopist's assessment of EoE activity, n (%)		
None	1 (2)	0 (0)
Mild	9 (15)	3 (10)
Moderate	30 (51)	17 (59)
Severe	19 (32)	9 (31)

Table 1. Continued

Characteristic	BOT 1 mg bid (n = 59)	Placebo (n = 29)
Blood, *eos/mm*^{3}, mean (SD)	427 (255)	455 (256)
Failed PPI trial (either previously or during the screening phase), n (%)	56 (100)	29 (100)
Concomitant treatment with PPI, n (%)	7 (12)	3 (10)
EoE medications/interventions used in the patient's history, n (%)[a]		
PPI	32 (54)	13(45)
Topical budesonide	12 (20)	3 (10)
Topical fluticasone	25 (42)	14 (48)
Systemic steroids	3 (5)	0 (0)
Other (Montelucast, Singulair)	4 (7)	0 (0)
Endoscopic dilation	9 (15)	5 (17)
Elemental diet	0 (0)	0 (0)
Directed elimination diet (based on allergy test)	4 (7)	4 (14)
Non-directed elimination diet	24 (41)	10 (35)

bid, twice daily; CI, confidence interval; n, valid number; PPI, proton pump inhibitor.
[a]Previously reported efficacy of drug interventions in the patient's history is presented in Supplementary Table 11.

group (BOT→BOT) and all 29 patients from the placebo groups (placebo→BOT) (Supplementary Table 3). As achievement of clinical remission (Figure 2*A–C*) takes longer than achievement of histologic remission under BOT 1 mg twice daily, the majority of BOT→BOT patients were already in histologic remission at EoT of DB phase (93.2%) (Table 2), but benefited clinically from a prolonged treatment with BOT 1 mg twice daily (Supplementary Figure 3). The overall cumulative clinico-histologic remission rate after up to 12 weeks of treatment with BOT 1 mg twice daily was therefore 84.7% (50 of 59 patients), providing evidence that a prolonged treatment for up to 12 weeks is beneficial to bring more patients into clinico-histologic remission.

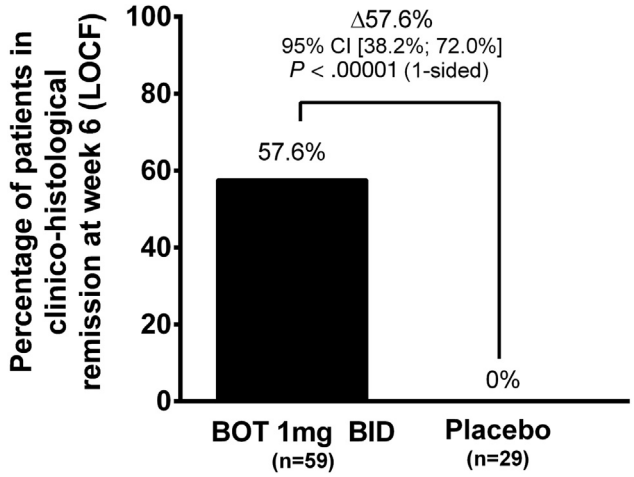

Figure 1. Primary study end point in EoE patients treated with BOT or placebo in the 6-week DB phase. Clinico-histologic remission was defined as achieving both histologic remission (peak eosinophil count <16 eos/mm^2 hpf; equivalent to <5 eos/hpf) at week 6 (LOCF) and clinical remission (symptoms severity of ≤2 points on 0–10 NRS for dysphagia and a severity of ≤2 points on 0–10 NRS for odynophagia on each day in the week before week 6 (LOCF) (1-sided Fisher's exact test). Patients who experienced food impaction needing endoscopic intervention, needed a dilation during the study, or withdrew prematurely were assessed as treatment failure. BID, twice daily; CI, confidence interval; LOCF, last observation carried forward.

All 4 a priori–ordered major secondary efficacy end points proved superiority of BOT 1 mg twice daily vs placebo in a confirmatory manner (Table 2). Clinical remission, as defined in the primary composite end point, was achieved in 59.3% vs 13.8% ($P < .0001$) in the BOT and placebo group, respectively (Table 2), and was in line with alternative definitions of clinical remission (EEsAI-PRO ≤20: 50.8% vs 6.9%; $P < .0001$); PatGA ≤2: 64.4% vs 24.1%; $P = .0006$; see also Figure 3*A–C* for course of clinical remission/response).

Histologic remission after 6 weeks of DB phase, irrespective of symptoms, was achieved in 93.2% and 0% in the BOT 1 mg twice daily and placebo groups, respectively ($P < .0001$). All but 3 patients in the BOT 1 mg twice daily group showed a dramatic decrease from baseline in peak eosinophil count, independently of the eosinophil load at baseline (Figure 3*A*), demonstrating that BOT 1 mg twice daily was able to induce remission, even in severely inflamed cases. Histologic remission in the BOT 1 mg twice daily group was independently achieved in all esophageal segments (Figure 3*B*), and irrespectively from the extent of the inflamed area, as even patients with a pan-esophageal inflammation where all 3 segments of the esophagus were affected, achieved histologic remission rates of 95.3% (Figure 3*C*) ($P < .0001$ for each comparison). Changes in peak eosinophil count (total and by esophageal segment) are provided in Supplementary Table 4.

In addition, the mean decrease in PatGA of EoE activity in the BOT 1 mg twice daily group (–3.6 points) was

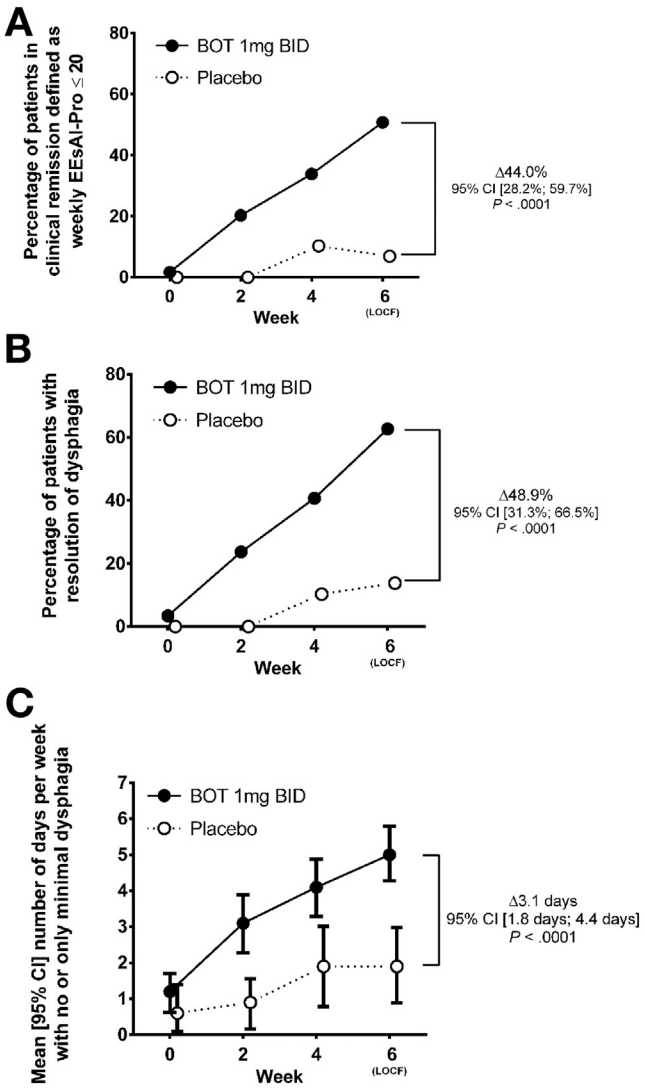

Figure 2. Course of clinical improvement and remission in EoE patients treated with BOT or placebo in the DB phase. (*A*) Course of achieved clinical remission defined as EEsAI-PRO score of ≤20 points (1-sided Fisher's exact test). (*B*) Course of achieved resolution of dysphagia defined as ≤2 points on a 0–10 point NRS for dysphagia on each day in the week before a visit (2-sided Fisher's exact test). (*C*) Course of the number of days in the week before a visit, with none or only minimal dysphagia (ie, dysphagia ≤2 points on a 0 to 10-point NRS for dysphagia (2-sided Wilcoxon rank sum test). BID, twice daily; BOT, budesonide oro-dispersible tablets; CI, confidence interval; LOCF, last observation carried forward.

significantly higher compared to placebo (−1.9 points; P = .0073). The PGA of EoE activity mirrored the findings observed with the PatGA, with a significantly higher decrease under BOT 1 mg twice daily (−3.8 points) compared to placebo (−0.8 points; $P < .0001$) (Table 2).

Mean reductions from baseline to EoT in modified EREFS total score and its inflammatory and fibrotic subscores were in the BOT 1 mg twice daily and placebo groups, respectively, −2.6 vs −0.1 ($P < .0001$), −2.1 vs 0.0 ($P < .001$), and −0.4 vs 0.0 (P = .2204). However, the change of −0.4 points in the fibrotic subscore under BOT 1 mg twice daily treatment was relevant and also significant (P = .0006; Table 2). Changes in each of the EREFS component are provided in Supplementary Table 5. A complete normalization of the esophageal appearance was reported in 61% vs 0% of the patients in the BOT 1 mg twice daily and placebo group, respectively ($P < .0001$) (Table 2).

QoL measured with the generic modified SHS instrument showed, for all 4 dimensions, a numerically higher and significant improvement (absolute change) in mean scores from baseline to week 6 for the BOT 1 mg twice daily group, but only a significant change from baseline to EoT for Symptom Burden and Social Function domain in the placebo group (Figure 4*A*). The comparison of absolute changes between the treatment groups revealed superiority of BOT 1 mg twice daily over placebo in the domains of Social Function and Disease-Related Worry, as the 95% confidence interval of the group differences (BOT 1 mg twice daily–placebo) excluded 0 (Figure 4*B*).

With the disease-specific EoE-QoL-A questionnaire and its subscores, the improvements from baseline to EoT in HRQoL were all significant for the BOT 1 mg twice daily group, but only significant for the 30-item, 24-item, social impact, emotional impact, and swallowing anxiety score in the placebo group (Supplementary Table 6). The intra-group comparison of the mean changes from baseline to EoT were significant for BOT 1 mg twice daily vs placebo for subscores "eating/diet impact 10 items": 0.7 vs 0.2, P = .0030 and for "eating/diet impact 4 items": 0.7 vs 0.2, P = .0082 (Supplementary Table 6). Quality of life data from the OLI phase are provided in Supplementary Table 7.

Safety

Overall, BOT 1 mg twice daily was well tolerated in this study. No serious adverse event was reported. However, food impaction requiring endoscopic emergency intervention occurred in 1 patient receiving placebo. No important differences were observed among the study groups in the most commonly reported adverse events, despite that a higher proportion of patients with suspected treatment-emergent adverse drug reactions at the end of DB phase were assigned to the budesonide group (27 of 59) than to the placebo group (1 of 29) (Table 3). Suspected local fungal infections were more common with budesonide than with placebo: suspected candidiasis in endoscopy carried out per protocol at EoT visit was confirmed histologically in only 10 of 59 (16.9%) patients. Finally, and clinically most important, only 3 (5.1%) of these patients presented with clinical symptoms (2 patients with esophageal symptoms and 1 with oral and esophageal symptoms), all of mild intensity, with no impact on daily life activities, and which recovered after medical treatment. No candidiasis appeared in patients assigned to placebo.

There were no laboratory-related treatment-emergent adverse events. Additionally, there were no significant differences between treatment groups in cortisol levels at the EoT assessment (Supplementary Table 8). A decrease in serum morning cortisol from normal at screening to a value

Table 2. A Priori–Ordered Major Secondary and Further Exploratory Efficacy End Points of Eosinophilic Esophagitis Patients Treated With Budesonide Orodispersible Tablet 1 mg Twice Daily or Placebo in the Double-Blind Phase

End point	BOT 1 mg bid (n = 59)	Placebo (n = 29)	*P* value
A priori–ordered major secondary efficacy end points (DB phase)			
1. Rate of patients with histologic remission (ie, peak eos <16 /mm^2 hpf; equivalent to <5 eos/hpf) at wk 6, n (%)	55 (93.2)	0 (0)	<.0001[a]
2. Change in the peak eos/mm^2 hpf from baseline to wk 6, mean (SD)	–226 (150.4)	–4 (135.6)	<.0001[b]
3. Rate of patients with clinical remission (as defined in the primary end point) at wk 6, n (%)	35 (59.3)	4 (13.8)	<.0001[a]
4. Rate of patients in clinical remission (total weekly EEsAI-PRO ≤20) at wk 6, n (%)	30 (50.8)	2 (6.9)	<.0001[a]
Further exploratory efficacy end points (DB phase)			
Clinic			
Weekly sum of daily 0–10 NRS dysphagia (range, 0–70)	‘		
Baseline, mean (SD)	34.6 (16.1)	36.4 (12.4)	—
EoT,[c] mean (SD)	14.5 (16.4)	24.9 (11.0)	—
Change from baseline to wk 6, mean (SD)	–20.1 (17.0)	–11.4 (11.0)	.0230[d]
PGA of EoE activity (NRS 0–10)			
Baseline, mean (SD)	6.1 (1.3)	6.2 (1.3)	—
EoT,[c] mean (SD)	2.3 (2.5)	5.5 (2.1)	—
Change from baseline to wk 6, mean (95% CI)	–3.8 (–4.4 to –3.2)	–0.8 (–1.6 to 0.1)	<.0001[d]
PatGA of EoE activity (NRS 0–10)			
Baseline, mean (SD)	5.9 (1.5)	6.0 (1.5)	—
EoT,[c] mean (SD)	2.3 (2.6)	4.1 (2.1)	—
Change from baseline to wk 6, mean (95% CI)	–3.6 (–4.3 to –2.9)	–1.9 (–3.0 to –0.9)	.0073[d]
Rate of patients with overall symptoms resolution defined as PatGA ≤2 at EoT,[c] n (%)	38 (64.4)	7 (24.1)	.0006[a]
Change from baseline to EoT[c] in blood eosinophil counts, *eos/mm^3*, mean (95% CI)	–219 (–288 to –150)	–28 (–124 to 68)	.0016[d]
Endoscopy			
Total modified EREFS endoscopic score (0–9)			
Baseline, mean (SD)	3.8 (1.5)	4.6 (1.3)	—
EoT,[c] mean (SD)	1.2 (1.4)	4.5 (1.6)	—
Change from baseline to EoT[c] mean (95% CI)	–2.6 (–3.1 to –2.1)	–0.1 (–0.8 to 0.5)	<.0001[d]
P value	<.0001[e]	.7358[e]	—
Modified EREFS inflammatory signs subscore (0–4)			
Baseline, mean (SD)	2.7 (1.0)	3.0 (1.0)	—
EoT,[c] mean (SD)	0.6 (0.9)	3.0 (1.0)	—
Change from baseline to EoT[c] mean (95% CI)	–2.1 (–2.5 to –1.7)	0.0 (–0.4 to 0.3)	<.0001[f]
P value	<.0001[g]	.9646[g]	—
Modified EREFS fibrotic signs subscore (0–4)			
Baseline, Mean (SD)	1.0 (1.0)	1.4 (0.9)	—
EoT,[c] Mean (SD)	0.6 (0.7)	1.4 (1.0)	—
Change from baseline to EoT[c] mean (95% CI)	–0.4 (–0.6 to –0.2)	–0.1 (–0.5 to 0.4)	.2204[f]
P value	*P* = .0006[g]	*P* = .8074[g]	—
Rate of patients with global assessment of endoscopic EoE activity of no signs of EoE at EoT,[c] n (%)	36 (61.0)	0 (0)	<.0001[a]
Histology			
Rate of patients with histologic remission (ie, peak eos <48/mm^2 hpf; equivalent to <15 eos/hpf) at wk 6, n (%)	56 (94.9)	0 (0)	<.0001[a]
Post-hoc analysis			
Rate of patients in deep histologic remission defined as peak eos/mm^2 hpf of 0 in all biopsies at EoT,[c] n (%)	53 (89.8)	0 (0)	<.0001[a]

bid, twice daily.
[a]Two-sided Fisher's exact test (test between groups).
[b]One-sided *P* value for effect between treatment groups from linear least squares model with treatment group and baseline value as covariate.
[c]Week 6, last observation carried forward.
[d]Two-sided *t* test (test between groups).
[e]Two-sided, 1-sample *t* test (test within group).
[f]Two-sided Wilcoxon rank sum test (test between groups).
[g]Two-sided Wilcoxon signed rank test (test within group).

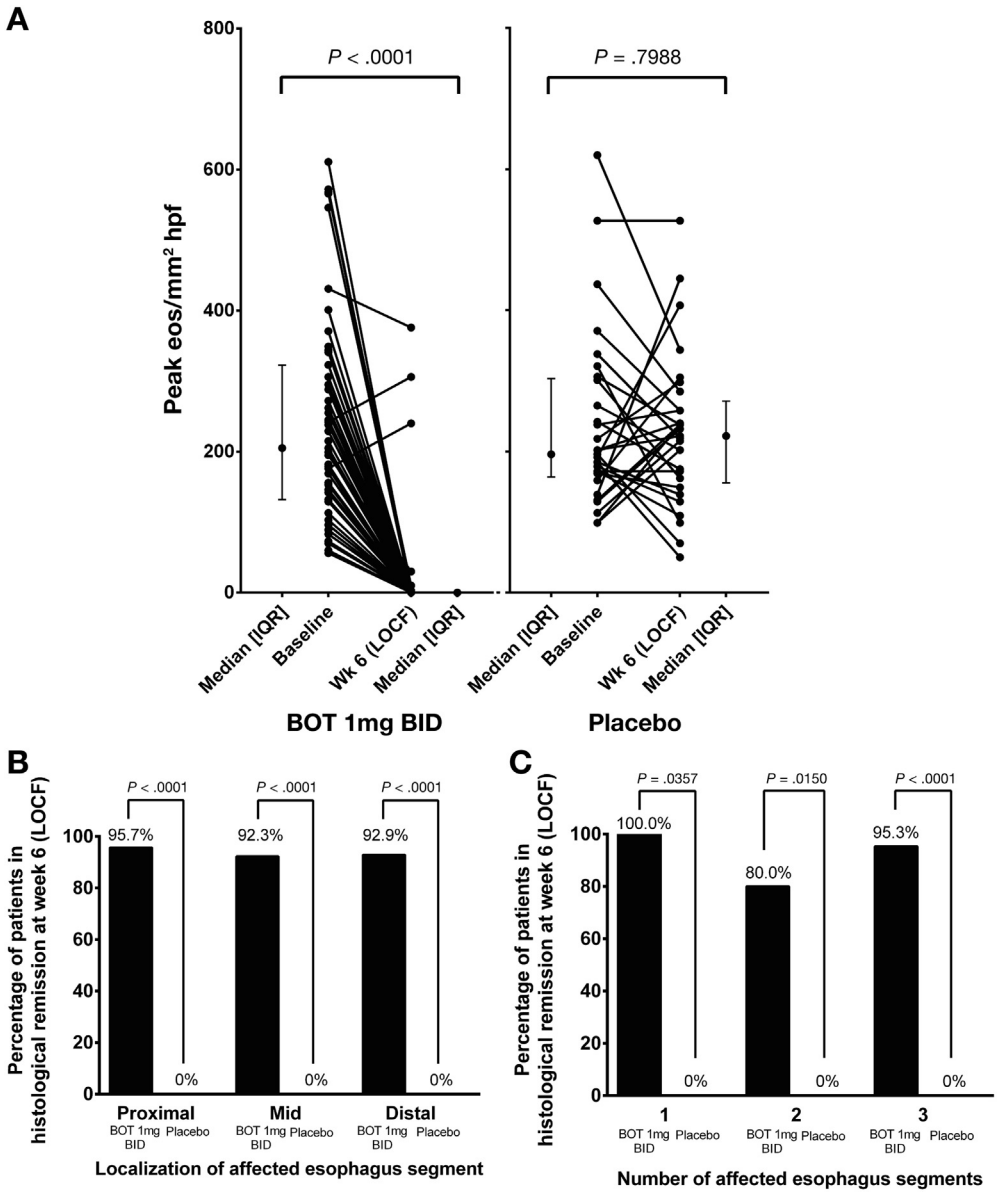

Figure 3. Histologic changes and remission in EoE patients treated with BOT 1 mg bid or placebo in the DB phase. (*A*) Individual pre- and post-treatment peak eos/mm^2 hpf counts and median group values with IQR (2-sided Wilcoxon signed rank test for intra-group changes); (*B*) histologic remission stratified by the localization of the affected esophagus segment (2-sided Fisher's exact test), and (*C*) stratified by the extent of the eosinophilic inflammation (either 1, 2, or all 3 segments involved) at baseline (2-sided Fisher's exact test). BID, twice daily; IQR, interquartile range; LOCF, last observation carried forward.

below the lower limit of normal (6.2 μg/dL) was recorded in only 3 (5.1%) patients in the budesonide arm (Supplementary Table 9). No patient had to prematurely stop administration of the study medication.

Safety results from the 6-week OLI phase did not reveal any new safety signal (Supplementary Table 10).

Discussion

This is a pivotal phase 3 trial reporting on the efficacy and safety of a medicinal product to treat active EoE in adults. In this multicenter trial, budesonide in an orodispersible tablet formulation was highly effective and safe in bringing adult patients with active EoE into clinical and histologic remission. As EoE is diagnosed by the presence of symptoms of esophageal dysfunction (mainly dysphagia) and histologic inflammation with >15 eos/hpf, a composite end point of achieving both clinical and histological remission is an appropriate readout. A 6-week treatment with 1 mg budesonide twice daily was highly superior over placebo with regard to all predefined primary and secondary outcomes.

Nevertheless, assessment of the clinical response in EoE is a challenge because the leading symptom of solid food dysphagia depends not only on the activity of the disease, but also on the eating behavior of the patient. Clinical remission as defined in the primary composite end point was highly superior under BOT 1 mg twice daily compared to placebo in a confirmatory manner. A direct comparison between other studies with STCs is difficult, as they used different readouts and cutoffs for defining clinical remission. However, our NRS for dysphagia was a simple tool with obvious face validity, and was also confirmed recently to be responsive to assess dysphagia severity in EoE in clinical practice.[26] The chosen cutoff of ≤2 was in line with all other important clinical end points based on different tools

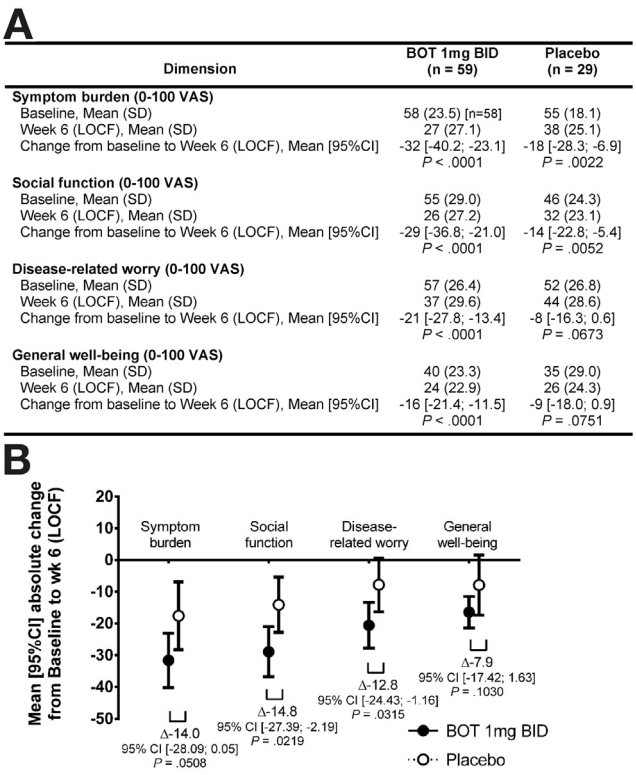

Figure 4. Changes in HRQoL by means of the modified SHS in EoE patients treated with BOT or placebo in the DB phase. (*A*) Mean pre- and post-treatment scores of the 4 dimensions of the modified SHS showed a greater improvement in BOT-treated patients, with lower values indicating better quality of life. All dimensions improved significantly from baseline to week 6 (LOCF) under BOT, whereas only Symptom Burden and Social Function improved significantly. (*B*) The 95% CI of the group differences (BOT 1 mg BID–Placebo) in mean absolute changes, which excluded 0, indicated a superiority of BOT 1 mg BID over placebo in the dimensions of Social Function and Disease-Related Worry. All intra- and inter-group comparisons were performed using 2-sided 1-sample *t* test and 2-sided *t* test, respectively. BID, twice daily; CI, confidence interval; LOCF, last observation carried forward; VAS, visual analogue scale.

(PatGA, PGA, and EEsAI-PRO), which also showed similar remission rates based on cutoffs $\leq$2 on a 1–10 scale (PatGA, PGA) or $\leq$20 on a 1–100 scale (EEsAI-PRO).

Recently, Hirano et al[27] used a similar PatGA and PGA in their trial with RPC4046, an anti–interleukin-13 monoclonal antibody. In that study, the pre–post PatGA in the highest RPC dose group decreased from 5.4 to 2.5 points and the PGA from 6.1 to 3.2, which was comparable to our study with PatGA, which decreased from 5.9 to 2.3 and PGA from 6.1 to 2.3. However, in the study by Hirano et al, approximately 50% of patients were steroid-refractory, whereas in our study only 11% of patients showed a previously poor response to steroids, which might explain the slightly better improvement in our study.

Histologic improvement of EoE is directly related to therapy with a higher mucosal contact time, which highlights the importance of using appropriate drug formulations with optimized esophageal targeting. Our data confirm the results of the phase 2 trial, which reported a 100% histologic remission rate[18] and showed that BOT 1 mg twice daily had similar anti-inflammatory effects in the entire esophagus, independent of severity, localization, or extent of inflammation (Figure 2*A*–*C*), indicating optimal esophageal targeting with BOT 1 mg twice daily.

More patients achieved histologic remission of EoE in our trial compared to clinical remission. Thus, nearly every

Table 3. Eosinophilic Esophagitis Patients Treated With Budesonide Orodispersible Tablets or Placebo in the Double-Blind Phase and Experiencing Treatment-Related Adverse Events

Variable	BOT 1 mg bid (n = 59)	Placebo (n = 29)
Any TEAE	37 (62.7)	12 (41.1)
Severe TEAE	0 (0)	1 (3.4)
Esophageal food impaction	0 (0)	1 (3.4)
TEAE related to study drug	23 (39.0)	1 (3.4)
Serious AEs	0 (0)	0 (0)
TEAE leading to withdrawal from the study	0 (0)	1 (3.4)
Esophageal food impaction of severe intensity requiring endoscopic intervention	0 (0)	1 (3.4)
TEAEs by occurring in $\geq$2 patients in any treatment group		
Gastrointestinal disorders	10 (16.9)	3 (10.3)
Gastroesophageal reflux disease	3 (5.1)	0 (0)
Nausea	2 (3.4)	0 (0)
Infections and infestations	21 (35.6)	6 (20.7)
Suspected local fungal infection,[a] thereof:	14 (23.7)	0 (0)
Histologically confirmed[b]	10 (16.9)	0 (0)
Histologically confirmed[b] with suspected endoscopic signs	8 (13.6)	0 (0)
Histologically confirmed[b] with suspected endoscopic signs and clinical symptoms	3 (5.1)	0 (0)
Nasopharyngitis	2 (3.4)	1 (3.4)
Pharyngitis	1 (1.7)	2 (6.9)
Investigations	5 (8.5)	0 (0)
Blood cortisol decreased	3 (5.1)	0 (0)
Nervous system disorders	5 (8.5)	1 (3.4)
Headache	4 (6.8)	1 (3.4)
Respiratory, thoracic and mediastinal disorders	2 (3.4)	2 (6.9)
Asthma	0 (0)	2 (6.9)
Vascular disorders	3 (5.1)	0 (0)
Hypertension	2 (3.4)	0 (0)

bid, twice daily; TEAE, treatment-emergent adverse events.
[a]Local fungal infection (included suspected cases of candida infection, esophageal candidiasis, oral candidiasis, and oropharyngeal candidiasis) was suspected and assessed as an adverse event if any of the following criteria was fulfilled: suspected clinical symptoms, suspected endoscopic findings, suspected histologic assessment in H&E-stained biopsies (even without any endoscopic signs or clinical symptoms).
[b]Histologically confirmed by Grocott staining.

patient in clinical remission at EoT was also in histologic remission, but not vice versa. The data underscore the repeatedly documented imperfect relationship between esophageal symptoms and the biological activity of EoE.[28,29] The potential causes for this might include the presence of mild esophageal strictures (15% in both arms in the present study), an esophageal narrow caliber underestimated with endoscopy,[30] a decreased esophageal distensibility,[31] or symptoms unrelated with EoE but due to coexistent comorbidities. In any case, it highlights the need to consider both aspects in the evaluation of patients with EoE.

Of note, the histologic remission rate of 93.2% was strikingly higher than those achieved in all previously performed trials with other budesonide formulations in adult EoE patients.[25,32] In a recent phase 2 trial with a viscous budesonide suspension with a high volume of 10 mL/application and doubled daily dose, only 39% of the patients achieved histologic remission, defined as $\leq$6 eos/hpf, after a 12-week course.[32] This difference might be explained by the different pharmaceutical formulations used. Although in a recent trial, the oral viscous suspension was more effective than a nebulized steroid preparation,[33] which was explained by a prolonged contact time, the scintigraphy points to the fact that the majority of the drug ended up in the stomach. In contrast to a twice-daily single swallow of a relative large volume of 10 mL viscous suspension, BOT 1 mg twice daily offered a unique method of delivery. As soon as BOT is put on the tongue, it stimulates the production of saliva via its effervescence characteristics for approximately 2–3 minutes—the period during which the BOT completely dissolves. During this period, budesonide-enriched saliva is continuously swallowed in small volumes. It can be speculated that the naturally mucus adhesive characteristic of the saliva then leads to optimal adhesion and prolonged contact time, such that even with 1 mg twice daily, histologic remission rates are twice as high as a 2-mg twice daily dosing with oral viscous suspension in a high volume.

Endoscopically, treatment with BOT 1 mg twice daily resulted in significant changes from baseline to EoT in the total modified EREFS, as well as in its inflammatory signs subscore. Surprisingly, a 6-week treatment with BOT 1 mg twice daily already significantly decreased the fibrotic signs subscore, indicating that prolonged treatment with BOT might have a substantial impact on re-modeling. Therefore, long-term data are needed and actually being addressed by the ongoing EOS-2 maintenance of remission trial (EudraCT number 2014-001485-99). Comparisons between different trials are hindered by the fact that either the original EREFS score or its modified version were used (as done in our trial), or that the EREFS score was assessed by separate segments, whereas we used the worst-case assessment resulting from the whole esophagus.

Both HRQoL tools (modified SHS and EoE-QoL-A) showed a significant improvement in HRQoL in all domains and items under BOT 1 mg twice daily, with numerically larger improvement compared to placebo. This was statistically significant already after a 6-week short treatment for the domains of Social Function and Disease-Related Worry using the modified SHS and the EoE-QoL-A "eating/diet impact 10 and 4 items (weighted average)" domains scores.

The main side effect of STCs is local fungal infection. In this study, we searched systematically for candidiasis, that is, clinically, endoscopically, and histologically regarding localization and clinical relevance. In a worst-case scenario, histologically suspected findings of local fungal infection were classified as adverse events, even without any endoscopic signs or clinical symptoms. Therefore, this approach reflects a worst-case scenario, which is uncommon in daily practice and also not used and reported in other trials. Far more important are the rates of histologically confirmed cases of local fungal infections associated with endoscopic and clinical signs. However, these cases occurred in only 5% of patients under a 6-week BOT 1 mg twice daily treatment, without a further increase in patients treated up to 12 weeks.

An additional concern when using topical corticosteroids is the risk of inducing adrenal axis suppression. The determination of the morning fasting cortisol levels showed no difference between the treatment groups, and a clinically significant decrease in serum cortisol levels was reported for only 3 patients under BOT 1 mg twice daily treatment, which normalized after the end of treatment.

The main strength of the study lies in its rigorous design and multicenter conduct: The use of clinico-histologic remission of EoE as the primary end point, in accordance with the definition of EoE, in which clinical manifestations or pathologic data should not be interpreted in isolation.[1,19] Validated instruments were used to evaluate symptoms, endoscopic features, and changes in HRQoL along the trial, and adverse events and safety issues were monitored comprehensively and assessed.

Our study also has some limitations. First, it was not designed to identify the time of the maximal effect of budesonide as induction therapy but to demonstrate a significant superiority compared to placebo at week 6. Greater efficacy may be obtained by extending induction treatment beyond 6 weeks, as most of the trials that assessed efficacy of topical steroids in EoE already did,[16,17,32–35] and also as the data of patients with a prolonged treatment of up to 12 weeks suggested in our OLI phase. Second, we did not identify a minimally effective dose regimen because we used the lower of the 2 doses (ie, 1 mg and 2 mg BOT twice daily), both of which demonstrated histologic remission in almost all of the patients who participated in our phase 2 trial.[18] Our histologic remission rate does not preclude that an even lower dose than 1 mg twice daily could still achieve disease remission in a significant proportion of patients compared to placebo. In contrast, we believe that a higher dose would not achieve a higher clinico-remission rate. Third, we excluded, at screening, patients with severe strictures unable to be passed with a standard gastroscope, ruling out the possibility that some strictures with a predominant inflammatory component may have responded to BOT. However, patients with mild strictures were included, and fibrotic features of the EREFS score overall improved at EoT. Fourth, symptomatic improvement during OLI phase could have overestimated the effect of therapy because

patients were unblinded and knew that they were receiving active medication. Finally, concomitant treatment with PPIs was allowed along the trial, which could have contributed to the symptomatic improvement at the EoT. However, every recruited patient has excluded a PPI response, and dysphagia was longitudinally assessed in every individual patient along the study period. Only <12% of patients recruited continued their underlying PPI treatment with stable dosing.

In conclusion, compared to placebo, BOT 1 mg twice daily is a highly effective therapy to rapidly induce disease remission in adult patients with active EoE; an ongoing trial with the same formulation will provide evidence on its efficacy to maintain this remission in the long term.

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.2019.03.025.

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Author contributions: Alfredo J Lucendo, Stephan Miehlke, and Alex Straumann: Development of the study protocol, patient recruitment, data analysis and interpretation, manuscript preparation; Michael Vieth: Development of the study protocol and central pathologist; Stephen Attwood and Alain Schoepfer: Development of the study protocol and manuscript preparation; Christoph Schlag, Ulrike von Arnim, Javier Molina-Infante, Dirk Hartmann, Albert Jan Bredenoord, Constanza Ciriza de los Rios, Stefan Schubert, Stefan Brückner, Ahmed Madisch, Jamal Hayat, and Jan Tack: Patient recruitment; Ralph Mueller and Roland Greinwald: Development of the study protocol, data analysis and interpretation, support for manuscript preparation.

Conflicts of interest
These authors disclose the following: Alfredo J Lucendo has received research funding from Dr Falk Pharma; Stephan Miehlke is a member of advisory boards for Celgene and EsoCap and has received speaker's fee from Dr Falk Pharma GmbH and Falk Foundation; Christoph Schlag has received consultant fees from EsoCap and speaker fees, travel and research funding from Dr Falk Pharma GmbH; Michael Vieth has received speaker and consultant fees from Dr Falk Pharma GmbH; Ulrike von Arnim is a member of MSD national advisory board, has received speaker fees from AbbVie, MSD, Falk Foundation, Pfizer, Takeda, and Vifor; Javier Molina-Infante has received speaker and consultant fees from Dr Falk Pharma GmbH; Dirk Hartmann has no conflicts of interest to declare; Albert Jan Bredenoord has received research funding from Nutricia, Norgine, and Bayer and received speaker and/or consulting fees from Laborie, EsoCap, Diversatek, Medtronic, Dr Falk Pharma GmbH, Calypso, Thelial, Regeneron, Celgene, Bayer, Norgine, AstraZeneca, Almirall, and Allergan; Constanza Ciriza de los Rios has received speaker fees from Casen Recordati; Ahmed Madisch has received speaker fees from Dr Falk Pharma GmbH and Falk Foundation; Jamal Hayat has received speaker fees from Dr Falk Pharma GmbH; Stephen Attwood has received speaker and consulting fees from Dr Falk Pharma GmbH; Ralph Mueller and Roland Greinwald are employees of Dr Falk Pharma GmbH; Alain Schoepfer is a member of an advisory board for Dr Falk Pharma GmbH, Adare Pharmaceuticals, Celgene Pharmaceuticals, and Regeneron Pharmaceuticals. He has received research funding from Dr Falk Pharma GmbH, Adare Pharmaceuticals, Celgene Pharmaceuticals, and Regeneron Pharmaceuticals. He has received speaker's fees from Dr Falk Pharma GmbH and Celgene Pharmaceuticals; Alex Straumann is a consultant of Calypso, EsoCap, Dr Falk Pharma GmbH, GSK, Receptos-Celgene, Regeneron-Sanofi, Shire and Tillotts, and has received speaker fees and research funding from Dr Falk Pharma GmbH. The remaining authors disclose no conflicts.

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Supplementary Appendix. List of International EOS-1 Study Group Investigators/Institutions who Screened Patients

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	Javier Molina-Infante, José Zamorano	Hospital Universitario San Pedro de Alcantara, Cáceres
	Cecilio Santander Vaquero, Sergio Casabona Francés, Teresa Pérez, Teresa Rodriguez	Hospital Universitario de la Princesa, Madrid
	Constanza Ciriza de los Ríos, Fernando Canga Rodríguez-Valcárcel, Isabel Castel de Lucas	Hospital Universitario 12 de Octubre, Madrid
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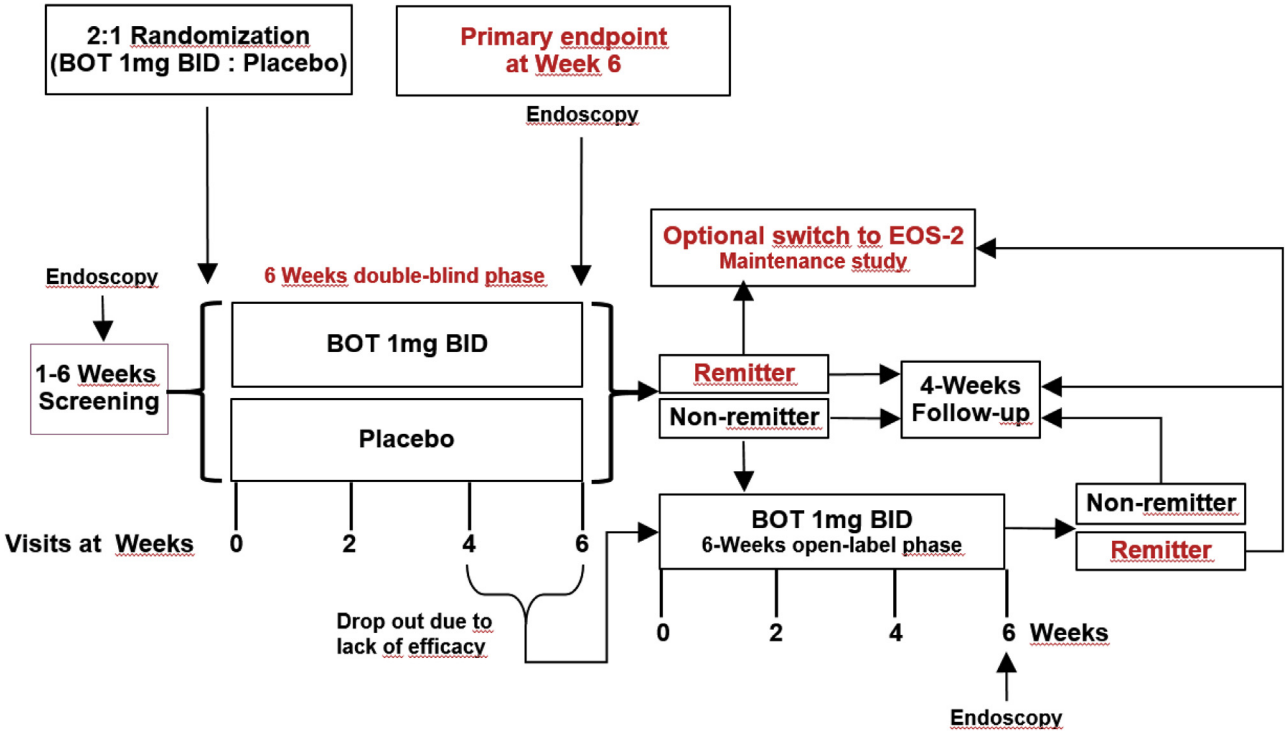
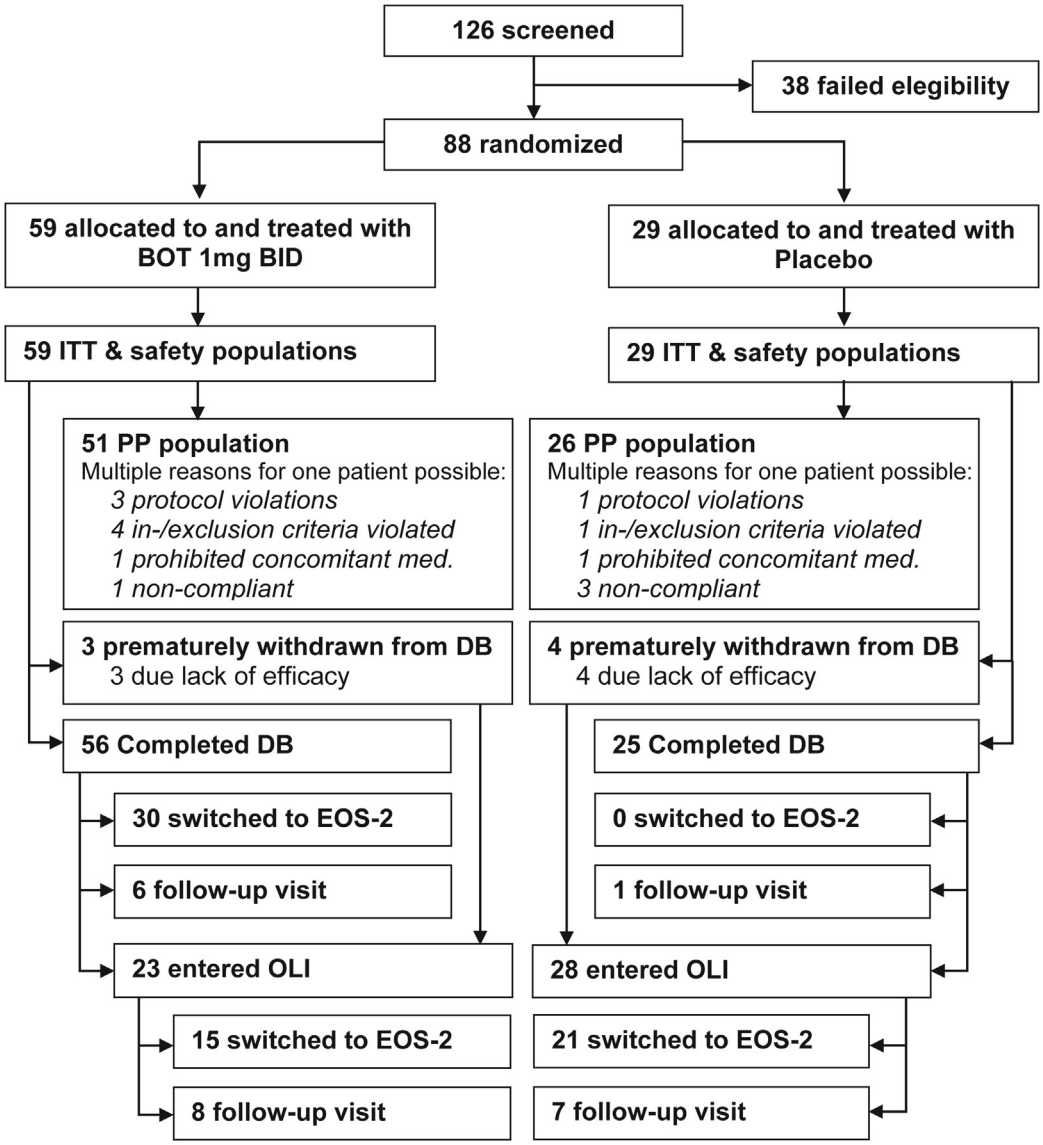
	Petr Hruz, Simon Brunner	University Hospital Basel, Basel
United Kingdom	**Jamal Hayat,** Andrew Poullis	St. George's Hospital, London

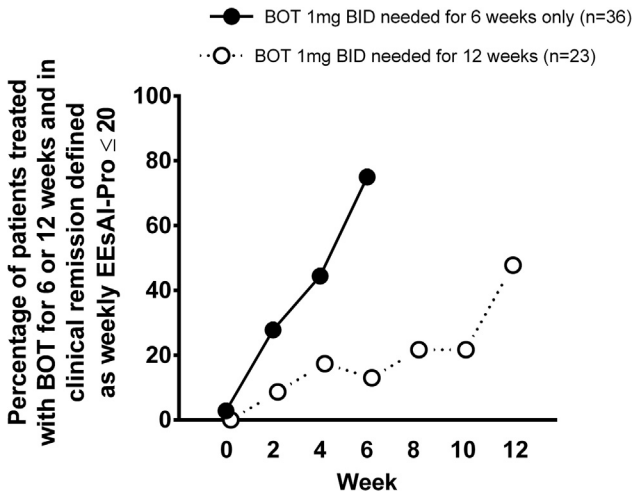
NOTE. Bold type indicates principal investigators.



Supplementary Figure 1. Study scheme. BID, twice daily; EOS-2, phase 3 maintenance study (EudraCT number 2014-001485-99) offered to be entered by patients achieving clinico-histologic remission either at the end of the 6-wk DB or 6-wk open-label induction phase.



Supplementary Figure 2. CONSORT (Consolidated Standards of Reporting Trials) diagram showing the patient flow in the study. BID, twice daily; DB, 6-wk double-blind treatment phase; EOS-2, phase 3 maintenance study (EudraCT number 2014-001485-99) offered to be entered by patients achieving clinico-histologic remission either at the end of the DB or OLI phase. ITT, intention-to-treat; OLI, 6-wk open-label induction phase; PP, per-protocol.



Supplementary Figure 3. Course of clinical remission in EoE patients treated with BOTs for only 6 wk or in patients who required a 12-wk treatment course. BID, twice daily.

Supplementary Table 1. Study End Points

DB phase
Primary efficacy variable
Rate of patients with clinico-histologic remission at wk 6 (LOCF), ie, achieving both, histologic remission (peak eosinophil count <16 eos/mm^2 hpf; equivalent to <5 eos/hpf) at wk 6 (LOCF), and clinical remission (symptoms severity of ≤ 2 points on 0–10 NRS for dysphagia and a severity of ≤ 2 points on 0–10 NRS for odynophagia on each day in the week before wk 6 (LOCF). Patients who experienced a food impaction needing endoscopic intervention, who needed a dilation during the study, or withdrew prematurely were assessed as treatment failures
Note: 0–10 NRS range: 0 = no symptoms, 10 = most severe symptoms; hpf area of 0.345 mm^2
A priori–ordered major secondary efficacy end points
1. Rate of patients with histologic remission (as defined in the primary end point) at wk 6 (LOCF),
2. Change in the peak eos/mm^2 hpf from baseline to wk 6 (LOCF)
Note: hpf area of 0.345 mm^2
3. Rate of patients with clinical remission (as defined in the primary end point) on each day in the week before wk 6 (LOCF)
4. Rate of patients in remission (total weekly EEsAI-PRO ≤ 20) at wk 6 (LOCF)
Note: score range 0–100: 0 = no EoE activity, 100 = most severe EoE activity
Further secondary efficacy variables
Clinical
Weekly sum of daily 0–10 NRS Dysphagia (range: 0–70)
Note: 0: no symptoms, 10: most severe symptoms
PGA of EoE Activity (NRS 0–10)
Note: score range 0–10: 0: no EoE activity, 10: most severe EoE activity
PatGA of EoE Activity (NRS 0–10)
Note: score range 0–10: 0: no EoE activity, 10: most severe EoE activity
Rate of patients with overall symptoms resolution defined as PatGA ≤ 2 at wk 6 (LOCF)
Note: score range 0–10: 0: no EoE activity, 10: most severe EoE activity
Change from baseline to wk 6 (LOCF) in blood eosinophil counts (eos/mm^3)
Endoscopy
Change from baseline to wk 6 (LOCF) in total modified EREFS endoscopic score
Note: score range 0–9: 0: no endoscopic EoE activity, 9: most severe endoscopic EoE activity
Change from baseline to wk 6 (LOCF) in modified EREFS inflammatory signs subscore (0–4)
Note: score range 0–4: 0: no inflammatory signs, 4: most severe inflammatory signs
Change from baseline to wk 6 (LOCF) in modified EREFS fibrotic signs subscore (0–4)
Note: score range 0–4: 0: no fibrotic signs, 4: most severe fibrotic signs
Rate of patients with global assessment of endoscopic EoE activity of no signs of EoE at wk 6 (LOCF)
Histology
Rate of patients with histologic remission (i.e., peak eos <48 /mm^2 hpf; equivalent to <15 eos/hpf) at wk 6 (LOCF), n (%)
HRQoL
Change from baseline to EoT DB phase in modified SHS Symptom Burden
Note: VAS 0–100; with lower values indicating better quality of life
Change from baseline to EoT DB phase in modified SHS Social Function
Note: VAS 0–100; with lower values indicating better quality of life
Change from baseline to EoT DB phase in modified SHS Disease–Related Worry
Note: VAS 0–100; with lower values indicating better quality of life
Change from baseline to EoT DB phase in modified SHS General Well-Being
Note: VAS 0–100; with lower values indicating better quality of life
Change from baseline to EoT DB phase in EoE-QoL-A 30 items (weighted average)
Note: 0 (very good HRQoL) to 4 (very poor HRQoL)
Change from baseline to EoT DB phase in EoE-QoL-A 24 items (weighted average)
Note: 0 (very good HRQoL) to 4 (very poor HRQoL)
Change from baseline to EoT DB phase in EoE-QoL-A eating/diet impact 10 items (weighted average)
Note: 0 (very good HRQoL) to 4 (very poor HRQoL)
Change from baseline to EoT DB phase in EoE-QoL-A eating/diet impact 4 items (weighted average)
Note: 0 (very good HRQoL) to 4 (very poor HRQoL)
Change from baseline to EoT DB phase in EoE-QoL-A social impact (weighted average)(weighted average)
Note: 0 (very good HRQoL) to 4 (very poor HRQoL)
Change from baseline to EoT DB phase in EoE-QoL-A emotional impact (weighted average)
Note: 0 (very good HRQoL) to 4 (very poor HRQoL)
Change from baseline to EoT DB phase in EoE-QoL-A disease anxiety (weighted average)
Note: 0 (very good HRQoL) to 4 (very poor HRQoL)
Change from baseline to EoT DB phase in EoE-QoL-A swallowing anxiety (weighted average)
Note: 0 (very good HRQoL) to 4 (very poor HRQoL)
Post-hoc analyses
Rate of patients in deep histologic remission at wk 6 defined as peak eos/mm^2 hpf of 0 in all biopsies

Supplementary Table 1. Continued

DB phase
Safety variables
Adverse events
Vital signs (blood pressure, heart rate) and body weight
Standard hematology, blood chemistry, urinalysis
Morning serum cortisol
Assessment of tolerability by investigator and patient
Open-label induction phase
Further secondary efficacy variables
Clinical
Rate of patients with clinico-histologic remission (as defined in the primary end point) at EoT OLI phase
Note: for definitions see DB primary end point
Rate of patients with clinical remission (as defined in the primary end point) at EoT OLI phase
Note: for definitions see DB primary end point
Rate of patients in remission (total weekly EEsAI-PRO $\leq$20) at EoT OLI phase
Change from EoT DB phase to EoT OLI phase in EEsAI-PRO
Rate of patients with no or only minimal problems defined as 0–10 NRS dysphagia $\leq$2 on each day in the week before EoT OLI phase
Change from EoT DB phase to EoT OLI phase in weekly sum of daily 0–10 NRS dysphagia (range, 0–70)
Change from EoT DB phase to EoT OLI phase in PGA of EoE Activity (NRS 0–10)
Change from EoT DB phase to EoT OLI phase in PatGA of EoE Activity (NRS 0–10)
Change from EoT DB phase to EoT OLI phase in blood eosinophil counts (eos/mm^3)
Endoscopy
Change from EoT DB phase to EoT OLI phase in total modified EREFS endoscopic score (0–9)
Change from EoT DB phase to EoT OLI phase in modified EREFS inflammatory signs subscore (0–4)
Change from EoT DB phase to EoT OLI phase in modified EREFS fibrotic signs subscore (0–4)
Rate of patients with global assessment of endoscopic EoE activity of no signs of EoE at wk6
Histology
Rate of patients with histologic remission (as defined in the primary end point) at EoT OLI phase
Rate of patients with histologic remission (ie, peak eos $<$48 /mm^2 hpf; equivalent to $<$15 eos/hpf) at EoT OLI phase
Change from EoT DB phase to EoT OLI phase in overall peak eos/mm^2 hpf
Note: hpf area of 0.345 mm^2
HRQoL
Change from EoT DB phase to EoT OLI phase in modified SHS Symptom Burden
Note: VAS 0–100; with lower values indicating better quality of life
Change from EoT DB phase to EoT OLI phase in modified SHS Social Function
Note: VAS 0–100; with lower values indicating better quality of life
Change from EoT DB phase to EoT OLI phase in modified SHS Disease–Related Worry
Note: VAS 0–100; with lower values indicating better quality of life
Change from EoT DB phase to EoT OLI phase in modified SHS General Well–Being
Note: VAS 0–100; with lower values indicating better quality of life
Change from EoT DB phase to EoT OLI phase in EoE-QoL-A 30 items (weighted average)
Note: 0 (very good HRQoL) to 4 (very poor HRQoL)
Change from EoT DB phase to EoT OLI phase in EoE-QoL-A 24 items (weighted average)
Note: 0 (very good HRQoL) to 4 (very poor HRQoL)
Change from EoT DB phase to EoT OLI phase in EoE-QoL-A eating/diet impact 10 items (weighted average)
Note: 0 (very good HRQoL) to 4 (very poor HRQoL)
Change from EoT DB phase to EoT OLI phase in EoE-QoL-A eating/diet impact 4 items (weighted average)
Note: 0 (very good HRQoL) to 4 (very poor HRQoL)
Change from EoT DB phase to EoT OLI phase in EoE-QoL-A social impact (weighted average)
Note: 0 (very good HRQoL) to 4 (very poor HRQoL)
Change from EoT DB phase to EoT OLI phase in EoE-QoL-A emotional impact (weighted average)
Note: 0 (very good HRQoL) to 4 (very poor HRQoL)
Change from EoT DB phase to EoT OLI phase in EoE-QoL-A disease anxiety (weighted average)
Note: 0 (very good HRQoL) to 4 (very poor HRQoL)
Change from EoT DB phase to EoT OLI phase in EoE-QoL-A swallowing anxiety (weighted average)
Note: 0 (very good HRQoL) to 4 (very poor HRQoL)
Safety variables
Adverse events
Vital signs (blood pressure, heart rate) and body weight
Standard hematology, blood chemistry, urinalysis
Morning serum cortisol
Assessment of tolerability by investigator and patient

bid, twice daily; CI, confidence interval; DB, double-blind; eos/hpf, eosinophils per high power field (400×); EoT, end of treatment (wk 6 [LOCF]); LOCF, last observation carried forward.

Supplementary Table 2. 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 clinico-pathologic remission at wk 6 (LOCF) stratified by protocol prespecified criteria	
	BOT 1 mg bid, n (%) (n = 59)	Placebo, n (%) (n = 29)
Localization of inflammation at baseline		
Proximal esophagus		
No	5/12 (41.7)	0/4 (0.0)
Yes	29/47 (61.7)	0/25 (0.0)
Middle esophagus		
No	4/7 (57.1)	0/3 (0.0)
Yes	30/52 (57.7)	0/26 (0.0)
Distal esophagus		
No	1/3 (33.3)	0/1 (0.0)
Yes	33/56 (58.9)	0/28 (0.0)
Extent of inflammation at baseline, no. of esophageal segments affected		
1	3/6 (50.0)	0/2 (0.0)
2	4/10 (40.0)	0/4 (0.0)
3	27/43 (62.8)	0/23 (0.0)
Peak eosinophil count/mm^2 hpf at baseline		
<Median	15/28 (53.6)	0/15 (0.0)
≥Median	19/31 (61.3)	0/14 (0.0)
Blood eosinophil count at baseline		
Not evaluable	0/2 (0.0)	0/0 (0.0)
<Median	15/27 (55.6)	0/12 (0.0)
≥Median	19/30 (63.3)	0/17 (0.0)
Concomitant use of PPIs during the DB phase		
No	29/52 (55.8)	0/26 (0.0)
Yes	5/7 (71.4)	0/3 (0.0)
History of allergic diseases		
No	8/12 (66.7)	0/6 (0.0)
Yes	26/47 (55.3)	0/23 (0.0)
PatGA at baseline		
3 or 4	9/12 (75.0)	0/5 (0.0)
5	11/16 (68.8)	0/7 (0.0)
6	5/8 (62.5)	0/5 (0.0)
7	4/13 (30.8)	0/8 (0.0)
8 or 9	5/10 (50.0)	0/4 (0.0)
Time since first symptoms (disease duration)		
Not evaluable	0/1 (0.0)	0/0 (0.0)
<Median	18/28 (64.3)	0/15 (0.0)
≥Median	16/30 (53.3)	0/14 (0.0)
History of any dietary approach to treat EoE		
No	22/31 (71.0)	0/17 (0.0)
Yes	12/28 (42.9)	0/12 (0.0)

bid, twice daily; LOCF, last observation carried forward; PPI, proton-pump inhibitor.

Supplementary Table 3. Exploratory Secondary Clinical, Histologic and Endoscopic Efficacy End Points of Eosinophilic Esophagitis Patients Treated With Budesonide Orodispersible Tablets 1 mg Twice Daily in the Optional 6-Weeks Open-Label Phase

End Points	BOT → BOT[a] (n = 23)	Placebo → BOT[b] (n = 28)
General		
Rate of patients with clinico-histologic remission (as defined in the primary end point) at EoT OLI phase, n (%)	16 (69.6)	22 (78.6)
Histology		
Rate of patients with histologic remission (ie, peak eos <16/mm^2 hpf; equivalent to <5 eos/hpf) at EoT OLI phase, n (%)	19 (82.6)	25 (89.3)
Rate of patients with histologic remission (ie, peak eos <48/mm^2 hpf; equivalent to <15 eos/hpf) at EoT OLI phase, n (%)	20 (87.0)	25 (89.3)
Overall peak eos/mm^2 hpf		
EoT DB phase, mean (SD)	42 (107.2)	224 (94.5)
EoT OLI phase, mean (SD)	18 (56.7)	30 (80.7)
Change from EoT DB phase to EoT OLI phase, mean (95% CI)	–12 (–39 to 15)	–206 (–247 to –165)[c]
Clinic		
Rate of patients with clinical remission (as defined in the primary end point) at EoT OLI phase, n (%)	17 (73.9)	23 (82.1)
Rate of patients in remission (total weekly EEsAI-PRO ≤20) at:		
EoT DB phase, n (%)	3 (13.0)	2 (7.1)
EoT OLI phase, n (%)	11 (47.8)	17 (60.7)
Total weekly EEsAI-PRO at:		
EoT DB phase, mean (SD)	50.1 (21.8)	42.7 (16.3)
EoT OLI phase, mean (SD)	28.9 (26.0)	19.1 (19.1)
Change from EoT DB phase to EoT OLI phase, mean (95% CI)	–21.2 (–31.5 to –10.9)[c]	–23.6 (–30.4 to –16.9)[c]
Rate of patients with no or only minimal problems defined as 0–10 NRS dysphagia ≤2 on each day in the week before:		
EoT DB phase, n (%)	2 (8.7)	4 (14.3)
EoT OLI phase, n (%)	17 (73.9)	23 (82.1)
Weekly sum of daily 0–10 NRS dysphagia (range, 0–70) at:		
EoT DB phase, mean (SD)	29.4 (16.7)	24.6 (11.1)
EoT OLI phase, mean (SD)	12.5 (12.0)	8.4 (10.6)
Change from EoT DB phase to EoT OLI phase, mean (95% CI)	–16.8 (–23.0 to –10.6)[c]	–16.1 (–20.7 to –11.6)[c]
PGA of EoE Activity (NRS 0–10) at:		
EoT DB phase, mean (SD)	4.5 (2.5)	5.4 (2.1)
EoT OLI phase, mean (SD)	1.3 (1.5)	1.3 (1.3)
Change from EoT DB phase to EoT OLI phase, mean (95% CI)	–3.3 (–4.5 to –2.2)[c]	–4.1 (–5.0 to –3.2)[c]
PatGA of EoE Activity (NRS 0–10) at:		
EoT DB phase, mean (SD)	4.8 (2.5)	4.0 (2.1)
EoT OLI phase, mean (SD)	1.9 (1.9)	1.4 (1.5)
Change from EoT DB phase to EoT OLI phase, mean (95% CI)	–2.9 (–4.0 to –1.7)[c]	–2.7 (–3.6 to –1.8)[c]
Blood eosinophil counts , *eos/mm^3*		
EoT DB phase, mean (SD)	193 (159)	412 (212)
EoT OLI phase, mean (SD)	201 (208)	208 (155)
Change from EoT DB phase to EoT OLI phase, mean (95% CI)	–5 (–99 to 89)	–211 (–287 to –135)[c]
Endoscopy		
Total modified EREFS endoscopic score (0–9):		
EoT DB phase, mean (SD)	2.1 (1.6)	4.5 (1.6)
EoT OLI phase, mean (SD)	1.0 (1.2)	1.1 (1.3)
Change from EoT DB phase to EoT OLI phase, mean (95% CI)	–1.3 (–1.9 to –0.7)[c]	–3.4 (–4.2 to –2.6)[c]

Supplementary Table 3. Continued

End Points	BOT → BOT[a] (n = 23)	Placebo → BOT[b] (n = 28)
Modified EREFS inflammatory signs subscore (0–4):		
EoT DB phase, mean (SD)	1.1 (1.1)	3.0 (1.0)
EoT OLI phase, mean (SD)	0.5 (0.9)	0.5 (0.8)
Change from EoT DB phase to EoT OLI phase, mean (95% CI)	–0.6 (–1.2 to –0.1)[c]	–2.4 (–3.0 to –1.9)[c]
Modified EREFS fibrotic signs subscore (0–4):		
EoT DB phase, mean (SD)	0.8 (0.8)	1.4 (1.0)
EoT OLI phase, mean (SD)	0.3 (0.6)	0.6 (0.6)
Change from EoT DB phase to EoT OLI phase, mean (95% CI)	–0.5 (–0.9 to –0.2)[c]	–0.9 (–1.2 to –0.5)[c]
Rate of patients with global assessment of endoscopic EoE activity of "no signs of EoE":	n = 23	n = 28
EoT DB phase, n (%)	11 (47.8)	0 (0)
EoT OLI phase, n (%)	15 (65.2)	17 (60.7)

bid, twice daily; CI, confidence interval; EoT, end of treatment (wk 6 [last observation carried forward]).
[a]BOT → BOT: Patients who received BOT 1 mg bid and who were not in clinico-histologic remission at the end of the 6-wk DB phase continued with a 6-wk open-label treatment with BOT 1 mg bid.
[b]Placebo → BOT: Patients who received placebo and who were not in clinico-histologic remission at the end of the 6-wk DB phase continued with a 6-wk open-label treatment with BOT 1 mg bid.
[c]Significant changes from EoT DB phase to EoT OLI, as 0 was excluded from the 95% CI.

Supplementary Table 4. Course and Absolute Changes from Baseline to Week 6 (Last Observation Carried Forward) of Peak Eosinophilic Count/mm^2 hpf (Total and by Esophageal Segment) in Eosinophilic Esophagitis Patients Treated With Budesonide Orodispersible Tablets or Placebo in the Double-Blind Phase

Peak eosinophil count per mm^2 hpf	BOT 1 mg bid (n = 59)	Placebo (n = 29)	BOT–placebo, mean difference (95% CI)
Total			
Baseline, mean (SD), n	242 (141), 59	239 (125), 29	—
EoT, mean (SD), n	16 (69), 59	224 (95), 28	—
Mean (95% CI) change from baseline to EoT	–226 (–265 to –186)	–4 (–56 to 47)	–221 (–287 to –156)
P value	<.0001[a]	.7988[a]	<.0001[b]
Proximal esophagus			
Baseline, mean (SD), n	125 (138), 59	185 (143), 29	—
EoT, mean (SD), n	5 (26), 59	137 (107), 28	—
Mean (95% CI) change from baseline to EoT	–120 (–157 to –83)	–38 (–98 to 21)	–82 (–148 to –15)
P value	<.0001[a]	.2463[a]	.0171[b]
Mid esophagus			
Baseline, mean (SD), n	148 (117), 59	178 (141), 29	—
EoT, mean (SD), n	10 (49), 59	168 (97), 28	—
Mean (95% CI) change from baseline to EoT	–138 (–171 to –105)	1 (–61 to 63)	–139 (–202 to –77)
P value	<.0001[a]	.9470[a]	<.0001[b]
Distal esophagus			
Baseline, mean (SD), n	200 (145), 59	159 (120), 29	—
EoT, mean (SD), n	16 (69), 59	182 (105), 28	—
Mean (95% CI) change from baseline to EoT	–184 (–223 to –145)	36 (–19 to 91)	–219 (–286 to –153)
P value	<.0001[a]	.1800[a]	<.0001[b]

bid, twice daily; CI, confidence interval; EoT, end of treatment (wk 6, last observation carried forward).
[a]Wilcoxon signed rank test (2-sided, test within group).
[b]Wilcoxon rank sum test (2-sided, test between groups).

Supplementary Table 5. Course and Absolute Changes From Baseline to Week 6 (Last Observation Carried Forward) of Individual Subscores of the Modified Endoscopic Reference Score in Eosinophilic Esophagitis Patients Treated With Budesonide Orodispersible Tablets or Placebo in the Double-Blind Phase

EREFS subscores	BOT 1 mg bid (n = 59)	Placebo (n = 29)	BOT-placebo, mean difference (95% CI)
Edema (range, 0–1)			
Baseline, mean (SD)	0.7 (0.44), n = 59	0.8 (0.38), n = 29	—
EoT, mean (SD)	0.2 (0.36), n = 59	0.8 (0.42), n = 28	—
Change from baseline to EoT, mean (95% CI)	–0.6 (–0.73 to –0.46)	0.0 (–0.20 to 0.13)	–0.6 (–0.79 to –0.33)
P value	<.0001	1.0000	<.0001
Exudates (range, 0–2)			
Baseline, mean (SD)	1.1 (0.69), n = 59	1.2 (0.77), n = 29	—
EoT, mean (SD)	0.2 (0.46), n = 59	1.2 (0.72), n = 28	—
Change from baseline to EoT, mean (95% CI)	–0.8 (–1.06 to –0.64)	0.0 (–0.28 to 0.28)	–0.8 (–1.20 to –0.49)
P value	<.0001	1.0000	<.0001
Furrows (range, 0–1)			
Baseline, mean (SD)	0.8 (0.36), n = 59	1.0 (0.00), n = 29	—
EoT, mean (SD)	0.2 (0.41), n = 58	1.0 (0.00), n = 28	—
Change from baseline to EoT, mean (95% CI)	–0.6 (–0.77 to –0.50)	0.0 (—)	–0.6 (–0.83 to –0.44)
P value	<.0001	—	<.0001
Fixed rings (range, 0–3)			
Baseline, mean (SD)	0.8 (0.84), n = 59	1.3 (0.76), n = 29	—
EoT, mean (SD)	0.5 (0.68), n = 59	1.3 (0.80), n = 28	—
Change from baseline to EoT, mean (95% CI)	–0.3 (–0.52 to –0.09)	–0.1 (–0.45 to 0.23)	–0.2 (–0.59 to 0.19)
P value	.0061	.6509	.3851
Stricture (range, 0–1)			
Baseline, mean (SD)	0.2 (0.36), n = 59	0.1 (0.35), n = 29	—
EoT, mean (SD)	0.1 (0.22), n = 59	0.2 (0.39), n = 28	—
Change from baseline to EoT, mean (95% CI)	–0.1 (–0.18 to –0.02)	0.0 (–0.16 to 0.23)	–0.1 (–0.31 to 0.04)
P value	*P*.0313	1.0000	.1384
Crêpe paper esophagus (range, 0–1)			
Baseline, mean (SD)	0.2 (0.38), n = 59	0.1 (0.31), n = 29	—
EoT, mean (SD)	0.1 (0.25), n = 59	0.1 (0.31), n = 28	—
Change from baseline to EoT, mean (95% CI)	–0.1 (–0.19 to –0.01)	0.0 (–0.15 to 0.15)	–0.1 (–0.27 to 0.07)
P value	.0703	1.0000	.2394

NOTE. All intra-group comparisons were performed using exploratory 2-sided Wilcoxon signed-rank test. All intergroup comparisons were performed using exploratory 2-sided Wilcoxon rank sum test.
bid, twice daily; CI, confidence interval; EoT, end of treatment (wk 6 [last observation carried forward]).

Supplementary Table 6. Course and Absolute Changes From Baseline to Week 6 (Last Observation Carried Forward) of the Total Eosinophilic Esophagitis Quality of Life Scale for Adults Questionnaire and its Subscores in Eosinophilic Esophagitis Patients Treated With Budesonide Orodispersible Tablets or Placebo in the Double-Blind Phase

Scores range: 0–4, with higher scores denote better HRQoL	BOT 1 mg bid (n = 59)	Placebo (n = 29)	BOT–placebo, mean difference (95% CI)
EoE-QoL-A 30-items (weighted average)			
Baseline, mean (SD)	2.3 (0.8)	2.3 (0.8)	—
EoT, mean (SD)	2.8 (0.9)	2.6 (0.7)	—
Change from baseline to EoT, mean (95% CI)	0.5 (0.32 to 0.62)	0.2 (0.06 to 0.42)	0.23 (–0.010 to 0.472)
P value	<.0001	.0115	.0602
EoE-QoL-A 24 items (weighted average)			
Baseline, mean (SD)	2.2 (0.8)	2.3 (0.8)	—
EoT, mean (SD)	2.7 (0.9)	2.6 (0.7)	—
Change from baseline to EoT, mean (95% CI)	0.5 (0.33 to 0.63)	0.2 (0.07 to 0.42)	0.24 (–0.004 to 0.476)
P value	<.0001	.0093	.0534
EoE-QoL-A eating/diet impact 10 items (weighted average)			
Baseline, mean (SD)	2.2 (1.0)	2.3 (0.8)	—
EoT, mean (SD)	2.9 (1.0)	2.5 (0.7)	—
Change from baseline to EoT, mean (95% CI)	0.7 (0.41 to 0.88)	0.2 (–0.08 to 0.38)	0.50 (0.174 to 0.817)
P value	<.0001	*P* = .1848	*P* = .0030
EoE-QoL-A eating/diet impact 4 items, (weighted average)			
Baseline, mean (SD)	2.1 (1.0)	2.2 (0.9)	—
EoT, mean (SD)	2.8 (1.0)	2.4 (0.8)	—
Change from baseline to EoT, mean (95% CI)	0.7 (0.46 to 0.92)	0.2 (–0.04 to 0.44)	0.49 (0.131 to 0.858)
P value	<.0001	.1039	.0082
EoE-QoL-A social impact (weighted average)			
Baseline, mean (SD)	2.1 (1.0)	2.2 (1.0)	—
EoT, mean (SD)	2.6 (1.1)	2.5 (0.9)	—
Change from baseline to EoT, mean (95% CI)	0.5 (0.27 to 0.65)	0.3 (0.02 to 0.58)	0.16 (–0.172 to 0.490)
P value	<.0001	.0364	.3430
EoE-QoL-A emotional impact (weighted average)			
Baseline, mean (SD)	2.6 (0.9)	2.7 (0.8)	—
EoT, mean (SD)	3.0 (0.9)	2.9 (0.7)	—
Change from baseline to EoT, mean (95% CI)	0.4 (0.28 to 0.60)	0.2 (0.04 to 0.43)	0.20 (–0.055 to 0.459)
P value	<.0001	.0186	.1216
EoE-QoL-A disease anxiety (weighted average)			
Baseline, mean (SD)	2.0 (0.9)	1.8 (0.9)	—
EoT, mean (SD)	2.3 (1.0)	2.0 (0.9)	—
Change from baseline to EoT, mean (95% CI)	0.3 (0.17 to 0.45)	0.2 (–0.04 to 0.34)	0.16 (–0.077 to 0.395)
P value	<.0001	.1078	.1840
EoE-QoL-A swallowing anxiety (weighted average)			
Baseline, mean (SD)	2.1 (1.0)	2.3 (1.1)	—
EoT, mean (SD)	2.7 (1.1)	2.8 (0.9)	—
Change from baseline to EoT, mean (95% CI)	0.6 (0.39 to 0.80)	0.4 (0.13 to 0.68)	0.19 (–0.150 to 0.539)
P value	<.0001	.0055	.2656

NOTE. All intra- and inter-group comparisons were performed using 2-sided, 2-sample *t* test and 2-sided *t* test, respectively.
bid, twice daily; CI, confidence interval; EoT, end of treatment (wk 6 [last observation carried forward]).

Supplementary Table 7. Exploratory Quality of Life End Points of Eosinophilic Esophagitis Patients Treated With Budesonide Orodispersible Tablets 1 mg Twice Daily in the Optional 6-Weeks Open-Label Phase

End points	BOT → BOT[a] (n = 23)	Placebo → BOT[b] (n = 29)
Modified SHS (scores range, 0–100, with lower scores denote better HRQoL)		
Modified SHS Symptom Burden:		
EoT DB phase, mean (SD)	51 (23.8)	37 (25.5)
EoT OLI phase, mean (SD)	23 (23.6)	14 (16.2)
Change from EoT DB phase to EoT OLI phase, mean (95% CI)	–28 (–40.7 to –14.8)[c]	–24 (–32.6 to –14.5)[c]
Modified SHS Social Function:		
EoT DB phase, mean (SD)	51 (24.5)	33 (23.5)
EoT OLI phase, mean (SD)	26 (25.6)	15 (16.7)
Change from EoT DB phase to EoT OLI phase, mean (95% CI)	–25 (–35.4 to –14.5)[c]	–18 (–26.7 to –9.3)[c]
Modified SHS Disease-Related Worry:		
EoT DB phase, mean (SD)	63 (21.2)	45 (28.6)
EoT OLI phase, mean (SD)	51 (23.7)	31 (24.4)
Change from EoT DB phase to EoT OLI phase, mean (95% CI)	–12 (–20.2 to –3.9) [c]	–14 (–22.9 to –5.0) [c]
Modified SHS General Well-Being:		
EoT DB phase, mean (SD)	45 (22.6)	27 (24.2)
EoT OLI phase, mean (SD)	27 (23.2)	14 (15.2)
Change from EoT DB phase to EoT OLI phase, mean (95% CI)	–18 (–26.9 to –8.4)[c]	–13 (–21.6 to –4.3)[c]
EoE-QoL-A (Scores range 0–4, with higher scores denote better HRQoL)		
EoE-QoL-A 30-items (weighted average)		
EoT DB phase, mean (SD)	2.0 (0.8)	2.5 (0.7)
EoT OLI phase, mean (SD)	2.2 (0.7)	2.8 (0.6)
Change from EoT DB phase to EoT OLI phase, mean (95% CI)	0.16 (0.003 to 0.327)[c]	0.29 (0.072 to 0.512)[c]
EoE-QoL-A 24-items (weighted average)		
EoT DB phase, mean (SD)	2.0 (0.8)	2.5 (0.7)
EoT OLI phase, mean (SD)	2.5 (0.7)	2.8 (0.6)
Change from EoT DB phase to EoT OLI phase, mean (95% CI)	0.17 (0.017 to 0.324)[c]	0.28 (0.061 to 0.505)[c]
EoE-QoL-A eating/diet impact 10 items (weighted average)		
EoT DB phase, mean (SD)	2.1 (0.9)	2.5 (0.8)
EoT OLI phase, mean (SD)	2.4 (1.0)	2.9 (0.7)
Change from EoT DB phase to EoT OLI phase, mean (95% CI)	0.33 (0.085 to 0.580)[c]	0.49 (0.217 to 0.754)[c]
EoE-QoL-A eating/diet impact 4 items (weighted average)		
EoT DB phase, mean (SD)	2.0 (0.9)	2.4 (0.8)
EoT OLI phase, mean (SD)	2.4 (0.9)	2.9 (0.8)
Change from EoT DB phase to EoT OLI phase, mean (95% CI)	0.39 (0.157 to 0.626)[c]	0.46 (0.164 to 0.747)[c]
EoE-QoL-A social impact (weighted average)		
EoT DB phase, mean (SD)	1.9 (1.2)	2.5 (0.9)
EoT OLI phase, mean (SD)	1.9 (1.1)	2.9 (0.8)
Change from EoT DB phase to EoT OLI phase, mean (95% CI)	0.04 (–0.212 to 0.299)	0.45 (0.073 to 0.820)[c]
EoE-QoL-A emotional impact (weighted average)		
EoT DB phase, mean (SD)	2.3 (0.9)	2.9 (0.7)
EoT OLI phase, mean (SD)	2.5 (0.7)	3.1 (0.5)
Change from EoT DB phase to EoT OLI phase, mean (95% CI)	0.15 (–0.025 to 0.318)	0.22 (–0.004 to 0.436)
EoE-QoL-A disease anxiety (weighted average)		
EoT DB phase, mean (SD)	1.5 (0.8)	2.0 (0.9)
EoT OLI phase, mean (SD)	1.7 (0.8)	2.1 (0.9)
Change from EoT DB phase to EoT OLI phase, mean (95% CI)	0.16 (–0.055 to 0.368)	0.16 (–0.080 to 0.397)
EoE-QoL-A swallowing anxiety (weighted average)		
EoT DB phase, mean (SD)	1.9 (1.1)	2.7 (0.9)
EoT OLI phase, mean (SD)	2.0 (1.0)	2.9 (0.8)
Change from EoT DB phase to EoT OLI phase, mean (95% CI)	0.13 (–0.077 to 0.338)	0.20 (–0.029 to 0.434)

bid, twice daily; CI, confidence interval; EoT, end of treatment (wk 6 [last observation carried forward]); HRQoL, Health-Related Quality of Life.

[a]BOT → BOT: Patients who received BOT 1 mg bid and who were not in clinico-histologic remission at the end of the 6-wk DB phase continued with a 6-wk open-label treatment with BOT 1 mg bid.

[b]Placebo → BOT: Patients who received placebo and who were not in clinico-histologic remission at the end of the 6-wk DB phase continued with a 6-wk open-label treatment with BOT 1 mg bid.

[c]Significant changes from EoT DB phase to EoT OLI, as 0 was excluded from the 95% CI.

Supplementary Table 8. Mean Serum Morning (8:00–09:00 AM) Cortisol Levels and Change from Baseline in Eosinophilic Esophagitis Patients Treated with Budesonide Orodispersible Tablets or Placebo in the Double-Blind Phase, the Optional 6-Week Open-Label Phase, and the Follow-Up Phase (if Not Switched to Study EOS-2 after Double-Blind End of Treatment or Open-Label Induction/End of Treatment

Cortisol levels, $\mu g/dL$	BOT 1 mg bid (n = 59)	Placebo (n = 29)	BOT–placebo, mean difference (95% CI)
Baseline, mean (SD), n	12.6 (4.8), 52	12.5 (4.4), 27	—
EoT, mean (SD), n	11.9 (4.6), 54	11.2 (4.5), 27	—
Change from baseline to EoT, mean (95% CI), n	–1.1 (–2.0 to –0.1), 52	–1.3 (–2.9 to 0.2), 27	0.3 (–1.4 to 1.9)
P value	—	—	.7272
	BOT→BOT[a] (n = 23)	Placebo→BOT[b] (n = 28)	BOT–placebo, mean difference (95% CI)
EoT DB phase, mean (SD), n	12.1 (4.5), 19	10.1 (3.3), 22	—
EoT OLI phase, mean (SD), n	12.4 (4.8), 20	10.11 (3.7), 26	—
Change from EoT DB phase to EoT OLI phase, mean (95% CI), n	0.04 (–1.9 to 2.0) , 19	0.5 (–0.9 to 1.9), 22	—
	Follow-up	Follow-up	
EoT DB or OLI phase, mean (SD), n	11.9 (4.9), 18	14.8, 1	—
EoT FU phase, mean (SD), n	13.1 (5.6), 18	4.0, 1[c]	—
Change from EoT DB or OLI phase to EoT FU phase, mean (95% CI)	1.3 (–0.4 to 2.9), 18	–10.8, 1	—

bid, twice daily; CI, confidence interval; EoT, end of treatment (wk 6, last observation carried forward); FU, follow-up.
[a]BOT→BOT: Patients who received BOT 1 mg bid and who were not in clinico-histologic remission at the end of the 6-wk DB phase continued with a 6-wk open-label treatment with BOT 1 mg bid.
[b]Placebo→BOT: Patients who received placebo and who were not in clinico-histologic remission at the end of the 6-wk DB phase continued with a 6-wk open-label treatment with BOT 1 mg bid.
[c]The patient experienced a food impaction during double-blind treatment phase requiring endoscopic emergency intervention outside the study setting and was treated throughout the FU phase with budesonide asthma medication twice daily, which explains the drop of serum morning cortisol from EoT to FU. The FU value was assessed by the investigator of being not clinically relevant.

Supplementary Table 9. Serum Morning Cortisol Levels of Patients With Clinically Relevant Abnormal Values Below Lower Limit of Normal (<6.2 μg/dL)

Variable	Baseline DB	EoT DB	EoT OLI	FU
BOT 1 mg bid				
Patient 1	10.1	3.7 [a]	—	—
Patient 2	6.5	5.8	10.2[c]	—
Patient 3	11.6	2.7 [a,b]	—	—
Placebo				
Patient 1	8.2	15.8	2.2[c]	—

bid, twice daily; EoT, end of treatment (wk 6, last observation carried forward); FU, follow-up.
[a]Patient switched over to EOS-2 maintenance trial after completion of DB phase. Therefore, no FU value is available.
[b]Sample was taken outside the requested window of 08:00-09:00 a.m.
[c]Patient switched over to EOS-2 maintenance trial after completion of OLI phase. Therefore, no FU value is available.

Supplementary Table 10. Eosinophilic Esophagitis Patients Treated With Budesonide Orodispersible Tablets 1 mg Twice Daily in the Optional 6-Week Open-label Phase and Experiencing Treatment-Related Adverse Events

Variable	BOT → BOT,[a] n (%) (n = 23)	Placebo → BOT,[b] n (%) (n = 28)
Any TEAE	13 (56.5)	16 (57.1)
Severe TEAE		
Esophageal food impaction		
TEAE related to study drug	6 (26.1)	13 (46.4)
Serious adverse events	0 (0)	0 (0)
TEAE leading to withdrawal from the study	0 (0)	1 (3.6)
Lip edema and oral paraesthesia, both of mild intensity and recovered	0 (0)	1 (3.6)
TEAE related to study drug and leading to withdrawal from the study	0 (0)	1 (3.6)
TEAEs by occurring in ≥2 patients in any treatment group:		
Gastrointestinal disorders	3 (13.0)	2 (7.1)
Gastroesophageal reflux disease	2 (8.7)	1 (3.6)
Infections and infestations	4 (17.4)	12 (42.9)
Suspected local fungal infection,[c] thereof:	4 (17.4)	10 (35.7)
Histologically confirmed[d]	2 (8.7)	7 (25.0)
Histologically confirmed[d] with suspected endoscopic signs	1 (4.3)	6 (21.4)
Histologically confirmed[d] with suspected endoscopic signs and clinical symptoms	0 (0)	0 (0)
Nervous system disorders	4 (17.4)	1 (3.6)
Headache	4 (17.4)	1 (3.6)

bid, twice daily; TEAE, treatment-emergent adverse events.

[a]BOT → BOT: Patients who received BOT 1 mg bid and who were not in clinico-histologic remission at the end of the 6-wk DB phase continued with a 6-wk open-label treatment with BOT 1mg bid

[b]Placebo → BOT: Patients who received placebo and who were not in clinico-histologic remission at the end of the 6-wk DB phase continued with a 6-wk open-label treatment with BOT 1 mg bid.

[c]Local fungal infection (included suspected cases of candida infection, esophageal candidiasis, oral candidiasis, and oropharyngeal candidiasis) was suspected and assessed as an adverse event if any of the following criteria was fulfilled: suspected clinical symptoms, suspected endoscopic findings, suspected histologic assessment in H&E-stained biopsies (even without any endoscopic signs or clinical symptoms).

[d]Histologically confirmed by Grocott staining.

Supplementary Table 11. Efficacy of Drug Interventions for Treating Eosinophilic Esophagitis in the Past (Previous Acute and/or Maintenance Treatment)

Previously reported efficacy	BOT 1 mg bid, n (%) (n = 59)	Placebo, n (%) (n = 29)
PPI	32 (54)[a]	13 (45)[a]
Poor	25/32 (78)	11/13 (85)
Satisfactory	2/32 (6)	1/13 (8)
Good	0/32 (0)	1/13 (8)
Very good	2/32 (6)	0/13 (0)
Unknown	3/32 (9)	0/13 (0)
Topical budesonide	12 (20)	3 (10)
Poor	0/12 (0)	0/3 (0)
Satisfactory	3/12 (25)	0/3 (0)
Good	6/12 (50)	2/3 (67)
Very good	3/12 (25)	1/3 (33)
Topical fluticasone	25 (42)	14 (48)
Poor	7/25 (28)	3/14 (21)
Satisfactory	1/25 (4)	2/14 (14)
Good	11/25 (44)	7/14 (50)
Very good	5/25 (20)	1/14 (7)
Unknown	1/25 (4)	1/14 (7)
Systemic steroids	3 (5)	0 (0)
Good	1/3 (33)	0/0 (0)
Very good	1/3 (33)	0/0 (0)
Unknown	1/3 (33)	0/0 (0)
Montelukast	4 (7)	0 (0)
Good	1/4 (25)	0/0 (0)
Poor	2/4 (50)	0/0 (0)
Unknown	1/4 (25)	0/0 (0)

bid, twice daily; n, valid numbers; PPI, proton pump inhibitor.
[a]All patients failed PPI trial (either in their history or during the screening phase.