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

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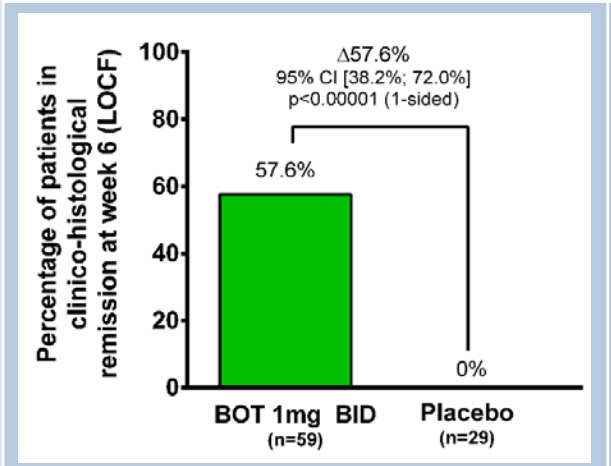
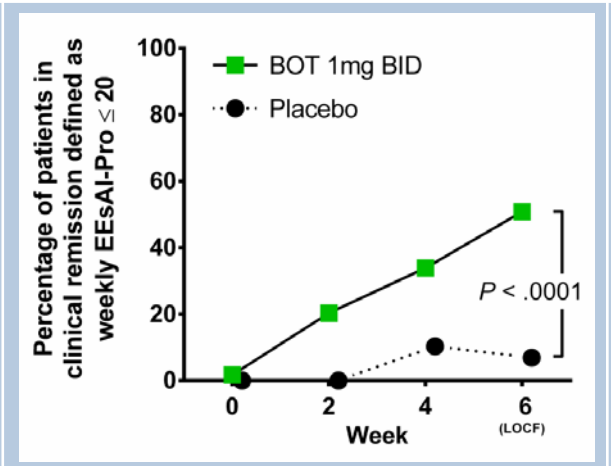
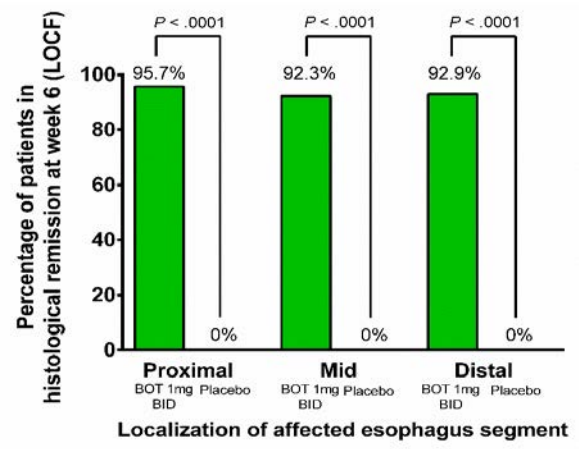
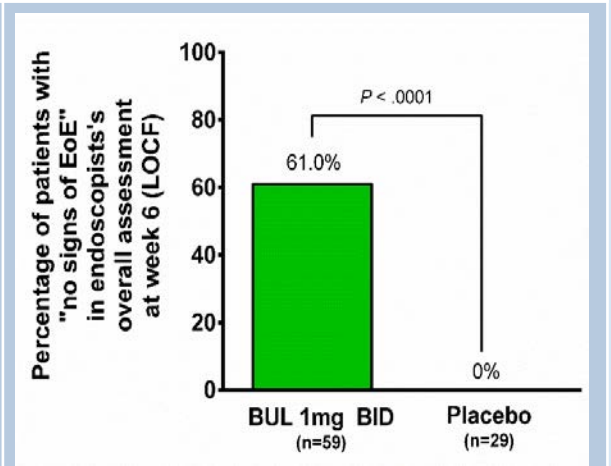
Active eosinophilic esophagitis

A 6-weeks twice daily treatment with Budesonide 1mg orodispersible tablets (BOT) was safe and highly effective for achieving:

Clinico-Histological remission (1° endpoint)	Clinical remission	Histological remission	Endoscopic remission
			

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

Short Title: Budesonide Orodispersible Tablets for EoE

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Abbreviations used in this paper: BID, twice daily; BOT, budesonide orodispersible tablet; CI, confidence interval; DB, double-blind; EEsAI-PRO, eosinophilic esophagitis activity index - patient

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reported outcome; EoE, eosinophilic esophagitis; EoE-QoL-A, eosinophilic esophagitis quality of life scale for adults; eos/hpf, eosinophils per high power field (400x) 0.345 mm^2; EoT, end of treatment (Week 6 [LOCF]); EREFS, Endoscopic Reference Score; GERD, gastroesophageal reflux disease; HRQoL, health-related quality of life; ITT, intention-to-treat; LOCF, last observation carried forward; 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; SD, standard deviation; SHS, short health scale; STC, swallowed topical-acting corticosteroids

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Abstract

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) that 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 endpoint 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-bind 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 endpoint 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- and 12-weeks administration of BOT 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 no: 2014-001485-99; ClinicalTrials.gov no: NCT02434029.

Keywords: phase 3 trial; immune response; esophagus; patient-reported outcomes

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Introduction

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 two 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 (GERD).[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.

Swallowed topical-acting corticosteroids (STC) are today an established first-line pharmacologic treatment for patients with EoE.[1] Proton pump inhibitors (PPI)[11] and dietary modifications[12] are alternatives. From the first positive attempt to treat EoE with STC, 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 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 STC over placebo in symptom improvement.[16-18]

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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% histological remission rate. Doses of 1 mg or 2 mg BOT twice daily (BID) 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 1mg BID over placebo for inducing symptomatic and histological remission in adults with active EoE.

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 treatment with budesonide (BOT 1mg BID) versus placebo in adult patients with active EoE (see Supplementary Figure 1). Patients not achieving clinico-histological remission at the end of the 6-week DB-phase, or who dropped out after at least 4-weeks DB treatment due to lack of efficacy, were offered a further 6-weeks open-label induction (OLI) treatment with BOT 1mg BID. Patients achieving clinico-histological remission either at end of treatment (EoT) of DB- or OLI-phase, could enter the maintenance of remission study EOS-2 (EudraCT No.: 2014-001485-99). The study was conducted at 26 centers in 6 countries from Nov 2015 to Oct 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

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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: Patients 18 to 75 years with clinico-histologic active EoE, and being refractory to treatment with a PPI used at least standard doses (e.g., omeprazole 20 mg/day, pantoprazole 40 mg/day, esomeprazole 40 mg/day, lansoprazole 30 mg/day, or rabeprazole 20 mg/day) for a 4-week period.[19] Patients had to have a severity of ≥4 points on a 0-10 numerical rating scale (NRS) for either dysphagia or odynophagia for ≥1 day in the week before randomization. Additionally, patient‘s global assessment (PatGA) of EoE activity was to be ≥4 points on a 0-10 NRS. Histological activity with peak eos ≥65/mm^2 hpf in at least 1 hpf (corresponding to ≥20 eos/hpf), as measured in a total of 6 hpfs derived from six biopsies, two each from the proximal, mid and distal segments of the esophagus.

Key exclusion criteria were: Clinical and endoscopic suspicion for GERD (at least Los Angeles Classification of Esophagitis Grade A); achalasia or scleroderma; evidence of causes other than EoE for esophageal eosinophilia; pathological eosinophilic infiltration in gastric and duodenal biopsies; history of esophageal surgery at any time or of esophageal dilation procedures within the last 8 weeks prior to screening; any relevant systemic disease; systemic glucocorticosteroids, immunosuppressants, biological drugs within 4 weeks prior to screening, or topical glucocorticosteroids within 2 weeks prior to screening; onset of dietary restrictions within 4 weeks prior to screening.

Randomization and interventions

At baseline, eligible patients were centrally randomized in a 2:1 ratio (verum: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,

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investigators and their study team, the sponsor, monitoring staff, central lab, 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 nor 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, whose production 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 90–120s). Patients were instructed to avoid eating, drinking or oral hygiene procedures for 30 min after study drug administration. Compliance was assessed by pill count. The use of other concomitant anti-inflammatory drugs (i.e., systemic or topical glucocorticoids, immunosuppressants, biological 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 daily assessed during the seven days prior to 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 patient's global assessment (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

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activity (0-10 NRS) was assessed at baseline and EoT. Patients completed the EoE-QoL-A questionnaire v.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, Illinois. USA. 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 four health dimensions: (1) symptom burden, (2) social function, (3) disease-related worry, and (4) 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) to 3), i.e. 'bowel' by the term '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, two biopsies each from the distal, mid, and proximal esophagus were obtained and analyzed in a blinded manner by the central pathologist (M.V.). 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 hematoxylin & eosin 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 cut-off level for histological remission of <16 eos/mm^2 hpf was chosen as the same microscope was used in the previous trial by Straumann

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et al.[25] and in the recent phase II trial with BOT,[18] and which corresponds to <5 eos/hpf as reported by Straumann *et al*.[25]

In patients with suspected local fungal infection (i.e., based either on clinical symptoms, endoscopic appearance or even from suspicious HE-stained histological 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 (08:00–09:00) levels were measured at Baseline and EoT visits. Tolerability was classified by the patient and the investigator independently at the EoT.

Study endpoints

The primary efficacy endpoint was the rate of patients with clinico-histological remission at week 6, i.e., achieving both, histological 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 prior to EoT). Occurrence of food impaction, needing for endoscopic intervention or dilation, or prematurely withdrawal was assessed as treatment failure.

Secondary *a priori*-ordered endpoints, which could be tested in a confirmatory manner, included (1) histological remission, (2) change in peak eosinophil count, (3) resolution of symptoms on each day in the week prior to the EoT, and (4) rate of clinical remission defined as EEsAI-PRO ≤20 at EoT. A full list of all clinical, endoscopic, histological, and HRQoL endpoints used is shown in Supplementary Table 1.

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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 FAS patients (2:1 randomization) were needed to detect this difference of 40% in true remission rates using Fisher's exact test (one-sided alpha=0.025) 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 one dose of the study drug.

For the primary endpoint, proportions of patients with clinico-histological remission at week 6 with last observation carried forward (LOCF) were compared between treatment groups using one-sided Fisher's exact test. Efficacy significance testing continued in hierarchical fashion for the *a priori* ordered key secondary endpoints. Once a one-sided non-significant p-value (>0.025) occurred, subsequent significance tests were considered exploratory. Dichotomous key secondary endpoints 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 endpoints between treatment groups or between baseline and end of treatment were performed using two-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 Inc., USA) and ADDPLAN® version 6.1.1 (licensed by ADDPLAN, Inc., an ICON Clinical Research, LLC company) and according to the intention-to-treat principle. Missing data at week 6 were replaced using the LOCF method.

Results

Patient Flow and Baseline Characteristics

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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 dys-, 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 endpoint of clinico-histological remission at Week 6 was achieved in 34 of 59 patients (57.6%) receiving budesonide but in none of the 29 patients (0%) 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-histological 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 1mg BID was offered to clinical or histological non-responders at EoT of DB-phase and was chosen by 23 patients from the BOT group (BOT→BOT) and all 29 patients from the placebo groups (Placebo→BOT; Supplementary Table 3). As achievement of clinical remission (Figure 2A-C) takes longer than achievement of histological remission under BOT 1mg BID, the majority of BOT→BOT patients were already in histological remission at EoT of DB-phase (93.2%; Table 2), but benefited clinically from a prolonged treatment with BOT 1mg BID (Supplementary Figure 3). The overall cumulative clinico-histological remission rate after up to 12 weeks of treatment with BOT 1mg BID was therefore 84.7% (50 of 59

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patients), providing evidence that a prolonged treatment for up to 12 weeks is beneficial to bring more patients into clinico-histological remission.

All four *a priori* ordered major secondary efficacy endpoints proved superiority of BOT 1mg BID vs placebo in a confirmatory manner (Table 2). Clinical remission, as defined in the primary composite endpoint, was achieved in 59.3% versus 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% versus 6.9%, $P < .0001$); PatGA≤2: 64.4% versus 24.1%, $P = .0006$; see also Figure 3A-C for course of clinical remission/response).

Histological remission after 6 week of DB-phase, irrespective of symptoms, was achieved in 93.2% and 0% in the BOT 1mg BID and placebo group, respectively ($P < .0001$). All but 3 patients in the BOT 1mg BID group showed a dramatic decrease from baseline in peak eosinophil count, independently of the eosinophil load at baseline (Figure 3A), demonstrating that BOT 1mg BID was able to induce remission even in severely inflamed cases. Histological remission in the BOT 1mg BID group was independently achieved in all esophageal segments (Figure 3B), 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 histological remission rates of 95.3%) (Figure 3C) ($P < .0001$ 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 1mg BID group (-3.6 points) was 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 1mg BID (-3.8 points) compared to placebo (-0.8 points; $P < .0001$; Table 2).

The mean reductions from baseline to EoT in modified EREFS total score and its 'inflammatory' and 'fibrotic' subscores were in the BOT 1mg BID and placebo group, respectively -2.6 versus -0.1 ($P < .0001$), -2.1 versus 0.0 ($P < .001$), and -0.4 versus 0.0 ($P = .8074$). However, the change of 0.4 points in the 'fibrotic' subscore under BOT 1mg BID treatment was relevant and also significant

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(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% versus 0% of the patients in the BOT 1mg BID and placebo group, respectively (P < .0001; Table 2).

Quality of life measured with the generic modSHS instrument showed for all four dimensions a numerically higher and significant improvement (absolute change) in mean scores from baseline to week 6 for the BOT 1mg BID group, but only a significant change from baseline to EoT for 'symptom burden' and 'social function' domain in the placebo group (Figure 4A). The comparison of absolute changes between the treatment groups revealed superiority of BOT 1mg BID over placebo in the domains 'social function' and 'disease-related worry', as the 95% CI of the group differences (BOT 1mg BID – Placebo) excluded '0' (Figure 4B).

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

Safety

Overall, BOT 1mg BID was well tolerated in this study. No serious adverse event was reported. However, food impaction requiring endoscopic emergency intervention occurred in one patient receiving placebo. No important differences were observed among the study groups in the most commonly reported adverse events, despite a higher proportion of patients with suspected treatment-emergent adverse drug reactions at the end of DB-phase were assigned to the budesonide (27/59) than in the placebo group (1/29) (Table 3). Suspected local fungal infections were more

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common with budesonide than with placebo: suspected candidiasis in endoscopy carried out per protocol at EoT visit were confirmed histologically in only 10/59 patients (16.9%). Finally, and clinically most important, only 3 of these patients (5.1%) presented with clinical symptoms (2 patients with esophageal, 1 with oral and esophageal symptoms), all of mild intensity, with no impact on daily life activities, 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 below the lower limit of normal (6.2 mcg/dL) was recorded only in 3 patients (5.1%) in the budesonide arm (Supplementary Table 9). No patient had to prematurely stop administration of the study medication.

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

Discussion

This is a pivotal Phase 3 trial reporting 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 histological remission. As EoE is diagnosed by the presence of symptoms of esophageal dysfunction (mainly dysphagia) and histological inflammation with >15 eos/hpf, a composite endpoint of achieving both clinically and histologically remission is an appropriate readout. A 6-week treatment with 1 mg budesonide BID was highly superior over placebo regarding 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

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eating behavior of the patient. Clinical remission as defined in the primary composite endpoint was highly superior under BOT 1mg BID compared to placebo in a confirmatory manner. A direct comparison between other studies with STCs is difficult as they used different read-outs and cut-offs for defining clinical remission. However, our NRS for dysphagia was a simple tool with obvious face validity. and which was also confirmed recently to be responsive to assess dysphagia severity in EoE in clinical practice.[26] The chosen cut-off of ≤2 was in line with all other important clinical endpoints based on different tools (PatGA, PGA and EEsAI-PRO), which also showed similar remission rates based on cut-offs ≤2 on a 0-10 (PatGA, PGA) or ≤20 on a 1-100 scale (EEsAI-PRO).

Recently, Hirano *et al*. used a similar PatGA and PGA in their trial with RPC4046, an anti-IL13 mAb.[27] 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 decreased from 5.9 to 2.3 and PGA from 6.1 to 2.3. However, in the study by Hirano approximately 50% of patients were steroid-refractory, whereas in our study only 11% patients showed a previously poor response to steroids, which might explain the slightly better improvement in our study.

Histological 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 100% histological remission rate[18] and showed that BOT 1mg BID had similar anti-inflammatory effects in the entire esophagus, independently of severity, localization, or extent of inflammation (Figure 2A-C), indicating an optimal esophageal targeting with BOT 1mg BID.

More patients achieved histological remission of EoE in our trial compared to clinical remission. Thus, nearly every patient in clinical remission at EoT was also in histological 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

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esophageal narrow caliber underestimated with endoscopy,[30] a decreased esophageal distensibility,[31] or symptoms unrelated with EoE but due to co-existent comorbidities. In any case, it demands the need of considering both aspects in the evaluation of patients with EoE.

Of note, the histological 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 10ml/application and doubled daily dose, only 39% of the patients after a 12-week course achieved histologic remission defined as $\leq$6 eos/hpf.[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 10ml viscous suspension, BOT 1mg BID offered a unique way of delivery. As soon as BOT is put on the tongue, it stimulates via its effervescence characteristics the production of saliva over 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 an optimal adhesion and a prolonged contact time, thus that even with 1mg BID histological remission rates are twice as high as compared to a 2mg BID dosing with oral viscous suspension in a high volume.

Endoscopically, treatment with BOT 1 mg BID resulted in significant changes from baseline to EoT in the total modified EREFS as well as in its 'inflammatory signs' subscore. Surprisingly, already a 6-week treatment with BOT 1mg BID also significantly decreased the 'fibrotic signs' subscore, indicating that a prolonged treatment with BOT might have a substantial impact on re-modelling. Therefore, long-term data are needed and actually being addressed by the ongoing EOS-2 maintenance of remission trial (EudraCT No. 2014-001485-99). Comparisons between different trials are hindered by the fact that either the original EREFS score or its modified version were used

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(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 (mod SHS and EoE-QoL-A) showed a significant improvement in HRQoL in all domains and items under BOT 1mg BID, with a numerical larger improvement compared to placebo. This was statistically significant already after a 6-week short treatment for the domains 'social function' and 'disease related worry' using the modSHS and the 'EoE.QoL-A 'eating/diet impact 10 and 4 items (weighted average)' domains score.

The main side effect of STC is local fungal infection. In this study, we searched systematically for candidiasis, i.e., clinically, endoscopically and histologically regarding localization and regarding 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 therefore the rates of histological 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 1mg BID 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 only for 3 patients under BOT 1mg BID treatment a clinically significant decrease in serum cortisol levels was reported, 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-histological remission of EoE, as the primary endpoint, 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 comprehensively monitored and assessed.

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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 as also 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 dose among the two doses (i.e., 1mg and 2mg BOT BID), which both demonstrated histological remission in almost all the patients who participated in our phase-2 trial.[18] Our histologic remission rate does not preclude that an even lower dose than 1mg BID could still achieve disease remission in a significant proportion of patients as 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. Four, symptomatic improvement during OLI phase could have overestimated the effect of therapy since patients were un-blinded and knew 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 less than 12% of patients recruited continued their underlying PPI treatment with stable dosing.

In conclusion, compared to placebo, BOT 1mg BID 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.

Supplemental Material

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Note: To access the supplementary material accompanying this article, visit the online version of Gastroenterology at www.gastrojournal.org.

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Figure Legends

Figure 1. Primary study endpoint in eosinophilic esophagitis patients treated with budesonide orodispersible tablets or placebo in the 6-week DB-phase. Clinico-histological remission was defined as achieving both histological 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 prior to Week 6 (LOCF); (1-sided Fisher exact test)). Patients who experienced a food impaction needing endoscopic intervention, who needed a dilation during the study, or withdrew prematurely were assessed as treatment failure.

Abbreviations: BID, twice daily; BOT, budesonide orodispersible tablet, CI, confidence interval; eos; eosinophils; hpf, high power field; LOCF, last observation carried forward

Figure 2. Course of clinical improvement and remission in eosinophilic esophagitis patients treated with budesonide orodispersible tablets or placebo in the DB-phase. (A) Course of achieved clinical remission defined as Eosinophilic Esophagitis Activity Index - Patient Reported Outcome score of ≤20 points (1-sided Fisher's exact test). (B) Course of achieved resolution of dysphagia defined as ≤2 points on a 0 to 10-point Numerical Rating Scale for dysphagia on each day in the week prior to a visit (2-sided Fisher's exact test). (C) Course of the number of days in the week prior to a visit, with none or only minimal dysphagia (i.e, dysphagia ≤2 points on a 0 to 10-point Numerical Rating Scale for dysphagia (2-sided Wilcoxon rank sum test).

Abbreviations: BID, twice daily; BOT, budesonide orodispersible tablet; CI, confidence interval; EEsAI-PRO, Eosinophilic Esophagitis Activity Index - Patient Reported Outcome; LOCF, last observation carried forward

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Figure 3. Histological changes and remission in eosinophilic esophagitis patients treated with BOT 1mg BID or placebo in the DB-phase. (A) Individual pre- and post-treatment peak eos/mm^2 hpf counts and median group values with interquartile range (2-sided Wilcoxon signed rank test for intra-group changes); (B) Histological 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 exact test)

Abbreviations: BID, twice daily; BOT, budesonide orodispersible tablet; eos; eosinophils; hpf, high power field; IQR, interquartile range; LOCF, last observation carried forward

Figure 4. Changes in Health-related Quality of Life by means of the modified Short Health Scales in eosinophilic esophagitis patients treated with budesonide orodispersible tablets or placebo in the DB-phase. (A) Mean pre- and post-treatment scores of the four dimensions of the modified Short Health Scale showed a greater improvement in BOT treated patients, with lower values indicating better quality of life. All dimensions significantly improved from baseline to Week 6 (LOCF) under BOT, whereas only 'symptom burden' and 'social function' significantly improved. (B) The 95% CI of the group differences (BOT 1mg BID – Placebo) in mean absolute changes, which excluded '0', indicated a superiority of BOT 1mg BID over placebo in the dimension of 'social function' and 'disease-related worry'. All intra- and intergroup comparisons were performed using 2-sided one-sample t-test and two-sided t-test, respectively.

Abbreviations: BID, twice daily; BOT, budesonide orodispersible tablet; CI, confidence interval; LOCF, last observation carried forward; SD, standard deviation; VAS, visual analogue scale

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

Characteristic	BOT 1mg BID (n = 59)	Placebo (n = 29)
Male, n (%)	48 (81)	25 (86)
White, n (%)	59 (100)	29 (100)
Age (years), Mean (SD)	37 (11.5)	37 (9.2)
BMI (kg/m^2), Mean (SD)	24.4 (2.9)	25.6 (4.1)
Time since first EoE symptoms (months), Mean (SD)	134 (104.6)	139 (98.8)
Time since EoE diagnosis (months), 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)
1-3x/week	21 (36)	12 (41)
4-6x/week	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 Short Health Scales (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)
Patient‘s Global Assessment of EoE activity (NRS 0-10), Mean (SD)	5.9 (1.5)	6.0 (1.5)
Physician‘s Global Assessment 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)
Number 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)

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Edema	44 (75)	24 (83)
Furrows	50 (85)	29 (100)
Strictures	9 (15)	4 (14)
Crepe 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)
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 (%) *		
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)

*Previously reported efficacy of drug interventions in the patient's history is presented in Supplementary Table 11

Abbreviations: BMI, body mass index; BOT, budesonide orodispersible tablet; CI, confidence interval; EEsAI-PRO, Eosinophilic Esophagitis Activity Index - Patient Reported Outcome; EoE , eosinophilic esophagitis; EoE-QoL-A, eosinophilic esophagitis quality of life scale for adults; eos; eosinophils; EREFS, Endoscopic Reference Score; hpf, high power field; n, valid numbers; NRS, numerical rating scale; PPI, proton pump inhibitor; SD, standard deviation

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Table 2. *A Priori* Ordered Major Secondary and Further Exploratory Efficacy Endpoints of Eosinophilic Esophagitis Patients Treated With BOT 1mg BID or Placebo in the DB-Phase

Endpoints	BOT 1mg BID (n=59)	Placebo (n=29)	*P* value
***A priori* ordered major secondary efficacy endpoints (DB-phase)**			
1. Rate of patients with histological remission (i.e., peak eos <16 /mm^2 hpf; equivalent to <5 eos/hpf) at week 6, n (%)	55 (93.2)	0 (0)	$P < .0001^{b}$
2. Change in the peak eos/mm^2 hpf from baseline to week 6, Mean (SD)	-226 (150.4)	-4 (135.6)	$P < .0001^{i}$
3. Rate of patients with clinical remission (as defined in the primary endpoint) at week 6, n (%)	35 (59.3)	4 (13.8)	$P < .0001^{b}$
4. Rate of patients in clinical remission (total weekly EEsAI-PRO ≤20) at week 6, n (%)	30 (50.8)	2 (6.9)	$P < .0001^{b}$
Further exploratory efficacy endpoints (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, Mean (SD)	14.5 (16.4)	24.9 (11.0)	
Change from baseline to wk6, Mean (SD)	-20.1 (17.0)	-11.4 (11.0)	$P = .0230^{a}$
Physician’s Global Assessment (PGA) of EoE Activity (NRS 0-10):			
Baseline, Mean (SD)	6.1 (1.3)	6.2 (1.3)	
EoT, Mean (SD)	2.3 (2.5)	5.5 (2.1)	
Change from baseline to wk6, Mean [95%CI]	-3.8 [-4.4; -3.2]	-0.8 [-1.6; 0.1]	$P < .0001^{a}$
Patient’s Global Assessment (PatGA) of EoE Activity (NRS 0-10):			
Baseline, Mean (SD)	5.9 (1.5)	6.0 (1.5)	
EoT, Mean (SD)	2.3 (2.6)	4.1 (2.1)	
Change from baseline to wk6, Mean [95%C])	-3.6 [-4.3; -2.9]	-1.9 [-3.0; -0.9]	$P = .0073^{a}$
Rate of patients with overall symptoms resolution defined as PatGA ≤2 at EoT, n (%)	38 (64.4)	7 (24.1)	$P = .0006^{b}$
Change from baseline to EoT in blood eosinophil counts [eos/mm^3], Mean [95%CI]	-219 [-288; -150]	-28 [-124; 68]	$P = .0016^{a}$
Endoscopy			
Total modified EREFS endoscopic score (0-9)			
Baseline, Mean (SD)	3.8 (1.5)	4.6 (1.3)	
EoT, Mean (SD)	1.2 (1.4)	4.5 (1.6)	
Change from baseline to EoT in, Mean [95%CI]	-2.6 [-3.1; -2.1]	-0.1 [-0.8; 0.5]	$P < .0001^{a}$
	$P < .0001^{d}$	$P = .7358^{d}$	

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Modified EREFS 'inflammatory signs' subscore (0-4)			
Baseline, Mean (SD)	2.7 (1.0)	3.0 (1.0)	
EoT, Mean (SD)	0.6 (0.9)	3.0 (1.0)	
Change from baseline to EoT in , Mean [95%CI]	-2.1 [-2.5; -1.7] $P < .0001^{e}$	0.0 [-0.4; 0.3] $P = .9646^{e}$	$P < .0001^{c}$
Modified EREFS 'fibrotic signs' subscore (0-4)			
Baseline, Mean (SD)	1.0 (1.0)	1.4 (0.9)	
EoT, Mean (SD)	0.6 (0.7)	1.4 (1.0)	
Change from baseline to EoT in , Mean [95%CI]	-0.4 [-0.6; -0.2] $P = .0006^{e}$	-0.1 [-0.5; 0.4] $P = .8074^{e}$	$P = .2204^{c}$
Rate of patients with global assessment of endoscopic EoE activity of 'no signs of EoE' at EoT, n (%)	36 (61.0)	0 (0)	$P < .0001^{b}$
Histology			
Rate of patients with histological remission (i.e., peak eos <48 /mm^2 hpf; equivalent to <15 eos/hpf) at week 6, n (%)	56 (94.9)	0 (0)	$P < .0001^{b}$
Post-hoc analysis			
Rate of patients in deep histological remission defined as peak eos/mm^2 hpf of '0' in all biopsies at EoT, n (%)	53 (89.8)	0 (0)	$P < .0001^{b}$

[a] t-test (2-sided; test between groups), [b] Fisher's exact test (2-sided; test between groups), [c] Wilcoxon rank sum test (2-sided; test between groups), [d] One-sample t-test (2-sided, test within group), [e] Wilcoxon signed rank test (2-sided, test within group)

[i] One-sided p-value for effect between treatment groups from linear least squares model with treatment group and baseline value as covariate.

Abbreviations: BOT, budesonide orodispersible tablet; EEsAI-PRO, Eosinophilic Esophagitis Activity Index - Patient Reported Outcome; eos, eosinophils; EoT, end of treatment (=Week 6, last observation carried forward); EREFS, Endoscopic Reference Score; hpf, high power field; n, number; NRS, numerical rating scale; PatGA, Patient's Global Assessment; PGA, Physician's Global Assessment; SD, standard deviation

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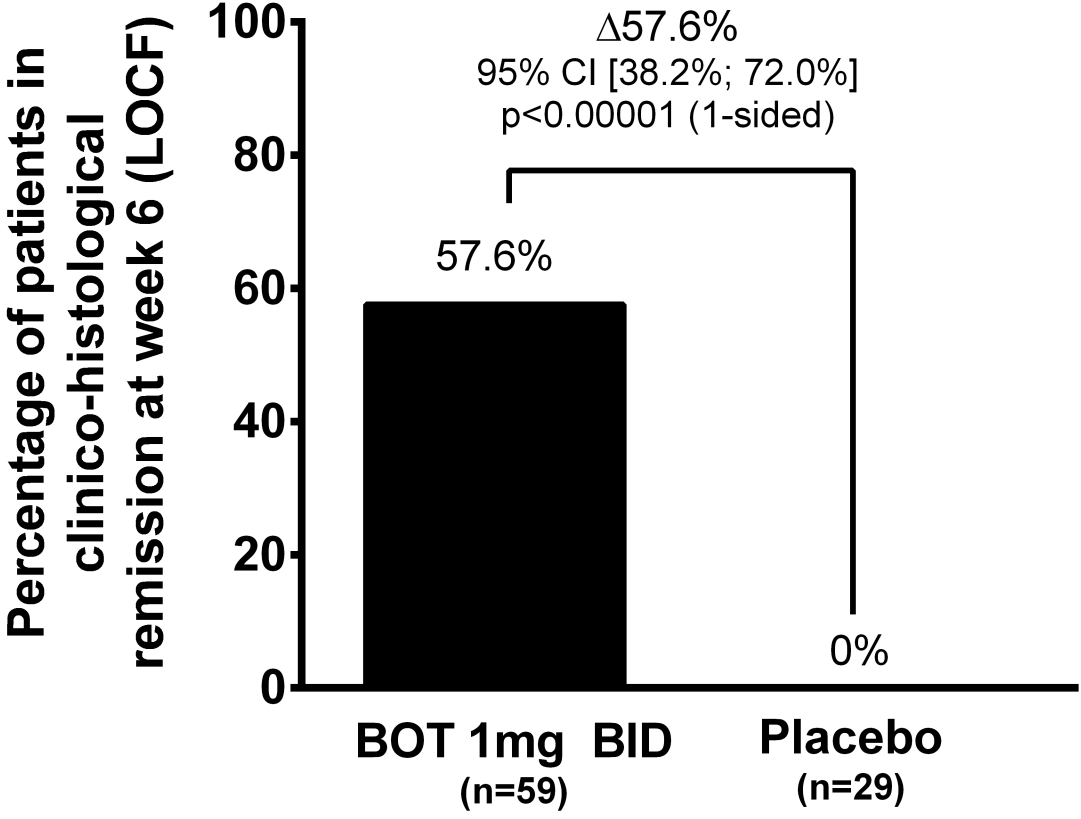
Table 3. Number (%) of Eosinophilic Esophagitis Patients Treated With Budesonide Orodispersible Tablets or Placebo in the Double-blind Phase and Experiencing Treatment-related Adverse Events

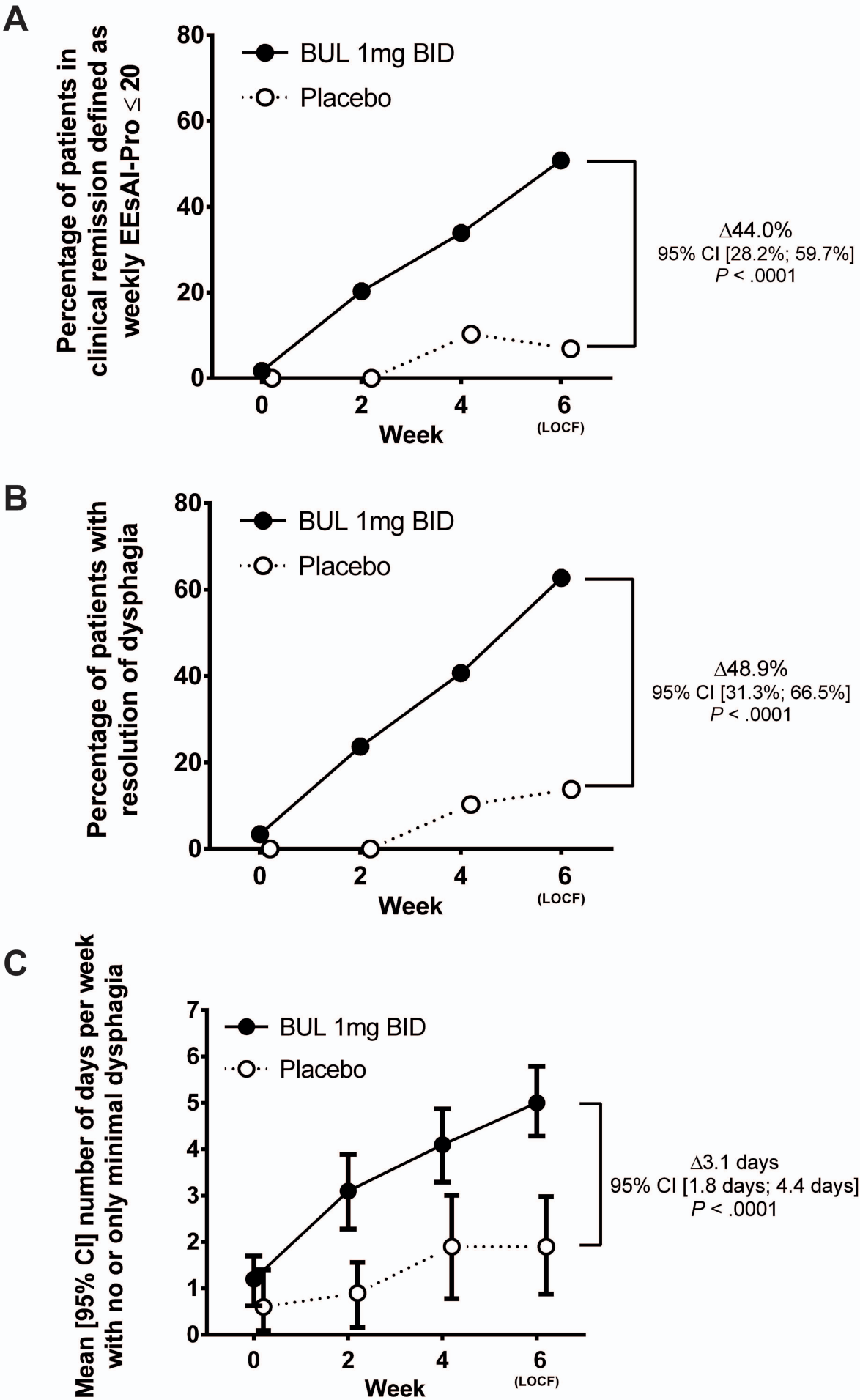
	BOT 1mg BID (n = 59)	**Placebo (n = 29)**
Any TEAE	37 (62.7)	12 (41.1)
Severe TEAE	0 (0)	1 (3.4)
Esophageal food impaction	0 (0)	1 (3.4)
TEAE related to study drug	23 (39.0)	1 (3.4)
Serious adverse events	0 (0)	0 (0)
TEAE leading to withdrawal from the study	0 (0)	1 (3.4)
Esophageal food impaction of severe intensity requiring endoscopic intervention	0 (0)	1 (3.4)
TEAEs by occurring in ≥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 [d] 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)

[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 <u>any</u> of the following criteria was fulfilled: suspected clinical symptoms, suspected endoscopic findings, suspected histological assessment in hematoxylin-eosin stained biopsies (even without any endoscopic signs or clinical symptoms).

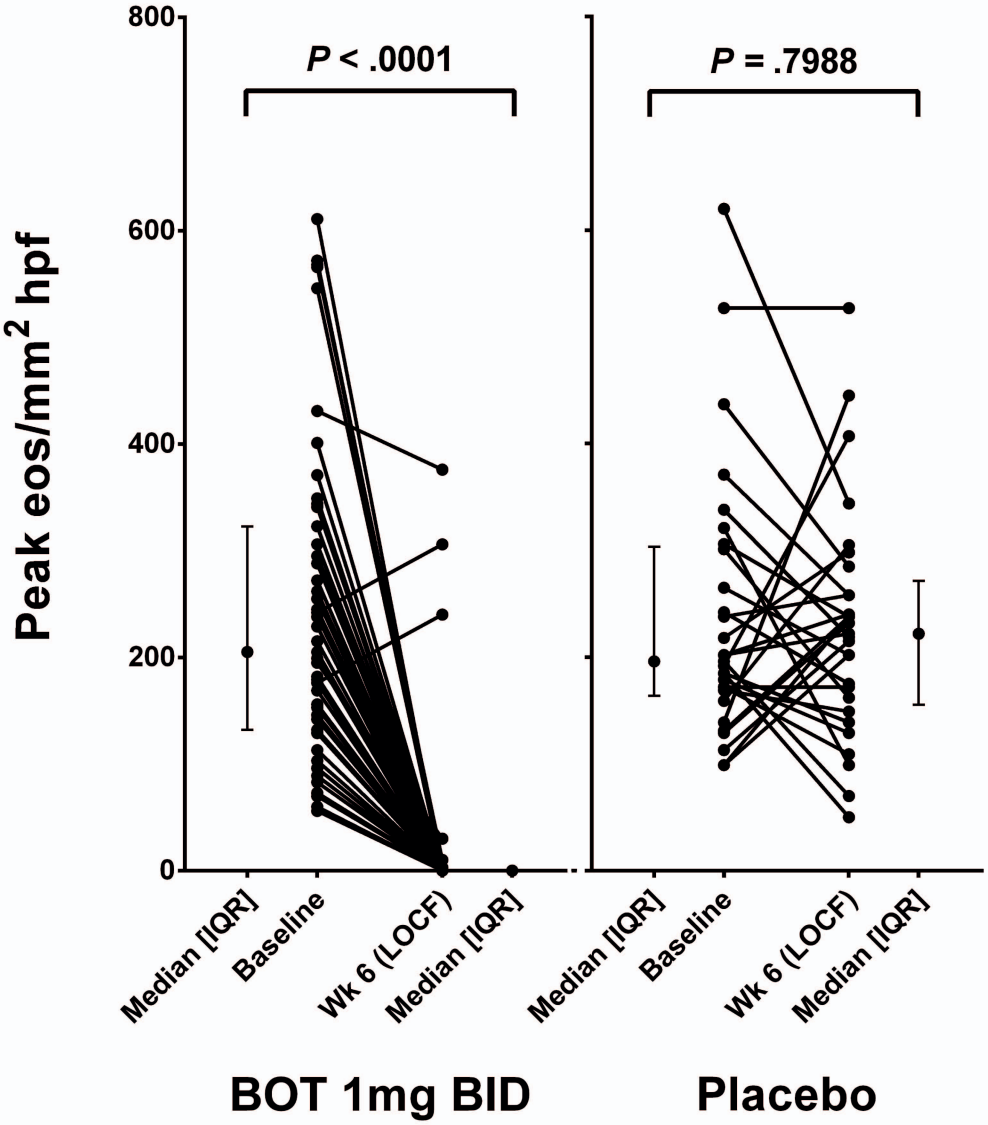
[b] Histologically confirmed by Grocott staining

Abbreviations: BID, twice daily; BOT, budesonide orodispersible tablet; TEAE, treatment-emergent adverse events

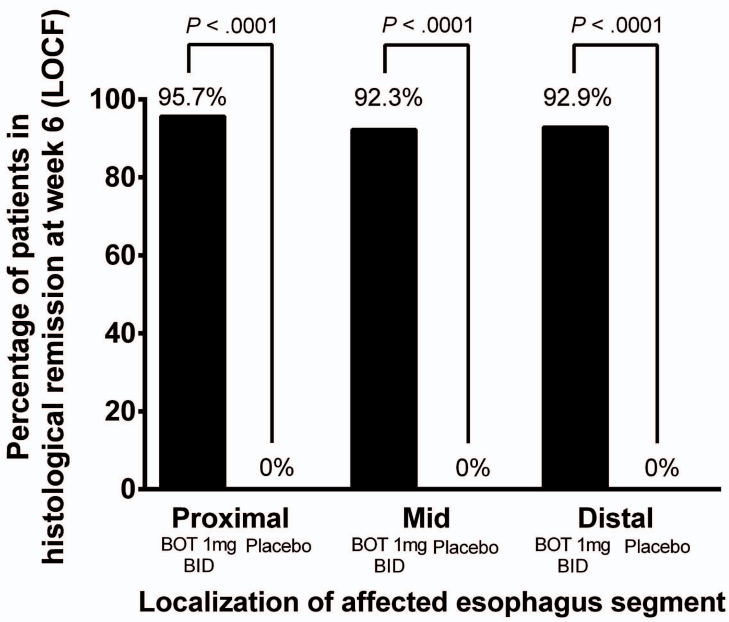

Percentage of patients in clinico-histological remission at week 6 (LOCF)
100
80
60
40
20
0
Δ57.6%
95% CI [38.2%; 72.0%]
p<0.00001 (1-sided)
57.6%
0%
BOT 1mg BID
(n=59)
Placebo
(n=29)


A
Percentage of patients in clinical remission defined as weekly EEsAI-Pro ≤ 20
BUL 1mg BID
Placebo
80
60
40
20
0
0
2
4
6
(LOCF)
Week
Δ44.0%
95% CI [28.2%; 59.7%]
P < .0001
B
Percentage of patients with resolution of dysphagia
BUL 1mg BID
Placebo
80
60
40
20
0
0
2
4
6
(LOCF)
Week
Δ48.9%
95% CI [31.3%; 66.5%]
P < .0001
C
Mean [95% CI] number of days per week with no or only minimal dysphagia
BUL 1mg BID
Placebo
7
6
5
4
3
2
1
0
0
2
4
6
(LOCF)
Week
Δ3.1 days
95% CI [1.8 days; 4.4 days]
P < .0001

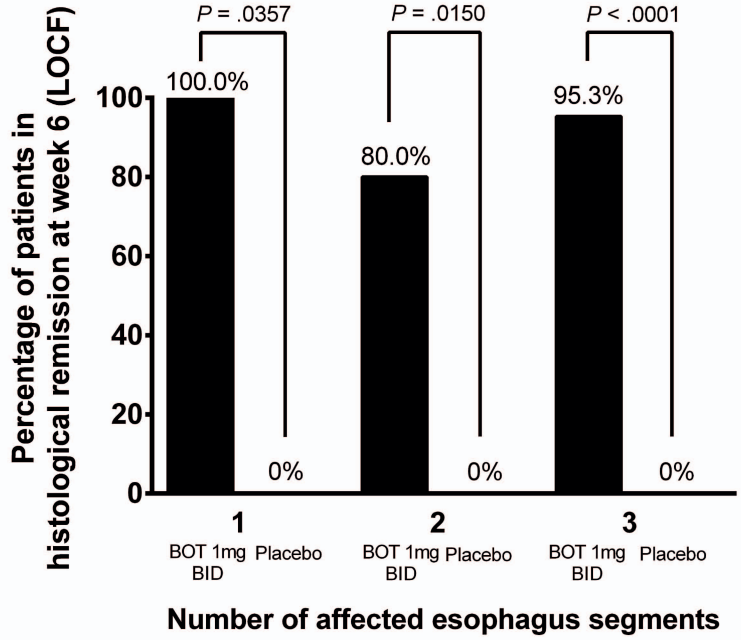
A


P < .0001
P = .7988
Peak eos/mm2 hpf
800
600
400
200
0
Median [IQR]
Baseline
Wk 6 (LOCF)
Median [IQR]
Median [IQR]
Baseline
Wk 6 (LOCF)
Median [IQR]
BOT 1mg BID
Placebo

B


P < .0001
P < .0001
P < .0001
95.7%
92.3%
92.9%
0%
0%
0%
Percentage of patients in histological remission at week 6 (LOCF)
100
80
60
40
20
0
Proximal
Mid
Distal
BOT 1mg BID
Placebo
Localization of affected esophagus segment

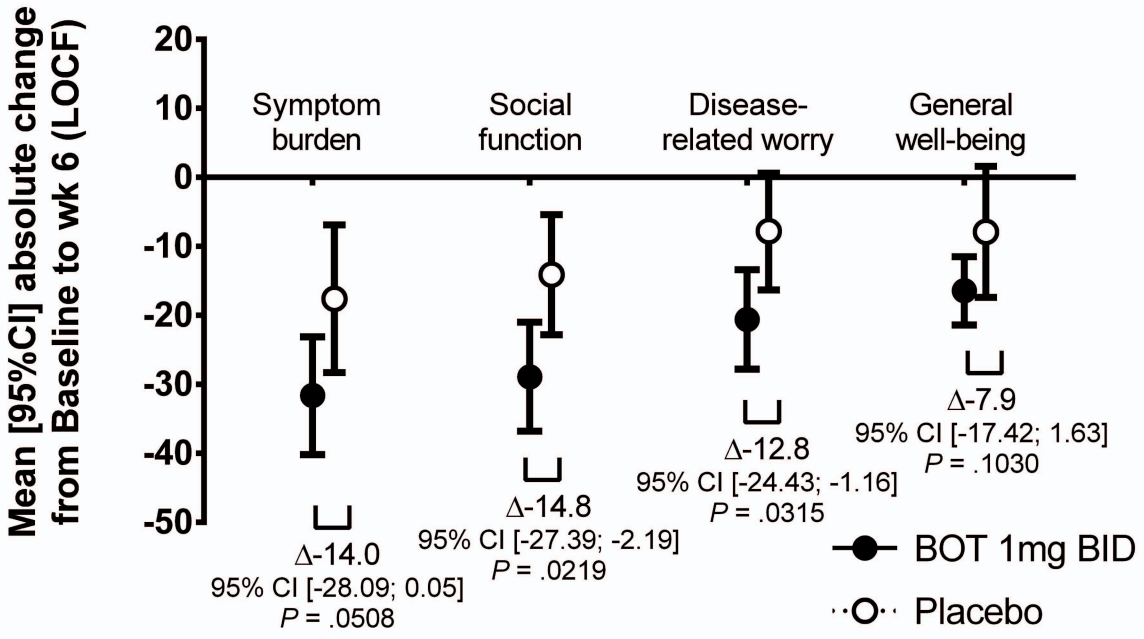
C

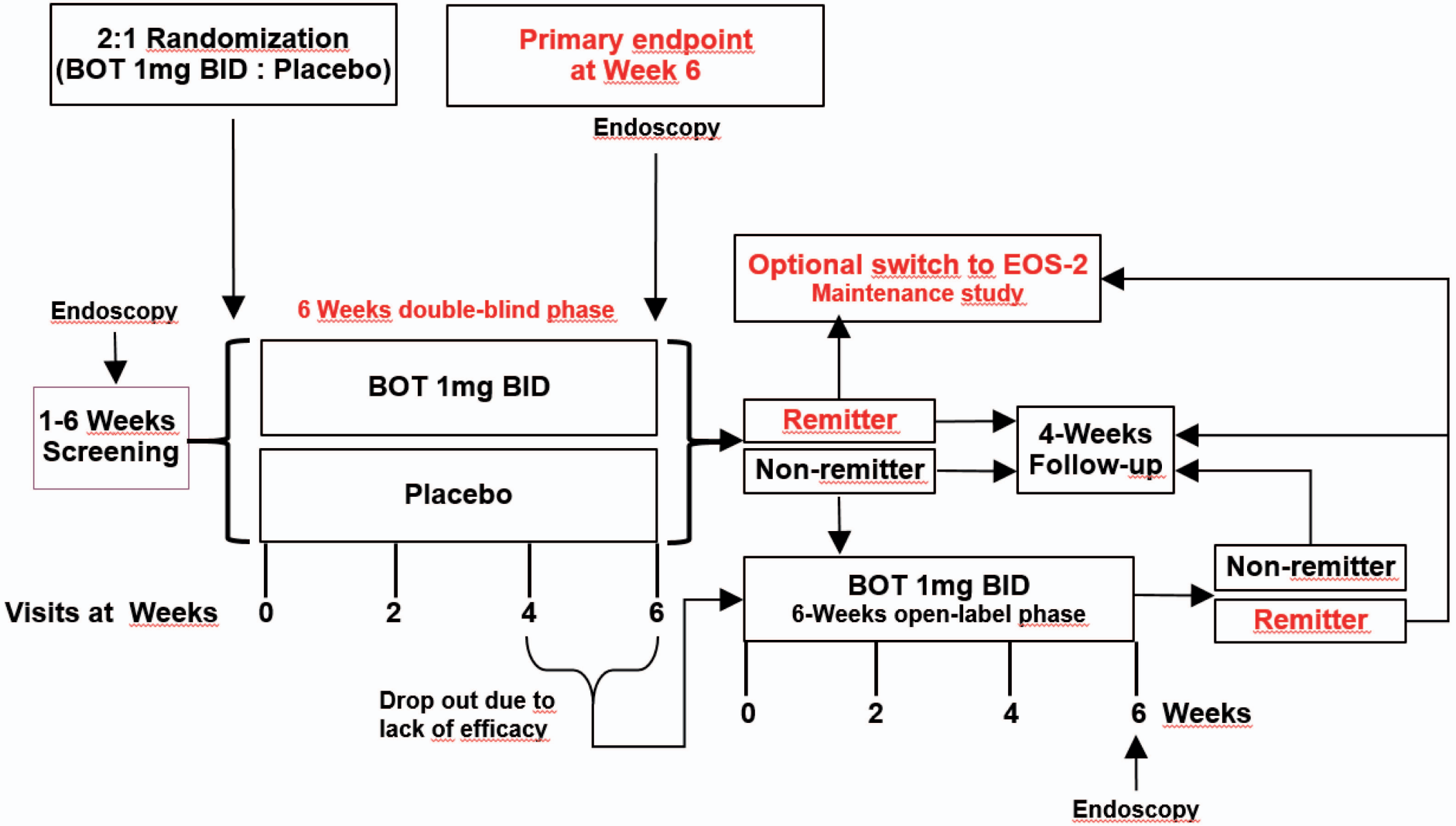

P = .0357
P = .0150
P < .0001
100.0%
80.0%
95.3%
0%
0%
0%
Percentage of patients in histological remission at week 6 (LOCF)
100
80
60
40
20
0
1
2
3
BOT 1mg BID
Placebo
Number of affected esophagus segments

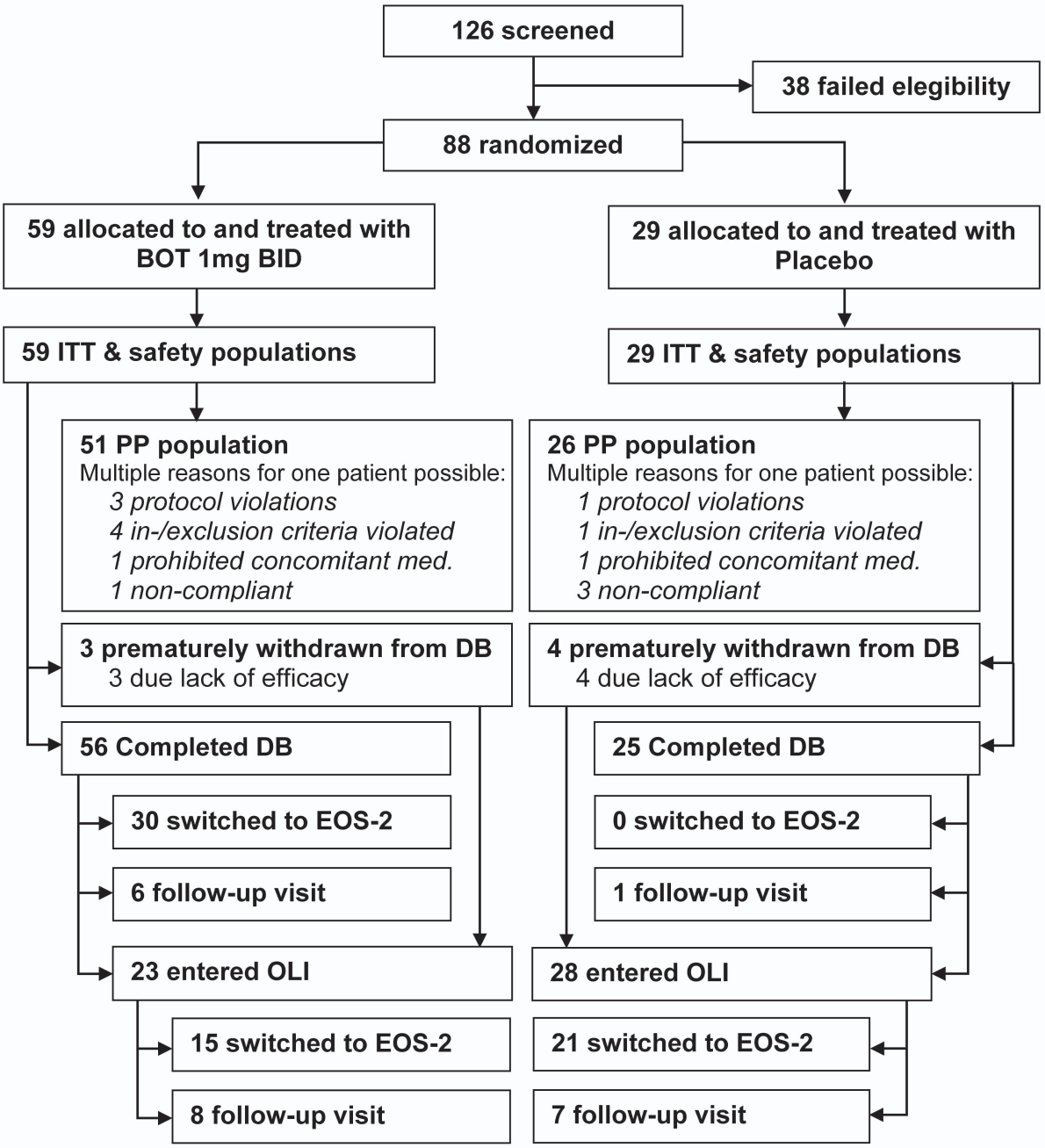
A

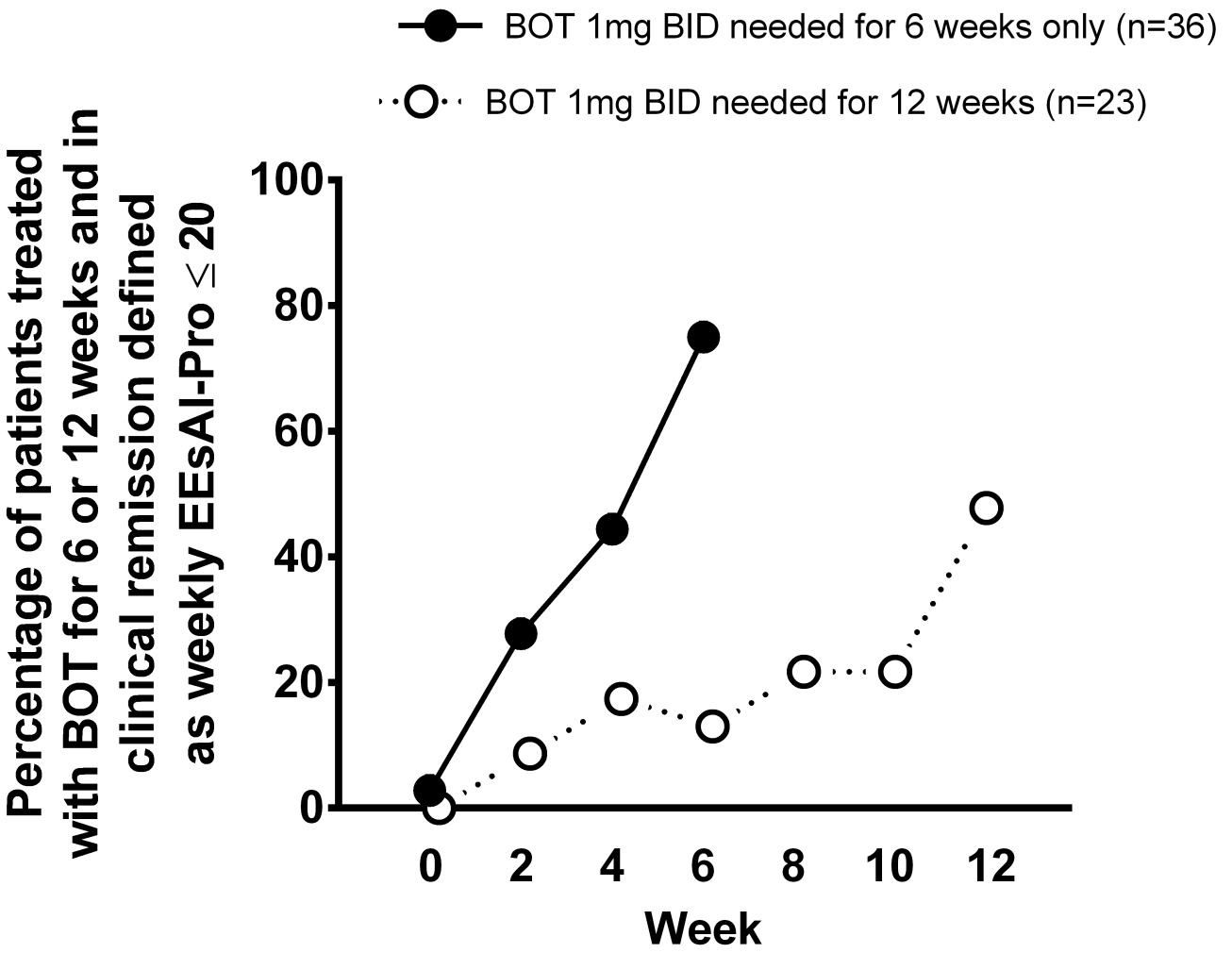
Dimension	BOT 1mg BID (n = 59)	Placebo (n = 29)
Symptom burden (0-100 VAS)		
Baseline, Mean (SD)	58 (23.5) [n=58]	55 (18.1)
Week 6 (LOCF), Mean (SD)	27 (27.1)	38 (25.1)
Change from baseline to Week 6 (LOCF), Mean [95%CI]	-32 [-40.2; -23.1]	-18 [-28.3; -6.9]
	P <.0001	*P* =.0022
Social function (0-100 VAS)		
Baseline, Mean (SD)	55 (29.0)	46 (24.3)
Week 6 (LOCF), Mean (SD)	26 (27.2)	32 (23.1)
Change from baseline to Week 6 (LOCF), Mean [95%CI]	-29 [-36.8; -21.0]	-14 [-22.8; -5.4]
	P <.0001	*P* =.0052
Disease-related worry (0-100 VAS)		
Baseline, Mean (SD)	57 (26.4)	52 (26.8)
Week 6 (LOCF), Mean (SD)	37 (29.6)	44 (28.6)
Change from baseline to Week 6 (LOCF), Mean [95%CI]	-21 [-27.8; -13.4]	-8 [-16.3; 0.6]
	P <.0001	*P* =.0673
General well-being (0-100 VAS)		
Baseline, Mean (SD)	40 (23.3)	35 (29.0)
Week 6 (LOCF), Mean (SD)	24 (22.9)	26 (24.3)
Change from baseline to Week 6 (LOCF), Mean [95%CI]	-16 [-21.4; -11.5]	-9 [-18.0; 0.9]
	P <.0001	*P* =.0751

B




2:1 Randomization
(BOT 1mg BID : Placebo)
Primary endpoint
at Week 6
Endoscopy
Endoscopy
6 Weeks double-blind phase
1-6 Weeks
Screening
BOT 1mg BID
Placebo
Optional switch to EOS-2
Maintenance study
Remitter
Non-remitter
4-Weeks
Follow-up
Visits at Weeks
0
2
4
6
Drop out due to
lack of efficacy
BOT 1mg BID
6-Weeks open-label phase
Non-remitter
Remitter
0
2
4
6 Weeks
Endoscopy


126 screened
38 failed elegibility
88 randomized
59 allocated to and treated with BOT 1mg BID
29 allocated to and treated with Placebo
59 ITT & safety populations
29 ITT & safety populations
51 PP population
Multiple reasons for one patient possible:
3 protocol violations
4 in-/exclusion criteria violated
1 prohibited concomitant med.
1 non-compliant
26 PP population
Multiple reasons for one patient possible:
1 protocol violations
1 in-/exclusion criteria violated
1 prohibited concomitant med.
3 non-compliant
3 prematurely withdrawn from DB
3 due lack of efficacy
4 prematurely withdrawn from DB
4 due lack of efficacy
56 Completed DB
25 Completed DB
30 switched to EOS-2
0 switched to EOS-2
6 follow-up visit
1 follow-up visit
23 entered OLI
28 entered OLI
15 switched to EOS-2
21 switched to EOS-2
8 follow-up visit
7 follow-up visit


BOT 1mg BID needed for 6 weeks only (n=36)
BOT 1mg BID needed for 12 weeks (n=23)
Percentage of patients treated with BOT for 6 or 12 weeks and in clinical remission defined as weekly EEsAI-Pro ≤ 20
100
80
60
40
20
0
0
2
4
6
8
10
12
Week

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Supplementary Material

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

Country	Principal Investigator and Co-Investigator(s)	Institution
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	Monther Bajbouj, Christoph Schlag, Simon Nennstiel	Klinikum Rechts der Isar, München
	Stefan Brückner, Renate Schmelz, Schmelz Heimerl, Anna-Magdalena Stephan	Universitätsklinikum Carl Gustav Carus TU Dresden, Dresden
	Christiane Fibbe, Niels Liedtke (née Laschinsky), Jutta Keller, Ulrich Rosien	Israelitisches Krankenhaus in Hamburg, Hamburg
	Sebastian Haag, Arne Schneider	Gastroenterologische Gemeinschaftspraxis, Wiesbaden
	Dirk Hartmann, Christoph Schmöcker, Hendrik Buchholz	Sana Klinikum Lichtenberg, Berlin
	Frank Lammert, Markus Casper, Matthias Reichert	Universitätsklinikum des Saarlandes, Homburg (Saar)
	Ahmed Madisch, Dirk Sommer	Klinikum Region Hannover GmbH, Klinikum Siloah, Hannover
	Hubert Mönnikes, Miriam Stengel, Marco Schmidtmann	Martin-Luther-Krankenhaus, Berlin
	Michaela Müller, Alexander Eckardt, Till Wehrmann	DKD HELIOS Klinik Wiesbaden GmbH, Wiesbaden
	Stefan Schubert, Peter Armerding, Wolf Peter Hofmann, Thomas Liceni	Praxis für Innere Medizin und Gastroenterologie, Berlin
	Ulrike von Arnim, Arne Kandulski, Jochen Weigt	Otto-von-Guericke-Universitäts Klinikum Magdeburg, Magdeburg
	Norbert Börner, Anne Lutz-Vorderbrügge	Gastroenterologische Gemeinschaftspraxis Mainz, Mainz
	Jörg Albert, Stefan Zeuzem, Irina Blumenstein, Kathrin Sprinzl, Johannes Hausmann	Klinikum der Johann Wolfgang Goethe-Universität, Frankfurt am Main
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Spain	**Alfredo Lucendo Villarin,** Ángel Arias Arias, Maria Ángeles Tejero Bustos, María Jesús Carrillo Ramos, José María Olalla Gallardo, Rocío Juárez Tosina	Hospital General de Tomelloso Tomelloso, Ciudad Real
	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
	Antonia Perelló Juan, Merce Barenys, Carlos Pons	Hospital de Viladecans, Barcelona
	Isabel Perez Martinez, M. Eugenia Lauret, Andrés Castaño García, Esmeralda Rubio	Hospital Universitario Central de Asturias, Oviedo
Switzerland	**Alex Straumann**	Praxis für Gastroenterologie, Olten
	Petr Hruz, Simon Brunner	University Hospital Basel, Basel
United Kingdom	**Jamal Hayat,** Andrew Poullis	St. George's Hospital, London

Note: Principal investigators are typed in bold letters

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Supplementary Figure Legends

Supplementary Figure 1. Study scheme

Abbreviations: BID, twice daily; BOT, budesonide orodispersible tablet; EOS-2, Phase 3 maintenance study (EudraCT No. 2014-001485-99) offered to be entered by patients achieving clinico-histological remission either at the end of the 6-weeks double-blind or 6-weeks open-label induction phase

Supplementary Figure 2. CONSORT (Consolidated Standards of Reporting Trials) diagram showing the patient flow in the study

Abbreviations: BID, twice daily; BOT, budesonide orodispersible tablet; DB, 6-week double-blind treatment phase; EOS-2, Phase 3 maintenance study (EudraCT No. 2014-001485-99) offered to be entered by patients achieving clinico-histological remission either at the end of the DB-or OLI-phase; ITT, intention-to-treat; OLI, 6-week open-label induction phase; PP, per-protocol

Supplementary Figure 3. Course of clinical remission in eosinophilic esophagitis patients treated with budesonide orodispersible tablets for only 6 weeks or in patients who required a 12-weeks treatment course.

Abbreviations: BID, twice daily; BOT, budesonide orodispersible tablet; EEsAI-PRO, Eosinophilic Esophagitis Activity Index - Patient Reported Outcome

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Supplementary Table 1. Study Endpoints

DOUBLE-BLIND PHASE

Primary efficacy variable

– Rate of patients with clinico-histological remission at week 6 (LOCF), i.e., achieving both, histological 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 prior to week 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 failure.

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 endpoints**

1. Rate of patients with histological remission (as defined in the primary endpoint) at week 6 (LOCF),
2. Change in the peak eos/mm^2 hpf from baseline to week 6 (LOCF)

   Note: hpf area of 0.345 mm^2
3. Rate of patients with clinical remission (as defined in the primary endpoint) on each day in the week prior to week 6 (LOCF)
4. Rate of patients in remission (total weekly EEsAI-PRO ≤20) at week 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
- Physician's Global Assessment (PGA) of EoE Activity (NRS 0-10)

  Note: score range 0-10: '0': no EoE activity, '10': most severe EoE activity
- Patient's Global Assessment (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 week 6 (LOCF)

  Note: score range 0-10: '0': no EoE activity, '10': most severe EoE activity
- Change from baseline to week 6 (LOCF) in blood eosinophil counts [eos/mm^3]

Endoscopy

- Change from baseline to week 6 (LOCF) in total modified EREFS endoscopic score

  Note: score range 0-9: '0': no endoscopic EoE activity, '10': most severe endoscopic EoE activity
- Change from baseline to week 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 week 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 week 6 (LOCF)

Histology

- Rate of patients with histological remission (i.e., peak eos <48 /mm^2 hpf; equivalent to <15 eos/hpf) at week 6 (LOCF), n (%)

Health-related Quality of Life

- 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 histological remission at week 6 defined as peak eos/mm^2 hpf of '0' in all biopsies

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-histological remission (as defined in the primary endpoint) at EoT OLI phase
  Note: for definitions see DB primary endpoint
- Rate of patients with clinical remission (as defined in the primary endpoint) at EoT OLI phase
  Note: for definitions see DB primary endpoint
- Rate of patients in remission (total weekly EEsAI-PRO ≤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 ≤2 on each day in the week prior to 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 Physician's Global Assessment of EoE Activity (NRS 0-10)
- Change from EoT DB phase to EoT OLI phase in Patient's Global Assessment 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 histological remission (as defined in the primary endpoint) at EoT OLI phase
- Rate of patients with histological remission (i.e., 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

Health-related Quality of Life

- 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

Abbreviations: BID, twice daily; BOT, budesonide orodispersible tablet; CI, confidence interval; 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 (400x); EoT, end of treatment (week 6 [LOCF]); EREFS,

Endoscopic Reference Score; HRQoL, health-related quality of life; LOCF, last observation carried forward; NRS, numerical rating scale; OLI, open-label induction; PatGA, patient‘s global assessment; PGA, Physician’s global assessment; SD, standard deviation; SHS, short health scale

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Supplementary Table 2. Protocol Pre-specified Subgroup Analyses of the Primary Study Endpoint in Eosinophilic Esophagitis Patients Treated With Budesonide Orodispersible Tablets or Placebo in the Double-blind Phase

Characteristic	Number (%) of patients in clinico-pathological remission at week 6 (LOCF) stratified by protocol pre-specified criteria	
	BOT 1mg BID (n = 59)	Placebo (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: Number 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 double-blind 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)

Abbreviations: BID, twice daily; BOT, budesonide orodispersible tablet; EoE, eosinophilic esophagitis; hpf; high power field; LOCF, last observation carried forward; PatGA, patient‘s global assessment; PPI, proton-pump inhibitor

Supplementary Table 3. Exploratory Secondary Clinical, Histological and Endoscopic Efficacy Endpoints of Eosinophilic Esophagitis Patients Treated With BOT 1mg BID in the Optional 6-Weeks Open-label Phase

Endpoints	BOT→BOT [a] (n=23)	Placebo→BOT [b] (n=28)
General		
Rate of patients with clinico-histological remission (as defined in the primary endpoint) at EoT OLI phase, n (%)	16 (69.6)	22 (78.6)
Histology		
Rate of patients with histological remission (i.e., 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 histological remission (i.e., 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; 15]	-206 [-247; -165]*
Clinic		
Rate of patients with clinical remission (as defined in the primary endpoint) 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; -10.9]*	-23.6 [-30.4; -16.9]*
Rate of patients with no or only minimal problems defined as 0-10 NRS Dysphagia ≤2 on each day in the week prior to:		
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; -10.6]*	-16.1 [-20.7; -11.6]*
Physician's Global Assessment 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; -2.2]*	-4.1 [-5.0; -3.2]*
Patient's Global Assessment 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; -1.7]*	-2.7 [-3.6; -1.8]*
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; 89]]	-211 [-287; -135]*
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; -0.7]*	-3.4 [-4.2; -2.6]*
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)

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Change from EoT DB phase to EoT OLI phase; Mean [95%CI]	-0.6 [-1.2; -0.1]*	-2.4 [-3.0; -1.9]*
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; -0.2]*	-0.9 [-1.2; -0.5]*
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)

*indicating significant changes from EoT DB phase to EoT OLI, as '0' was excluded from the 95% CI

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

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

Abbreviations: BID, twice daily; BOT, budesonide orodispersible tablet; CI, confidence interval; DB, double-blind; EEsAI-PRO, Eosinophilic Esophagitis Activity Index - Patient Reported Outcome; eos; eosinophils; EoT, end of treatment (Week 6 [LOCF]); EREFS, Endoscopic Reference Score; hpf, high power field; LOCF, last observation carried forward; n, number; NRS, numerical rating scale; OLI, open-label induction; SD, standard deviation

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Supplementary Table 4. Course and Absolute Changes from Baseline to Week 6 (LOCF) 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 1mg BID (n = 59)	Placebo (n = 29)	Mean Difference [95% CI] BOT-Placebo
Total:			
Baseline, Mean (SD)	242 (141), n=59	239 (125), n=29	
EoT, Mean (SD)	16 (69), n=59	224 (95), n=28	
Mean [95%CI] change from baseline to EoT	-226 [-265; -186]	-4 [-56; 47]	-221 [-287; -156]
	$P < .0001$[a]	$P = .7988$[a]	$P < .0001$[b]
Proximal esophagus:			
Baseline, Mean (SD)	125 (138), n=59	185 (143), n=29	
EoT, Mean (SD)	5 (26), n=59	137 (107), n=28	
Mean [95%CI] change from baseline to EoT	-120 [-157; -83]	-38 [-98; 21]	-82 [-148; -15]
	$P < .0001$[a]	$P = .2463$[a]	$P = .0171$[b]
Mid esophagus:			
Baseline, Mean (SD)	148 (117), n=59	178 (141), n=29	
EoT, Mean (SD)	10 (49), n=59	168 (97), n=28	
Mean [95%CI] change from baseline to EoT	-138 [-171; -105]	1 [-61; 63]	-139 [-202; -77]
	$P < .0001$[a]	$P = .9470$[a]	$P < .0001$[b]
Distal esophagus:			
Baseline, Mean (SD)	200 (145), n=59	159 (120), n=29	
EoT, Mean (SD)	16 (69), n=59	182 (105), n=28	
Mean [95%CI] change from baseline to EoT	-184 [-223; -145]	36 [-19; 91]	-219 [-286; -153]
	$P < .0001$[a]	$P = .1800$[a]	$P < .0001$[b]

[a] Wilcoxon signed rank test (2-sided, test within group); [b] Wilcoxon rank sum test (2-sided, test between groups)

Abbreviations: BID, twice daily; BOT, budesonide orodispersible tablet; CI, confidence interval; EoT, end of treatment (=Week 6, last observation carried forward); hpf, high power field; n, number; SD, standard deviation

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Supplementary Table 5. Course and Absolute Changes from Baseline to Week 6 (LOCF) of Individual Subscores of the modified EREFS Endoscopic Score in Eosinophilic Esophagitis Patients Treated With Budesonide Orodispersible Tablets or Placebo in the Double-blind Phase

EREFS Subscores	BOT 1mg BID (n = 59)	Placebo (n = 29)	Difference [95% CI] BOT-Placebo in Mean
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; -0.46] *P* < .0001	0.0 [-0.20; 0.13] *P* = 1.0000	-0.6 [-0.79; -0.33] *P* < .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; -0.64] *P* < .0001	0.0 [-0.28; 0.28] *P* =1.0000	-0.8 [-1.20; -0.49] *P* < .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; -0.50] *P* < .0001	0.0 [---]	-0.6 [-0.83; -0.44] *P* < .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; -0.09] *P* = .0061	-0.1 [-0.45; 0.23] *P* = .6509	-0.2 [-0.59; 0.19] *P* = .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; -0.02] *P* = .0313	0.0 [-0.16; 0.23] *P* = 1.0000	-0.1 [-0.31; 0.04] *P* = .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; -0.01] *P* = .0703	0.0 [-0.15; 0.15] *P* = 1.0000	-0.1[-0.27; 0.07] *P* = .2394

All intra- group comparisons were performed using exploratory two-sided Wilcoxon signed-rank test. All intergroup comparisons were performed using exploratory two-sided Wilcoxon rank sum test.

Abbreviations: BID, twice daily; BOT, budesonide orodispersible tablet; CI, confidence interval; EREFS, Endoscopic Reference Score; EoT, end of treatment (Week 6 [LOCF]); LOCF, last observation carried forward; n, number; SD, standard deviation

Supplementary Table 6. Course and Absolute Changes from Baseline to Week 6 (LOCF) of the Total EoE-QoL-A 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 1mg BID (n = 59)	Placebo (n = 29)	Mean [95% CI] difference BOT-Placebo
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; 0.62]	0.2 [0.06; 0.42]	0.23 [-0.010; 0.472]
	P < .0001	*P* = .0115	*P* = .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; 0.63]	0.2 [0.07; 0.42]	0.24 [-0.004; 0.476]
	P < .0001	*P* = .0093	*P* = .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; 0.88]	0.2 [-0.08; 0.38]	0.50 [0.174; 0.817]
	P < .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; 0.92]	0.2 [-0-04; 0.44]	0.49 [0.131; 0.858]
	P < .0001	*P* = .1039	*P* = .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; 0.65]	0.3 [0.02; 0.58]	0.16 [-0.172; 0.490]
	P < .0001	*P* = .0364	*P* = .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; 0.60]	0.2 [0.04; 0.43]	0.20 [-0.055; 0.459]
	P < .0001	*P* = .0186	*P* = .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; 0.45]	0.2 [-0.04; 0.34]	0.16 [-0.077; 0.395]
	P < .0001	*P* = .1078	*P* = .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; 0.80]	0.4 [0.13; 0.68]	0.19 [-0.150; 0.539]
	P < .0001	*P* = .0055	*P* = .2656

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All intra- and intergroup comparisons were performed using two-sided one-sample t-test and two-sided t-test, respectively.

Abbreviations: BID, twice daily; BOT, budesonide orodispersible tablet; CI, confidence interval; EoE-QoL-A, eosinophilic esophagitis quality of life scale for adults; EoT, end of treatment (Week 6 [LOCF]); HRQoL, health-related quality of life; LOCF, last observation carried forward; SD, standard deviation

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Supplementary Table 7. Exploratory Quality of Life Endpoints of Eosinophilic Esophagitis Patients Treated With BOT 1mg BID in the Optional 6-Weeks Open-label Phase

Endpoints	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; -14.8]*	-24 [-32.6; -14.5]*
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; -14.5]*	-18 [-26.7; -9.3]*
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; -3.9]*	-14 [-22.9; -5.0]*
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; -8.4]*	-13 [-21.6; -4.3]*
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; 0.327]*	0.29 [0.072; 0.512]*
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; 0.324]*	0.28 [0.061; 0.505]*
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; 0.580]*	0.49 [0.217; 0.754]*
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; 0.626]*	0.46 [0.164; 0.747]*
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; 0.299]	0.45 [0.073; 0.820]*
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; 0.318]	0.22 [-0.004; 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; 0.368]	0.16 [-0.080; 0.397]
EoE-QoL-A swallowing anxiety (weighted average)		
EoT DB phase, Mean (SD)	1.9 (1.1)	2.7 (0.9)

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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; 0.338]	0.20 [-0.029; 0.434]

*indicating significant changes from EoT DB phase to EoT OLI, as '0' was excluded from the 95% CI

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

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

Abbreviations: BID, twice daily; BOT, budesonide orodispersible tablet; CI, confidence interval; DB, double-blind; EoE-QoL-A, eosinophilic esophagitis quality of life scale for adults; EoT, end of treatment (Week 6 [LOCF]); HRQoL, health-related quality of life; LOCF, last observation carried forward; OLI, open-label induction; SD, standard deviation; SHS, short health scales

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Supplementary Table 8. **Mean Serum Morning (8:00-09:00 a.m) Cortisol Levels [µg/dL] and Change from Baseline in Eosinophilic Esophagitis Patients Treated with Budesonide Orodispersible Tablets or Placebo in the Double-blind Phase, the Optional 6-Weeks Open-label Phase, and the Follow-up Phase (if not switched to study BUL-2 after DB/EoT or OLI/EoT**

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

*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.

Abbreviations: BID, twice daily; BOT, budesonide orodispersible tablet; CI, confidence interval; DB, double-blind; EoT, end of treatment (week 6, last observation carried forward); FU, follow-up; OLI, open-label induction; SD, standard deviation

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

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

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

	Baseline DB	EoT DB	EoT OLI	Follow-up
BOT 1mg 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]	---

[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.

Abbreviations: BID, twice daily; BOT, budesonide orodispersible tablet; DB, double-blind; EoT, end of treatment (week 6, last observation carried forward); FU, follow-up; OLI, open-label induction

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Supplementary Table 10. Number (%) of Eosinophilic Esophagitis Patients Treated With BOT 1mg BID in the Optional 6-Weeks Open-label Phase and Experiencing Treatment-related Adverse Events

	BOT→BOT[a] (n=23)	Placebo→BOT[b] (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)

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

[b] Placebo→BOT: Patients who received placebo and who were not in clinico-histological remission at the end of the 6-week DB phase continued with a 6-week open-label treatment with BOT 1mg 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 histological assessment in hematoxylin-eosin stained biopsies (even without any endoscopic signs or clinical symptoms).

[d] Histologically confirmed by Grocott staining

Abbreviations: BID, twice daily; BOT, budesonide orodispersible tablet; TEAE, treatment-emergent adverse events

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

Previously reported efficacy	BOT 1mg BID (n = 59)	Placebo (n = 29)
PPI, n (%)	**32 (54) ***	**13 (45) ***
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, n (%)	**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, n (%)	**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, n (%)	**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, n (%)	**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)

*All patients failed PPI trial (either in their history or during the screening phase

Abbreviations: BID, twice daily; BOT, budesonide orodispersible tablet; n, valid numbers; PPI, proton pump inhibitor

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