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ESOPHAGUS

Efficacy and Safety of Budesonide Orodispersible Tablets for Eosinophilic Esophagitis up to 3 Years: An Open-Label Extension Study

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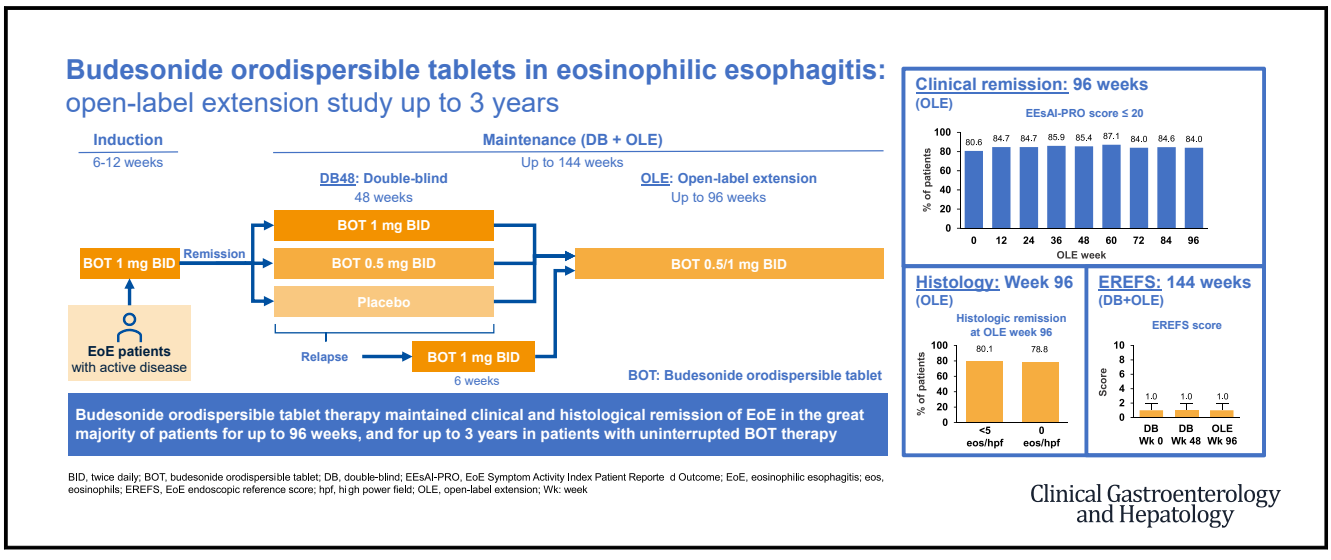

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Abbreviations used in this paper: ADR, adverse drug reaction; AE, adverse event; BOT, budesonide orodispersible tablet; DB48, 48-week double-blind study of EOS-2 trial; EEsAI-PRO, Eosinophilic Esophagitis Activity Index Patient Reported Outcome; EoE, eosinophilic esophagitis; EoE-QoL-A, Eosinophilic Esophagitis Quality of Life in Adults; eos, eosinophils; EREFS, Endoscopic Reference Score; hpf, high-power field; MedDRA, Medical Dictionary for Regulatory Activities; NRI, non-responder imputation; NRS, Numerical Rating Scale; OCs, observed cases; OLE, open-label extension; OLRI, open-label re-induction; QoL, quality of life; SAE, serious adverse event; STC, swallowed topical corticosteroids; TEAE, treatment-emergent adverse event.

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BACKGROUND & AIMS: **Budesonide orodispersible tablets (BOT) have been shown to be safe and effective in phase III double-blind trials of induction and 48-week maintenance therapy of eosinophilic esophagitis (EoE). We now analyzed the long-term efficacy and safety of BOT in a 96-week open-label extension (OLE) study.**

METHODS: **All patients with EoE in the 48-week double-blind maintenance study were eligible to receive BOT treatment for up to 96 weeks. Dosage was 0.5 or 1.0 mg BOT, twice daily, at investigator's discretion. Clinical, histologic, endoscopic, quality of life, and safety measures were assessed.**

RESULTS: **A total of 186 patients participated in the OLE up to 96 weeks. At week 96, 81.9% of patients had clinical remission, defined as an EoE Symptom Activity Index (EEsAI) score of ≤20 vs 77.7% at OLE baseline. A further 80.1% of patients were in histologic remission, defined as peak eosinophils per high-power field of <5, at week 96 vs 91.8% at OLE baseline. Mean EoE endoscopic reference scores (EREFS) were 1 at all time points measured. Mean EoE Quality of Life (EoE-QoL-A) Scale scores improved from 3.3 at OLE baseline to 3.5 at week 96. No new safety concerns were observed across 96 weeks of treatment. Suspected symptomatic candidiasis occurred at similar rates to prior BOT studies and was predominantly mild and resolved with treatment.**

CONCLUSIONS: **Clinical and histologic remission of EoE could be maintained with BOT in a large majority of patients for up to 96 weeks, and for up to 144 weeks in patients with uninterrupted BOT therapy across all trials. No additional safety concerns were identified with long-term BOT treatment (ClinicalTrials.gov, Number: NCT02493335).**

Keywords: Eosinophilic Esophagitis; Maintenance Therapy; Remission; Safety; Topical Corticosteroid.

See editorial on page 2086.

Eosinophilic esophagitis (EoE) is a chronic, immune-mediated, inflammatory disease characterized by eosinophil-predominant inflammation and esophageal dysfunction. Although proton pump inhibitors and swallowed topical corticosteroids (STC) were once the primary, albeit off-label, medical treatment options for EoE,[1,2] esophageal-specific formulations of budesonide[3–5] and a monoclonal antibody targeting interleukin-4/-13 receptor α[6] have recently been approved in multiple countries.

Although EoE is a chronic condition, published data on the long-term effectiveness past 1 year remains limited, and questions have been raised regarding the long-term efficacy of some recently approved treatments.[7–10] Although many patients relapse within months after discontinuation of effective therapy,[4,11,12] most trials to date have been limited to 1 year of treatment or less.[4,12,13] Loss of efficacy has also been reported during long-term treatment with off-label topical corticosteroids,[14] and concerns exist over the safety of long-term corticosteroid use in EoE treatment.[15] Data on the long-term use of effective medical therapeutics in EoE is thus urgently needed.

Budesonide orodispersible tablet (BOT) is a novel topical corticosteroid formulation approved for adults with EoE in numerous countries. BOT utilizes effervescence to stimulate saliva production, while also utilizing the adhesive properties of mucin in saliva to coat the esophageal mucosa with active substance.[16,17] In a phase III, double-blind trial of 6-week induction therapy (EOS-1), BOT led to clinicohistologic remission in 57.6% of adult patients with EoE vs 0% in patients receiving placebo.[3] In a subsequent trial of maintenance therapy (EOS-2), up to 75.0% maintained clinicohistologic remission for 48 weeks with BOT compared with 4.4% receiving placebo.[4]

Here, we report on an open-label, long-term extension of up to 96 weeks to the double-blind 48-week study in the EOS-2 trial on maintenance therapy of EoE with BOT.

Patients and Methods

Study Design, Patients, and Treatments

This study was an optional open-label extension (OLE) to a randomized, double-blind, placebo-controlled, 48-week maintenance study (hereinafter termed "DB48")[4] within the phase III EOS-2 trial on BOTs (Jorveza, Dr Falk Pharma GmbH) for EoE in adults responding to 6- to 12-week prior BOT induction therapy.[3,18] All patients in the DB48 study were eligible for the optional OLE study (Figure 1). Details on inclusion and exclusion criteria as well as concomitant medications in the DB48 study have been previously reported.[4] The OLE study was conducted from August 2016 to November 2020. Patients with clinical and/or histologic relapse during the DB48 study were offered optional 6-week open-label reinduction (OLRI) therapy with 1 mg BOT twice daily before entering the OLE (Figure 1).

The duration of the OLE study was originally limited to 48 weeks. This was extended by a further optional 48 weeks to up to 96 weeks total by a protocol amendment enacted approximately 14 months after enrollment of the first patient into the OLE. This extension was implemented in response to requests by participating physicians and patients. For administrative and logistical reasons, the study was still conducted and presented to patients as an initial 48-week OLE phase followed by a second 48-week OLE phase.

Dosage was either 1 × or 2 × 0.5 mg BOT, twice daily, at investigators' discretion. Guidance was given to prescribe the lower dose whenever clinically feasible. As the intentions and reasons for dose changes and to patients were not systematically recorded, treatment adherence could not be meaningfully analyzed. BOT was administered as previously described.[4]

This study was conducted in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. The study protocol was approved by the Institutional Review Board or independent ethics committee at each participating center. All patients provided written informed consent. All authors had access to the study data and reviewed and approved the final manuscript.

What You Need to Know

Background

Budesonide orodispersible tablet (BOT) has been shown to be effective in eosinophilic esophagitis (EoE) for up to 1 year. This study investigates BOT in EoE for up to 3 years.

Findings

In this single-arm, open-label extension study, clinical, histologic, and endoscopic remission were maintained in the vast majority of patients for up to 3 years. Long-term BOT therapy was well-tolerated.

Implications for patient care

Long-term BOT therapy safely and effectively maintains clinical, histologic, and endoscopic remission of EoE. Durable symptom control also leads to continuous improvements in patients' quality of life.

Assessments and Measurements

Clinical, histologic, and endoscopic assessments and measures were performed as in the DB48 study.[4] See Supplementary Information for details. Safety analyses included recording of adverse events (AEs), treatment-emergent AEs (TEAEs), adverse drug reactions (ADRs), and serious adverse events (SAEs). All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Clinical and quality of life (QoL) outcomes were recorded at visits every 12 weeks, whereas safety was recorded at these visits and during phone calls every 4 weeks between these visits. Endoscopy with biopsy collection was performed at the concurrent DB48 end of treatment/OLE baseline visit (except for OLRI participants, who did not undergo additional endoscopy after the OLRI) and optionally at OLE weeks 48 and 96. Morning (8 a.m. to 9 a.m.) serum cortisol levels were measured at OLE baseline and at OLE weeks 48 and 96, whereas eye examinations were performed every 24 weeks.

Statistical Analyses

Safety analyses were performed using all subjects who entered the OLE study. Primary efficacy analyses for all 96 weeks were performed using all subjects who entered the second 48-week phase, whereas a confirmatory analysis for the first 48 weeks was performed using all subjects. No formal hypothesis testing was performed. Efficacy and safety outcomes were summarized using descriptive statistics. Clinical and QoL outcomes were evaluated by observed cases (OCs) and non-responder imputation (NRI) analyses, whereas endoscopic and histologic assessments were performed

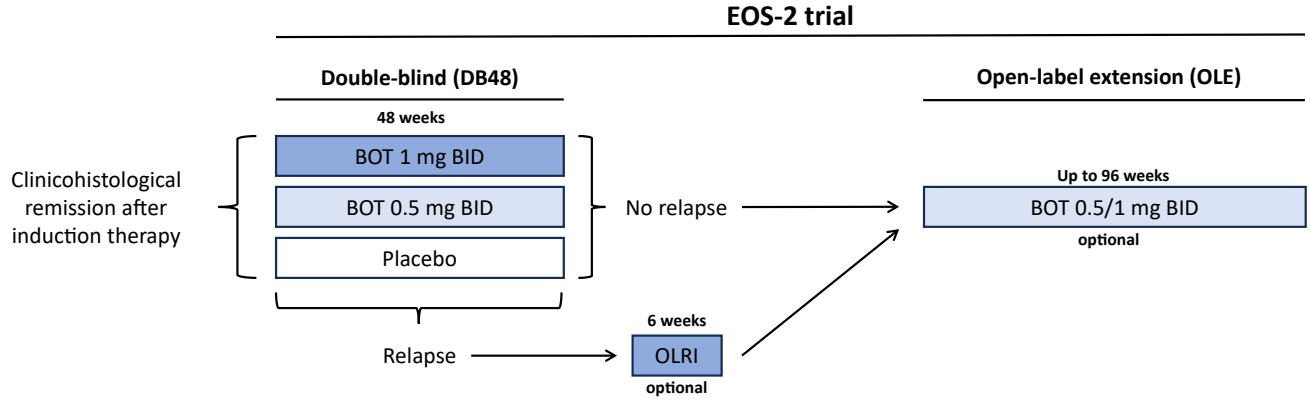

Figure 1. Design of EOS-2 trial including DB48, OLRI, and OLE studies.

using OC analyses, as endoscopy was optional at end of treatment. OLE baseline was defined as the last assessment of the DB48 study, or the last assessment of the OLRI study for OLRI patients.

Results

Patient Disposition and Baseline Characteristics

Among the 204 patients in the 48-week, double-blind BOT maintenance study (DB48), 186 elected to enter the OLE (Supplementary Figure 1): 100 patients entered directly from the BOT arms (0.5 mg or 1 mg, twice daily) and 5 directly from the placebo arm, whereas 81 patients from all 3 DB48 arms underwent OLRI before entering the OLE study (see Supplementary Information and Supplementary Tables 1 and 2 for a description and results of the OLRI study). Three OLE patients completed week 48 prior to the amendment extending the OLE study to 96 weeks, whereas an additional 7 patients who enrolled after the amendment declined the option to continue up to 96 weeks after the initial 48 weeks. Of the 186 patients in the total population, 166 continued into the second 48-week phase and comprised the efficacy population. Three participants discontinued at the OLE week 96 visit (one due to an AE), and thus after completion of the final treatment assessment. There were no documented cases of Covid-19 among trial participants. The pandemic had no effect on efficacy or safety results, aside from several cases in which treatment was extended due to postponed visits.

The demographics of the total OLE population were generally equivalent to those in the preceding DB48 study (Table 1). The mean (± standard deviation) Eosinophilic Esophagitis Activity Index Patient Reported Outcome (EEsAI-PRO) score at OLE baseline was 9 ± 13.5, and 75.8% of patients were in clinical remission. Among patients with an endoscopy at OLE baseline, mean peak eos counts were 13 ± 54.5 eos/mm^2 hpf; 93.3% of patients were in histologic remission and 87.6% in deep histologic remission. Mean total modified Endoscopic Reference Score (EREFS) scores were 1 ± 0.9, and 64.7% had a total EREFS score of 0. Disease parameters at OLE baseline were generally equivalent between prior treatment groups (DB48 BOT vs DB48 placebo vs OLRI), with the exception of peak eos counts (5 ± 30.5 [n = 100] for DB48 BOT vs 177 ± 138.2 [n = 5] for DB48 placebo, not determined for OLRI patients). The baseline characteristics of the efficacy population were generally comparable to the total population.

Across the entire OLE study, 131 patients (70.4%) received a uniform dosage of 0.5 mg BOT twice daily, whereas 13 (7.0%) received solely 1.0 mg BOT twice

Table 1. Baseline Demographic and Clinical Characteristics in the BOT OLE Study

	Total population N = 186	Efficacy population n = 166
Age, *years*	36.7 ± 10.6	36.9 ± 10.7
Male sex	154 (82.8)	141 (84.9)
Concomitant treatment with PPI	48 (25.8)	56 (33.7)
Daily dysphagia NRS last 7 days	1 ± 0.8 (184)	0 ± 0.7 (165)
Daily odynophagia NRS last 7 days	0 ± 0.6 (184)	0 ± 0.6 (165)
EEsAI-PRO score	10 ± 13.9 (180)	9 ± 13.5 (160)
EEsAI-PRO score ≤20 points	141 (75.8)	129 (77.7)
EoE-QoL-A 30 items weighted questionnaire	3.3 ± 0.52 (181)	3.3 ± 0.49 (163)
Overall peak eos/mm^2 hpf	13 ± 54.5 (105)	14 ± 56.5 (97)
Histologic remission	98/105 (93.3)	89/97 (91.8)
Deep histologic remission	92/105 (87.6)	85/97 (87.6)
Histologic relapse	5/105 (4.8)	5/97 (5.2)
Total modified EREFS score (0–9 points)	1 ± 0.9 (105)	1 ± 0.9 (97)
Inflammatory signs subscore (0–4 points)	0 ± 0.6 (105)	0 ± 0.6 (97)
Fibrotic signs subscore (0–4 points)	0 ± 0.5 (105)	0 ± 0.5 (97)
Total EREFS score of 0 points	68/105 (64.7)	63/97 (64.9)

Note: Data are presented as number (%), number/total (%), or mean ± standard deviation (number).
BOT, budesonide orodispersible tablet; EEsAI-PRO, EoE Symptom Activity Index Patient-Reported Outcome; EoE-QoL-A, EoE Quality of Life in Adults instrument; eos, eosinophils; EREFS, EoE endoscopic reference score; hpf, high-power field; NRS: numerical rating scale; OLE, open-label extension; PPI, proton pump inhibitor.

daily across the entire study period. The remaining 42 patients (22.6%) switched between these 2 doses at personalized intervals.

Efficacy

Clinical remission was stably maintained in the efficacy population at all visits throughout the 96-week study period, with rates above 84.0% at all post-OLE baseline visits compared with 80.6% at OLE baseline as analyzed by OC (Figure 2*A*). Using a more conservative NRI analysis, over 81.9% of patients were in clinical remission at each post-baseline visit compared with 77.7% at OLE baseline (Figure 2*B*). The mean EEsAI-PRO score remained between 7 and 8 across all visits through OLE week 96 (Figure 2*C*). An increase in EEsAI-PRO score of >15 points from OLE baseline was recorded for fewer than 5% of patients at all visits (Supplementary Figure 2). Mean Numerical Rating Scale (NRS) scores for the symptoms of dysphagia and odynophagia remained at 0 at all post-baseline time points (Figure 2*D and E*), with symptomatic relapse recorded in a total of 7 patients and at 0.6% of total visits across the OLE (Supplementary Table 3). There were 2 cases of food impaction requiring endoscopic intervention; both patients continued on BOT therapy. No patients required endoscopic dilation. Similar findings were observed among the total population (n = 186) up to week 48 (Supplementary Information and Supplementary Figure 3).

At OLE week 96, 80.1% and 78.8% of patients in the efficacy population exhibited histologic remission and deep histologic remission, respectively (Table 2). Among patients with deep histologic remission at DB48 baseline, 62.6% maintained deep histologic remission through OLE week 96 (ie, across ≥ 144 weeks in total). At week 96, 78.1% of patients were in combined clinico-histologic remission. Patients' EREFS scores remained stable through OLE weeks 48 and 96, respectively, with mean total and subscores of 0 at all assessments. At OLE week 96, 66.4% of patients undergoing endoscopy had a total EREFS score of 0.

Patients' QoL improved across the 96-week OLE, with a mean improvement on the 4-point Eosinophilic Esophagitis Quality of Life in Adults (EoE-QoL-A) of 0.1 points from OLE baseline to OLE week 96 and of 0.4 points from DB48 baseline (Table 2). At OLE week 96, 97.6% of patients reported being satisfied or extremely satisfied with BOT treatment. Similar results were achieved in the total population (Supplementary Table 4).

Because the efficacy population of this OLE study (n = 166) comprises both patients who received BOT or placebo during the DB48 study, the total duration of uninterrupted BOT therapy varied greatly. Therefore, we analyzed the subset of patients (n = 93) who received BOT continuously during both the DB48 and 96-week OLE studies without OLRI, as this group received nearly 3 years (≥150 weeks) of uninterrupted BOT therapy (Table 3). Of these 93 patients, 68.8%, 88.2%, and 86.0% were in clinical remission at DB48 baseline, OLE baseline, and OLE week 96, respectively. Mean EEsAI-PRO scores and symptom NRS scores also improved or remained stable. EREFS scores were also equivalent across the same period, with 66.7% of

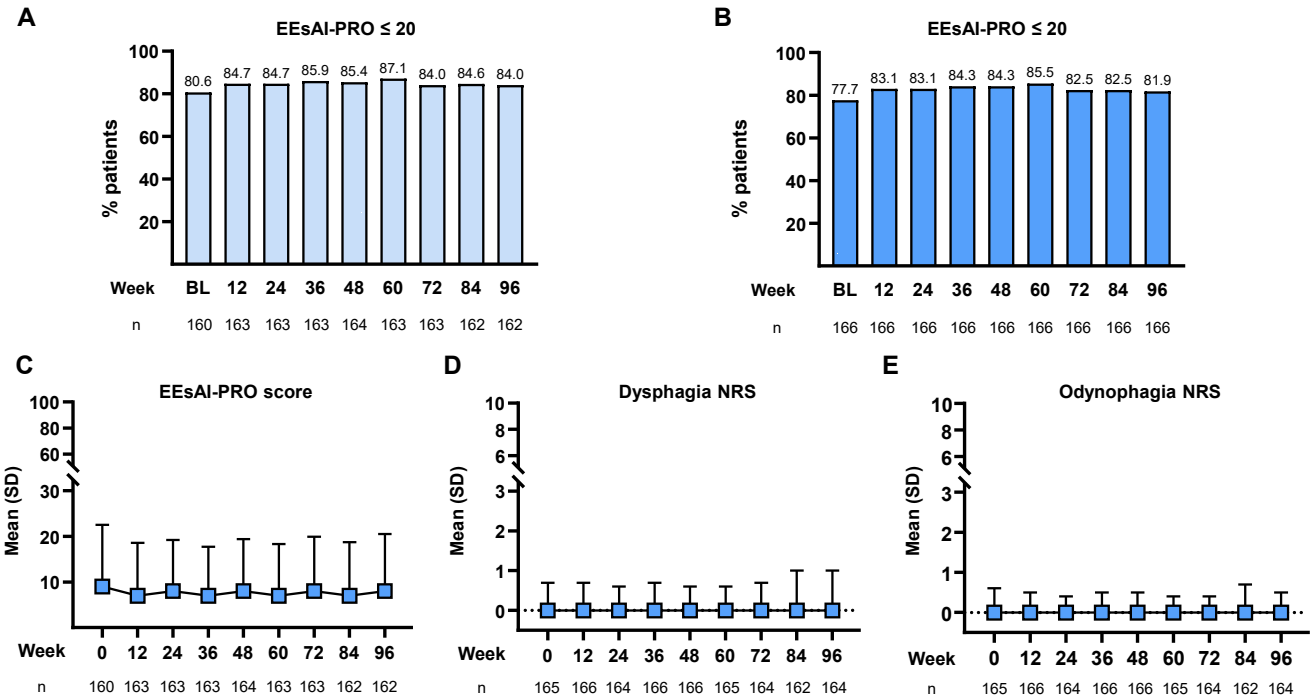

Figure 2. Clinical efficacy of long-term BOT therapy. Rates of clinical remission (EEsAI-PRO score of ≤20) at each visit by OC analysis (*A*) and NRI analysis (*B*). (*C*) Mean (standard deviation) EEsAI-PRO score at each visit. Patient-reported severity of dysphagia (*D*) and odynophagia (*E*) at each visit, by NRS.

Table 2. Histologic, Endoscopic, QoL and Patient Satisfaction Outcomes With Long-term BOT Therapy

	Week 48	Week 96
Histologic		
Histologic remission	99/113 (87.6)	117/146 (80.1)
Deep histologic remission	95/113 (84.1)	115/146 (78.8)
Histologic relapse	12/113 (10.6)	22/146 (15.1)
Peak eos/mm^2 hpf	26 ± 99.0 (113)	26 ± 69.2 (146)
Maintaining deep histologic remission from DB48 BL to time point[a]	53/72 (73.6)	57/91 (62.6)
Clinico-histologic		
Clinico-histologic remission[b]	n.d.	114/146 (78.1)
Endoscopic		
Total EREFS score	1 ± 1.0 (113)	1 ± 1.0 (146)
EREFS inflammatory subscore	0 ± 0.6 (113)	0 ± 0.7 (146)
EREFS fibrotic subscore	0 ± 0.6 (113)	0 ± 0.5 (146)
Total EREFS score of 0 points	64/113 (56.6)	97/146 (66.4)
Change in total EREFS score from OLE BL	0 ± 0.9 (69)	0 ± 1.1 (82)
QoL		
EoE-QoL-A score[c]	3.5 ± 0.46 (149)	3.5 ± 0.46 (160)
Absolute change in EoE-QoL-A score from OLE BL	0.1 (0.06 to 0.16); 146	0.1 (0.08 to 0.18); 158
Absolute change in EoE-QoL-A score from DB48 BL	0.4 (0.27 to 0.44); 141	0.4 (0.33 to 0.52); 150
Patient satisfaction		
Patient global satisfaction		
Extremely satisfied	126 (75.9)	129 (77.7)
Satisfied	37 (22.3)	33 (19.9)
Neither satisfied nor dissatisfied	2 (1.2)	1 (0.6)
Dissatisfied	0 (0.0)	0 (0.0)
Extremely dissatisfied	0 (0.0)	0 (0.0)
Missing	1 (0.6)	3 (1.8)

Note: Data are presented as, number/total (%), mean ± standard deviation (number), or mean (95% CI).
BL, baseline; BOT, budesonide orodispersible tablet; CI, confidence interval; DB48, 48-week double-blind study; EoE-QoL-A, EoE Quality of Life in Adults instrument; eos, eosinophils; EREFS, Endoscopic Reference Score; hpf, high-power field; n.d., not determined; OLE, open-label extension; QoL, quality of life.
[a]Defined as patients with deep histologic remission at DB48 baseline who remained in deep histologic remission at each time point tested up to and including week 48/96.
[b]Defined as in reference 3.
[c]Higher values denote greater QoL.

patients exhibiting a total EREFS score of 0 at OLE week 96 vs 49.5% at DB48 baseline. Among patients in this subpopulation with evaluable data at both time points, mean EoE-QoL-A scores improved by 0.5 ± 0.60 points (95% confidence interval [CI], 0.34–0.60) from DB48 baseline to OLE week 96.Mean peak eosinophil counts increased from 0 ± 1.5 eos/mm^2 hpf at DB48 baseline to 34 ± 84.4 at OLE week 96, whereas patients in deep histologic remission declined from 95.7% to 75.6%, respectively.

Safety

Among the 186 patients who entered the OLE, 161 (86.6%) experienced at least one TEAE, and 70 (37.6%) experienced at least one ADR across the 96-week OLE (Table 4). A total of 15 SAEs were recorded in 14 patients across the OLE study, 2 of which were classified by investigators as having at least a possible relationship to BOT (see Supplementary Information for details). The rates of TEAEs and ADRs were consistent between the first and second year of the OLE at 76.35 to 78.3% and 28.9% to 30.1%, respectively. Study participation was discontinued for 5 patients due to TEAEs. Similar rates of TEAEs were observed during the OLRI study (Supplementary Table 3).

The most common ADRs in the OLE were localized candidiasis: 34 patients (18.3%) had suspected candidiasis, with 6 (3.2%) confirmed by histology (Table 4). There were 9 cases of esophageal candidiasis, 17 cases of oral candidiasis, and 17 cases of oropharyngeal candidiasis—several patients had recurrent infections or infections at multiple locations. No cases of candidiasis were serious, the majority were of mild intensity, and all were treated successfully. There were 5 cases of esophageal food impaction, with 2 requiring endoscopic intervention. No dose-related trends were observed with regard to any AEs (data not shown).

Mean morning serum cortisol levels were 11.8, 11.2, and 11.3 μg/dL at OLE baseline, OLE week 48, and OLE week 96, respectively (Table 4). The mean absolute change in serum cortisol levels from OLE baseline was −0.4 (95% CI, −1.56 to 0.72) to OLE week 48 and −0.3 (95% CI, −1.43 to 0.88) to OLE week 96, neither of which was clinically relevant. The ADR 'blood

Table 3. Efficacy Outcomes Among the Group of n = 93 Patients Receiving BOT (0.5 mg and/or 1.0 mg Twice Daily) Continuously Through the BOT DB48 and OLE Studies (≥144 Weeks Uninterrupted Treatment)

	DB48 BL	OLE BL	OLE week 96
Clinical			
EEsAI-PRO score ≤20 points	64 (68.8)	82 (88.2)	80 (86.0)
EEsAI-PRO score	15 ± 13.7 (92)	6 ± 9.8 (92)	6 ± 10.4 (91)
Daily dysphagia NRS last 7 days	1 ± 0.9 (93)	0 ± 0.6 (93)	0 ± 0.7 (92)
Histologic			
Peak eos/mm^2 hpf	0 ± 1.5 (93)	6 ± 31.6 (93)	34 ± 84.4 (78)
Histologic remission	93/93 (100.0)	90/93 (96.8)	61/78 (78.2)
Deep histologic remission	89/93 (95.7)	85/93 (91.4)	59/78 (75.6)
Histologic relapse	0/93 (0.0)	1/93 (1.1)	12/78 (15.4)
Endoscopic			
Total EREFS score	1 ± 1.2 (93)	1 ± 0.9 (93)	1 ± 1.0 (78)
EREFS inflammatory subscore	0 ± 0.7 (93)	0 ± 0.6 (93)	0 ± 0.7 (78)
EREFS fibrotic subscore	1 ± 0.7 (93)	0 ± 0.5 (93)	0 ± 0.5 (78)
Total EREFS score of 0 points	46/93 (49.5)	60/93 (64.5)	52/78 (66.7)
QoL			
EoE-QoL-A score	3.1 ± 0.60 (86)	3.4 ± 0.42 (93)	3.5 ± 0.35 (91)

Note: Data are presented as number (%), number/total (%), or mean ± standard deviation (number).
BL, baseline; BOT, budesonide orodispersible tablet; DB48, 48-week double-blind study; EEsAI-PRO, EoE Symptom Activity Index Patient-Reported Outcome; EoE-QoL-A, EoE Quality of Life in Adults instrument; eos, eosinophils; EREFS, EoE endoscopic reference score; hpf, high-power field; NRS, numerical rating scale; OLE, open-label extension.

cortisol decreased' was recorded for 6 patients (3.2%). In all cases, this decrease was mild and treatment was not interrupted. Among corticosteroid-related ADRs of special interest (Supplementary Information), 1 case each of dysgeusia and depression and 2 cases of weight increased were observed.

Discussion

In this OLE study on maintenance therapy of adults with EoE using BOT for up to 96 weeks, disease control was durably and safely maintained as measured by clinical, histologic, endoscopic, QoL, and safety parameters. Clinical remission (EEsAI-PRO ≤20) rates were consistently above 84.0% at all post-baseline visits, compared with 80.6% at OLE baseline, whereas mean severity of dysphagia and odynophagia was 0 (on an NRS scale of 0–10) at all visits. Quality of life improved from 3.1 points at DB48 baseline to 3.5 at OLE week 96 on the 4-point EoE-QoL-A questionnaire, and 97.6% of respondents were satisfied or extremely satisfied with BOT treatment at 96 weeks. Endoscopic remission was maintained, with mean total EREFS scores of 0 at OLE weeks 48 and 96, whereas 80.1% of patients achieved histologic remission (peak eos <16 eos/mm^2 hpf [<5 eos/hpf]) at OLE week 96 compared with 91.8% at OLE baseline.

In addition to mitigating debilitating symptoms such as dysphagia and urgent events including food impaction, the clinical management of EoE encompasses long-term objectives such as reducing behavioral impacts on patients' daily lives and preventing fibrostenotic esophageal remodeling.[19] While 24-hour recall NRS symptom scales reflect patients' perception of symptom severity, the 7-day EEsAI-PRO also surveys food avoidance behavior, food modification, and eating, which may mask symptoms.[20] The positive findings on both measures reflect an amelioration of symptoms without the need for dietary or lifestyle modifications, and may also explain the continued improvement in patients' QoL.

Similarly, the consistent EREFS fibrotic and inflammatory subscores of 0 at all time points suggest that long-term BOT therapy may halt fibrostenotic remodeling of the esophagus, in contrast to increased EREFS fibrotic subscores without long-term therapy in the DB study.[4] Rates of histologic and deep histologic remission also remained stable, with 78.8% of patients having no detectable esophageal eosinophils at OLE week 96. Although mean peak eosinophil counts increased from 14 to 26 eos/mm^2 hpf between OLE baseline and week 96, this did not correlate with any negative trend in clinical or endoscopic findings, consistent with other reports decoupling histologic and clinical outcomes in EoE therapy.[21,22]

In addition to high rates of stringent response, relapse rates were also low: only 15.1% of patients exhibited histologic relapse at OLE week 96, whereas only 7 patients experienced symptomatic relapse at any visit. Moreover, many cases of symptomatic or clinical relapse were transient and resolved with further treatment, as demonstrated by the low percentage of patients (11.8%) with sustained lack of clinical remission and the high percentage of patients (90.4%) who regained

Table 4. Summary of Safety Findings in the BOT OLE Study

	OLE weeks 1–48 (n = 186)	OLE weeks 49–96 (n = 166)[a]	Total (N = 186)
Total person-years of exposure	167.2	153.7	320.9
Patients with ≥1 TEAE[b]	142 (76.3)	130 (78.3)	161 (86.6)
Patients with ≥1 ADR	56 (30.1)	33 (19.9)	70 (37.6)
Patients with ≥1 SAE	4 (2.2)	10 (6.0)	14 (7.5)
Patients with ≥1 SAE with at least possible relationship to study drug	2 (1.1)	–	2 (1.1)
Nervous system disorder	1 (0.6)	–	1 (0.6)
Intracranial pressure increased	1 (0.6)		1 (0.6)
Patients with TEAE leading to discontinuation by preferred term	3 (1.6)	2 (1.2)	5 (2.7)
Chest pain	1 (0.5)	–	1 (0.5)
Oropharyngeal candidiasis	1 (0.5)	–	1 (0.5)
Laryngeal nerve dysfunction	–	1 (0.6)	1 (0.5)
Clear cell renal cell carcinoma	–	1 (0.6)	1 (0.5)
Intracranial pressure increased	1 (0.5)	–	1 (0.5)
Food impaction needing endoscopic intervention	–	2 (1.2)	2 (1.1)
Food impaction without need for endoscopic intervention	1 (0.5)	2 (1.2)	3 (1.6)
Patients with ADR by system organ class and preferred term (if of special interest)[c]			
Cardiac disorders	–	1 (0.6)	1 (0.5)
Ear and labyrinth disorders	–	1 (0.6)	1 (0.5)
Eye disorders	2 (1.1)	3 (1.8)	5 (2.7)
Gastrointestinal disorders	14 (7.5)	3 (1.8)	16 (8.6)
General disorders and administration site conditions	2 (1.1)	1 (0.6)	3 (1.6)
Immune system disorders	1 (0.5)	–	1 (0.5)
Infections and infestations	24 (12.9)	18 (10.8)	36 (19.4)
Candidiasis overall	23 (12.4)	17 (10.2)	34 (18.3)
Suspected symptomatic candidiasis	21 (11.3)	16 (9.6)	33 (17.7)
Histologically confirmed candidiasis	4 (2.2)	2 (1.2)	6 (3.2)
Histologically confirmed and symptomatic candidiasis	3 (1.6)	2 (1.2)	5 (2.7)
Injury, poisoning and procedural complications	–	1 (0.6)	1 (0.5)
Investigations	7 (3.8)	4 (2.4)	11 (5.9)
Blood cortisol decreased[d]	4 (2.2)	2 (1.2)	6 (3.2)
Weight increased	2 (1.1)	–	2 (1.1)
Musculoskeletal and connective tissue disorders	1 (0.5)	1 (0.6)	2 (1.1)
Bone metabolism disorder[e]	–	1 (0.6)	1 (0.5)
Nervous system disorders	5 (2.7)	2 (1.2)	6 (3.2)
Dysgeusia	1 (0.5)	–	1 (0.5)
Psychiatric disorders	1 (0.5)	–	1 (0.5)
Depression	1 (0.5)	–	1 (0.5)
Respiratory, thoracic and mediastinal disorders	1 (0.5)	–	1 (0.5)
Morning serum cortisol, *μg/dL*			
OLE baseline			11.8 ± 5.79 (141)
Week 48 OLE	11.2 ± 4.13 (125)		
Week 96 OLE		11.3 ± 4.24 (113)	
Absolute change from OLE baseline to week 48[f]	-0.4 (-1.56 to 0.72); 96		
Absolute change from OLE baseline to week 96[f]		-0.3 (-1.43 to 0.88); 92	

Note: Data are presented as number (%), mean ± standard deviation (number), or mean (95% CI).
ADR. adverse drug reaction; AE, adverse event; BOT, budesonide orodispersible tablet; CI, confidence interval; OLE, open-label extension; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
[a]Comprises all patients in OLE after week 48 + 1 day.
[b]TEAEs defined as any event with onset or worsening (if pre-existing) after first administration of BOT during the OLE.
[c]See Supplementary Information for definition.
[d]None with clinical symptoms of adrenal insufficiency, values normalized without change in the medication.
[e]Low bone alkaline phosphatase.
[f]Calculated among patients with values at OLE baseline and time point specified.

symptomatic remission during the OLRI following clinical relapse in DB48.

Although several studies have previously reported diminishing efficacy with long-term STC treatment of EoE,[14,23] we observed clear durability and even improvement of disease control based on clinical, endoscopic, histologic, and QoL parameters. However, improvement in patients receiving placebo during DB48 might mask waning among patients with uninterrupted BOT therapy. We therefore analyzed the subgroup of patients (n = 93) who received continuous BOT therapy for at least 144 weeks across the DB48 and OLE studies. This analysis revealed no diminishing efficacy over nearly 3 years in any parameters except histology endpoints, consistent with our results for the aggregated population. This lack of waning underscores the importance of formulation in treating EoE with STC,[24–26] as BOT was specifically designed to use saliva as a vehicle to robustly coat the esophageal mucosa.[16]

In the OLE study, investigators had the option of prescribing 0.5 mg or 1.0 mg BOT twice daily based on patients' symptoms and overall presentation, with guidance to use the lower dose whenever feasible. Consistent with this guidance, 70.4% of patients (131/186) received exclusively the lower dose in the OLE study, whereas 7.0% (13/186) received exclusively high-dose BOT. Many of the remaining patients received high-dose BOT for a short period at the start of the OLE following high-dose therapy in the OLRI study. In light of the low percentage of patients taking only high-dose BOT and the absence of specific dose selection criteria, no analyses were performed by dosage group for the OLE study. In the DB48 study, equivalent efficacy and safety were shown for both doses, although a subgroup analysis revealed greater efficacy of 1.0 mg BOT twice daily in patients with longstanding (>9.8 years) disease, pointing to a potential benefit of 2.0 mg BOT per day in certain maintenance therapy settings.

BOT was well-tolerated during the 96-week OLE study. Rates of TEAEs, ADRs, and SAEs remained nearly constant across the 48-week DB48 trial and each of the 2 48-week phases of the OLE trial, with ADRs rates of 32.4%, 30.1%, and 28.9% in these consecutive 48-week periods.[4] Hence, there were no indications of cumulative toxicity. The most frequent ADRs were oral and esophageal candidiasis, recorded for 18.3% of OLE patients vs 17.6% for 0.5 mg BOT twice daily in DB48. As in the DB48 study, no dose effect trends were generally observed. The vast majority of candidiasis was mild with no serious cases reported, and all cases were successfully managed. Mean morning cortisol levels remained within normal range. Although the ADR was 'blood cortisol decreased' in 3.2% of patients, there were no signs of adrenal insufficiency in these patients. There were 2 SAEs with at least a possible relationship to BOT, both of which resolved fully.

This study had several limitations. It was implemented as an open-label study with no placebo comparator, even though a placebo effect on EoE symptoms has been described.[27] Furthermore, because response to BOT induction therapy was an inclusion criterion for the prior DB48 study, primary nonresponders to BOT were excluded from both the DB48 and the OLE studies. Due to the pragmatic nature of BOT dosage, it was not possible to meaningfully assess treatment adherence. Because the OLE was extended from 48 weeks to 96 weeks approximately 1 year after initiation, some patients completed the study at week 48 who might have otherwise remained longer. To address this ambiguity, the primary efficacy analyses were performed using patients who participated in both 48-week phases of the OLE, while a secondary analysis including all patients who entered the OLE was performed up to week 48.

In summary, our results show that BOT therapy can durably maintain clinical and histologic remission for up to 144 weeks in the majority of adult patients with EoE. The adverse effect profile was favorable, and no cumulative effects were observed. BOT therapy also halted and may even sustainably reverse fibrostenotic remodeling of the esophagus, raising hope of disease modification in EoE.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2024.10.034.

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Data Availability
Individual participant data will not be shared.

Supplementary Information

Assessments and Measurements

Clinical outcomes were measured using the validated Eosinophilic Esophagitis Activity Index Patient Reported Outcome (EEsAI-PRO),[1] with scores of ≤20 defined as clinical remission.[2] The symptoms of dysphagia and odynophagia were additionally assessed using an 11-point numerical rating scale (NRS, 0–10 points) as described previously, with symptomatic relapse defined as NRS ≥4.[3] Endoscopic findings were graded using the modified EoE Endoscopic Reference Score (EREFS),[4] which ranges from 0 to 9 and is subdivided into a fibrotic signs and an inflammatory signs subscore, each ranging from 0 to 4 points. During endoscopies, 2 biopsies were collected from each esophageal third to measure the eosinophil (eos) count, as described previously.[3] Histologic remission was defined as a peak eos count of <16 eos/mm^2 high-power field (hpf), (corresponding to <5 eos/hpf), deep histologic remission was defined as 0 eos/mm^2 hpf, whereas histologic relapse was defined as ≥48 eos/mm^2 hpf (≥15 eos/hpf). Clinico-histologic remission was calculated as previously described.[3] Health-related quality of life (QoL) was measured using the validated Eosinophilic Esophagitis Quality of Life Scale for Adults version 2.0 (EoE-QoL-A).[5,6]

Open-label Reinduction Phase

The 6-week open-label re-induction (OLRI) phase was designed to reinduce remission in patients who experienced relapse during the 48-week double-blind study of EOS-2 trial (DB48) study prior to entering the open-label extension (OLE). For the purposes of OLRI participation, the definitions of clinical and histological relapse from the DB48 study were used.[4] Because the recommended dosage for the OLE study was 0.5 mg budesonide orodispersible tablet (BOT) twice daily, reinduction was achieved using a higher dose of 1 mg BOT twice daily. Participation in the OLRI was optional, and there were no prespecified endpoints. After 6 weeks, clinical and QoL outcomes were recorded, but no endoscopy was performed.

A total of 82 patients entered the OLE: 25 who received BOT in the DB48, and 57 who received placebo. Four placebo patients with histologic but not clinical relapse entered the OLE study directly from the DB48 study. At OLRI baseline, 84.1% of patients (69 of 82) had histologic relapse, 63.4% (52 of 82) had clinical relapse, and 48.8% (40 of 82) had both. Other demographic characteristics were generally similar to the total OLE population (data not shown).

Key efficacy and QoL outcomes are shown in Supplementary Table 2. The proportion of patients in clinical remission increased from 22.0% at OLRI baseline to 65.9% at OLRI week 6. The percentage of patients with symptom resolution (defined as dysphagia and odynophagia NRS ≤2) increased from 36.6% at OLRI baseline to 92.7% at OLRI week 6. Of the 52 patients with clinical relapse at OLRI baseline, 47 (90.4%) achieved symptom resolution by OLRI week 6. Mean EoE-QoL-A scores increased from 2.9 to 3.2.

During the OLRI study, 33 patients (40.2%) experienced a treatment-emergent adverse event (TEAE), and 13 (15.9%) experienced an adverse drug reaction (ADR) (Supplementary Table 3). There were 7 cases (8.5% of patients) of suspected candidiasis. One patient in clinical remission at OLRI baseline experienced symptomatic relapse during the OLRI and did not continue onto the OLE study, while the other 81 patients (98.8%) proceeded directly to the OLE with no pause in treatment. Of these 81 patients, 26 (32.1%) initially received 2 × 0.5 mg BOT twice daily during the OLE phase, equivalent to the OLRI dosage of 1 mg BOT twice daily.

Efficacy Outcomes for the N = 186 Total Population

The EOS-2 study was originally designed with a 48-week OLE phase following the DB48 phase. However, investigators and patients began requesting longer treatment with BOT only several months into the double-blind phase. Responding to this request, the study sponsor implemented a protocol amendment extending the OLE phase to 96 weeks. This amendment took effect approximately 1 year after entry of the first patients into the OLE phase, causing several to complete the study at week 48 with no option to extend.

For administrative and logistical reasons, the OLE phase was still presented to patients after the amendment as 2 distinct phases: one optional 48-week phase, with an additional option to extend by a further 48 weeks. Accordingly, patients were asked to actively consent to continued participation at the OLE week 48 visit. Because this procedural complication resulted in some patients not participating in the full 96 week OLE due to administrative reasons, the primary efficacy analyses were performed using the 166 patients who actively consented to participate in both 48-week OLE treatment phases.

For completeness, efficacy data up to week 48 are shown here for all 186 patients who entered the OLE. Key clinical outcomes for the n = 186 population are shown in Supplementary Figure 3, while key histologic, endoscopic, and quality of life outcomes are shown in Supplementary Table 4. Results for all parameters were similar or nearly identical between the n = 166 and n = 186 populations. All safety analyses in the study encompassed the entire duration of participation for the n = 186 total population.

Serious Adverse Events With at Least a Possible Relationship to Study Drug

Two serious adverse events (SAEs) in 2 patients were classified by investigators as having at least a possible relationship to BOT. A 30-year-old man experienced a

combination of vision disturbances, speech disorders, and headaches after 484 days of continuous BOT therapy, which spontaneously resolved within 1 day of onset; the patient continued with the study treatment. A 41-year-old man experienced idiopathic elevated intracranial pressure after 49 days of continuous BOT therapy, which resolved after 22 days of treatment with acetazolamide; the patient subsequently withdrew from the study.

Corticosteroid-related Adverse Events

As the present study describes the long-term use of the locally-acting corticosteroid budesonide, the following adverse events (AEs) (by preferred term)were defined post-hoc as being corticosteroid-related events of special interest potentially indicative of systemic steroid side effects: Cushing's syndrome, skin striae, hirsutism, mood altered, insomnia, depression, glaucoma, cataract, central serous retinopathy, visual impairment, blurred vision, dysgeusia, fractures, impaired healing, bone metabolism disorder, hypertension, diabetes, blood cortisol decreased, obesity, weight fluctuation and weight increased. These events are reported here (Table 4; Supplementary Table 2) when judged as having at least a possible relationship to the study drug by investigators (ie, ADRs).

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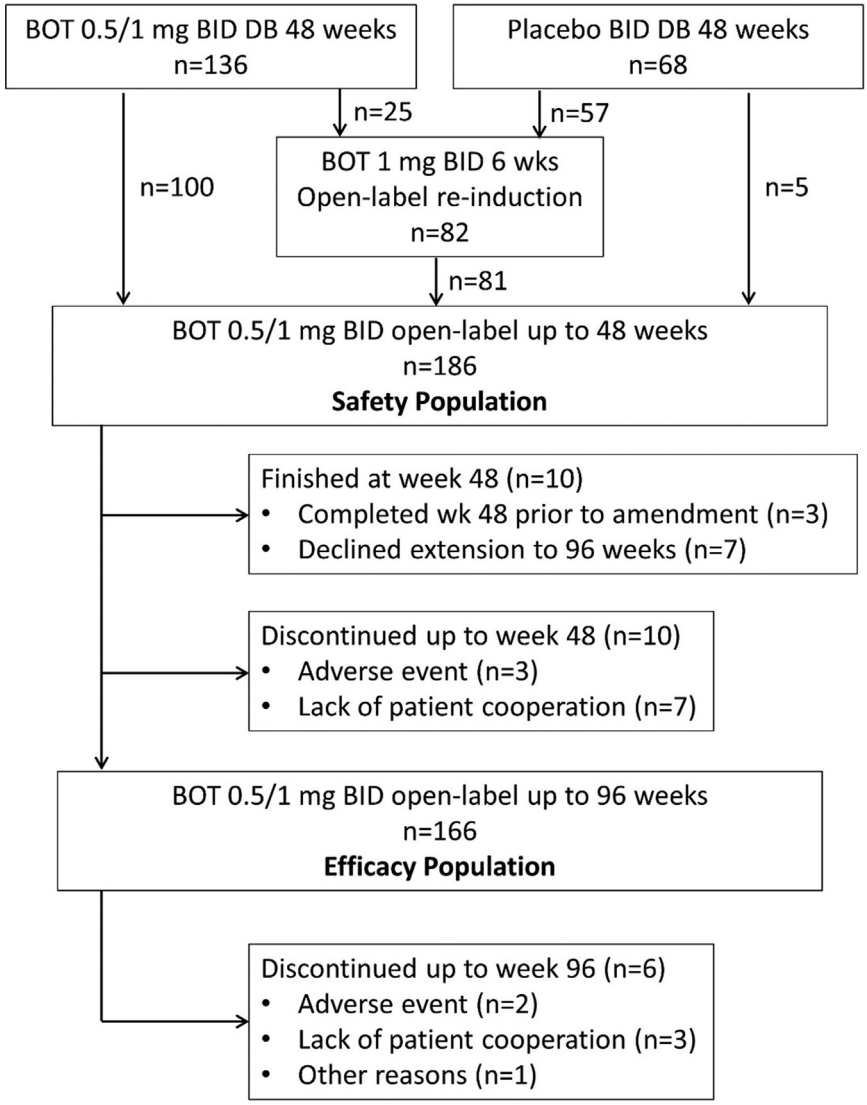
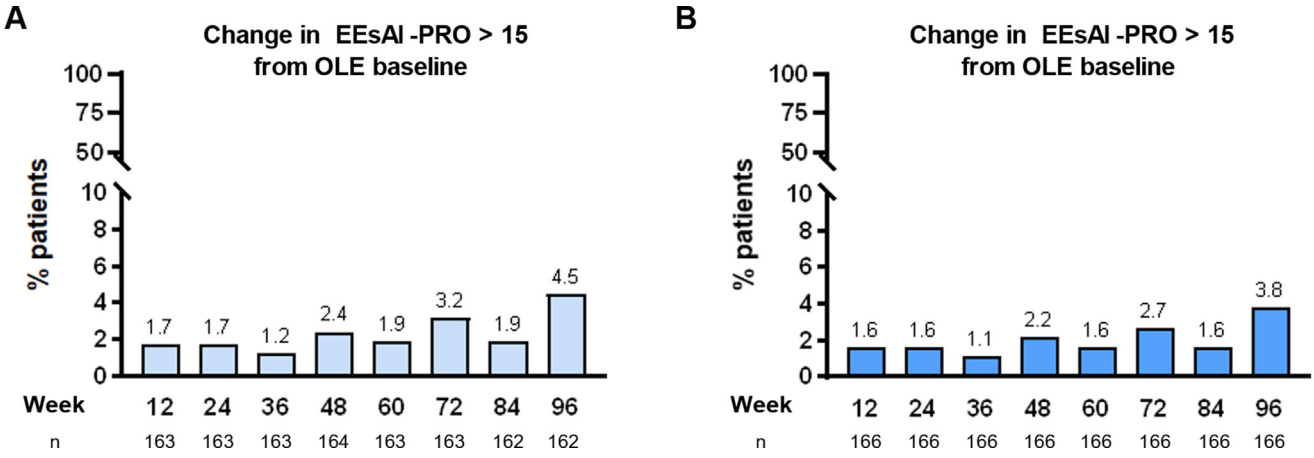
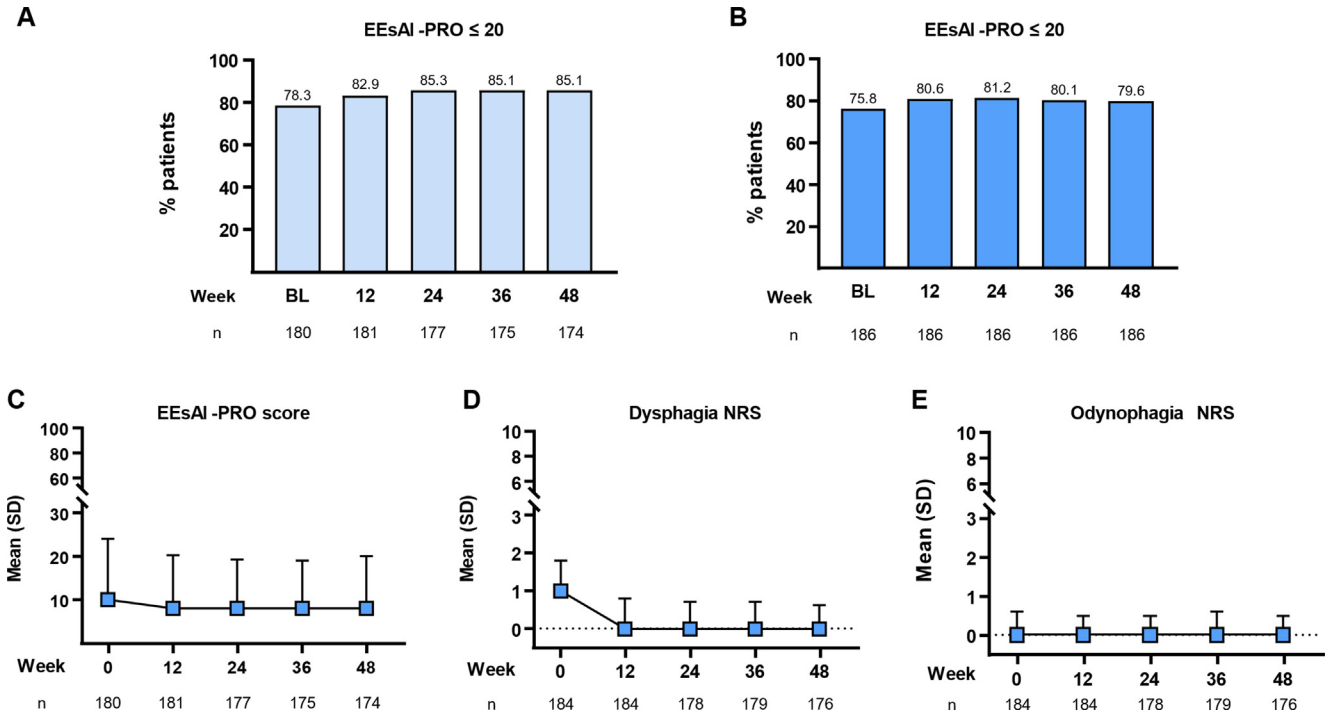


Supplementary Figure 1. Patient disposition in the BUL-2 OLE study.



Supplementary Figure 2. Rates of increase in EEsAI-PRO score of >15 points from OLE baseline, by OC analysis (*A*) and NRI analysis (*B*).



Supplementary Figure 3. Clinical efficacy in the total population (N = 186) up to week 48. Percentage of patients with an EEsAI-PRO score of ≤20 at each visit by OC analysis (*A*) and NRI analysis (*B*). (*C*) Mean (standard deviation) EEsAI-PRO score at each visit (higher scores denote worse outcomes). Patient-reported severity of dysphagia (*D*) and odynophagia (*E*) at each visit, captured by an NRS (0–10, higher scores denote worse symptoms).

Supplementary Table 1. Key Efficacy Results for the OLRI Phase

	OLRI baseline	OLRI week 6
EEsAI-PRO score ≤20 points	18/82 (22.0)	54/82 (65.9)
EEsAI-PRO score	40 ± 22.3 (80)	15 ± 17.6 (76)
Daily dysphagia NRS last 7 days	4 ± 2.7 (81)	1 ± 1.1 (79)
Daily odynophagia NRS last 7 days	2 ± 2.7 (81)	0 ± 0.9 (79)
Dysphagia and odynophagia ≤2	30/82 (36.6)	76/82 (92.7)
EoE-QoL-A score	2.9 ± 0.74 (81)	3.2 ± 0.57 (81)
Absolute change in EoE-QoL-A score from OLRI BL		0.3 (0.24 to 0.45); 81

Note: Data are presented as number/total (%), mean ± standard deviation (number), or mean (95% CI).
BL, baseline; CI, confidence interval; EEsAI-PRO, EoE Symptom Activity Index Patient-Reported Outcome; EoE-QoL-A, EoE Quality of Life in Adults instrument; EREFS, EoE endoscopic reference score; NRS, numerical rating scale; OLRI, open-label reinduction.

Supplementary Table 2. Summary of Safety Findings in the OLRI Phase

	OLRI population (n = 82)
Total person-years of exposure	10.1
Patients with ≥1 TEAE,[a] n (%)	33 (40.2)
Patients with ≥1 ADR, n (%)	13 (15.9)
Patients with ADR by system organ class and preferred term (if of special interest),[b] n (%)	
Gastrointestinal disorders	3 (3.7)
Infections and infestations	8 (9.8)
Candidiasis overall	7 (8.5)
Suspected symptomatic candidiasis	7 (8.5)
Investigations	1 (1.2)
Blood cortisol decreased	1 (1.2)
Nervous system disorders	1 (1.2)
Dysgeusia	1 (1.2)
Psychiatric disorders	2 (2.4)
Morning serum cortisol, *μg/dL*	
OLRI baseline	11.1 ± 4.88 (59)
Week 6 OLRI	11.4 ± 4.49 (64)
Absolute change from OLRI baseline to week 6[c]	0.2 (-0.90 to 1.32); 53

Note: Data are presented as number (%), mean ± standard deviation (number), or mean (95% CI).
ADR, adverse drug reaction; AE, adverse event; BL, baseline; BOT, budesonide orodispersible tablet; CI, confidence interval; OLE, open-label extension; OLRI, open-label reinduction; TEAE, treatment-emergent adverse event.
[a]TEAEs defined as any event with onset or worsening (if pre-existing) after first administration of BOT during the OLE.
[b]See Supplementary Information for definition.
[c]Calculated among patients with values at OLRI baseline and time point specified.

Supplementary Table 3. Frequency of Clinical Findings Above Remission/Relapse Thresholds Across All Aggregated Patient Visits

EEsAI-PRO	
Patients with	
EEsAI-PRO score >20 at ≥ 1 post-baseline visit	70 (37.6)
EEsAI-PRO score >20 at 1 post-baseline visit	26 (14.0)
EEsAI-PRO score >20 at ≥4 post-baseline visits	22 (11.8)
Dysphagia/odynophagia NRS	
Patients with	
Dysphagia and/or odynophagia NRS >2 at ≥1 post-baseline visit	27 (14.5)
Dysphagia and/or odynophagia NRS ≥4 at ≥1 post-baseline visit	7 (3.8)
Visits	
Total no. of visits with evaluable dysphagia/odynophagia NRS results[a]	1372
Dysphagia and/or odynophagia NRS 3, visits (% of total visits)[b]	28 (2.0)
Dysphagia and/or odynophagia NRS ≥4, visits (% of total visits)[b]	8 (0.6)

Note: Data are presented as number (%) unless otherwise indicated.
EEsAI-PRO, EoE Symptom Activity Index Patient-Reported Outcome; NRS, numerical rating scale.
[a]Across all 8 post-baseline visits for all patients in total population (n = 186).
[b]Total number of individual visits (among all patients) at which symptomatic finding was recorded.

Supplementary Table 4. Histologic, Endoscopic, QoL, and Patient Satisfaction Outcomes in the Total Population (N = 186) at Week 48

	Week 48
Histologic	
Histologic remission	105/120 (87.5)
Deep histologic remission	101/120 (84.2)
Histologic relapse	12/120 (10.0)
Peak eos/mm^2 hpf	28 ± 102.9 (120)
Maintaining deep histologic remission from DB48 BL to time point[a]	57/78 (73.1)
Clinico-histologic	
Clinico-histologic remission[b]	104/120 (86.0)
Endoscopic	
Total EREFS score	1 ± 0.9 (120)
EREFS inflammatory subscore	0 ± 0.6 (120)
EREFS fibrotic subscore	0 ± 0.6 (120)
Total EREFS score of 0 points	69/120 (57.5)
Change in total EREFS score from OLE BL	0 ± 0.9 (73)
QoL	
EoE-QoL-A score[c]	3.4 ± 0.47 (159)
Absolute change in EoE-QoL-A score from OLE BL	0.1 (0.06 to 0.16); 156
Absolute change in EoE-QoL-A score from DB48 BL	0.3 (0.25 to 0.41); 151
Patient satisfaction	
Patient global satisfaction	
Extremely satisfied	135 (72.6)
Satisfied	39 (21.0)
Neither satisfied nor dissatisfied	2 (1.1)
Dissatisfied	0 (0.0)
Extremely dissatisfied	0 (0.0)
Missing	10 (5.4)

Note: Data are presented as, number/total (%), mean ± standard deviation (number), or mean (95% CI).
BL, baseline; BOT, budesonide orodispersible tablet; CI, confidence interval; DB48, 48-week double-blind study; EoE-QoL-A, EoE Quality of Life in Adults instrument; eos, eosinophils; EREFS, Endoscopic Reference Score; hpf, high-power field; OLE, open-label extension; QoL, quality of life.
[a]Defined as patients with deep histologic remission at DB48 baseline who remained in deep histologic remission at each time point tested up to and including week 48/96.
[b]Defined as in reference 3.
[c]Higher values denote greater QoL.