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CADTH COMMON DRUG REVIEW

Clinical Review Report

BUDESONIDE (JORVEZA)

(AVIR Pharma Inc.)

Indication: For the induction of clinicopathologic remission in adults with eosinophilic esophagitis

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Abbreviations

AE	adverse event
AMS	avoidance, modification, and slow eating
budesonide	budesonide orodispersible tablets
CI	confidence interval
EEsAI-PRO	Eosinophilic Esophagitis Activity Index Patient Reported Outcome
EGID	eosinophilic gastrointestinal disease
EoE	eosinophilic esophagitis
EoE-QoL-A	Adult Eosinophilic Esophagitis Quality of Life
EOT	end of treatment
FAS	full analysis set
GERD	gastroesophageal reflux disease
HPF	high-power field
HRQoL	health-related quality of life
LOCF	last observation carried forward
MID	minimal important difference
modSHS	modified Short Health Scale
NRS	numerical rating scale
OLI	open-label induction
PatGA	Patient's Global Assessment
PGA	Physician's Global Assessment
PPI	proton pump inhibitor
PPI-REE	PPI-responsive esophageal eosinophilia
PRO	patient-reported outcome
SAE	serious adverse event
SAS	safety analysis set
SD	standard deviation
SHS	Short Health Scale
TEAE	treatment-emergent adverse event
VDQ	Visual Dysphagia Question

Executive Summary

An overview of the submission details for the drug under review is provided in Table 1.

Table 1: Submitted for Review

Item	Description
Drug product	Budesonide orodispersible tablets (Jorveza), 1 mg, oral
Indication	Induction of clinicopathologic remission in adults with eosinophilic esophagitis
Reimbursement request	As per indication
Health Canada approval status	NOC
Health Canada review pathway	Priority review
NOC date	November 5, 2019
Sponsor	AVIR Pharma Inc.

Introduction

Eosinophilic esophagitis (EoE) is a chronic, local immune-mediated, esophageal disease characterized histologically by eosinophil-predominant inflammation and clinically by symptoms related to esophageal dysfunction.[1, 2] The most commonly reported symptoms in older children and adults are dysphagia (difficulty swallowing), food impactions (food getting stuck in the esophagus), and non–swallowing-associated chest pain.[1, 2] EoE impairs patients' social and psychological functioning and significantly impacts their health-related quality of life (HRQoL).[2] In Canada, the most recent estimates of EoE were published in a 2018 systematic review that reported an incidence rate of 2.1 to 10.7 EoE cases per 100,000 adults and children per year.[3] The diagnostic criteria of EoE include the following: the presence of clinical symptoms indicative of esophageal dysfunction, eosinophil-predominant inflammation on esophageal biopsy consisting of a peak value of at least 15 eosinophils per high-power field (HPF) (or 60 eosinophils per mm^2), and the exclusion of any non-EoE disorders that may be responsible for or contributing to symptoms and esophageal eosinophilia.[1, 4]

The management of EoE includes a variety of dietary, pharmacologic, and endoscopic interventions.[5] The aim of therapy is symptomatic relief, with histologic improvement in esophageal eosinophilia, and in the case of pediatric patients, restoration of normal growth and development.[6] Dietary therapy is one of the first-line treatment options in children and adults, and involves avoidance of diets to minimize allergen exposure.[2, 6] Before the approval of budesonide orodispersible tablets in Canada there have been no approved pharmacological drugs for the treatment of EoE. As a result, proton pump inhibitors (PPIs) and topical corticosteroids are used off-label to treat the disease.[2, 7] Both PPIs and topical corticosteroids might be offered as first-line anti-inflammatory pharmacologic therapy.[2, 7] Topical corticosteroids fluticasone propionate and nebulized budesonide are generally prescribed. Fluticasone, as per its instructions, is to be sprayed into the patient's mouth and then swallowed, while budesonide can be administered using a nebulizer and patients are then instructed to mix budesonide with sucralose or another thickener to form an aqueous gel (termed "slurry") prior to administration.[2, 6] Topical corticosteroids are associated with several limitations, preventing the development of an optimized formulation.

Budesonide orodispersible tablets (also referred to as "budesonide") are indicated for the induction of clinicopathologic remission in adults with EoE.[8] The recommended daily dose

of budesonide is one 1 mg orodispersible tablet in the morning and one 1 mg orodispersible tablet in the evening (a total dose of 2 mg of budesonide daily). The usual treatment duration is six weeks. Budesonide is recommended after a meal and no food or liquid should be taken during or after 30 minutes of administration.[8]

The objective of this report is to perform a systematic review of the beneficial and harmful effects of budesonide 1 mg orodispersible tablets for the induction of clinicopathologic remission in adults with EoE.

Stakeholder Engagement

The information in this section is a summary of input provided by the patient groups that responded to CADTH's call for patient input and from a panel of six clinical experts consulted by CADTH for the purpose of this review.

Patient Input

A total of six patient group submissions were received for this review: one Canadian patient group submission (the Gastrointestinal Society) and five international patient group submissions (the Families Affected by Eosinophilic Disorders in the UK, the American Partnership for Eosinophilic Disorders and the Campaign Urging Research for Eosinophilic Disease in the US, ausEE Inc. in Australia, and the Spanish Association for Eosinophilic Esophagitis in Spain).

The patient groups collected information using a combination of published studies, self-reported data that patients or caregivers (including parents of patients) shared with various online platforms, and personal experiences shared by the patients and/or caregivers or members of the patient groups.

According to the patient input received, the symptoms of EoE vary among individuals and can include difficulty swallowing, choking, regurgitation, nausea, vomiting, fatigue, reflux, and abdominal and/or chest pain, as well as malnutrition and failure to thrive in the case of young children.

It was noted that living with EoE greatly impacts the daily lives of patients and their families — socially, mentally, and financially. Dietary restriction presents the biggest burden to the lives of patients and/or caregivers, negatively impacting activities such as holidays and family gatherings, social engagements, dining away from home, and travel.

The patient groups reported that corticosteroids generally resulted in remission; however, they are primarily asthma medications used beyond the Health Canada indication that are swallowed from an inhaler or mixed, and the non-specific nature of drug delivery makes the effectiveness varied and uncertain.

Patients expressed a desire for convenience in medication administration as well as clear instructions to maintain compliance. Patients expressed a need for a treatment that improves their day-to-day quality of life (i.e., eating, working, and socializing) and indicated that an effective therapy that resolves clinicopathologic symptoms and has minimum long-term complications is of high importance.

Clinician Input

The clinical experts indicated that every treatment option currently available has some limitations. The dietary approach is challenging for patients to follow. It has a significant impact on the patient's quality of life and it often requires the assistance of a dietitian; also, maintaining food avoidance over a long period is cumbersome for patients. PPI therapy is the most straightforward treatment to receive and is well tolerated. PPIs are effective treatment in a subgroup of patients with mild symptoms. However, a substantial proportion of patients are nonresponders to PPI therapy, and for patients who respond to PPI therapy, there is a risk of relapse upon discontinuation of the PPI. Response rates to topical corticosteroids are high; however, recurrence rates on withdrawal of the medication are high as well. Currently in Canada, these agents are not commercially formulated for the EoE indication and are used off-label; hence, they must be compounded or administered via a different route than approved. Patients, physicians, and pharmacists are left to adapt these corticosteroid formulations to the EoE patient. This can be confusing and cumbersome, leading to reduced patient compliance. Hence, other formulations of topical corticosteroids are needed to improve convenience and compliance.

The clinical experts indicated that budesonide orodispersible tablets will take the role of the compounded topical corticosteroids, which will not, by itself, present a large treatment paradigm shift.

The approach to treatment of adult patients was variable among panel members. One approach considered that adult patients best suited for treatment with budesonide orodispersible tablets are symptomatic patients with eosinophilic inflammation who have not responded to PPI treatment. Another approach considered that, in adult patients with severe symptoms, budesonide orodispersible tablets would be initiated as the first line of treatment without having to try PPI first.

The panel indicated that it may be difficult to determine a set of distinct characteristics for patients who would best respond to treatment with budesonide, given the limited data available. The panel also indicated that patients with reflux-like symptomatology and patients who respond to PPIs are the least suitable for treatment with budesonide orodispersible tablets.

In practice, clinicians would assess patients symptomatically. No scales are currently used in the clinical practice to assess symptomatic response. Meaningful responses to treatment include the complete resolution of symptoms of dysphagia and food impaction. Other important assessments would include an overall improvement in patient symptoms allowing for the consumption of solid food of all consistencies, reduced hospitalization, and a decrease in the frequency and severity of dysphagia. Histologic evaluation using endoscopy is not frequently used in clinical practice; it is mainly used in the case of worsening symptoms or the non-resolution of symptoms while on therapy, or for monitoring response to an elimination diet.

The clinical experts suggested that treatment discontinuation can be considered in cases where unacceptable side effects are present (such as recurrent candidiasis, systemic side effects from topical corticosteroids, and hypersensitivity), or if patients are intolerant to the drug.

The clinical experts agreed that budesonide orodispersible tablets for the treatment of EoE should be prescribed by specialists in gastroenterology or allergy who have expertise in EoE.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

The BUL-1/EEA trial (N = 88) was a pivotal phase III, double-blind, randomized, multi-centre, placebo-controlled study that compared the efficacy and tolerability of a six-week treatment with budesonide effervescent tablets with placebo for the induction of clinicopathologic remission in adult patients with active EoE. Patients enrolled in the trial were adults (18 to 75 years of age) with a confirmed clinicopathologic diagnosis of EoE, and active symptomatic and histologic EoE, and must have undergone a documented trial with PPIs in order to exclude PPI-responsive esophageal eosinophilia (PPI-REE). Patients were assigned to one of two treatment groups via a central randomization procedure using a 2:1 allocation ratio to receive either budesonide 1 mg orodispersible tablet (budesonide 1 mg) twice daily or a placebo orodispersible tablet (placebo) twice daily. The budesonide 1 mg and placebo treatments were identical in physical appearance, which assured treatment blinding. No stratification of randomized treatment assignment was performed. The screening period of up to six weeks was followed by a six-week double-blind treatment period and an optional six-week open-label induction (OLI). The primary efficacy end point in the BUL-1/EEA trial was the percentage of patients with clinicopathologic remission at week 6, defined as fulfilling histologic remission (defined as a peak of fewer than 16 eosinophils per mm^2 HPF at week 6), and resolution of symptoms (i.e., no or only minimal problems), defined as a severity of 2 points or less on a numerical rating scale (NRS) of 0 to 10 points for dysphagia and a severity of 2 points or less on a NRS of 0 to 10 points for pain during swallowing on each day of the week prior to week 6. Key secondary end points included percentage of patients with histologic remission and percentage of patients with resolution of symptoms. HRQoL was assessed using the modified Short Health Scale (modSHS) and the Adult Eosinophilic Esophagitis Quality of Life (EoE-QoL-A) questionnaire.

In the BUL-1/EEA trial, the average age of participants was 37 years in both treatment groups, and the majority were men (81% and 86% for the budesonide 1 mg and placebo treatment groups, respectively). The mean time since an established EoE diagnosis was 49 months and 58 months for the budesonide 1 mg and placebo study groups, respectively, with a mean time since symptom onset of 134 months and 139 months, respectively. Almost all patients had current dysphagia symptoms at baseline. The mean Dysphagia NRS values at screening were 5.8 and 5.9, respectively, and the mean Pain During Swallowing NRS values at screening were 3.5 and 3.4 in the budesonide 1 mg and placebo groups, respectively. Nine patients in the budesonide 1 mg group (15.3%) and five patients in the placebo group (17.2%) had previous esophageal dilation.

Efficacy Results

The percentage of patients achieving resolution of symptoms (dysphagia and pain during swallowing) was 59.3% in the budesonide 1 mg group versus 13.8% in the placebo group. The difference between the budesonide 1 mg group and placebo group was 45.5% (95% confidence interval [CI], 27.8 to 63.3; $P < 0.0001$), which was clinically relevant and

statistically significant in favour of budesonide. The clinical experts indicated that using a questionnaire to assess resolution of symptoms is not common in clinical practice; they also indicated that the questionnaire used in the trial is simple to use. However, no studies validating the Dysphagia NRS and Pain During Swallowing NRS in patients with EoE were identified from the literature. A post-hoc analysis of resolution of symptoms used a more stringent criteria, which was defined as a severity of 0 points on a NRS of 0 to 10 points (0 to 10) for dysphagia and pain during swallowing on each day of the week prior to week 6. According to this most stringent criterion, none of the 29 patients in the placebo group (0.0%) versus 15 of the 59 patients in the budesonide 1 mg group (25.4%) achieved resolution of symptoms at week 6. The difference between the budesonide 1 mg group and placebo treatment group was 25.4% (95% CI, 14.3 to 36.5). The clinical experts indicated that the post-hoc analysis using the more stringent criteria was very strict, and they are comfortable with the definition of resolution of symptoms that was used in the main analysis.

Food impaction needing endoscopic intervention occurred in only one patient in the placebo group and none in the budesonide 1 mg group, and no endoscopic dilation was needed in either group during the study. It is uncertain if treatment with budesonide 1 mg effervescent tablets would actually decrease the risk of impaction and the need for endoscopic dilation.

In the BUL-1/EEA trial, HRQoL was assessed using EoE-QoL-A and modSHS. The mean change from baseline to week 6 was higher in the budesonide 1 mg group than in the placebo group for both the EoE-QoL-A 30-item total scores (mean difference = 0.24; 95% CI, −0.01 to 0.47) and consistently for each of the six subscales (eating/diet impact [10 items], eating/diet impact [four items], social impact, emotional impact, disease anxiety, and swallowing anxiety). Of note, the between-group difference in the eating/diet impact (10 items) subscale (0.50; 95% CI, 0.17 to 0.82) and the eating/diet impact (four items) subscale (0.49; 95% CI, 0.13 to 0.86) was significantly improved in favour of budesonide 1 mg, whereas these differences were less evident in the other four subscales in which the 95% CIs of the differences were all crossed as null, as shown in Table 2. Similarly, the modSHS also showed a consistent change from baseline to week 6, with between-group difference significantly improved in favour of budesonide 1 mg for social function and disease-related worry questions of the modSHS, but not for symptom burden and general well-being. A minimal important difference (MID) for the EoE-QoL-A and modSHS was not identified for patients with EoE. Also, the analysis of modSHS and EoE-QoL-A were not specifically tested for statistical significance with methods adjusted for multiplicity, despite a reporting of 95% CI. It is likely, however, that budesonide 1 mg may have substantially improved patients' eating/diet, whereas the clinical importance of the magnitude of improvement on other outcomes is uncertain.

Fifty-five of the 59 patients (93.2%) in the budesonide 1 mg group versus none of the 29 patients (0%) in the placebo group achieved histologic remission at week 6 (between-group difference was 93.2% [95% CI, 86.8 to 99.6; P < 0.0001]). In a post-hoc analysis of histologic remission that used a more stringent criteria, which was defined as peak eosinophils per mm^2 HPF of 0 in all biopsies at week 6, the difference between the budesonide 1 mg twice daily and placebo treatment groups was 89.8% (95% CI, 82.1 to 97.5; P < 0.0001).

The primary end point in the BUL-1/EEA trial was percentage of patients with clinicopathologic remission; this end point encompasses both histologic remission and patient-reported symptom resolution. Thirty-four of 59 patients (57.6%) in the budesonide

1 mg group versus none of the 29 patients (0%) in the placebo group achieved clinicopathologic remission at week 6. The difference between the budesonide 1 mg group and placebo treatment group on this composite outcome was 57.6% (95% CI, 38.2 to 72.0; P < 0.0001) in favour of budesonide. It is noteworthy that post-hoc analyses using a more stringent criteria for severity in symptoms remissions (severity of 0 points for dysphagia and pain during swallowing on each day of the week prior to week 6) and more stringent criteria for clinical remission (a peak of zero eosinophils per mm^2 HPF at week 6) was performed. The results showed that the difference on clinicopathologic remission was still favouring budesonide 1 mg (the between-group difference was 22.0% [95% CI, 11.5% to 32.6%; P = 0.0034]). Results from the primary end point and its main criteria (resolution of symptoms and histologic remission) indicate that almost every patient who achieved resolution of symptoms was also in histologic remission, but not vice versa. The clinical experts indicated that these results underscore the imperfect relationship between esophageal symptoms and the biological activity of EoE.

Harms Results

A higher proportion of patients reported treatment-emergent AEs (TEAEs) following treatment with budesonide 1 mg (37 patients, 62.7%) in comparison to patients treated with placebo (12 patients, 41.1%). The most frequently reported TEAE in the budesonide 1 mg group was suspected AEs of candidiasis, which occurred in 14 patients (23.7%) in the budesonide 1 mg treatment group and in none of the patients in the placebo group.

Of the 14 patients (23.7%) affected with local fungal infection in the budesonide 1 mg treatment group, 10 patients (16.9%) had esophageal candidiasis, three patients (5.1%) had oropharyngeal candidiasis, two patients (3.4%) had oral candidiasis, and two patients (3.4%) had Candida infection. Some patients had more than one fungal infection in different subcategories.

No deaths or serious adverse events (SAEs) occurred during the study in any of the treatment groups. One adverse event (AE) in the placebo group led to discontinuation of the treatment; there were no AEs in the budesonide 1 mg group. The one AE leading to discontinuation of treatment in the placebo group was an esophageal food impaction that was severe and needed endoscopic intervention.

There were 17 suspected AEs of candidiasis in the budesonide 1 mg treatment group versus none in the placebo group. Only four events (three esophageal candidiasis events and one oral candidiasis) in three patients (5.1%) were histologically confirmed and showed endoscopic and clinical signs.

Table 2: Summary of Key Results From Pivotal Studies, LOCF

	BUL-1/EEA trial	
	Budesonide 1 mg b.i.d. N = 59	Placebo N = 29
Patients with resolution of symptoms (i.e., no or only minimal problems), defined as a severity of ≤ 2 points on 0 to 10 NRS for dysphagia *and* a severity of ≤ 2 points on 0 to 10 NRS for pain during swallowing on each day of the week prior to week 6		
n (%)	35 (59.3)	4 (13.8)
Difference in proportions: Budesonide vs. placebo (95% CI)	45.5% (27.8% to 63.3%)	
P value	< 0.0001[a]	
Patients with no or only minimal problems in dysphagia defined as a severity of ≤ 2 points on 0 to 10 NRS for dysphagia on each day of the week prior to week 6		
n (%)	37 (62.7)	4 (13.8)
Difference in proportions: Budesonide vs. placebo (95% CI)	48.9% (31.3% to 66.5%)	
P value	NR	
Patients with no or only minimal problems in pain during swallowing defined as a severity of ≤ 2 points on 0 to 10 NRS for pain during swallowing on each day of the week prior to week 6		
n (%)	38 (64.4)	16 (55.2)
Difference in proportions: Budesonide vs. placebo (95% CI)	9.2% (−12.6% to 31.1%)	
P value	NR	
Change from baseline to week 6 in modSHS[b, c]		
Symptom burden		
Mean change from baseline (95% CI) at week 6	−31.6 (−40.2 to −23.1)	−17.6 (−28.3 to −6.9)
Treatment group difference vs. placebo	−14.0 (−28.1 to 0.05)	
P value	NR	
Social function		
Mean change from baseline (95% CI) at week 6	−28.9 (−36.8 to −21.0)	−14.1 (−22.8 to −5.4)
Treatment group difference vs. placebo	−14.8 (−27.4 to −2.2)	
P value	NR	
Disease-related worry		
Mean change from baseline (95% CI) at week 6	−20.6 (−27.8 to −13.4)	−7.8 (−16.3 to 0.6)
Treatment group difference vs. placebo	−12.8 (−24.4 to −1.2)	
P value	NR	
General well-being		
Mean change from baseline (95% CI) at week 6	−16.5 (−21.4 to −11.5)	−8.6 (−18.0 to 0.9)
Treatment group difference vs. placebo	−7.9 (−17.4 to 1.6)	
P value	NR	
Changes from baseline to week 6 of the total EoE-QoL-A questionnaire and its subscores[d, e]		
EoE-QoL-A, 30 items (weighted average)		
Mean change from baseline (95% CI) at week 6	0.47 (0.32 to 0.62)	0.24 (0.06 to 0.42)
Treatment group difference vs. placebo	0.24 (−0.01 to 0.47)	
P value	NR	
EoE-QoL-A eating/diet impact, 10 items (weighted average)		
Mean change from baseline (95% CI) at week 6	0.65 (0.41 to 0.88)	0.15 (−0.08 to 0.38)

	BUL-1/EEA trial	
	Budesonide 1 mg b.i.d. N = 59	Placebo N = 29
Treatment group difference vs. placebo	0.50 (0.17 to 0.82)	
P value	NR	
EoE-QoL-A social impact (weighted average)		
Mean change from baseline (95% CI) at week 6	0.46 (0.27 to 0.65)	0.30 (0.02 to 0.58)
Treatment group difference vs. placebo	0.16 (−0.17 to 0.49)	
P value	NR	
EoE-QoL-A emotional impact (weighted average)		
Mean change from baseline (95% CI) at week 6	0.44 (0.28 to 0.60)	0.23 (0.04 to 0.43)
Treatment group difference vs. placebo	0.20 (−0.05 to 0.46)	
P value	NR	
EoE-QoL-A disease anxiety (weighted average)		
Mean change from baseline (95% CI) at week 6	0.31 (0.17 to 0.45)	0.15 (−0.04 to 0.34)
Treatment group difference vs. placebo	0.16 (−0.08 to 0.39)	
P value	NR	
EoE-QoL-A swallowing anxiety (weighted average)		
Mean change from baseline (95% CI) at week 6	0.60 (0.39 to 0.80)	0.40 (0.13 to 0.68)
Treatment group difference vs. placebo	0.19 (−0.15 to 0.54)	
P value	NR	
Patients with histologic remission, defined as a peak of < 16 EOS/mm^2 HPF at week 6[f]		
n (%)	55 (93.2)	0 (0)
Difference in proportions: Budesonide vs. placebo (95% CI)	93.2% (86.8% to 99.6%)	
P value	< 0.0001[a]	
Patients in deep histologic remission, defined as peak EOS/mm^2 HPF of 0 in all biopsies at week 6[g]		
n (%)	53 (89.8)	0 (0)
Difference in proportions: Budesonide vs. placebo (95% CI)	89.8% (82.1% to 97.5%)	
P value	< 0.0001[b]	
Patients with clinicopathologic remission at week 6		
n (%)	34 (57.6)	0 (0)
Difference in proportions: Budesonide vs. placebo (95% CI)	57.6% (38.2% to 72.0%)	
P value	< 0.0001[a]	
Patients with clinicopathologic remission at week 6, based on peak of 0 EOS/mm˙ HPF and overall resolution of symptoms with maximal NRS = 0 points[g]		
n (%)	13 (22.0)	0 (0)
Difference in proportions: Budesonide vs. placebo (95% CI)	22.0% (11.5% to 32.6%)	
P value	0.0034[b]	
Harms, n (%) (safety analysis set)		
AEs	37 (62.7)	12 (41.1)
SAEs	0	0
WDAEs (from study treatment)	0	1 (3.4)
Deaths	0	0

	BUL-1/EEA trial	
	Budesonide 1 mg b.i.d. N = 59	Placebo N = 29
Notable harms, n (%)		
Local fungal infection	14 (23.7)	0
Candida infection	2 (3.4)	0
Esophageal candidiasis	10 (16.9)	0
Oral candidiasis	2 (3.4)	0
Oropharyngeal candidiasis	3 (5.1)	0
Psychiatric disorders	0	1 (3.4)
Insomnia	0	1 (3.4)
Symptoms of sore throat (pharyngitis)	1 (1.7)	2 (6.9)

AE = adverse event; b.i.d. = twice a day; CI = confidence interval; EoE-QoL-A = Adult Eosinophilic Esophagitis Quality of Life; EOS = eosinophil; HPF = high-power field; LOCF = last observation carried forward; modSHS = modified Short Health Scale; NR = not reported; NRS = numerical rating scale; SAE = serious adverse event; vs. = versus; WDAE = withdrawal due to adverse event.

[a] Fisher exact test (test for superiority, one-sided alpha level of 0.025).

[b] Range of each score: 0 to 100. Lower numbers indicate higher quality of life.

[c] Two-sided 95% CIs for the mean modSHS: Symptom burden, social function, disease-related worry, and general well-being per group and for the group difference in means, based on t-distribution.

[d] The EoE-QoL-A yields an overall score and five subscale scores. Scores range from 0 to 4. Higher scores indicate better quality of life.

[e] Two-sided 95% CIs for the mean EoE-QoL-A: Overall score (30 items, weighted average), overall score (24 items, weighted average), eating/diet impact (10 items, weighted average), eating/diet impact (four items, weighted average), social impact (weighted average), emotional impact (weighted average), disease anxiety (weighted average), and swallowing anxiety (weighted average). Absolute change from baseline per group and for the group difference in means, based on t-distribution.

[f] For this analysis, results that were not evaluable were set to “no.”

[g] Post-hoc analysis.

Source: Clinical Study Report of the BUL-1/EEA trial.[9]

Critical Appraisal

The BUL-1/EEA trial used accepted methods to conceal allocation and randomize patients to treatments; in addition, matched placebo was used to maintain blinding. The patients’ baseline characteristics and prior treatment experience appeared to be roughly balanced at baseline between groups, despite certain large variations observed between the treatment groups, perhaps due to a small sample size in the placebo group (N = 29). Notably, more patients previously received PPI (54% versus 45%) and topical budesonide (20% versus 10%) in the budesonide 1 mg group compared to placebo. The validity, test-retest reliability, and responsiveness of the outcome measures Dysphagia NRS, Pain During Swallowing NRS, Physician’s Global Assessment (PGA) of EoE activity, and Patient’s Global Assessment (PatGA) concerning the severity of EoE symptoms used were not established in the BUL-1/EEA trial. Also, MID in the EoE population is not available for any of the patient-reported outcomes (PROs) assessed. Subjective recall biases were highly likely, particularly when such recall was differential between treatment groups, due perhaps to patients’ or assessing physicians’ awareness of the treatment assignment as a result of drug-related side effects, such as local fungal infections, gastroesophageal reflux disease (GERD), or nausea.

Patients enrolled in the BUL-1/EEA trial appear to be similar, in general, to patients with EoE in Canada. The clinical experts indicated that patients enrolled in the trial can be categorized as being moderate to severe. The BUL-1/EEA trial excluded patients with

severe strictures, which may limit the interpretations of the efficacy findings to patients who have strictures with a predominant inflammatory component.

The use of systemic or topical glucocorticoids, biologics, or immunosuppressants (except for PPI) as concomitant medication or the initiation of dietary restrictions were prohibited during the study treatment period. However, in clinical practice, symptomatic patients often receive dietary or pharmacologic treatment. Hence, the beneficial treatment effect as observed in the BUL-1/EEA trial may not be generalizable to real-world settings, i.e., as an add-on to those patients on concurrent treatment with dietary restriction or PPI.

In order to enrol in the BUL-1/EEA trial, patients had to have undergone a documented trial with PPIs in order to exclude PPI-REE. Health Canada approved budesonide 1 mg for the induction of clinicopathologic remission in adults with EoE without restrictions on prior PPI use. It is uncertain whether patients who are PPI naive would respond to budesonide 1 mg in the same manner as patients who were included in the trial.

EoE is a chronic condition where patients experience recurrences of inflammation requiring re-treatment or changes in therapy over time. The BUL-1/EEA trial was not long enough to assess how long the remission would be maintained. Also, it is uncertain whether patients who relapse would respond to a subsequent course of treatment with budesonide 1 mg in the same manner as they responded the first time they received budesonide 1 mg.

Indirect Comparisons

No indirect comparisons were identified or submitted by the sponsor.

Other Relevant Evidence

Description of Studies

In the BUL-1/EEA trial, patients eligible to enroll in the OLI treatment phase of the study were those patients who were not in clinicopathologic remission at completion of the double-blind treatment phase, or who were prematurely withdrawn due to lack of efficacy after at least four weeks of treatment and showed no change or a deterioration in the PatGA concerning the severity of EoE symptoms compared to baseline at their last visit in the double-blind treatment phase, or who were experiencing a food impaction at any time that needed endoscopic intervention. All patients eligible for OLI treatment had the option to enter a six-week OLI treatment with budesonide 1 mg twice daily. Overall, 51 patients (58.0%) participated in the OLI phase of the study: 28 patients (96.6%) from the double-blind, placebo-treated patient group and 23 patients (39.0%) from the double-blind budesonide 1 mg twice daily treatment patient group.

Study BUU-2/EEA (N = 77) was a phase II, double-blind, double-dummy, randomized, placebo-controlled trial. Study BUU-2/EEA compared twice daily oral treatment with budesonide 1 mg or 2 mg effervescent tablets for orodispersible use, 5 mL viscous budesonide suspension (0.4 mg/mL) twice daily, or placebo in adult patients with clinico-histologic active EoE. The screening period of up to five weeks was followed by a two-week treatment period and a two-week follow-up period. The patients were assigned in a ratio of 1:1:1:1 to one of the following: one budesonide 1 mg effervescent tablet (budesonide 1 mg) twice daily plus 5 mL viscous placebo suspension twice daily for 14 days, one budesonide 2 mg effervescent tablet twice daily plus 5 mL viscous placebo suspension twice daily for 14 days, 5 mL budesonide viscous suspension (0.4 mg/mL) twice daily plus one placebo effervescent tablet twice daily for 14 days, or one placebo effervescent tablet twice daily

plus 5 mL viscous placebo suspension twice daily for 14 days. Budesonide 2 mg effervescent tablet twice daily is not a dosage approved by Health Canada; hence, results of this treatment group were not further reported. The primary efficacy end point in the BUU-2/EEA trial was the percentage of patients with histologic remission, defined as a mean of fewer than 16 eosinophils per mm^2 HPF at week 2. The main secondary efficacy end points were percentage of patients with histologic remission (defined as a peak of < 16 eosinophils per mm^2 HPF at week 2), course and change of the Dysphagia Score within the study, and change from baseline in modSHS.

Efficacy Results

In the OLI phase of the BUL-1/EEA trial, 17 patients (73.9%) in the budesonide followed by budesonide group and 23 patients (82.1%) in the placebo followed by budesonide group achieved resolution of symptoms on each day prior to week 6 OLI. There was no food impaction and there was no need for an endoscopic dilation during the OLI treatment phase in any treatment group. Nineteen patients (82.6%) in the budesonide followed by budesonide group and 25 patients (89.3%) in the placebo followed by budesonide group achieved histologic remission at week 6 OLI. Sixteen patients (69.6%) in the budesonide followed by budesonide group and 22 patients (78.6%) in the placebo followed by budesonide group achieved clinicopathologic remission at week 6 OLI.

In the OLI phase of the BUL-1/EEA trial, in both treatment groups, there was improvement from week 6 double-blind (end of treatment [EOT] or withdrawal) to week 6 OLI in the four health dimensions of modSHS (symptom burden, social function, disease-related worry, and general well-being). The between-group difference did not favour any treatment group in any of the four health dimensions. Also, the between-group difference did not favour any treatment group for any subscale measured by the total EoE-QoL-A questionnaire. Due to the lack of MID for the modSHS questionnaire and the total EoE-QoL-A questionnaire, the clinical importance of the reported improvements is unknown.

In the BUU-2/EEA trial, 10 out of the 19 patients (52.6%) in the budesonide 1 mg group, nine out of the 19 patients (47.4%) in the budesonide viscous suspension 2 mg group, and seven out of the 19 patients (36.8%) in the placebo group experienced clinical improvement (defined as a decrease of ≥ 3 points in the Dysphagia Score) at week 2. The difference between the budesonide 1 mg group and placebo treatment group was 15.8% (95% CI, −15.4 to 47.0; P = not reported), and the difference between the budesonide viscous suspension 2 mg group and the placebo treatment group was 10.5% (95% CI, −20.7% to 41.7%; P = not reported). The between-group difference did not favour any treatment group. No comparison between the budesonide 1 mg group and the budesonide viscous suspension 2 mg group was conducted.

In the BUU-2/EEA trial, the four scores of the modSHS questionnaire showed a decrease from baseline to the EOT or withdrawal visit in all treatment groups. However, due to the large variability of the four scores and due to large differences between treatment groups at baseline, no differences in changes from baseline to the EOT or withdrawal visit of the four scores of the modSHS questionnaire between treatment groups can be concluded.

In the BUU-2/EEA trial, none of the 19 patients (0%) in the placebo group, all of the 19 patients (100%) in the budesonide 1 mg group, and 18 out of the 19 patients (94.7%) in the budesonide viscous suspension 2 mg group achieved histologic remission, defined as the mean of fewer than 16 eosinophils per mm^2 HPF at week 2. The difference between the budesonide 1 mg group and placebo treatment group was 100% (95% CI, 64.7 to 100; P =

< 0.0001), and the difference between the budesonide viscous suspension 2 mg group and the placebo treatment group was 94.7% (95% CI, 57.6 to 99.5; P = < 0.0001). The between-group difference showed that both budesonide treatment groups were superior to placebo. No comparison between the budesonide 1 mg group and the budesonide viscous suspension 2 mg group was conducted.

Harms Results

In the OLI phase of the BUL-1/EEA trial, the nature of the reported AEs appears to be in line with those presented in the pivotal trial. In total, 24 TEAEs occurred in 16 patients (57.1%) in the placebo followed by budesonide group and 35 TEAEs occurred in 13 patients (57.1%) in the budesonide followed by budesonide group. The most frequently reported TEAEs were esophageal candidiasis with eight patients (28.6%) affected in the placebo followed by budesonide group and one patient (4.3%) in the budesonide followed by budesonide group, and headache with one patient (3.6%) in the placebo followed by budesonide group and four patients (17.4%) in the budesonide followed by budesonide group. No deaths or SAEs occurred during the course of the OLI phase. Two AEs in one patient led to discontinuation of budesonide in the placebo followed by budesonide group. The AEs leading to discontinuation of budesonide were lip edema and oral paresthesia.

In the BUU-2/EEA trial, proportions of patients with at least one TEAE were larger in the budesonide groups (36.8% and 57.9% in the budesonide 1 mg group and budesonide viscous suspension 2 mg twice daily treatment group, respectively) than in the placebo group (10.5%). The most frequently reported TEAEs in the budesonide 1 mg treatment group were suspected cases of esophageal candidiasis, which occurred in two patients (10.5%) in the budesonide 1 mg treatment group, in three patients (15.8%) in the budesonide viscous suspension 2 mg twice daily treatment group, and in none of the patients in the placebo group. No deaths or SAEs occurred during the course of the trial. One patient in the budesonide viscous suspension 2 mg twice daily treatment group experienced an edema of the lips five days after first intake of study medication.

Critical Appraisal

The main limitations associated with the OLI phase of the BUL-1/EEA trial arise from the open-label study design, lacking randomization, and the within-group comparisons to week 6 of the double-blind phase in the trial. These may have an impact on the subjective patient-reported questionnaires on dysphagia symptoms, pain during swallowing, and HRQoL where reported improvement to these questionnaires could have been overestimated.

In the BUU-2/EEA trial, the sample size per group was relatively small, and the baseline characteristics were not well-balanced across treatment groups. However, these differences were not clearly suggestive of a specific bias toward favouring unduly the active treatments groups. The Health Canada product monograph for budesonide orodispersible tablets indicates that the usual treatment duration is six weeks. Patients enrolled in the BUU-2/EEA trial received budesonide for only two weeks; hence, the generalizability of the study results for the budesonide 1 mg twice daily treatment group to Canadian patient population is unclear. Finally, budesonide viscous suspension is not indicated for treatment of EoE, and it is used off-label for the treatment of EoE. The clinical experts indicated that the regular dose used in clinical practice is 1 mg twice daily budesonide viscous suspension; however, patients in the BUU-2/EEA trial received budesonide viscous suspension 2 mg twice daily, which is double the dose used in the clinical practice. Hence,

the generalizability of the study results for the budesonide viscous suspension 2 mg twice daily treatment group to Canadian patient population is unclear.

Conclusions

The BUL-1/EEA trial provided evidence on the efficacy and safety of budesonide effervescent tablets 1 mg for the induction of clinicopathologic remission in adult patients with active EoE. The BUL-1/EEA trial demonstrated a statistically significant and clinically meaningful improvement of budesonide 1 mg twice daily in inducing clinicopathologic remission in patients with active EoE when compared to placebo, following six weeks of treatment. In addition, budesonide effervescent tablets 1 mg twice daily demonstrated a statistically significant and clinically meaningful improvement on symptomatic remission, following pre-specified criteria that the clinical expert recognized as appropriate. It is uncertain if treatment with budesonide 1 mg effervescent tablets would decrease the risk of impaction and the need for endoscopic dilation. In association with the improvement of patients' symptoms, there were likely consistent improvements of patients' HRQoL, particularly impact on eating and/or diet, even though the assessment of these outcomes may have suffered methodological limitations. The effect of budesonide effervescent tablets 1 mg seemed to be more pronounced on the histologic component and somewhat less so on the symptomatic remission, where 93% achieved histologic remission. The duration of the remission, however, is uncertain. It is also uncertain whether patients who relapse would respond to a subsequent course of treatment with budesonide 1 mg in the same manner as they responded the first time they received budesonide 1 mg. Safety data from the BUL-1/EEA trial did not demonstrate any notable concern. Long-term safety, particularly in combination with other pharmacological therapies, remains unknown.

Introduction

Disease Background

EoE is a chronic, local immune-mediated, esophageal disease characterized histologically by eosinophil-predominant inflammation and, clinically, by symptoms related to esophageal dysfunction.[1, 2] The most commonly reported symptoms in older children and adults are dysphagia (difficulty swallowing), food impactions (food getting stuck in the esophagus), and non–swallowing-associated chest pain.[1, 2] EoE is considered to be a progressive condition and is not outgrown. Left untreated, EoE can progress to a fibrostenotic condition that is characterized by stricture formation and functional abnormalities, such as food bolus impaction (choking on food) requiring removal by means of an emergency endoscopic procedure.[2, 10] Another serious and potentially life-threatening complication of EoE is esophageal perforation and/or rupture, termed spontaneous Boerhaave syndrome, which can occur following prolonged and severe vomiting, resulting from vomiting during an endoscopy or as a complication of esophageal food bolus impaction.[11] EoE impairs patients' social and psychological functioning and significantly impacts their HRQoL.[2]

EoE can occur at any age; as well, there is a male predominance, it is more common in white people, and there is a strong association with atopic diseases.[12] Epidemiologic data on EoE is relatively sparse due to the poor awareness and recognition of the disease in the past. Recent literature suggests that the prevalence of EoE is on the rise, in part due to the increased recognition and improvement in diagnosis.[13] In Canada, the most recent estimates of EoE were published in a systematic review in 2018, which reported an incidence rate of 2.1 to 10.7 EoE cases per 100,000 per year.[3] Notably, separate estimates for pediatric and adult populations were not provided. In contrast, the global incidence of EoE is estimated at 7.7 per 100,000 adults with no significant differences between the results from different countries.[14]

The diagnosis of EoE is based upon symptoms, histologic findings, and endoscopic appearance. Patients with chronic symptoms of esophageal dysfunction (e.g., food impaction, dysphagia, odynophagia, abdominal pain, heartburn, food refusal, regurgitation, or chest pain) are suspected of having EoE.[1] The index of suspicion is raised if the patient has a history of atopic comorbidities (e.g., atopic dermatitis, asthma, or immediate food-type allergies) and a family history of dysphagia or EoE. A history of severe pain after dilation of a stricture or esophageal perforation also raises suspicion of this disorder. The diagnosis is established by upper endoscopy with esophageal biopsies in addition to an evaluation to exclude other disorders that can cause esophageal eosinophilia.[1] Because the symptoms of EoE are not specific, the diagnosis may be missed. [1] The diagnostic criteria of EoE are based on an updated international consensus published by Dellon et al. (2018),[4] and include the following: presence of clinical symptoms indicative of esophageal dysfunction, eosinophil-predominant inflammation on esophageal biopsy, consisting of a peak value of at least 15 eosinophils per HPF (or 60 eosinophils per mm^2), and the exclusion of any non-EoE disorders that may be responsible for or contributing to symptoms and esophageal eosinophilia.[1,4]

Standards of Therapy

The management of EoE includes a variety of dietary, pharmacologic, and endoscopic interventions.[5] The aim of therapy is symptomatic relief, with histologic improvement in

esophageal eosinophilia and, in the case of pediatric patients, restoration of normal growth and development.[6] The clinical experts consulted for this review indicated that there is no formal Canadian guideline for this condition; evidence from literature is generally consulted and personal experience is followed when prescribing treatments. The most recent treatment guidelines identified from the literature were developed by authors participating on behalf of the United European Gastroenterology, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition, the European Academy of Allergy and Clinical Immunology, and the European Society of Eosinophilic Oesophagitis and published by Lucendo et al. (2017);[2] the guidelines provided a treatment algorithm that was used in the updated international consensus guidelines[4] and a recent Canadian article entitled "Practical Guide to Allergy and Immunology in Canada."[15] Commonly used treatments can be broadly classified into dietary therapy, pharmacotherapy, and surgical interventions.

Dietary therapy is one of the first-line treatment options in children and adults, and involves avoidance of diets to minimize allergen exposure.[2, 6] The empirical six- or four-food elimination diet involves the avoidance of the most common allergy-triggering food groups (e.g., milk, eggs, wheat and gluten, soy and legumes, peanut, tree nuts, fish and shellfish) and is a common dietary management for EoE. This is sometimes modified into targeted elimination diets where foods are typically added back one at a time with follow-up endoscopies to pinpoint the allergy-causing agent(s).[16] In elemental diets, all forms of food are removed from the diet and instead replaced with amino acid formula as well as simple sugars and oils. Generally reserved for children with multiple food allergies, this form of treatment sometimes requires a feeding tube to avoid the poor taste of the formula and is reserved for those who are refractory to other therapies.[16] Dietary management with food restriction poses a risk of nutritional deprivation resulting from unnecessary food aversion, can be difficult for caregivers (particularly if nasogastric feedings or gastrostomy tubes are required), and adds burden to the cost and convenience of the treatment.[6] Both elemental and elimination diets should be administered under the supervision of a registered dietitian; they have shown moderate to high clinical and histologic improvement depending on adherence.[6]

Prior to the approval of budesonide orodispersible tablets in Canada, there were no approved pharmacological drugs for the treatment of EoE. As a result, PPIs and topical corticosteroids are used off-label to treat the disease.[2 ,7] Both might be offered as first-line anti-inflammatory pharmacologic therapy.[2, 7] The efficacy of any pharmacological or dietary therapy should be checked after a six- to 12-week initial course by means of a follow-up endoscopy.[2, 7] If patients respond to PPI therapy, it is recommended to continue the PPI therapy at the lowest dose successful at controlling symptoms; however, the best maintenance doses have yet to be defined.[2, 6] It is worth noting that the diagnostic criteria for EoE have evolved since EoE was first conceptually defined, where one of the diagnostic criteria in prior guidelines was the persistence of mucosal eosinophilia in the esophagus after two months of treatment with a PPI.[1, 4, 17] However, PPIs are currently considered one of the treatment options for EoE. The rationale for exclusion of a PPI trial from the EoE diagnostic criteria is that patients with clinical and histologic features compatible with EoE but who respond histologically to a PPI do not appear to be distinct from those with EoE,[1, 17] and the most recent diagnostic guidelines for EoE considered PPI-REE as a subset of EoE rather than a distinct disease.[1, 4]

Patients who are nonresponsive to PPIs are treated with corticosteroids — in particular, drugs used for the treatment of asthma, given the pathological similarities between the two conditions.[2] Two drugs, fluticasone propionate and nebulized budesonide, are generally

prescribed. Fluticasone, as per its instructions, is to be sprayed into the patient's mouth and then swallowed, while budesonide can be administered using a nebulizer and patients are then instructed to mix budesonide with sucralose or another thickener to form an aqueous gel (slurry) prior to administration.[2, 6] Topical corticosteroids are associated with several limitations, preventing the development of an optimized formulation. Their efficacy has been investigated in a limited number of studies and patients, and those studies have limited comparability since the agents, daily dosages, length of treatment, methods of administration, and definition of outcomes were not standardized.[2] Maintenance therapy with topical steroids and/or dietary restriction should be mainly considered in patients with food impaction or severe dysphagia, high-grade esophageal stricture, and rapid symptomatic or histologic relapse following initial therapy.[17] Systemic corticosteroids, such as prednisone, are not recommended for the treatment of EoE.[2] A number of recent biologics show promising results; however, these are not yet approved in Canada.[2]

Esophageal dilation is a non-pharmacological treatment where the narrowed area of the esophagus is dilated, or stretched, using either a bougie (cone-shaped tube) or a balloon as the dilator.[18] This procedure is effective for relieving dysphagia, but has no effect on underlying inflammation.[6] Esophageal dilation is generally reserved for patients with strictures or rings who have not responded to medical therapy.[6] Esophageal dilation should be performed carefully since sometimes it leads to complications such as chest pain and life-threatening esophageal perforation.[6, 17]

Drug

Budesonide orodispersible tablets (also referred to as budesonide) is indicated for the induction of clinicopathologic remission in adults with EoE.[8]

Budesonide is formulated as a 1 mg orodispersible tablet, which is designed to dissolve by effervescence in the mouth and mix with saliva prior to swallowing. It should be placed on the tip of the tongue and gently pressed against the top of the mouth, where it will dissolve. This will usually take about two minutes. The effervescence process of the tablet starts after budesonide comes into contact with saliva and stimulates the production of further saliva. The dissolved material should be swallowed with saliva little by little while the orodispersible tablet disintegrates. The orodispersible tablet should not be chewed or swallowed undissolved.[8] The recommended daily dose of budesonide is one 1 mg orodispersible tablet in the morning and one 1 mg orodispersible tablet in the evening (total dose of 2 mg of budesonide daily). The usual treatment duration is six weeks. Budesonide is recommended after a meal and no food or liquid should be taken during or after 30 minutes of administration.[8]

Budesonide is a non-halogenated glucocorticosteroid, which acts primarily as an anti-inflammatory. Following its binding to the glucocorticoid receptor, budesonide will inhibit the antigen-stimulated secretion of various pro-inflammatory signal molecules, in the esophageal epithelium. The inhibition of these pro-inflammatory signals may significantly reduce the eosinophilic infiltration of the esophagus.[8]

The sponsor is requesting that budesonide be reimbursed for the induction of clinicopathologic remission in adults with EoE, which is concordant with the Health Canada indication.[19]

Budesonide underwent a priority review by Health Canada, as the drug is intended for the treatment of a life-threatening or severely debilitating disease or condition for which there is

no existing drug on the Canadian market with the same profile.[19] A table describing key characteristics of commonly recommended drugs for EoE is presented in Table 3.

Table 3: Key Characteristics of Budesonide Orodispersible Tablets, Proton Pump Inhibitors, Budesonide Nebules, and Topical Fluticasone

	Budesonide orodispersible tablets (Jorveza)	PPIs	Budesonide nebules	Topical fluticasone
Mechanism of action	Reduces the eosinophilic infiltration of the esophagus	Effectively block acid secretion	Anti-inflammatory corticosteroid	Anti-inflammatory corticosteroid
Indication[a]	Induction of clinicopathologic remission in adults with EoE	Reflux esophagitis	Asthma	Asthma
Route of administration	Oral	Oral	Can be administered using a nebulizer and patients are then instructed to swallow the accumulated liquid or take as an oral viscous slurry	Administered using a metered dose inhaler without a spacer. The medication is sprayed into the patient's mouth and then swallowed.
Recommended dosage	2 mg as 1 tablet (1 mg) in the morning and 1 tablet (1 mg) in the evening	Varies by drug	• Induction dosing (usually divided doses): 2 mg/day to 4 mg/day • Maintenance dosing (usually divided doses): 2 mg/day Budesonide nebules come in concentrations of 0.125 mg/mL, 0.25 mg/mL, or 0.5 mg/mL.	• Induction dosing (usually divided doses): 1,760 mcg/day • Maintenance dosing (usually divided doses): 880 mcg/day to 1,760 mcg/day
Serious adverse effects or safety issues	Fungal infections (candidiasis) of the mouth, pharynx, and esophagus	**Warnings and precautions** • There is an increased risk for CDI and CDAD. • There is an increased risk for osteoporosis-related fractures of the hip, wrist, or spine.	• Systemic corticosteroid effects (especially high-dose inhaled corticosteroid) • Localized candidiasis	• Systemic corticosteroid effects (especially high-dose inhaled corticosteroid) • Localized candidiasis

	Budesonide orodispersible tablets (Jorveza)	PPIs	Budesonide nebules	Topical fluticasone
		• Effects of long-term treatment include hypergastrinemia, possible enterochromaffin-like cell hyperplasia and carcinoid formation in the stomach, adenomas, and carcinomas in the liver, and neoplastic changes in the thyroid.		

CDAD = *Clostridium difficile*-associated diarrhea; CDI = *Clostridium difficile* infection; EoE = eosinophilic esophagitis; PPI = proton pump inhibitor.

[a] Health Canada–approved indication.

Source: CADTH Common Drug Review clinical expert, e-CPS,[20] Lucendo et al. (2017),[2] and Jorveza product monograph.[8]

Stakeholder Engagement

Patient Group Input

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Groups Supplying Input

A total of six Canadian and international patient group submissions were received for this review. The Gastrointestinal Society in Canada acts as a liaison between patients with gastrointestinal and liver conditions and health care professionals, other patient groups, and governments at all levels. It is involved in providing evidence-based information in all areas of the gastrointestinal tract, supporting research, advocating for appropriate patient access to health care, responding to information requests, participating in community initiatives, and promoting gastrointestinal and liver health. The international submissions included a number of non-profit and patient advocacy groups, including the Families Affected by Eosinophilic Disorders in the UK, the American Partnership for Eosinophilic Disorders and the Campaign Urging Research for Eosinophilic Disease in the US, ausEE Inc. in Australia, and the Spanish Association for Eosinophilic Esophagitis in Spain. These organizations aim to raise awareness among the public and health care professionals of eosinophilic conditions through education, advocacy, creating awareness, and providing support to families, patients, and caregivers.

All the patient groups indicated that they had no help from outside their organizations to collect and analyze data, or to complete the submission. With the exception of the Gastrointestinal Society and ausEE, all the remaining patient groups received funding from a number of pharmaceutical companies and advocacy groups. Families Affected by Eosinophilic Disorders and the Spanish Association for Eosinophilic Esophagitis received less than $5,000 over the past two years from Dr. Falk Pharma GmbH, the sponsor of budesonide orodispersible in Europe.

2. Condition-Related Information

The patient groups collected information using a combination of published studies, self-reported data that patients or caregivers (including parents of patients) shared with various online platforms, and personal experiences shared by the patients and/or caregivers or members of the patient groups. Notably, the American Partnership for Eosinophilic Disorders, the Campaign Urging Research for Eosinophilic Disease, Families Affected by Eosinophilic Disorders, and ausEE provided information from parents of children suffering from various eosinophilic gastrointestinal diseases (EGIDs). ausEE conducted a member survey in 2019 through an online platform, with respondents across all Australian states and a small proportion of non-Australian members. The survey included 157 people with direct experience with EGID, of whom 89% had a diagnosis of EoE, with an age range at diagnosis of six months to 66 years.

EGID is a rare disease characterized by chronic inflammation in the gastrointestinal tract resulting from an unusual increase in the number of eosinophils without evidence of infections or cancer. EoE is the most common form of EGID, where there is an accumulation of eosinophils in the esophagus, the tube that carries food from the mouth to the stomach. The symptoms of EoE vary among individuals and can include difficulty swallowing, choking, regurgitation, nausea, vomiting, fatigue, reflux, abdominal and/or chest pain, as well as malnutrition and failure to thrive in the case of young children. Left

untreated, EoE may lead to malnutrition, poor growth, and anemia. In some patients, EoE is complicated by the development of narrowing in the esophagus (strictures) that can cause issues with swallowing and choking. In addition, living with EoE greatly impacts the daily lives of patients and their families — socially, mentally, and financially. Dietary restriction presents the biggest burden to the lives of patients and caregivers, negatively impacting activities such as holidays and family gatherings, social engagements, dining away from home, and travel. Specialty foods or ingredients are time consuming and cumbersome to prepare, difficult to find in local grocery stores, often expensive; they almost exclusively require preparation at home. The simple act of eating and chewing food takes longer, which — combined with difficulty swallowing, choking, and regurgitation — makes it difficult to share regular meals with others and eat with companions. Patients are therefore seriously limited in attending social events with family, relationships, and work as their experiences are not shared by others. This often results in social isolation, anxiety, and an overall decrease in quality of life.

The symptoms of EoE are often similar to other well-known gastrointestinal diseases, such as GERD. Many individuals can therefore go years without a proper diagnosis. Being a chronic disease that can be triggered by any food or aeroallergen that a particular patient is allergic to, it takes a lot of trial and error through the process of elimination to pinpoint the specific allergen(s). The process of diagnosis may therefore take a long time for some patients, which adds to the burden of the disease. The following are quotes from patients to reflect their daily hardships from EoE:

"*My quality of life is effected daily. Imagine living your life without food? Our world revolves around food no matter what the occasion is.*"

"*EoE severely affects my day-to-day life, restricting many activities and causing time off work. This disease is isolating to say the least.*"

3. Current Therapy-Related Information

There is presently no cure for EoE; the goal of treatment is to eliminate the eosinophils in the affected area, thereby alleviating symptoms and reducing inflammation. Treatment is generally tailored to the patient's needs and responses, and includes a combination of diet management and medications.

Patients with EoE often have high rates of food allergies, and those allergies may contribute to the accumulation of eosinophils. Therefore, dietary therapy typically involves following some form of diet restriction, notably elimination diet, elemental diet, and food trial. Elimination diet involves excluding common allergy-causing foods (milk, eggs, wheat, soy, peanuts, tree nuts, fish, and shellfish) instead of basing dietary elimination on allergy-testing results. However, the currently available allergy-testing methods (skin prick test, blood test or patch test) are not reliable enough to detect specific food allergens consistently. While some patients already live with food allergies, some individuals may develop immunoglobulin-mediated food allergies, including anaphylaxis to previously tolerated foods after prolonged avoidance of certain foods. In cases where EoE cannot be controlled with medication or elimination diets, a prescribed elemental formula may be advised to meet nutritional needs, either for short-term or long-term use, depending on the individual. In an elemental diet, all sources of protein are removed from the diet and supplemented with only a cocktail of amino acids, sugars, vitamins, minerals, and fats. This form of treatment is common in infants and young children; however, some individuals may not consume adequate calories or tolerate the elemental diet due to the foul taste and

therefore require feeding tubes, which come at additional costs (as they are not always covered by insurance) and affect quality of life. In extreme cases, feeding tubes and feeding pumps may be used, but this can have huge impacts on daily life for patients and caregivers and can need 24-hour support. Lastly, a food trial involves removing specific foods from the diet and then adding them back one at a time to pinpoint which food(s) causes a reaction. The impact of food trials and putting foods in and taking them away again after a positive scope is emotionally very challenging and makes restrictive diets even harder. Overall, restricted diets can result in nutritional inadequacies, many patients struggle to access knowledgeable dietitians, and compliance of a highly restricted diet is very difficult if not impossible on a long-term basis.

Pharmacologic management includes a variety of steroids (fluticasone or budesonide) and acid suppressors (antacid and/or PPIs, e.g., omeprazole, esomeprazole, or lansoprazole). Current corticosteroids generally result in remission; however, these are primarily asthma medications used off-label, administered with an inhaler or mixture. The non-specific nature of the drug delivery method makes the effectiveness uncertain and varied. Budesonide is used as a mixture with a thickener, which can be prepared at home or bought at pharmacies. Preparation at home may be cost-effective but is sometimes difficult to prepare in the right mixture, while buying from pharmacies adds to the cost. Fluticasone is available in vials, which are swallowed directly, is well tolerated, and easy to use. However, there is some evidence of suprarenal impairment in kids taking fluticasone; therefore, a blood assessment is necessary to reassure kidney function. Systemic corticosteroids such as prednisone are not used for chronic management but may be prescribed for acute situations and short periods of time. PPIs may help relieve inflammation and control acid production in some patients; however, there is concern about long-term usage of reflux medications. Overall, current medications provide some relief for damage to the esophagus and allow patients to slightly increase their diet; however, there are few available options that are not always covered by insurance as they are used off-label and not currently approved for the treatment of EoE.

Finally, continuous disease surveillance is prescribed in patients to determine tolerance and/or effectiveness, which involves repeat endoscopies with biopsies as foods and/or medications are introduced. These procedures are invasive, require additional hospital visits, and add to the cost of already expensive and variedly effective treatment regimens.

4. Expectations About the Drug Being Reviewed

Patients across the six submissions had similar expectations from the new therapy. Patients overwhelmingly expressed an unmet need for a treatment that is specifically designed and prescribed for EoE, and that is covered through insurance. Additionally, patients expressed a desire for convenience in medication administration as well as clear instructions to maintain compliance. Patients acknowledged the unfortunate reality of not having a curative treatment for this chronic condition; however, there is a hope and need for a treatment that improves their day-to-day quality of life (i.e., for eating, working, and socializing). Finally, patients indicated that an effective therapy that resolves clinicopathologic symptoms and has minimum long-term complications is of high importance. One caregiver of a patient with EoE captured the unmet needs and expectations from a new treatment the following way: "*Convenience, cost, insurance coverage, accessibility, [the therapy's] effect on daily life such as work/travel/school, side effects, treatment effect on symptoms and scope results, ability to eat more foods with drug therapy, risks, research proof of concept and successful trials are things considered when*

choosing a therapy." Overall, administration of a medication that is targeted for EoE, has adequate effectiveness, minimal and manageable side effects and cost burden, and would improve quality of life were the most commonly mentioned things that should be evaluated when considering new therapies.

One patient group reported findings from a clinical trial involving patients receiving Jorveza, after being nonresponsive to PPIs. Patients confirmed good tolerability and an improvement in clinical symptoms as well as histology. High cost and some oral candidiasis were among the major negatives. Similar findings were reported in one patient in a separate submission, in which the patient-reported convenience and simplicity of taking the right dose of medication when not in home as a major plus point. The patient also reported fewer episodes of choking on food and a general improvement in symptoms since taking Jorveza. One submission reported findings from published studies in which budesonide treatment resulted in reduced symptoms and eosinophils count, endoscopic and histologic improvement, and an overall better quality of life. Overall, while Jorveza is not a curative treatment for EoE, it was reported as an easy medication to take, since patients only need to take two pills per day for six to 12 weeks, and it has demonstrated to be an effective treatment for a disease with few options. One patient group indicated that further studies and patient follow-up should be undertaken for ongoing assessment, treatment, and management after the 12-week course.

Clinician Input

All CADTH review teams include at least one clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results and providing guidance on the potential place in therapy). In addition, as part of the budesonide review, a panel of six clinical experts from across Canada was convened to characterize unmet therapeutic needs, assist in identifying and communicating situations where there are gaps in the evidence that could be addressed through the collection of additional data, promote the early identification of potential implementation challenges, gain further insight into the clinical management of patients living with a condition, and explore the potential place in therapy of the drug (e.g., potential reimbursement conditions). The following is a summary of this panel discussion.

Description of the Current Treatment Paradigm for the Disease

Current treatment for EoE depends on a proper diagnosis, which is determined by a history of clinical symptoms related to esophageal dysfunction and by endoscopy, which reveals the eosinophilia. Patients with EoE have 15 or more eosinophils per HPF.

The currently available treatment for EoE includes dietary treatment, pharmacologic treatment, and endoscopic treatment. The endoscopic treatment is used to treat complications of persistent EoE. Current treatments for EoE mainly manage symptoms as opposed to modifying the underlying disease mechanisms. While a high proportion of patients treated with dietary and/or pharmacologic treatment achieves histologic remission and resolution of symptoms, the recurrence of symptoms and inflammation is common after treatment discontinuation.

Dietary treatment is among the first line of treatment for EoE. There are three main dietary therapies. One of the dietary therapies is an elemental diet, such as amino acid-based therapy. However, it is rarely used, given that it is very restrictive, costly, and not very palatable. Another dietary therapy is the targeted elimination diet, where patients would avoid food based on positive skin test results to specific foods. This food elimination diet is not as effective as amino acid therapy. In general, skin testing to identify culprit food(s) has a poor predictive value in treating EoE. There is also empiric food elimination of the main allergenic foods, which can consist of six-food, four-food, two-food, and one-food elimination groups. Some panellists indicated that, in general, any elimination diet is preferable to no treatment at all. However, it is hard to comply with a food elimination diet, especially in the long term. Elimination diets can negatively impact quality of life, lead to social isolation, be expensive, and necessitate a dietitian monitoring to avoid nutritional deficiencies. Some panellists indicated that dietary avoidance also comes with issues of developing actual food allergies that may not have existed previously due to continued avoidance. Also, in pediatrics, growth is affected due to broad food elimination.

PPIs, which reduce esophageal exposure to acid, are the first line of pharmacologic therapy for EoE. They can be used in conjunction with dietary eliminations. The second line of pharmacological treatment is topical corticosteroids, which can be administered as an inhaler such as fluticasone propionate inhalers, but unlike the inhaled method used for asthma, instead of inhaling the spray, patients swallow the spray. Other topical corticosteroids available are budesonide nebules, which need to be thickened with a sugar substitute, something like Splenda, in order to be viscous enough to adhere to the esophagus. Compliance and taste are issues of the inhaled corticosteroids. After the topical corticosteroids, biologics such as anti-interleukin-5s or dupilumab medications might be used. However, they are not approved by Health Canada or reimbursed for the treatment of EoE. Budesonide orodispersible tablets (Jorveza) is the first pharmacologic treatment for EoE approved in Canada. Topical corticosteroids and PPIs are currently the mainstays of treatment.

Esophageal dilatation might be used in symptomatic patients with strictures that persist despite dietary and pharmacologic treatment.

With any therapy, monitoring is difficult. Endoscopy is required for the initial diagnosis of EoE, but repeat endoscopy becomes unwieldy and difficult for individuals.

Treatment Goals

The ideal treatment in adults would result in the resolution of symptoms (i.e., elimination of the symptom of dysphagia and the prevention of food impaction), as well as the reversal of the histologic changes in the esophagus. The panel also indicated that reversing the endoscopic changes in the esophagus is also an important goal as it would prevent long-term complications and the need for repeat dilation. However, in some cases of adults who present with esophageal strictures and persistent dysphagia, it might not be possible to achieve endoscopic improvement, given that the disease's progression may have already run its course. The panel indicated that relying only on symptomatology might not be accurate to assess disease activity, given that patients might not have symptoms while still having inflammation in the esophagus. Also, there is no good non-invasive method that assesses esophageal inflammation in these patients. Due to the difficulty of conducting endoscopy frequently, the symptomatic response is used to measure the success of therapy. However, there is a poor correlation between symptoms and inflammation. Also, patients might adapt by changing the way they eat to avoid symptoms, and hence indicate

that they no longer have symptoms, while the histologic response is not achieved. Hence, both symptomatic response and histologic improvement are important goals of the treatment. In addition, there are no good data that indicate that endoscopic and histologic remissions would improve disease course and long-term prognosis.

Unmet Needs

EoE is a chronic disease; lasting remission is not frequently seen in patients. Currently, no treatment that can induce long-term remission in the majority of patients is available. Also, it is sometimes difficult to assess treatment efficacy, given that there is no non-invasive measure of the inflammation in the esophagus. Hence, patients could be subject to several endoscopies to confirm that the patient responded to treatment. Some patients who still have inflammation in their esophagus but who achieved symptomatic response will stop taking any medication for their condition.

Every treatment option currently available has some limitations. The dietary approach is challenging for patients to follow; it has a significant impact on the patient's quality of life, and it often requires the assistance of a dietitian. Also, maintaining food avoidance over a long period is cumbersome for patients. Although PPI therapy is the most straightforward treatment to receive and is well tolerated, PPIs seem to be effective in less than a third of patients with mild symptoms. A substantial proportion of patients are nonresponders to PPI therapy, and for patients who respond to PPI therapy, there is a risk of relapse upon discontinuation of the PPI. Corticosteroids with topical activity and low systemic bioavailability are the mainstay of treatment for patients with EoE. Response rates are high but recurrence rates on withdrawal of the medication are high as well. Currently, in Canada, these agents are not commercially formulated for the EoE indication and they are used off-label; hence, they must be compounded or administered via a different route than that approved. Patients, physicians, and pharmacists are left to adapt these corticosteroid formulations to the EoE patient, which can be confusing and cumbersome, leading to reduced patient compliance. Hence, other formulations of topical corticosteroids are needed to improve convenience and compliance. Esophageal dilation is effective; however, it can lead to very significant complications ranging from severe transient pain to life-threatening perforation. There are patients with long-standing disease with strictures and fibrosis who may not respond to topical corticosteroids. However, it is unclear what is the best treatment option for these patients, and there is no good indicator to identify patients who will progress to strictures and fibrosis.

Place in Therapy

Currently, topical corticosteroids (which are often thickened with something like Splenda to be viscous enough to adhere to the esophagus) are used without a Health Canada indication for the treatment of adult patients with EoE. However, current topical corticosteroids used are cumbersome (some panellists indicated that some patients prefer esophageal dilation over topical corticosteroids). Also, the compliance rate in patients receiving topical corticosteroids is low. The drug under review, budesonide orodispersible tablets (Jorveza), will take the role of the compounded topical corticosteroids. Commercially available budesonide orodispersible tablets will be mainly used in patients who fail to achieve symptomatic or histologic response after a trial of PPI, which will not, by itself, present a large treatment paradigm shift.

The place in therapy of budesonide orodispersible tablets in the treatment of adult patients with EoE was variable among panel members. One approach indicated that as accessibility

to the Health Canada–approved budesonide increases, and familiarity with patients' responses and compliance to the drug rises, budesonide orodispersible tablets may become a first-line treatment as a monotherapy or in combination with a PPI for patients presenting with severe EoE and then budesonide orodispersible tablets may be stopped upon resolution of symptoms. This use could present a shift in the treatment paradigm. Another approach is that, given it is not possible to predict who will respond to PPI treatment and that PPIs have fewer side effects than corticosteroids, then all patients, regardless of severity, should have a six-week to eight-week trial of PPI therapy. If patients respond to PPI therapy, then they continue receiving a PPI; however, if patients fail to respond to PPI therapy, it is expected that patients would initiate budesonide orodispersible tablets.

Patient Population

The diagnosis of EoE requires that patients have chronic symptoms of esophageal dysfunction, which include but are not limited to dysphagia and food impaction. Also, patients have to have an eosinophil-predominant inflammation on esophageal biopsy, characteristically consisting of at least 15 eosinophils per HPF, and the exclusion of other causes of esophageal eosinophilia. The condition is not challenging to diagnose by a gastroenterologist specialist. As such, misdiagnosis is unlikely. However, it is highly likely that EoE is underdiagnosed by primary care.

The approach to treatment of adult patients was variable among panel members. One approach considered was that adult patients best suited for treatment with budesonide orodispersible tablets are symptomatic patients with eosinophilic inflammation who have not responded to PPI treatment, where those PPI nonresponders are patients who still have dysphagia, food impaction, and strictures after receiving a PPI for eight weeks. Another approach considered that in adult patients with severe symptoms, budesonide orodispersible tablets would be initiated as the first line of treatment without having to try a PPI first. The panel indicated that it may be difficult to determine a set of distinct characteristics for patients who would best respond to treatment with budesonide, given the limited data available. The panel also indicated that patients with reflux-like symptomatology and patients who respond to PPIs are the least suitable for treatment with budesonide orodispersible tablets.

Assessing Response to Treatment

In practice, clinicians would assess patients symptomatically. No scales are currently used in clinical practice to assess symptomatic response. Meaningful responses to treatment include the complete resolution of symptoms of dysphagia and food impaction. Other important assessments would include an overall improvement in patient symptoms allowing for the consumption of solid food of all consistencies, reduced hospitalization, and a decrease in the frequency and severity of dysphagia. While symptomatic response generally occurs after patients achieve histologic remission, this might not always be the case as some patients might feel better even if they still have a significant number of residual eosinophils. Histologic evaluation using endoscopy is not frequently used in clinical practice; it is mainly used in the case of worsening symptoms or the non-resolution of symptoms while on therapy, or for monitoring response to an elimination diet. If patients have persistence of symptoms and are not responding to treatment or titration of therapy, then a clinical follow-up and endoscopy are required.

The panel indicated that patients would initiate treatment with budesonide orodispersible tablets for a period of six weeks and, if there was no resolution of symptoms (i.e., elimination of the symptom of dysphagia and prevention of food impaction), they would renew treatment with budesonide orodispersible tablets for an additional six weeks. Patients would usually be assessed after 12 weeks of treatment.

Patients who respond after six or 12 weeks of treatment with budesonide orodispersible tablets would stop treatment until symptoms recur. Patients who respond to the initial treatment with budesonide orodispersible tablets would have their treatment with budesonide orodispersible tablets restarted if symptoms recur. If symptoms frequently recur after the discontinuation of budesonide orodispersible tablets (every few weeks), despite being on continuous PPI therapy, then patients could start on maintenance treatment with budesonide orodispersible tablets for one year. If symptoms recur less frequently (every eight months, for example), then patients should not receive maintenance therapy but rather only six to 12 weeks of treatment with budesonide orodispersible tablets based on response.

Discontinuing Treatment

If patients do not respond after a 12-week trial of budesonide orodispersible tablets, patients need to be reassessed, and endoscopy would be required to check for fibrosis or stenosis that is refractory to topical corticosteroids, as those patients may need dilation. Some panellists indicated that all patients, whether or not they respond to the initial treatment with budesonide orodispersible tablets, have to stop treatment after a maximum period of 12 weeks of therapy, while other panellists indicated that response to treatment or its absence must be re-evaluated after 12 weeks, and possibly stopped or modified with some patients requiring long-term maintenance treatment with budesonide orodispersible tablets at a lower dose.

The clinical experts suggested that treatment discontinuation can be considered in cases where unacceptable side effects are present (such as recurrent candidiasis, systemic side effects from topical corticosteroids, or hypersensitivity), or if patients are intolerant to the drug.

Prescribing Conditions

The clinical experts agreed that budesonide orodispersible tablets for the treatment of EoE should be prescribed by specialists in gastroenterology or allergy who have expertise in EoE. The expertise necessary to monitor response are available in outpatient clinics.

Additional Considerations

The panel indicated that the delivery route of budesonide orodispersible tablets is undoubtedly an improvement over current topical corticosteroids and will likely lead to better treatment response due to enhanced adherence.

Clinical Evidence

The clinical evidence included in the review of budesonide is presented in two sections. The first section, the systematic review, includes pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those studies that were selected according to an a priori protocol. The second section includes sponsor submitted long-term extension studies and additional relevant studies that were considered to address important gaps in the evidence included in the systematic review.

Systematic Review (Pivotal and Protocol Selected Studies)

Objectives

To perform a systematic review of the beneficial and harmful effects of budesonide orally, 1 mg orodispersible tablets for the induction of clinicopathologic remission in adults with EoE

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the sponsor's submission to CADTH and Health Canada, as well as those meeting the selection criteria presented in Table 4.

Table 4: Inclusion Criteria for the Systematic Review

Patient population	Adults with EoE Subgroups: • prior treatment with PPIs • concomitant use of PPIs • history of strictures (mild to moderate vs. severe)
Intervention	Budesonide orally, 1 orodispersible tablet (1 mg) in the morning and 1 orodispersible tablet (1 mg) in the evening
Comparators	• PPI • Topical budesonide • Topical fluticasone • Systemic steroids • Montelukast • Food elimination diets • Placebo
Outcomes	**Efficacy outcomes** • Clinical response (e.g., improvement in dysphagia and odynophagia)[a] • Treatment failure (e.g., stricture formation, occurrence of food impaction, need for endoscopic intervention or dilation) • HRQoL based on a validated scale[a] • Histologic response • EoE activity (e.g., EEsAI-PRO, PGA of EoE activity) • Relapse

	Harms outcomes AEs, SAEs, WDAEs, mortality, notable harms/harms of special interest (local fungal infection, dysgeusia, decreased bone mineral density, cataract, glaucoma, psychiatric behavioural effects, symptoms of sore throat [pharyngitis], and avascular necrosis of the hip)
Study design	Published and unpublished phase III and IV RCTs

AE = adverse events; EEsAI-PRO = Eosinophilic Esophagitis Activity Index Patient Reported Outcome; EoE = eosinophilic esophagitis; HRQoL = health-related quality of life; PGA = Physician's Global Assessment; PPI = proton pump inhibitor; RCT = randomized controlled trial; SAE = serious adverse event; vs. = versus; WDAE = withdrawal due to adverse event.

[a] These outcomes were identified as being of particular importance to patients in the input received by CADTH from patient groups.

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the *PRESS Peer Review of Electronic Search Strategies* checklist.[21]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, and PubMed. The search strategy comprised both controlled vocabulary, such as the U.S. National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Jorveza (budesonide) and EoE. The clinical trial registries were searched: the U.S. National Library of Medicine's ClinicalTrials.gov and the World Health Organization's International Clinical Trials Registry Platform search portal.

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on December 9, 2019. Regular alerts updated the search until the meeting of the CADTH Canadian Drug Expert Committee on May 20, 2020.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist:[22] Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Clinical Trials Registries, and Databases (Free). Google was used to search for additional internet-based materials. These searches were supplemented by reviewing bibliographies of key papers and through contacts with appropriate experts. In addition, the sponsor of the drug was contacted for information regarding unpublished studies. See Appendix 2 for more information on the grey literature search strategy.

Two CADTH clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Findings From the Literature

A total of one study was identified from the literature for inclusion in the systematic review (Figure 1). The included study is summarized in Table 5. A list of excluded studies is presented in Appendix 2.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

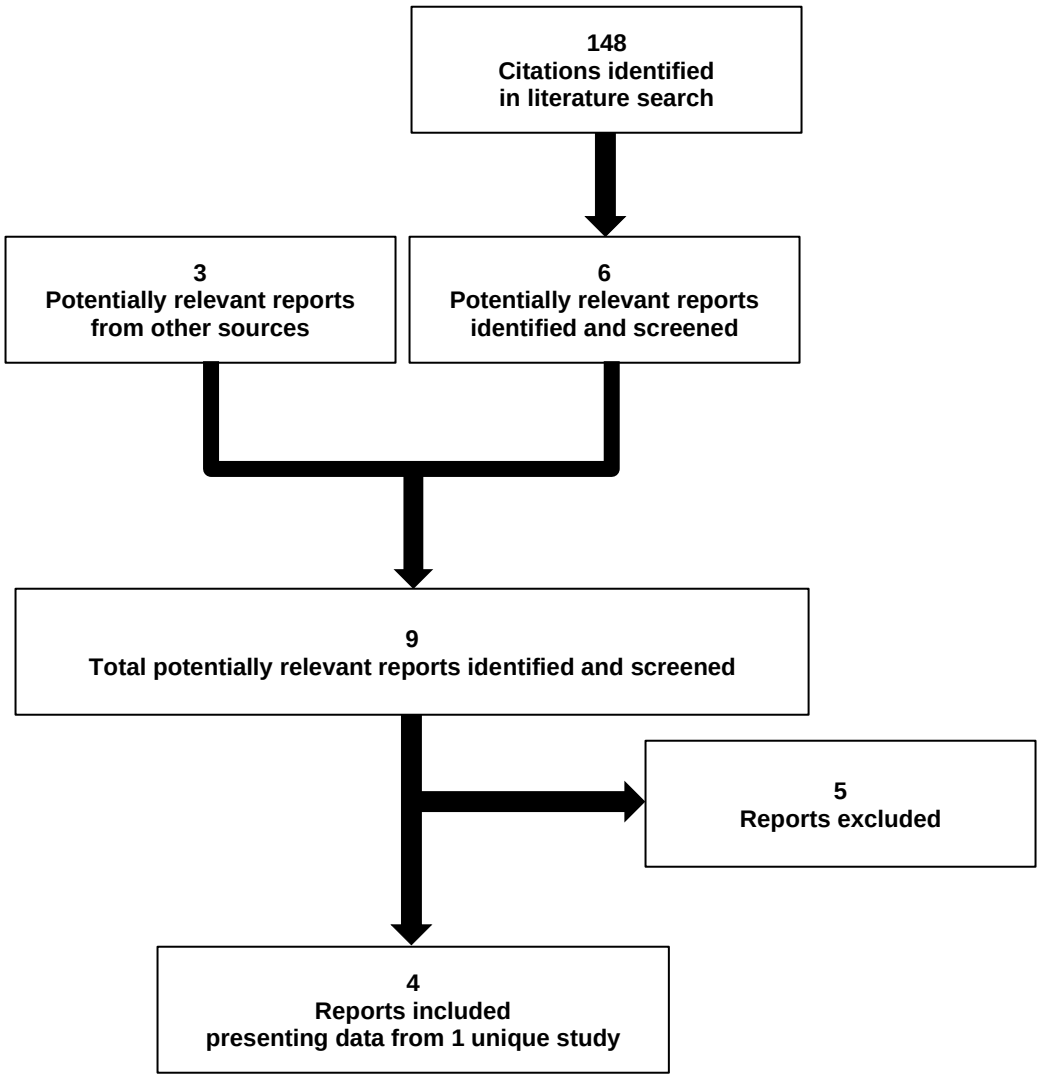

Table 5: Details of Included Studies

		Study BUL-1/EEA
DESIGNS AND POPULATIONS	**Study design**	Phase III, double-blind, multi-centre, placebo-controlled RCT
	Locations	Germany, Netherlands, Spain, and Switzerland
	Randomized (N)	88

	Inclusion criteria	• Male or female patients, 18 to 75 years of age
		• Confirmed clinicopathologic diagnosis of EoE according to established diagnostic criteria:
		  ○ history of symptoms of esophageal dysfunction (at least 1 of the following: transient or self-cleared food impaction, chest pain, epigastric discomfort, vomiting/regurgitation)
		  ○ peak EOS ≥ 15 in at least 1 HPF; (magnification = ×400) at screening procedure or previous endoscopy
		• Active symptomatic and histologic EoE fulfilling the following criteria:
		  ○ occurrence of at least 1 of the following clinical symptoms of esophageal dysfunction:
		  ▪ dysphagia (trouble swallowing) on at least 1 day in the last 7 days prior to baseline with a severity of ≥ 4 points on a NRS of 0 points (no trouble swallowing) to 10 points (the most severe trouble swallowing), or
		  ▪ pain during swallowing on at least 1 day in the last 7 days prior to baseline with a severity of ≥ 4 points on a NRS of 0 points (no pain during swallowing) to 10 points (most severe pain during swallowing), and
		  ○ peak eosinophils ≥ 65/mm^2 HPF in at least 1 HPF, out of a total of 6 HPFs derived from 6 biopsy specimens at screening endoscopy (2 each from the proximal, mid, and distal segment of the esophagus)
		• At least 4 points in PatGA concerning the severity of EoE symptoms (based on weekly overall assessment including all symptoms of EoE) on a NRS of 0 points (no symptoms) to 10 points (most severe symptoms) at baseline visit
		• A documented trial with PPIs in order to rule out PPI-responsive esophageal eosinophilia (PPI-REE)
		• Negative pregnancy test in females of childbearing potential at baseline visit

	Exclusion criteria	• Clinical and endoscopic signs of GERD
		• History of abnormal results in case of an optionally performed pH monitoring of the distal esophagus
		• Patients with PPI-REE are defined as having:
		  ○ a typical EoE symptom presentation
		  ○ had GERD diagnostically excluded
		  ○ demonstrated a clinicopathologic response to PPIs.[a]
		• Achalasia, scleroderma esophagus, or systemic sclerosis
		• Clinically evident causes other than EoE for esophageal eosinophilia
		• Any concomitant esophageal disease and relevant gastrointestinal disease (celiac disease, inflammatory bowel disease, oropharyngeal or esophageal bacterial, viral, or fungal infection [Candida esophagitis])
		• Any relevant systemic disease (e.g., AIDS, active tuberculosis)
		• Diseases if careful medical monitoring is not ensured: Cardiovascular disease, diabetes mellitus, osteoporosis, active peptic ulcer disease, glaucoma, cataract, or infection
		• Liver cirrhosis or portal hypertension
		• History of cancer in the last 5 years
		• History of esophageal surgery at any time or of esophageal dilation procedures within the last 8 weeks prior to screening visit
		• Upper gastrointestinal bleeding within 8 weeks prior to screening visit

		Study BUL-1/EEA
		• Any severe concomitant cardiovascular, renal, endocrine, or psychiatric disorder, which in the opinion of the investigator might have had an influence on the patient's compliance or the interpretation of the results
DRUGS	**Intervention**	1 mg budesonide orodispersible tablet twice daily
	Comparator(s)	Placebo orodispersible tablet twice daily
DURATION	**Phase**	
	Screening	Up to 6 weeks
	Double-blind	6 weeks
	Optional OLI	6 weeks
	Follow-up	4 weeks
OUTCOMES	**Primary end point**	Percentage of patients with clinicopathologic remission at week 6 (LOCF) defined as fulfilling both of these criteria: • histologic remission, i.e., peak of < 16 EOS/mm^2 HPF at week 6 (LOCF) • resolution of symptoms (i.e., no or only minimal problems), defined as a severity of ≤ 2 points on a NRS of 0 to 10 points (0 to 10) for dysphagia *and* a severity of ≤ 2 points on a NRS of 0 to 10 points for pain during swallowing on each day of the week prior to week 6 (LOCF).
	Secondary and exploratory end points	**Secondary** • Percentage of patients with histologic remission, defined as a peak of < 16 EOS/mm^2 HPF at week 6 (LOCF) • Change in the peak EOS/mm^2 HPF from baseline to week 6 (LOCF) • Percentage of patients with resolution of symptoms (i.e., no or only minimal problems), defined as a severity of ≤ 2 points on a NRS of 0 to 10 points for dysphagia *and* a severity of ≤ 2 points on a NRS of 0 to 10 points for pain during swallowing on each day of the week prior to week 6 (LOCF) • Percentage of patients with total weekly EEsAI-PRO score of ≤ 20 at week 6 (LOCF) • Percentage of patients with an improvement from baseline to week 6 (LOCF) in the weekly VDQ score • Percentage of patients with an improvement from baseline to week 6 (LOCF) in the weekly AMS score • Percentage of patients with histologic response, defined as a peak of < 48 EOS/mm^2 HPF at week 6 (LOCF) • Change from baseline in the PGA of EoE activity (NRS of 0 to 10) • Percentage of patients with no or only minimal problems in dysphagia defined as a severity of ≤ 2 points on a NRS of 0 points to 10 points for dysphagia on each day of the week prior to week 6 • Percentage of patients with no or only minimal problems in pain during swallowing defined as a severity of ≤ 2 points on a NRS of 0 points to 10 points for pain during swallowing on each day of the week prior to week 6 • Percentage of patients with overall symptoms resolution defined as PatGA concerning the severity of EoE symptoms (NRS of 0 to 10) ≤ 2 points at week 6 (LOCF) • Percentage of patients experiencing a food impaction during the DB treatment phase that needs endoscopic intervention • Percentage of patients needing endoscopic dilation during the DB treatment phase • Mean change from baseline in modSHS • Mean change from baseline in the EoE-QoL-A questionnaire

		Study BUL-1/EEA
NOTES	**Publications**	Lucendo et al. (2019)[23]

AMS = avoidance, modification, and slow eating; DB = double-blind; EEsAI-PRO = Eosinophilic Esophagitis Activity Index Patient Reported Outcome; EoE = eosinophilic esophagitis; EoE-QoL-A = Adult Eosinophilic Esophagitis Quality of Life; EOS = eosinophil; GERD = gastroesophageal reflux disease; HPF = high-power field; LOCF = last observation carried forward; modSHS = modified Short Health Scale; NRS = numerical rating scale; OLI = open-label induction; PatGA = Patient's Global Assessment; PGA = Physician's Global Assessment; PPI = proton pump inhibitor; PPI-REE = PPI-responsive esophageal eosinophilia; RCT = randomized controlled trial; VDQ = Visual Dysphagia Question.

Note: Three additional reports were included — CDR Submission,[19] Health Canada Reviewer's Report,[24] and the Clinical Study Report of the BUL-1/EEA trial.[9]

[a] A clinicopathologic response to PPIs was defined as having original symptoms of esophageal dysfunctions, with marked improvement of symptoms and peak eosinophils of fewer than 15 per HPF after four to eight weeks treatment with PPIs. The PPI dose used for a minimum of four weeks should have been at least the standard dose, according to the authorized summary of product characteristics of the respective PPI (e.g., omeprazole at 20 mg/day, pantoprazole at 40 mg/day, esomeprazole at 40 mg/day, lansoprazole at 30 mg/day, or rabeprazole at 20 mg/day).

Source: Lucendo et al. (2019)[23] and the Clinical Study Report of the BUL-1/EEA trial.[9]

Description of Studies

One trial (BUL-1/EEA) met the inclusion criteria. The BUL-1/EEA trial (N = 88) was a pivotal phase III, double-blind, randomized, multi-centre, placebo-controlled study that compared the efficacy and tolerability of a six-week treatment with budesonide effervescent tablets with placebo for the induction of clinicopathologic remission in adult patients with active EoE. The BUL-1/EEA trial was conducted in 26 centres across six countries (Belgium, Germany, the Netherlands, Spain, Switzerland, and the UK). The BUL-1/EEA trial was performed according to an adaptive two-stage group sequential design with the possibility for sample size adaptation and early stopping for efficacy at the interim analysis. The interim analysis was planned to be carried out when the data of 54 full analysis set (FAS) patients were available. If the trial was continued until completion and no adaptation was made at the interim analysis, the sample size was planned to be 81 FAS patients.

The screening period of up to six weeks was followed by a six-week double-blind treatment period and an optional six-week OLI treatment with budesonide 1 mg orodispersible tablet (budesonide 1 mg) twice daily in patients eligible for OLI treatment (clinicopathologic non-remitters), and a four-week follow-up period (if the patient did not further continue in the program). Patients, care providers, investigators, and all individuals involved in the outcome assessment and data analysis were blinded to treatment assignment. Patients were assigned to one of the two treatment groups via a central randomization procedure using a 2:1 allocation ratio to receive either budesonide 1 mg twice daily or placebo orodispersible tablet twice daily. The budesonide 1 mg and placebo treatments were identical in physical appearance, which assured treatment blinding. No stratification of randomized treatment assignment was performed.

All patients eligible for OLI treatment had the option to enter a six-week OLI treatment with budesonide 1 mg twice daily. Eligible were patients who were not in clinicopathologic remission at completion of the double-blind treatment phase or who were prematurely withdrawn due to lack of efficacy after at least four weeks of treatment and who showed no change or a deterioration in the PatGA concerning the severity of EoE symptoms compared to baseline at their last visit in the double-blind treatment phase, or patients who were experiencing a food impaction at any time that needed endoscopic intervention. The four-week follow-up phase after the end of the six-week double-blind treatment phase or after the end of the six-week OLI treatment phase (or after the respective premature withdrawal visit) primarily served to assess safety outcome. Patients without clinical symptoms at the

EOT or withdrawal visit double-blind or EOT or withdrawal visit OLI were to remain untreated during this follow-up period or, alternatively, could participate in a double-blind, randomized, placebo-controlled maintenance of remission trial, if eligible. Patients still suffering from clinical symptoms at EOT or withdrawal visit double-blind or EOT or withdrawal visit OLI could be treated symptomatically during the follow-up period in accordance with treatment as decided by the investigator. The placebo-controlled maintenance of remission trial was not included in this report as it was ongoing at the time of the submission to CADTH; in addition, the use of budesonide 1 mg as a maintenance therapy is not aligned with the usual treatment duration recommended by Health Canada.

Populations

Inclusion and Exclusion Criteria

Patients enrolled in the BUL-1/EEA trial were adults (18 to 75 years of age) with a confirmed diagnosis of active EoE and refractory to PPI treatment. Specifically, patients must have experienced dysphagia (trouble swallowing) or odynophagia (painful swallowing) for at least one day during the week preceding randomization, a PatGA concerning the severity of EoE symptoms of at least 4 out of 10, and histologic activity with peak eosinophils of at least 15 in at least one HPF, as measured in a total of six HPF derived from six biopsies (two each from the proximal, mid, and distal segments of the esophagus). Furthermore, patients must have undergone a documented trial with PPIs in order to exclude PPI-REE.

Patients were excluded from the BUL-1/EEA trial if they were pregnant or breastfeeding; were responsive to PPI treatment; were intolerant or hypersensitive to the study drug; had a history of abnormal pH monitoring of the distal esophagus; had clinical evidence of any causes other than EoE for eosinophilia of the esophagus; had signs or symptoms of GERD, achalasia, scleroderma, abnormal renal or hepatic function, AIDS, active tuberculosis, a relevant gastrointestinal disease, or relevant systemic disease without proper medical monitoring (cardiovascular disease, diabetes mellitus, osteoporosis, active peptic ulcer disease, glaucoma, cataract, or infection); had a history of topical glucocorticoids within two weeks of screening; had a history of systemic glucocorticoids, biologics, or immunosuppressants within four weeks of screening; previously had esophageal surgery at any time; had undergone dietary restrictive therapy in the preceding four weeks; had experienced esophageal dilation or upper gastrointestinal bleeding in the preceding eight weeks; or had cancer in the preceding five years.

Baseline Characteristics

As shown in Table 6, the patients' baseline characteristics and prior treatment experience appeared to be roughly balanced, despite certain large variations between the treatment groups, perhaps due to a small sample size in the placebo group (N = 29); notably, more patients received a PPI in the past (54% versus 45%) and topical budesonide in the past (20% versus 10%) in the active treatment group compared to the placebo group. The average age of the participants was 37 years in both treatment groups, and the majority were men (81% and 86% for the budesonide 1 mg and placebo study arms, respectively), which is representative of the EoE adult patient population. The mean time since an established EoE diagnosis was 49 months and 58 months for the budesonide 1 mg and placebo study groups, respectively, with a mean time since symptom onset of 134 months and 139 months, respectively.

In terms of clinical characteristics, the endoscopist assessment of EoE activities of the study patients showed that 83% and 90% of the patients in the budesonide 1 mg group and placebo group, respectively, had moderate or severe EoE. The PatGA concerning the severity of EoE symptoms and PGA of EoE activity mean scores were above 6 (NRS range of 0 to 10) in both treatment groups. The median overall peak of eosinophils per mm^2 HPF was 205 and 197, for the budesonide 1 mg group and placebo treatment group, respectively. Baseline symptoms of daily dysphagia were similar between both treatment groups, with a total weekly Eosinophilic Esophagitis Activity Index Patient Reported Outcome (EEsAI-PRO) score of 54 and 55, respectively. Almost all patients had current dysphagia symptoms at baseline. Nine patients in the budesonide 1 mg group (15.3%) and five patients in the placebo group (17.2%) had previous esophageal dilation.

The reported efficacy of previous pharmaceutical treatments are presented in Table 7. It remains difficult to interpret the findings as only a various small fraction (PPI: 32 versus 13, topical budesonide: 12 versus 3 and topical fluticasone: 25 versus 14) of the total randomized study patients (59 versus 29) in the budesonide 1 mg and placebo groups, respectively, reported prior experience of use of those drugs.

None of the patients had a history of treatment with an elemental diet with an amino acid-based complete liquid formulation. Overall, four of 59 patients (6.8%) in the budesonide 1 mg group and four of 29 patients (13.8%) in the placebo group had a history with directed elimination diet based on allergy results to treat EoE. Overall, 24 of 59 patients (40.7%) in the budesonide 1 mg group and 10 of 29 patients (34.5%) in the placebo group had a history with non-directed elimination diet. The most frequent foods that were eliminated were cow's milk protein, soy, wheat, egg, peanuts, tree nuts, fish, and shellfish.

Table 6: Summary of Baseline Characteristics in Study BUL-1/EEA, Full Analysis Set

Baseline characteristics	BUL-1/EEA	
	Budesonide 1 mg b.i.d. (N = 59)	Placebo (N = 29)
Sex, n (%)		
Male	48 (81.4)	25 (86.2)
Female	11 (18.6)	4 (13.8)
Age (years)		
Mean (SD)	37.0 (11.47)	36.9 (9.20)
Median (range)	37.0 (18 to 69)	34.0 (26 to 64)
Race, n (%)		
White	59 (100)	29 (100)
Smoking habits, n (%)		
Current	3 (5.1)	0 (0)
Former	5 (8.5)	3 (10.3)
Never	51 (86.4)	26 (89.7)
BMI (kg/m^2)		
Mean (SD)	24.4 (2.86)	25.6 (4.08)
Range	18.0 to 34.7	20.3 to 35.3
Time since EoE diagnosis, months		
Mean (SD)	48.8 (44.3)	57.6 (49.3)

Baseline characteristics	BUL-1/EEA	
	Budesonide 1 mg b.i.d. (N = 59)	Placebo (N = 29)
Median (range)	27.2 (2 to 186)	47.9 (1 to 227)
Time since first EoE symptoms, months		
Mean (SD)	134.2 (104.6)	139.0 (98.8)
Median (range)	114.8 (10 to 509)	106.9 (21 to 346)
No previous esophageal surgeries, n (%)	59 (100)	29 (100)
Previous esophageal dilations, n (%)	9 (15.3)	5 (17.2)
History of allergic disease, n (%)	47 (79.7)	23 (79.3)
History, previous and/or current, of these diseases, n (%)		
Dysphagia	58 (98.3)	29 (100.0)
Odynophagia	35 (59.3)	14 (48.3)
Food impaction	56 (94.9)	26 (89.7)
Frequency of dysphagia, n (%)		
Never	2 (3.4)	0 (0)
1 to 3 times per week	21 (35.6)	12 (41.4)
4 to 6 times per week	10 (16.9)	2 (6.9)
Daily	24 (40.7)	13 (44.8)
Missing	2 (3.4)	2 (6.9)
Dysphagia (NRS of 0 to 10), last 7 days		
Mean (SD)	5.8 (2.02)	5.9 (1.69)
Median (range)	6.0 (0 to 10)	6.0 (4 to 10)
Weekly sum dysphagia (NRS of 0 to 10), mean (95% CI)	34.6 (30.4 to 38.8)	36.4 (31.7 to 41.1)
Pain during swallowing (NRS of 0 to 10), last 7 days		
Mean (SD)	3.5 (2.78)	3.4 (3.17)
Median (range)	4.0 (0 to 9)	2.0 (0 to 10)
Number of inflamed segments, n (%)		
1 segment	6 (10.2)	2 (6.9)
2 segments	10 (16.9)	4 (13.8)
3 segments	43 (72.9)	23 (79.3)
Localization of inflammation, n (%)		
Proximal	47 (79.7)	25 (86.2)
Mid	52 (88.1)	26 (89.7)
Distal	56 (94.9)	28 (96.6)
Overall peak EOS/mm^2 HPF		
Mean (SD)	242 (140.7)	239 (125.0)
Median (range)	205 (56 to 611)	197 (99 to 620)
Blood EOS/mm^3 (baseline), mean (SD)	427 (255.4)	455 (255.5)
Endoscopist assessment of EoE activity, n (%)		
None	1 (1.7)	0 (0)
Mild	9 (15.3)	3 (10.3)
Moderate	30 (50.8)	17 (58.6)

Baseline characteristics	BUL-1/EEA	
	Budesonide 1 mg b.i.d. (N = 59)	Placebo (N = 29)
Severe	19 (32.2)	9 (31.0)
EoE: Duration of last acute episode in months		
n	32	15
Median (range)	1.8 (0 to 36)	3.0 (0 to 13)
EoE: Time since end of last acute episode in months		
n	33	15
Median (range)	19.4 (1 to 140)	14.3 (1 to 63)
EoE: Duration of last remission phase in months		
n	27	12
Median (range)	9.1 (0 to 64)	7.8 (0 to 62)
EoE: Time since end of last remission phase		
n	27	12
Median (range)	2.1 (1 to 53)	1.6 (1 to 12)
EoE: Time since start of current acute episode		
n	40	22
Median (range)	2.6 (1 to 246)	2.1 (1 to 150)
Weekly sum of pain during swallowing (NRS of 0 to 10), mean (95% CI)	27.4 (22.8 to 32.0)	25.6 (18.9 to 32.2)
Patient's Global Assessment of EoE activity (NRS of 0 to 10), mean (SD)	5.9 (1.5)	6.0 (1.5)
Physician's Global Assessment of EoE activity (NRS of 0 to 10), mean (SD)	6.1 (1.3)	6.2 (1.3)
Total weekly EEsAI-PRO, mean (SD)	54.1 (15.5)	55.3 (15.8)
modSHS (VAS 0 to 100), mean (SD)[a]		
Symptom burden	58 (23.5)	55 (18.1)
Social function	55 (29.0)	46 (24.3)
Disease-related worry	57 (26.4)	52 (26.8)
General well-being	40 (23.3)	35 (29.0)
PPI trial conducted (in the past or during the screening phase of this study), n (%)		
Yes	59 (100)	29 (100)
Concomitant use of PPIs	7 (11.9)	3 (10.3)

b.i.d. = twice a day; BMI = body mass index; CI = confidence interval; EEsAI-PRO = Eosinophilic Esophagitis Activity Index Patient Reported Outcome; EoE = eosinophilic esophagitis; EOS = eosinophil; HPF = high-power field; modSHS = modified Short Health Scale; NRS = numerical rating scale; PPI = proton pump inhibitor; SD = standard deviation; VAS = visual analogue scale.

[a] Range of each score: 0 to 100. Lower numbers indicate higher quality of life.

Source: Clinical Study Report of the BUL-1/EEA trial.[9]

Table 7: Efficacy of Drug Interventions for Treating Eosinophilic Esophagitis in the Past — Previous Acute and/or Maintenance Treatment — in Study BUL-1/EEA

Baseline characteristics	BUL-1/EEA	
	Budesonide 1 mg b.i.d. (N = 59)	Placebo (N = 29)
PPI, n (%)[a]	32 (54)	13 (45)
Poor	25 out of 32 (78)	11 out of 13 (85)
Satisfactory	2 out of 32 (6)	1 out of 13 (8)
Good	0 out of 32 (0)	1 out of 13 (8)
Very good	2 out of 32 (6)	0 out of 13 (0)
Unknown	3 out of 32 (9)	0 out of 13 (0)
Topical budesonide, n (%)	12 (20)	3 (10)
Poor	0 out of 12 (0)	0 out of 3 (0)
Satisfactory	3 out of 12 (25)	0 out of 3 (0)
Good	6 out of 12 (50)	2 out of 3 (67)
Very good	3 out of 12 (25)	1 out of 3 (33)
Topical fluticasone, n (%)	25 (42)	14 (48)
Poor	7 out of 25 (28)	3 out of 14 (21)
Satisfactory	1 out of 25 (4)	2 out of 14 (14)
Good	11 out of 25 (44)	7 out of 14 (50)
Very good	5 out of 25 (20)	1 out of 14 (7)
Unknown	1 out of 25 (4)	1 out of 14 (7)
Systemic steroids, n (%)	3 (5)	0 (0)
Good	1 out of 3 (33)	NA
Very good	1 out of 3 (33)	NA
Unknown	1 out of 3 (33)	NA
Montelukast, n (%)	4 (7)	0 (0)
Poor	2 out of 4 (50)	NA
Good	1 out of 4 (25)	NA
Unknown	1 out of 4 (25)	NA

b.i.d. = twice a day; NA = not applicable; PPI = proton pump inhibitor.

[a] All patients failed the PPI trial, either in their history or during the screening phase.

Source: Lucendo et al. (2019)[23]

Interventions

In the BUL-1/EEA, the patients received either budesonide 1 mg twice daily or placebo orodispersible tablet twice daily. The placebo orodispersible tablets were indistinguishable in appearance and size from the budesonide orodispersible tablets. One orodispersible tablet was taken in the morning and one in the evening after the meal. The orodispersible tablet had to be placed on the tongue, which allowed rapid disintegration. The orodispersible tablet was to dissolve rapidly and to be swallowed with saliva little by little. Patients were advised not to drink or eat during the 30 minutes after study drug administration.

The use of systemic or topical glucocorticoids, biologics, or immunosuppressants was not permitted during treatment phase as concomitant medication. In addition, the initiation of dietary restrictions was also not permitted within four weeks prior to screening visit or during treatment. Concomitant PPI treatment was to be kept stable during the double-blind treatment phase of the trial.

Patients were prematurely withdrawn from the trial due to lack of efficacy, which was defined as no change or a deterioration in the weekly PatGA concerning the severity of EoE symptoms after at least four weeks of treatment compared to baseline, or experiencing a food impaction at any time that needed endoscopic intervention, or requiring an endoscopic dilation. Patients were also prematurely withdrawn from the trial if they experienced intolerable AEs.

Outcomes

A list of efficacy end points identified in the CADTH review protocol that were assessed in the clinical trials included in this review is provided in Table 8. These end points are further summarized below. A detailed discussion and critical appraisal of the outcome measures is provided in Appendix 4.

Table 8: Summary of Outcomes of Interest Identified in the CADTH Review Protocol

Outcome measure	Study BUL-1/EEA
Percentage of patients with clinicopathologic remission at week 6 (LOCF) defined as fulfilling both of these criteria[a]: • histologic remission, i.e., peak of < 16 EOS/mm^2 HPF at week 6 (LOCF) • resolution of symptoms (i.e., no or only minimal problems), defined as a severity of ≤ 2 points on a NRS of 0 to 10 points (0 to 10) for dysphagia *and* a severity of ≤ 2 points on a NRS of 0 to 10 points for pain during swallowing on each day of the week before week 6 (LOCF)	Primary efficacy end point
Percentage of patients with histologic remission, defined as a peak of < 16 EOS/mm^2 HPF at week 6 (LOCF)	Key secondary end point[b]
Change in the peak EOS/mm^2 HPF from baseline to week 6 (LOCF)	Key secondary end point[b]
Percentage of patients with resolution of symptoms (i.e., no or only minimal problems), defined as a severity of ≤ 2 points on a NRS of 0 to 10 points for dysphagia *and* a severity of ≤ 2 points on a NRS of 0 to 10 points for pain during swallowing on each day of the week before week 6 (LOCF)	Key secondary end point[b]
Percentage of patients with total weekly EEsAI-PRO score of ≤ 20 at week 6 (LOCF)	Key secondary end point[b]
Percentage of patients with an improvement from baseline to week 6 (LOCF) in the weekly VDQ score	Key secondary end point[b]
Percentage of patients with an improvement from baseline to week 6 (LOCF) in the weekly AMS score	Key secondary end point[b]
Percentage of patients with histologic response, defined as a peak of < 48 EOS/mm^2 HPF at week 6 (LOCF)	Other secondary efficacy end point
Change from baseline in the PGA of EoE activity (NRS of 0 to 10)	Other secondary efficacy end point
Percentage of patients with no or only minimal problems in dysphagia defined as a severity of ≤ 2 points on a NRS of 0 to 10 points for dysphagia on each day in the week before week 6	Other secondary efficacy end point
Percentage of patients with no or only minimal problems in pain during swallowing defined as a severity of ≤ 2 points on a NRS of 0 to 10 points for pain during swallowing on each day of the week before week 6	Other secondary efficacy end point

Outcome measure	Study BUL-1/EEA
Percentage of patients with overall symptoms resolution defined as PatGA concerning the severity of EoE symptoms (NRS of 0 to 10) ≤ 2 points at week 6 (LOCF)	Other secondary efficacy end point
Percentage of patients experiencing a food impaction during the DB treatment phase that needs endoscopic intervention	Other secondary efficacy end point
Percentage of patients needing endoscopic dilation during the DB treatment phase	Other secondary efficacy end point
Change from baseline in modSHS	Other secondary efficacy end point
Change from baseline in the EoE-QoL-A questionnaire	Other secondary efficacy end point

AMS = avoidance, modification, and slow eating; DB = double-blind; EEsAI-PRO = Eosinophilic Esophagitis Activity Index Patient Reported Outcome; EoE = eosinophilic esophagitis; EoE-QoL-A = Adult Eosinophilic Esophagitis Quality of Life; EOS = eosinophil; HPF = high-power field; LOCF = last observation carried forward; modSHS = modified Short Health Scale; NRS = numerical rating scale; PatGA = Patient's Global Assessment; PGA = Physician's Global Assessment; VDQ = Visual Dysphagia Question.

[a] Patients experiencing a food impaction at any time during the double-blind treatment phase that needed endoscopic intervention or who needed an endoscopic dilation during the double-blind treatment phase were assessed as treatment failures, and thus did not fulfill, by definition, the clinicopathologic remission criterion.

[b] In order to control the family-wise error rate at the 0.05 level, a gatekeeping and a priori hierarchical ordering strategy was used for the key secondary efficacy variables. The sequence used was in the same order as the key secondary outcomes presented in Table 8.

Source: Clinical Study Report of the BUL-1/EEA trial.[9]

Histologic Remission

The peak number of eosinophils per mm^2 HPF was derived from the evaluation of a total of up to six HPFs derived from six esophageal biopsies. Two biopsy specimens each had to be taken from the proximal, mid, and distal part of the esophagus for the assessment of six HPFs. In each biopsy specimen, the number of eosinophils per HPF were counted and transformed to the number of eosinophils per mm^2 HPF. The highest number of eosinophils per mm^2 HPF by segment and overall was determined to define the peak number per segment and overall. If a patient discontinued the double-blind treatment phase prematurely without a follow-up endoscopy being documented, nonresponse with regard to the primary end point was assumed and the screening values were carried forward.

There is no clear threshold of eosinophils per HPF universally established as an end point in EoE, but other literature reports used this cut-off, and the diagnosis of EoE is commonly based on the presence of esophageal eosinophilia being greater than 15 per HPF.[25] It is important to note that the number of eosinophils per HPF is often less than the number of eosinophils per mm^2 HPF. For example, an area of each HPF can be 0.307 mm^2; thus, one has to multiply the reported numbers and cut-off values of eosinophils per HPF by a factor of 3.25 to standardize them per mm^2 HPF. Therefore, a cut-off value of fewer than five eosinophils per HPF corresponds to fewer than 16 eosinophils per mm^2 HPF. Eosinophils of at least 15 per HPF is equivalent to 60 eosinophils per mm^2.

It is also worth noting that in the FDA draft guidance for industry for developing drugs for the treatment of EoE, it was reported that the assessment of histologic response should be documented and the histologic response was defined as "*peak esophageal eosinophil per HPF count of less than or equal to 6 across all available esophageal levels at the final treatment period evaluation*."[26]

Dysphagia Numerical Rating Scale

The Dysphagia NRS is a 10-point rating scale where patients provide an assessment of the severity of dysphagia symptoms experienced in the past 24 hours or seven days. The scale ranges from 0 to 10 (0 represents no trouble swallowing, 10 represents the most severe trouble swallowing). The Dysphagia NRS captures dysphagia symptoms associated with

EoE only and not symptoms associated with cold, e.g., sore throat. Patients in the trial received the scale in the form of a diary and daily ratings were used to calculate a weekly sum.[9] No studies validating the Dysphagia NRS in patients with EoE were identified from the literature; neither was an MID found. In the BUL-1/EEA trial, one of the co-primary end points, resolution of symptoms (i.e., no or only minimal problems), was based on a Dysphagia NRS score of 2 or less.[9]

Pain During Swallowing Numerical Rating Scale

The Pain During Swallowing NRS is a 10-point rating scale where patients provide an assessment of the severity of pain during swallowing experienced in the past 24 hours or seven days. The scale ranges from 0 to 10 (0 represents no pain during swallowing, 10 represents most severe pain during swallowing).[9] Evidence regarding the validity, reliability, and MID of the Pain During Swallowing NRS was not found for patients with EoE in the literature. In the BUL-1/EEA trial, one of the co-primary end points, resolution of symptoms (i.e., no or only minimal problems), was based on a Pain During Swallowing NRS score of 2 or less.[9]

The Eosinophilic Esophagitis Activity Index Patient Reported Outcome

The EEsAI-PRO score is used to assess EoE activity over a seven-day recall period in adult patients that consists of the following five items: frequency of trouble swallowing, duration of dysphagia episodes, pain during swallowing, Visual Dysphagia Questions (VDQs), and behavioural change strategies. The scores of each item are added to provide an overall score out of 100, with disease severity rated as remission (0 to 20), mild (21 to 40), moderate (41 to 65), and severe (66 to 100).[9] Construct and content validity was demonstrated;[27] no information on reliability and responsiveness were found in the literature. A response to treatment was defined by the authors of the BUL-1/EEA trial as a 20-point or more decrease in the EEsAI-PRO score from baseline.[9] However, it is not clear how this MID was established.

Visual Dysphagia Question Score

The VDQ is a subscale in the EEsAI-PRO questionnaire that aims to address the severity of dysphagia when consuming food of eight different consistencies. The types of food consistencies and corresponding examples to illustrate those consistencies are generally consumed foods in the US, Europe, and Canada. They included 1) solid meat (such as steak, chicken, turkey, and lamb), 2) soft foods (such as pudding, jelly, and apple sauce), 3) dry rice or sticky Asian rice, 4) ground meat (hamburger and meatloaf), 5) fresh white untoasted bread or similar foods (such as doughnut, muffins, or cake), 6) grits, porridge (oatmeal), or rice pudding, 7) raw fibrous foods (such as apple, carrots, or celery), and 8) French fries.[9] Patients are evaluated on the occurrence of dysphagia upon “virtual” consumption of each of these reference foods without any modification (such as blending, mashing, cutting in tiny pieces, or dunking into liquid), i.e., the degree of difficulty swallowing the different food types if consumed at that moment. The VDQ score ranges from 0 to 10 (0 represents no difficulties, 10 represents severe difficulties). The VDQ was not validated separately; however, the trial by Schoepfer et al. validated the full EEsAI-PRO instrument, which assessed dysphagia caused by eating foods of different consistencies, i.e., the VDQ score.[27] An MID was not reported for the VDQ score.

Avoidance, Modification, and Slow Eating Score

The avoidance, modification, and slow eating (AMS) domain of EEsAI-PRO aims to address the change in eating behaviour due to the symptoms of dysphagia in order for patients to avoid potential food impaction. Patients are asked if the aforementioned eight categories of food resulted in behavioural adaptations, e.g., avoidance of the food altogether, whether the food is eaten, whether any modification is done, or whether the food is eaten more slowly than normal. Similar to the VDQ score, patients who are vegetarian or allergic to wheat answered "no" to questions concerning meat or wheat-based foods, respectively.[9] The AMS score ranges from 0 to 10, with 0 corresponding to no behavioural changes and 10 corresponding to completely avoiding all of the assessed food categories. The AMS was not validated separately; however, the aforementioned trial by Schoepfer et al. validated the full EEsAI-PRO instrument, which took into account behavioural adaptation strategies in response to EoE symptoms; i.e., the AMS score.[27] An MID was not reported for the AMS score.

Physician's Global Assessment of EoE Activity

In this scale, physicians are asked to provide an overall assessment of the patients' EoE activity and severity, taking into consideration the symptoms, endoscopy, histology, and laboratory markers. The EoE activity is rated on a 10-point scale, ranging from 0 (inactive EoE) to 10 (most active EoE).[9] Evidence of validity and reliability as well as MID were not found from the literature.

Patient's Global Assessment Concerning the Severity of EoE Symptoms

The PatGA scale evaluates the severity of EoE symptoms from a patient's perspective. Patients were asked to rate the severity of their EoE symptoms in the past seven days on a scale that ranges from 0 to 10 (0 represents no symptoms, 10 represents most severe symptoms).[9] Evidence of validity and reliability as well as MID were not found for the PatGA from the literature. In the BUL-1/EEA trial, resolution of symptoms was defined as having a PatGA score of 2 or less. Additionally, a decrease of 3 points or more in the PatGA score from baseline was used as an outcome.

Modified Short Health Scale

The modSHS is a four-item questionnaire, representing each of four health dimensions: (1) symptom burden, (2) social function, (3) disease-related worry, and (4) general well-being. The patient answers a total of four questions (health dimensions) that assess the effects of esophageal disease on the patient's QoL.[9]

Patients respond to each of the following questions representing the four health dimensions, which is scored on a scale of 0 to 100: how severe are the symptoms from esophageal disease (0 represents no symptoms, 100 represents very severe symptoms), do the symptoms interfere with activities in daily life due to esophageal problems (0 represents not at all, 100 represents that they interfere to a very high degree), does the patient feel worry caused by esophageal disease (0 represents no worry, 100 represents constant worry), and what is the patient's general feeling of well-being (0 represents very good, 100 represents dreadful)?

While the Short Health Scale (SHS) demonstrated discrimination validity, reliability (including internal consistency and test-retest reliability), and responsiveness in gastrointestinal conditions such as ulcerative colitis[28] and Crohn disease,[29] a psychometric

analysis of the modified version of the SHS in EoE was not found from the literature. Additionally, MID was not identified for any of these conditions.

Adult Eosinophilic Esophagitis Quality of Life Questionnaire

The EoE-QoL-A is a self-reported questionnaire in which there is an original version and a refined version. The refined version was used in the BUL-1/EEA trial. The refined 30-item questionnaire (a 24-item scale with a six-question addendum for those on elimination diet therapies) is categorized according to the following five dimensions: impact of the disease on eating patterns and diet, social impact, emotional impact, disease anxiety, and swallowing anxiety. Patients provide responses based on their life over the past week that best describes their experiences with living with EoE. Each question had five answers ranging from 4, which corresponds to "does not describe their experiences at all," to 0, which corresponds to "extremely describes their experiences." Based on the responses, an overall score and five subscale scores are generated. Higher scores indicate better quality of life. Notably, there is a standard version (24 items) and a standard plus dietary restrictions version (30 items) of the EoE-QoL-A questionnaire. The latter is used for patients on elimination diet therapy. Since the dietary restrictions section is not applicable to all patients, a weighted average is calculated for the overall score and the five subscales by adding the value of the response for each item answered, then dividing by the total number of questions answered.[9] Validity, reliability, and responsiveness shown for the original version[30] only construct validity assessed for the shorter version.[31] An MID for the total score of the five domains was not reported by the authors or identified from the literature.

Safety

TEAEs were defined as any event with an onset occurring after the first administration of the investigational products or, if pre-existing, worsening after the first administration of investigational products, and occurring within the period of treatment with the investigational products.

An SAE was defined as any untoward medical occurrence that at any dose results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability and/or incapacity, or is a congenital anomaly or birth defect.

Statistical Analysis

Power Calculation

The sample size in the BUL-1/EEA trial was calculated using a Fisher exact test for rates based on a one-sided alpha level of 0.025. The determination of sample size assumed that the percentage of patients with remission would be 10% in the placebo group and 50% in the active treatment group. Given these assumptions, with a 2:1 randomization rate, a sample size of 54 patients in the active group and 27 patients in the placebo group would provide an overall power of at least 90% to detect a difference of 40% in remission rates. In total, 81 patients were needed. This sample size was increased to account for up to 10% of randomized patients who did not take at least one dose of the investigational products.

The trial was performed according to an adaptive two-stage group sequential design with the possibility for sample size adaptation and early stopping for efficacy at the interim analysis. There were no binding stopping for futility boundaries. The interim analysis was performed after 66.6% of the planned number of patients had been included. The interim

analysis was performed based on 54 patients included in the FAS. Based on these results, the Independent Data Monitoring Committee stated that the study had reached its aim to show significant results in the primary end point, proving superiority of budesonide 1 mg twice daily versus placebo, and recommended terminating further study recruitment. The committee recommendation was accepted by the sponsor as the originally planned sample size had been reached. Meanwhile, recruitment for the study was stopped. However, as recruitment continued while the interim analysis was being performed, another 34 patients were randomized. The study carried on with these patients and these patients were included in the final analysis as overrun patients.

Primary Outcome(s) of the Studies

The primary efficacy variable in this clinical trial was the percentage of patients with clinicopathologic remission at week 6 (last observation carried forward [LOCF]), which was defined as fulfilling both of these criteria:

- histologic remission, i.e., a peak of fewer than 16 eosinophils per mm^2 HPF at week 6 (LOCF)
- resolution of symptoms (i.e., no or only minimal problems), defined as a severity of 2 points or less on a NRS of 0 to 10 points (0 to 10) for dysphagia *and* a severity of 2 points or less on a NRS of 0 to 10 points for pain during swallowing on each day of the week prior to week 6 (LOCF).

Patients experiencing a food impaction at any time during the double-blind treatment phase that needed endoscopic intervention or who needed an endoscopic dilation during the double-blind treatment phase were assessed as treatment failures, and thus did not fulfill, by definition, the clinicopathologic remission criterion. The evaluation of the primary efficacy outcome was performed for the FAS.

The hypothesis was tested at a one-sided type I error rate level of 0.025 using a Fisher exact test. For estimating the treatment effect, the difference between the remission rates of active treatment against placebo and the corresponding two-sided 95% repeated CI was provided.

Handling of Missing Data

Patients received a diary for daily documentation of the Dysphagia NRS and Pain During Swallowing NRS. The entries on the patient diary cards had to be made every day during the last seven days of the screening period prior to baseline visit and during the double-blind treatment period. One patient diary card contained the data for seven days. If the patient's documentation was incomplete, the investigator had to ask the patient to give the information on the missing data retrospectively. If the patient could not remember, the corresponding fields remained empty. Missing values at the EOT or withdrawal visit were replaced by the last measurement (last measured week, if appropriate) obtained during double-blind treatment phase (LOCF). Baseline values will be carried forward for patients who provide no post-baseline data. This approach was justified by the fact that the patients have been off anti-inflammatory or EoE-specific treatment, or have been off dietary restrictions for at least four weeks prior to the baseline assessments, meaning that no worsening after baseline was to be expected and that spontaneous remissions are highly unlikely to occur. Patients without a post-baseline endoscopy were considered as not assessable and their screening values were carried forward. In case of missing diary values (NRS for dysphagia and pain during swallowing, respectively) within a week prior to the respective visit for one or two days, the weekly sum of these values was calculated for valid

data only and the sum was divided by the number of days with valid data and multiplied by seven. If data of less than five days were available (> two days missing), the weekly variables were not evaluable for the respective week.

Subgroup Analysis

The primary analysis was not adjusted for covariates. However, the primary and key secondary end points were analyzed descriptively by subgroup of patients with or without concomitant use of PPIs.

No subgroup analysis by prior treatment with PPIs or by history of strictures was conducted.

Sensitivity Analysis

Two post-hoc analyses for the clinicopathologic remission in the most stringent way were performed, with one of the analyses defining the clinicopathologic remission as follows:

- histologic remission, i.e., a peak of zero eosinophils per mm^2 HPF at week 6 (LOCF)
- resolution of symptoms defined as a severity of 0 points on a NRS of 0 to 10 points (0 to 10) for dysphagia and a severity of 0 points on a NRS of 0 to 10 points for pain during swallowing on each day of the week prior to week 6 (LOCF).

The other post-hoc analysis was based on overall resolution of symptoms with a maximal NRS of 0 points. For this post-hoc analysis, the overall resolution of symptoms was defined as a severity of 0 points on a NRS of 0 to 10 points for dysphagia and a severity of 0 points on a NRS of 0 to 10 points for pain during swallowing on each day of the week prior to double-blind week 6 (LOCF).

Secondary Outcomes of the Studies

In order to control the family-wise error rate at the 0.05 level, significance testing was performed in hierarchical fashion for the following six key secondary end points. The test stopped when the first of these comparisons showed a one-sided P value greater than 0.025. Once a non-significant P value occurred, all subsequent significance tests were considered exploratory in nature. While some secondary end points included measurements at interim visits, the statistical tests were performed only on week 6 using LOCF data. Here is the hierarchy of the key secondary end points:

1. the percentage of patients with histologic remission defined as a peak of fewer than 16 eosinophils per mm^2 HPF at week 6 (LOCF)
2. the change in the peak eosinophils per mm^2 HPF from baseline to week 6 (LOCF)
3. the percentage of patients with resolution of symptoms (i.e., no or only minimal problems), defined as a severity of 2 points or less on a NRS of 0 to 10 points for dysphagia and a severity of 2 points or less on a NRS of 0 to 10 points for pain during swallowing on each day of the week prior to week 6 (LOCF)
4. the percentage of patients with a total weekly EEsAI-PRO score of 20 or less at week 6 (LOCF)
5. the percentage of patients with an improvement from baseline to week 6 (LOCF) in the weekly VDQ score
6. the percentage of patients with an improvement from baseline to week 6 (LOCF) in the weekly AMS score.

Analyses performed on all other secondary efficacy variables, primary (subgroup analyses), and safety variables were considered exploratory.

Dichotomous key secondary end points (key secondary end points from the aforementioned list of numbers 1, 3, 4, 5, and 6) were analyzed using a Fisher exact test (test for superiority, one-sided alpha level of 0.025). The denominator was all patients included in the respective analysis set. Dichotomous target variables with a corresponding baseline measurement (key secondary end points numbers 1, 4, 5, and 6) were analyzed in addition to using logistic regression and included the baseline value(s) in addition to treatment group. Change in the peak eosinophils per mm^2 HPF was analyzed by fitting a linear least squares model with treatment effect and baseline value as covariates.

All analyses for key secondary end points were done on a one-sided alpha level of 0.025 with the intent to show the superiority of active treatment over placebo in the context of the hierarchical testing procedure.

For non-key secondary efficacy variables, two-sided 95% CIs for treatment group differences in means or proportions were presented at double-blind week 6 (LOCF).

For the only two secondary end points indicating treatment failure (i.e., percentage of patients experiencing a food impaction during the double-blind treatment phase that needs endoscopic intervention and percentage of patients needing endoscopic dilation during the double-blind treatment phase), missing values were not replaced for the calculation of two-sided 95% CIs for treatment group differences as no missing values were expected.

Table 9: Statistical Analysis of Efficacy End Points

End point	Statistical model	Post-hoc analyses
Primary outcome		
Percentage of patients with clinicopathologic remission at week 6 (LOCF) defined as fulfilling both of these criteria: • histologic remission, i.e., peak of < 16 EOS/mm^2 HPF at week 6 (LOCF) • resolution of symptoms (i.e., no or only minimal problems), defined as a severity of ≤ 2 points on a NRS of 0 to 10 points (0 to 10) for dysphagia *and* a severity of ≤ 2 points on a NRS of 0 to 10 points for pain during swallowing on each day of the week prior to week 6 (LOCF)	Fisher exact test (test for superiority, one-sided alpha level of 0.025)	For the post-hoc analysis, clinicopathologic remission in the most stringent way was defined as fulfilling both of these criteria: • histologic remission, i.e., peak of 0 EOS/mm^2 HPF at week 6 (LOCF) • resolution of symptoms defined as a severity of 0 points on a NRS of 0 to 10 points (0 to 10) for dysphagia *and* a severity of 0 points on a NRS of 0 to 10 points for pain during swallowing on each day of the week prior to week 6 (LOCF)
Key secondary outcomes		
Percentage of patients with histologic remission defined as a peak of < 16 EOS/mm^2 HPF at week 6 (LOCF)	Fisher exact test (test for superiority, one-sided alpha level of 0.025)	Percentage of patients with histologic remission defined as a peak of 0 EOS/mm^2 HPF at week 6 (LOCF)
Change in the peak EOS/mm^2 HPF from baseline to week 6 (LOCF)	One-sided P value for effect between treatment groups from linear least squares model with treatment group and baseline value as covariate (test for superiority, one-sided alpha level of 0.025)	None

End point	Statistical model	Post-hoc analyses
Percentage of patients with resolution of symptoms (i.e., no or only minimal problems), defined as a severity of ≤ 2 points on a NRS of 0 to 10 points for dysphagia and a severity of ≤ 2 points on a NRS of 0 to 10 points for pain during swallowing on each day of the week prior to week 6 (LOCF)	Fisher exact test (test for superiority, one-sided alpha level of 0.025)	Percentage of patients with resolution of symptoms at week 6 (LOCF) based on overall resolution of symptoms with maximal NRS of 0 points. For this post-hoc analysis, resolution of symptoms is defined as a severity of 0 points on a NRS of 0 to 10 points for dysphagia and a severity of 0 points on a NRS of 0 to 10 points for pain during swallowing on each day of the week prior to DB week 6 (LOCF)
Percentage of patients with a total weekly EEsAI-PRO score of ≤ 20 at week 6 (LOCF)	Fisher exact test (test for superiority, one-sided alpha level of 0.025)	None
Percentage of patients with an improvement from baseline to week 6 (LOCF) in the weekly VDQ score	Fisher exact test (test for superiority, one-sided alpha level of 0.025)	None
Percentage of patients with an improvement from baseline to week 6 (LOCF) in the weekly AMS score	Fisher exact test (test for superiority, one-sided alpha level of 0.025)	None

AMS = avoidance, modification, and slow eating; DB = double-blind; EEsAI-PRO = Eosinophilic Esophagitis Activity Index Patient Reported Outcome; EOS = eosinophil; HPF = high-power field; LOCF = last observation carried forward; NRS = numerical rating scale; VDQ = Visual Dysphagia Question.

Source: Clinical Study Report of the BUL-1/EEA trial.[9]

Analysis Populations

The FAS included all randomized patients (as randomized) who received at least one dose of therapy.

The safety analysis set (SAS) included all randomized patients (as treated) who received at least one dose of therapy. If the administration of any therapy was not certain, the patient was included in the SAS.

The evaluation of primary and secondary efficacy end points was performed for the FAS. The SAS was used for the evaluation of safety.

Results

Patient Disposition

In the BUL-1/EEA trial, a total of 126 patients were screened. Thirty-eight of these patients were not eligible for the study. A total of 88 patients were randomized to the double-blind phase, and all 88 patients were treated. Of those, 81 patients completed the double-blind treatment phase and seven patients were prematurely withdrawn from the double-blind treatment phase (all due to lack of efficacy): four patients (13.8%) in the placebo group and three patients (5.1%) in the budesonide 1 mg twice daily treatment group. A total of 30 patients rolled over to the maintenance study BUL-2/EER after the double-blind treatment phase, and 51 patients entered the OLI treatment phase. Complete details are presented in Table 10.

Table 10: Patient Disposition

	BUL-1/EEA	
	Budesonide 1 mg b.i.d.	Placebo
Screened, N	126	
Randomized, N	59	29
Discontinued DB treatment phase, N (%)	3 (5.1)	4 (13.8)
Reason for discontinuation, N (%)		
Lack of efficacy	3 (5.1)	4 (13.8)
Full DB treatment phase completed, N (%)	56 (94.9)	25 (86.2)
OLI phase entered and treated, N (%)	23 (39.0)	28 (96.6)
Full OLI phase completed, N (%)	23 (39.0)	27 (93.1)
OLI phase prematurely terminated, N (%)	0 (0.0)	1 (3.4)
Follow-up visit not performed,[a] N (%)	45 (76.3)	21 (72.4)
Follow-up visit performed, N (%)	14 (23.7)	8 (27.6)
FAS-DB, N (%)	59 (100)	29 (100)
SAS-DB, N (%)	59 (100)	29 (100)
PP-DB, N (%)	51 (86.4)	26
FAS-OLI, N (%)	23 (39.0)	28 (96.6)
SAS-OLI, N (%)	23 (39.0)	28 (96.6)

b.i.d. = twice a day; DB = double-blind; FAS = full analysis set; OLI = open-label induction; PP = per-protocol; SAS = safety analysis set.

[a] A "follow-up visit not performed" means that the patient was considered for immediate transition into the subsequent BUL-2/EER trial.

Source: Clinical Study Report of the BUL-1/EEA trial.[9]

Exposure to Study Treatments

Placebo medication was administered on average on 41 days (standard deviation [SD] = 7.5 days, median = 42 days) and budesonide 1 mg twice daily was administered on average on 41 days (SD = 4.1 days, median = 41 days) in the FAS.

Compliance (%) was calculated as the number of used tablets divided by the number of tablets to be used, then multiplied by 100. Mean values (SD) for the compliance were 98.0% (6.55%) in the budesonide 1 mg group and 96.9% (7.56%) in the placebo group. Median values (range) for compliance were 98.1% (79.3% to 127.9%) in the budesonide 1 mg group and 100.0% (74.0% to 109.1%) in the placebo group.

Efficacy

Only those efficacy outcomes and analyses of subgroups identified in the review protocol are reported as follows. See Appendix 3 for detailed efficacy data.

Clinical Response (Improvement in Dysphagia and Odynophagia)

The percentage of patients with resolution of symptoms (i.e., no or only minimal problems), defined as a severity of 2 points or less on a NRS of 0 to 10 points for dysphagia and a severity of 2 points or less on a NRS of 0 to 10 points for pain during swallowing on each day of the week prior to week 6 was one of the two components of the composite primary end point in the BUL-1/EEA trial.

The percentage of patients with no or only minimal problems in dysphagia defined as a severity of 2 points or less on a NRS of 0 to 10 points for dysphagia on each day of the week prior to week 6, and the percentage of patients with no or only minimal problems with pain during swallowing defined as a severity of 2 points or less on a NRS of 0 to 10 points for pain during swallowing on each day of the week prior to week 6 were other secondary end points and were considered exploratory in the BUL-1/EEA trial.

Resolution of Symptoms

Four of the 29 patients (13.8%) in the placebo group and 35 of the 59 patients (59.3%) in the budesonide 1 mg group achieved resolution of symptoms at week 6. The difference between the budesonide 1 mg group and the placebo treatment group was 45.5% (95% CI, 27.8 to 63.3; P < 0.0001) in favour of budesonide (Table 11).

Subgroup analysis by concomitant use of a PPI were aligned with the overall study population (Table 11).

The post-hoc analysis of complete resolution of symptoms showed that none of the 29 patients (0.0%) in the placebo group and 15 of the 59 patients (25.4%) in the budesonide 1 mg group achieved resolution of symptoms at week 6. The difference between the budesonide 1 mg group and the placebo treatment group was 25.4% (95% CI, 14.3 to 36.5) in favour of budesonide (Table 11).

No or Only Minimal Problems With Dysphagia

Four patients (13.8%) in the placebo group and 37 patients (62.7%) in the budesonide 1 mg group had no or only minimal problems with dysphagia defined as a severity of 2 points or less on a NRS of 0 to 10 for dysphagia on each day of the week prior to week 6. The difference between the budesonide 1 mg group and the placebo treatment group was 48.9% (95% CI, 31.3 to 66.5) in favour of budesonide (Table 11).

The post-hoc analysis of no or only minimal problems in dysphagia in the most stringent way was defined as a severity of 0 points on a NRS of 0 to 10 points (0 to 10) for dysphagia each day in the week prior to week 6. According to this most stringent criterion, none of the 29 patients (0.0%) in the placebo group and 17 of the 59 patients (28.8%) in the budesonide 1 mg group achieved no or only minimal problems in dysphagia at week 6. The difference between the budesonide 1 mg and placebo treatment groups was 28.8% (95% CI, 17.3 to 40.4) in favour of budesonide (Table 11).

No or Only Minimal Problems With Pain

Sixteen patients (55.2%) in the placebo group and 38 patients (64.4%) in the budesonide 1 mg treatment group had no or only minimal problems with pain during swallowing, defined as a severity of 2 points or less on a NRS of 0 to 10 points for pain during swallowing on each day of the week prior to week 6. The difference between the budesonide 1 mg group and the placebo group was 9.2% (95% CI, −12.6 to 31.1) (Table 11).

Table 11: Resolution of Symptoms in the BUL-1/EEA Trial, LOCF

	Total N	n (%)	Difference in proportions: Budesonide vs. placebo (95% CI)	P value
Percentage of patients with resolution of symptoms (i.e., no or only minimal problems), defined as a severity of ≤ 2 points on a NRS of 0 to 10 points for dysphagia *and* a severity of ≤ 2 points on a NRS of 0 to 10 points for pain during swallowing on each day of the week prior to week 6				
Budesonide 1 mg b.i.d.	59	35 (59.3)	45.5% (27.8% to 63.3%)	< 0.0001[a]
Placebo	29	4 (13.8)	Reference	
Subgroup analysis for resolution of symptoms at week 6 (LOCF) for patients who used concomitant PPI				
Budesonide 1 mg b.i.d.	7	5 (71.4)	NR	NR
Placebo	3	0 (0)		
Subgroup analysis for resolution of symptoms at week 6 (LOCF) for patients who did not use concomitant PPI				
Budesonide 1 mg b.i.d.	52	30 (57.7)	NR	NR
Placebo	26	4 (15.4)		
Post-hoc analysis: Percentage of patients with resolution of symptoms at week 6 based on overall resolution of symptoms with maximal NRS of 0 points				
Budesonide 1 mg b.i.d.	59	15 (25.4)	25.4% (14.3% to 36.5%)	NR
Placebo	29	0	Reference	
Percentage of patients with no or only minimal problems in dysphagia defined as a severity of ≤ 2 points on a NRS of 0 to 10 points for dysphagia on each day of the week prior to week 6				
Budesonide 1 mg b.i.d.	59	37 (62.7)	48.9% (31.3% to 66.5%)	NR
Placebo	29	4 (13.8)	Reference	
Post-hoc analysis: Percentage of patients with resolution of symptom dysphagia at week 6 based on maximal NRS of 0 points in diary in the week preceding the visit				
Budesonide 1 mg b.i.d.	59	17 (28.8)	28.8% (17.3% to 40.4%)	NR
Placebo	29	0 (0)	Reference	
Percentage of patients with no or only minimal problems in pain during swallowing defined as a severity of ≤ 2 points on a NRS of 0 to 10 points for pain during swallowing on each day of the week prior to week 6				
Budesonide 1 mg b.i.d.	59	38 (64.4%)	9.2% (−12.6% to 31.1%)	NR
Placebo	29	16 (55.2%)	Reference	

b.i.d. = twice a day; CI = confidence interval; LOCF = last observation carried forward; NR = not reported; NRS = numerical rating scale; PPI = proton pump inhibitor; vs. = versus.

[a] Fisher exact test (test for superiority, one-sided alpha level of 0.025).

Source: Clinical Study Report of the BUL-1/EEA trial.[9]

Treatment Failure

Food Impaction

A food impaction at any time during the double-blind treatment phase that needed endoscopic intervention occurred in one out of 29 patients (3.4%) in the placebo group and in zero out of 59 patients (0.0%) in the budesonide 1 mg group.

Endoscopic Dilation

There was no need for an endoscopic dilation during the double-blind treatment phase in any treatment group.

Health-Related Quality of Life

Change from baseline in modSHS and change from baseline in the total EoE-QoL-A questionnaire were other secondary end points and were considered exploratory in the BUL-1/EEA trial.

Modified Short Health Scale

The difference between the budesonide 1 mg and placebo treatment groups in mean absolute changes (95% CI) from baseline to week 6 for symptom burden, social function, disease-related worry, and general well-being were −14.0 (−28.1 to 0.05), −14.8 (−27.4 to −2.2), −12.8 (−24.4 to −1.2), and −7.9 (−17.4 to 1.6), respectively. These between-group differences were in favour of budesonide 1 mg for the social function and disease-related worry dimensions only (Table 12).

Total Eosinophilic Esophagitis Quality of Life Scale for Adults Questionnaire

The difference between the budesonide 1 mg group and the placebo treatment group in mean absolute changes (95% CI) from baseline to week 6 for EoE-QoL-A (30 items), EoE-QoL-A (24 items), EoE-QoL-A eating/diet impact (10 items), EoE-QoL-A eating/diet impact (four items), EoE-QoL-A social impact, EoE-QoL-A emotional impact, EoE-QoL-A disease anxiety, and EoE-QoL-A swallowing anxiety were 0.24 (−0.01 to 0.47), 0.24 (−0.004 to 0.48), 0.50 (0.17 to 0.82), 0.49 (0.13 to 0.86), 0.16 (−0.17 to 0.49), 0.20 (−0.05 to 0.46), 0.16 (−0.08 to 0.39), and 0.19 (−0.15 to 0.54), respectively. These between-group differences were in favour of budesonide 1 mg for the subscales eating/diet impact (10 items) and eating/diet impact (four items) only (Table 13).

Table 12: Changes From Baseline to Week 6, LOCF, of the Modified Short Health Scale in Patients With EoE in the BUL-1/EEA Trial

	Total N	Baseline	EOT time point (week 6)		Treatment group difference vs. control		
		Mean (SD)	Mean (SD)	Mean change from baseline (95% CI)	N	Mean difference (95% CI)	P value
Change from baseline to week 6 in modified Short Health Scale[a, b]							
Symptom burden							
Budesonide 1 mg b.i.d.	58	58 (23.5)	27 (27.1)	−31.6 (−40.2 to −23.1)	58	−14.0 (−28.1 to 0.05)	NR[c]
Placebo	29	55 (18.1)	38 (25.1)	−17.6 (−28.3 to −6.9)	29	Reference	
Social function							
Budesonide 1 mg b.i.d.	58	55 (29.0)	26 (27.1)	−28.9 (−36.8 to −21.0)	58	−14.8 (−27.4 to −2.2)	NR[c]
Placebo	29	46 (24.3)	32 (23.1)	−14.1 (−22.8 to −5.4)	29	Reference	
Disease-related worry							
Budesonide 1 mg b.i.d.	58	57 (26.4)	37 (29.6)	−20.6 (−27.8 to −13.4)	58	−12.8 (−24.4 to −1.2)	NR[c]
Placebo	29	52 (26.8)	44 (28.6)	−7.8 (−16.3 to 0.6)	29	Reference	
General well-being							
Budesonide 1 mg b.i.d.	58	40 (23.3)	24 (22.9)	−16.5 (−21.4 to −11.5)	58	−7.9 (−17.4 to 1.6)	NR[c]

	Total N	Baseline	EOT time point (week 6)		Treatment group difference vs. control		
		Mean (SD)	Mean (SD)	Mean change from baseline (95% CI)	N	Mean difference (95% CI)	P value
Placebo	29	35 (29.0)	26 (24.3)	−8.6 (−18.0 to 0.9)	29	Reference	

b.i.d. = twice a day; CI = confidence interval; EoE = eosinophilic esophagitis; EOT = end of treatment; LOCF = last observation carried forward; NR = not reported; SD = standard deviation; vs. = versus.

[a] Range of each score: 0 to 100. Lower numbers indicate higher quality of life.

[b] Two-sided 95% CIs for the mean modified Short Health Scale: Symptom burden, social function, disease-related worry, and general well-being per group and for the group difference in means, based on t-distribution.

[c] Modified Short Health Scale was outside the statistical testing hierarchy.

Source: Clinical Study Report of the BUL-1/EEA trial.[9]

Table 13: Changes From Baseline to Week 6, LOCF, of the Total Eosinophilic Esophagitis Quality of Life Scale for Adults Questionnaire and its Subscores in the BUL-1/EEA Trial

	Total N	Baseline	EOT time point (week 6)		Treatment group difference vs. control		
		Mean (SD)	Mean (SD)	Mean change from baseline (95% CI)	N	Mean difference (95% CI)	P value
Changes from baseline to week 6 of the total EoE-QoL-A questionnaire and its subscores[a, b]							
EoE-QoL-A, 30 items (weighted average)							
Budesonide 1 mg b.i.d.	57	2.3 (0.8)	2.8 (0.9)	0.47 (0.32 to 0.62)	57	0.24 (−0.01 to 0.47)	NR[c]
Placebo	29	2.3 (0.8)	2.6 (0.7)	0.24 (0.06 to 0.42)	29	Reference	
EoE-QoL-A, 24 items (weighted average)							
Budesonide 1 mg b.i.d.	57	2.2 (0.8)	2.7 (0.9)	0.48 (0.33 to 0.63)	57	0.24 (−0.004 to 0.48)	NR[c]
Placebo	29	2.3 (0.8)	2.6 (0.7)	0.24 (0.07 to 0.42)	29	Reference	
EoE-QoL-A eating/diet impact, 10 items (weighted average)							
Budesonide 1 mg b.i.d.	57	2.2 (1.0)	2.9 (1.0)	0.65 (0.41 to 0.88)	57	0.50 (0.17 to 0.82)	NR[c]
Placebo	29	2.3 (0.8)	2.5 (0.7)	0.15 (−0.08 to 0.38)	29	Reference	
EoE-QoL-A eating/diet impact, 4 items (weighted average)							
Budesonide 1 mg b.i.d.	57	2.1 (1.0)	2.8 (1.0)	0.69 (0.46 to 0.92)	57	0.49 (0.13 to 0.86)	NR[c]
Placebo	29	2.2 (0.9)	2.4 (0.8)	0.20 (−0.04 to 0.44)	29	Reference	
EoE-QoL-A social impact (weighted average)							
Budesonide 1 mg b.i.d.	57	2.1 (1.0)	2.6 (1.1)	0.46 (0.27 to 0.65)	57	0.16 (−0.17 to 0.49)	NR[c]
Placebo	29	2.2 (1.0)	2.5 (0.9)	0.30 (0.02 to 0.58)	29	Reference	
EoE-QoL-A emotional impact (weighted average)							
Budesonide 1 mg b.i.d.	57	2.6 (0.9)	3.0 (0.9)	0.44 (0.28 to 0.60)	57	0.20 (−0.05 to 0.46)	NR[c]
Placebo	29	2.7 (0.8)	2.9 (0.7)	0.23 (0.04 to 0.43)	29	Reference	
EoE-QoL-A disease anxiety (weighted average)							
Budesonide 1 mg b.i.d.	57	2.0 (0.9)	2.3 (1.0)	0.31 (0.17 to 0.45)	57	0.16 (−0.08 to 0.39)	NR[c]

	Total N	Baseline	EOT time point (week 6)		Treatment group difference vs. control		
		Mean (SD)	Mean (SD)	Mean change from baseline (95% CI)	N	Mean difference (95% CI)	P value
Placebo	29	1.8 (0.9)	2.0 (0.9)	0.15 (−0.04 to 0.34)	29	Reference	
EoE-QoL-A swallowing anxiety (weighted average)							
Budesonide 1 mg b.i.d.	57	2.1 (1.0)	2.7 (1.1)	0.60 (0.39 to 0.80)	57	0.19 (−0.15 to 0.54)	NR[c]
Placebo	29	2.3 (1.1)	2.8 (0.9)	0.40 (0.13 to 0.68)	29	Reference	

b.i.d. = twice a day; CI = confidence interval; EoE-QoL-A = Adult Eosinophilic Esophagitis Quality of Life; EOT = end of treatment; LOCF = last observation carried forward; NR = not reported; SD = standard deviation; vs. = versus.

[a] The EoE-QoL-A yields an overall score and five subscale scores. Scores range from 0 to 4. Higher scores indicate better quality of life.

[b] Two-sided 95% CIs for the mean EoE-QoL-A: Overall score (30 items, weighted average), overall score (24 items, weighted average), eating/diet impact (10 items, weighted average), eating/diet impact (four items, weighted average), social impact (weighted average), emotional impact (weighted average), disease anxiety (weighted average), and swallowing anxiety (weighted average). Absolute change from baseline per group and for the group difference in means, based on t-distribution.

[c] EoE-QoL-A scores were outside the statistical testing hierarchy.

Source: Clinical Study Report of the BUL-1/EEA trial.[9]

Histologic Response

The percentage of patients with histologic remission, defined as a peak of fewer than 16 eosinophils per mm^2 HPF at week 6, was a key secondary end point; it was one of the two components of the composite primary end point. The change in the peak eosinophils per mm^2 HPF from baseline to week 6 was a key secondary end point in the BUL-1/EEA trial.

Histologic Remission

None of the 29 patients (0%) in the placebo group and 55 of the 59 patients (93.2%) in the budesonide 1 mg group achieved histologic remission at week 6. The difference between the budesonide 1 mg group and the placebo treatment group was 93.2% (95% CI, 86.8 to 99.6; P < 0.0001) in favour of budesonide (Table 14).

Subgroup analysis by concomitant use of a PPI was aligned with the overall study population (Table 14).

The post-hoc analysis of histologic remission in the most stringent way was defined as peak eosinophils per mm^2 HPF of 0 in all biopsies at week 6. According to this most stringent criterion, none of the 29 patients (0.0%) in the placebo group and 53 of the 59 patients (89.8%) in the budesonide 1 mg group achieved histologic remission at week 6. The difference between the budesonide 1 mg group and the placebo treatment group was 89.8% (95% CI, 82.1 to 97.5; P < 0.0001) in favour of budesonide (Table 14).

Change in the Peak Eosinophils per mm^2 HPF From Baseline

The mean change in the peak eosinophils per mm^2 HPF from baseline to week 6 was −225.5 (95% CI, −264.7 to −186.4) in the budesonide 1 mg group and −4.3 (95% CI, −55.9 to 47.3) in the placebo group. The mean (95% CI) difference between treatment groups at week 24 was −221.3 (95% CI, −287.0 to −155.6; P < 0.0001) in favour of budesonide (Table 31).

Table 14: Percentage of Patients With Histologic Remission at Week 6, LOCF, in the BUL-1/EEA Trial

	Total N	n (%)	Difference in proportions: Budesonide vs. placebo (95% CI)	P value
Percentage of patients with histologic remission, defined as a peak of < 16 EOS/mm^2 HPF at week 6[a]				
Budesonide 1 mg b.i.d.	59	55 (93.2)	93.2% (86.8% to 99.6%)	< 0.0001[b]
Placebo	29	0 (0)	Reference	
Percentage of patients with histologic remission, defined as a peak of < 16 EOS/mm^2 HPF at week 6				
Budesonide 1 mg b.i.d.	59	53 (89.8)	89.8% (82.1% to 97.5%)	NR
Placebo	29	0 (0)	NR	
Subgroup analysis for histologic remission at week 6 (LOCF) for patients who used concomitant PPI				
Budesonide 1 mg b.i.d.	7	7 (100)	NR	NR
Placebo	3	0 (0)		
Subgroup analysis for histologic remission at week 6 (LOCF) for patients who did not use concomitant PPI				
Budesonide 1 mg b.i.d.	52	48 (92.3)	NR	NR
Placebo	26	0 (0)		
Post-hoc analysis: Percentage of patients in deep histologic remission defined as peak EOS/mm^2 HPF of 0 in all biopsies at week 6				
Budesonide 1 mg b.i.d.	59	53 (89.8)	89.8% (82.1% to 97.5%)	< 0.0001[c]
Placebo	29	0 (0)	Reference	
Percentage of patients with histologic response, defined as peak of < 48 EOS/mm^2 HPF at week 6				
Budesonide 1 mg b.i.d.	59	56 (94.9)	NR	NR
Placebo	29	0 (0)		

b.i.d. = twice a day; CI = confidence interval; EOS = eosinophil; HPF = high-power field; LOCF = last observation carried forward; NR = not reported; PPI = proton pump inhibitor; vs. = versus.

[a] For this analysis, results that were not evaluable were set to "no."

[b] Fisher exact test (test for superiority, one-sided alpha level of 0.025).

[c] Outcome not adjusted for multiplicity.

Source: Clinical Study Report of the BUL-1/EEA trial.[9]

Clinicopathologic Remission

The primary end point in the BUL-1/EEA trial was the percentage of patients with clinicopathologic remission at week 6, defined as fulfilling both criteria histologic remission (i.e., a peak of fewer than 16 eosinophils per mm^2 HPF at week 6), and the resolution of symptoms (i.e., no or only minimal problems), defined as a severity of 2 points or less on a NRS of 0 to 10 points (0 to 10) for dysphagia *and* a severity of 2 points or less on a NRS of 0 to 10 points for pain during swallowing on each day of the week prior to week 6.

None of the 29 patients (0.0%) in the placebo group and 34 out of 59 patients (57.6%) in the budesonide 1 mg treatment group were in clinicopathologic remission at week 6. The difference between the budesonide 1 mg group and the placebo treatment group was 57.6% (95% CI, 38.2 to 72.0; P < 0.0001) in favour of budesonide (Table 15).

Subgroup analysis by concomitant use of a PPI was aligned with the overall study population (Table 15).

The post-hoc analysis of clinicopathologic remission in the most stringent way was defined as histologic remission, i.e., a peak of zero eosinophils per mm^2 HPF at week 6, and resolution of symptoms, defined as a severity of 0 points on a NRS of 0 to 10 points (0 to 10) for dysphagia and a severity of 0 points on a NRS of 0 to 10 points for pain during swallowing on each day of the week prior to week 6. According to this most stringent criterion, none of the 29 patients (0.0%) in the placebo group and 13 of the 59 patients (22.0%) in the budesonide 1 mg group achieved clinicopathologic remission at week 6. The difference between the budesonide 1 mg group and the placebo treatment group was 22.0% (95% CI, 11.5% to 32.6%; P = 0.0034) in favour of budesonide (Table 15).

Table 15: Clinicopathologic Remission in the BUL-1/EEA Trial, LOCF

	Total N	n (%)	Difference in proportions: Budesonide vs. placebo (95% CI)	P value
Percentage of patients with clinicopathologic remission at week 6				
Budesonide 1 mg b.i.d.	59	34 (57.6)	57.6% (38.2% to 72.0%)	< 0.0001[a]
Placebo	29	0 (0)	Reference	
Post-hoc analysis: Percentage of patients with clinicopathologic remission at week 6 based on overall resolution of symptoms with maximal NRS of 0 points				
Budesonide 1 mg b.i.d.	59	14 (23.7)	NR	NR
Placebo	29	0 (0)		
Post-hoc analysis: Percentage of patients with clinicopathologic remission at week 6 based on peak of 0 EOS/mm² HPF and overall resolution of symptoms with maximal NRS of 0 points				
Budesonide 1 mg b.i.d.	59	13 (22.0)	22.0% (11.5% to 32.6%)	0.0034[b]
Placebo	29	0 (0)	Reference	
Subgroup analysis for clinicopathologic remission at week 6 for patients who used concomitant PPI				
Budesonide 1 mg b.i.d.	7	5 (71.4)	NR	NR
Placebo	3	0 (0)		
Subgroup analysis for clinicopathologic remission at week 6 for patients who did not use concomitant PPI				
Budesonide 1 mg b.i.d.	52	29 (55.8)	NR	NR
Placebo	26	0 (0)		

b.i.d. = twice a day; CI = confidence interval; EOS = eosinophil; HPF = high-power field; LOCF = last observation carried forward; NR = not reported; NRS = numerical rating scale; vs. = versus.

[a] Fisher exact test (test for superiority, one-sided alpha level of 0.025).

[b] Outcome not adjusted for multiplicity.

Source: Health Canada Reviewer's Report[24] and Clinical Study Report of the BUL-1/EEA trial.[9]

Eosinophilic Esophagitis Activity

Eosinophilic Esophagitis Activity Index Patient Reported Outcome

The percentage of patients with a total weekly EEsAI-PRO score of 20 or less at week 6 was a key secondary end point.

Two of the 29 patients (6.9%) in the placebo group and 30 of the 59 patients (50.8%) in the budesonide 1 mg group achieved a total weekly EEsAI-PRO score of 20 or less at week 6. The difference between the budesonide 1 mg group and the placebo treatment group was 44.0% (95% CI, 28.2 to 59.7; P < 0.0001) in favour of budesonide (Table 32).

Visual Dysphagia Question

The percentage of patients with an improvement from baseline to week 6 in the weekly VDQ score was a key secondary end point.

Eleven of the 29 patients (37.1%) in the placebo group and 30 of the 59 patients (50.8%) in the budesonide 1 mg group had an improvement from baseline to week 6 in the weekly VDQ score. The difference between the budesonide 1 mg group and the placebo treatment group was 12.9% (95% CI, −9.9 to 34.7; P = 0.1804), which was not statistically significant (Table 32).

Avoidance, Modification, and Slow Eating

The percentage of patients with an improvement from baseline to week 6 in the weekly AMS score was a key secondary end point and was considered exploratory.

Three of the 29 patients (10.3%) in the placebo group and seven of the 59 patients (11.9%) in the budesonide 1 mg group had an improvement from baseline to week 6 in the weekly AMS score. The difference between the budesonide 1 mg group and the placebo treatment group was 1.5% (95% CI, −12.3 to 15.3; P = 0.5703), which was not statistically significant (Table 32).

Patient's Global Assessment

The percentage of patients with overall symptoms resolution defined as PatGA concerning the severity of EoE symptoms (NRS of 0 to 10) of 2 points or less at week 6 was other secondary end points and were considered exploratory in the BUL-1/EEA trial.

The PatGA concerning the severity of EoE symptoms on a NRS of 0 to 10 showed a much higher percentage of patients achieving overall symptoms resolution (PatGA ≤ 2 points) at week 6 in the budesonide 1 mg group (with 38 out of 59 patients, or 64.4%) than in the placebo group (with seven out of 29 patients, or 24.1%). The difference between the budesonide 1 mg group and the placebo treatment group was 40.3% (95% CI, 20.5 to 60.1) in favour of budesonide (Table 33).

Physician's Global Assessment

The change from baseline in the PGA of EoE activity (NRS of 0 to 10) was other secondary end points and were considered exploratory in the BUL-1/EEA trial.

The mean change in the PGA of EoE activity from baseline to week 6 was −3.8 (95% CI, −4.40 to −3.19) in the budesonide 1 mg group and −0.8 (95% CI, −1.58 to 0.06) in the placebo group. The mean (95% CI) difference between treatment groups at week 24 was −3.0 (95% CI, −4.06 to −2.01) in favour of budesonide (Table 34).

Relapse

Relapse was not assessed in the BUL-1/EEA trial.

Harms

Only those harms identified in the review protocol are reported as follows. See Table 16 for detailed harms data.

Adverse Events

A higher proportion of patients reported TEAEs following treatment with budesonide 1 mg (37 out of 59 patients, 62.7%) in comparison to patients treated with placebo (12 out of 29 patients, 41.1%) (Table 16).

The most frequently reported TEAEs in the budesonide 1 mg treatment group were suspected AEs of candidiasis (a fungal infection due to any type of Candida), which occurred in 14 patients (23.7%) in the budesonide 1 mg treatment group and in none of the patients in the placebo group. Of the 14 patients (23.7%) affected with local fungal infection in the budesonide 1 mg treatment group, 10 patients (16.9%) had esophageal candidiasis, three patients (5.1%) had oropharyngeal candidiasis, two patients (3.4%) had oral candidiasis, and two patients (3.4%) had Candida infection. Some patients had more than one fungal infection in different subcategories.

No patients in the placebo group versus three patients (5.1%) in the budesonide 1 mg treatment group experienced decreased blood cortisol values. All three events were assessed as possibly related to the study drugs. No patients in the placebo group versus three patients (5.1%) in the budesonide 1 mg group experienced GERD. Two of these events were assessed as possibly related to the study drugs, one as unlikely. More patients were affected by asthma in the placebo group (two patients, or 6.9%) than in the budesonide 1 mg group (no patients). One patient (3.4%) in the placebo group versus four patients (6.8%) in the budesonide 1 mg group experienced headache. All headache AEs were assessed as either unlikely related or not related to the study drugs.

Serious Adverse Events

No SAEs occurred during the course of the BUL-1/EEA trial.

Withdrawals due to Adverse Events

One AE in the placebo group (there were none in the budesonide 1 mg group) led to discontinuation of the treatment. The one AE leading to discontinuation of treatment in the placebo group was an esophageal food impaction that was severe and needed endoscopic intervention. The AE was assessed as a deterioration of the underlying disease, and the primary reason for withdrawal from the double-blind treatment phase for this patient was lack of efficacy.

Mortality

No deaths occurred during the course of the BUL-1/EEA trial.

Notable Harms

The most frequently reported TEAEs in the budesonide 1 mg treatment group were 17 suspected AEs of candidiasis, reported either by the investigator based on endoscopic or clinical signs and symptoms, or by the central pathologist based on the assessment of esophageal biopsies, and occurring in 14 patients (23.7%) in the budesonide 1 mg treatment group versus none in the placebo group. These are known AEs caused by the anti-inflammatory and immunosuppressive action of budesonide. However, these treatment-emergent suspected candidiasis cases were histologically confirmed by positive Grocott staining in only 10 patients (16.9%), whereas in eight patients (13.6%), they were histologically confirmed and showed endoscopic signs, and finally, only four events (three esophageal candidiasis events and one oral candidiasis) in three patients (5.1%) were

histologically confirmed and showed endoscopic and clinical signs. All four of these events were of mild severity and did not interfere with normal daily activities. Twelve of the treatment-emergent suspected candidiasis patients recovered during the course of the trial; for five events, the outcome was unknown at the end of the trial.

A psychiatric disorder was reported in one patient (3.4%) in the placebo group versus none in the budesonide 1 mg treatment group.

Symptoms of sore throat (pharyngitis) were reported in two patients (6.9%) in the placebo group and in one patient (1.7%) in the budesonide 1 mg treatment group.

Table 16: Summary of Harms

	BUL-1/EEA	
	Budesonide 1 mg b.i.d. (N = 59)	Placebo (N = 29)
Patients with ≥ 1 adverse event		
n (%)	37 (62.7)	12 (41.1)
Most common events[a]		
Gastroesophageal reflux disease	3 (5.1)	0
Nausea	2 (3.4)	0
Suspected local fungal infection[b]	14 (23.7)	0
Candida infection	2 (3.4)	0
Esophageal candidiasis	10 (16.9)	0
Oral candidiasis	2 (3.4)	0
Oropharyngeal candidiasis	3 (5.1)	0
Nasopharyngitis	2 (3.4)	1 (3.4)
Pharyngitis	1 (1.7)	2 (6.9)
Blood cortisol, decreased	3 (5.1)	0
Headache	4 (6.8)	1 (3.4)
Asthma	0	2 (6.9)
Hypertension	2 (3.4)	0
Patients with ≥ 1 SAE		
n (%)	0	0
Patients who stopped treatment due to adverse events		
n (%)	0	1 (3.4)
Most common events[a]		
Esophageal food impaction of severe intensity requiring endoscopic intervention	0	1 (3.4)
Deaths		
n (%)	0	0
Notable harms, N (%)		
Local fungal infection	14 (23.7)	0
Candida infection	2 (3.4)	0
Esophageal candidiasis	10 (16.9)	0
Oral candidiasis	2 (3.4)	0

	BUL-1/EEA	
	Budesonide 1 mg b.i.d. (N = 59)	Placebo (N = 29)
Oropharyngeal candidiasis	3 (5.1)	0
Dysgeusia	0	0
Decreased bone mineral density	0	0
Cataract	0	0
Glaucoma	0	0
Psychiatric disorders	0	1 (3.4)
Insomnia	0	1 (3.4)
Symptoms of sore throat (pharyngitis)	1 (1.7)	2 (6.9)
Avascular necrosis of the hip	0	0

b.i.d. = twice a day; SAE = serious adverse event.

[a] Treatment-emergent adverse events occurring in at least two patients in any treatment group.

[b] Patients with more than one fungal infection event may appear several times in different subcategories but are counted only once in the "Suspected local fungal infection" category.

Source: Clinical Study Report of the BUL-1/EEA trial.[9]

Critical Appraisal

Internal Validity

The BUL-1/EEA trial used accepted methods to conceal allocation and randomize patients to treatments; in addition, matched placebo was used to maintain blinding. Also, randomization was performed using randomly permuted blocks. The patients' baseline characteristics and prior treatment experience appeared to be roughly balanced at baseline between groups, despite certain large variations observed between the treatment groups, perhaps due to a small sample size in the placebo group (N = 29). Notably, more patients previously received a PPI (54% versus 45%) and topical budesonide (20% versus 10%) in the budesonide 1 mg group compared to the placebo group. It is unknown what would be the impact of such imbalance on the treatment effect assessment.

Subgroup analysis by concomitant treatment with PPIs was conducted in the BUL-1/EEA trial. The sample size was too small to draw any meaningful conclusion from the subgroup analyses, i.e., regarding the consistency of effect between patients with or without concomitant treatment of PPIs. Subgroup analysis on other patient characteristics of interest were not reported, such as patients with stricture or prior PPI treatment.

The clinical expert consulted on this review indicated that due to the short duration of the BUL-1/EEA trial, it is not possible to draw any firm conclusions about effects of budesonide 1 mg twice daily on HRQoL. Of note, however, there was a consistent trend of improvements, shown by using different HRQoL outcome measures. Particularly, the between-group difference over the six-week period in the EoE-QoL-A eating/diet impact (10 items) subscale was significantly improved in favour of budesonide 1 mg (0.50; 95% CI, 0.17 to 0.82).

The validity, test-retest reliability, and responsiveness of the outcome measures (e.g., Dysphagia NRS, Pain During Swallowing NRS, PGA of EoE activity, and PatGA concerning the severity of EoE symptoms, used in the BUL-1/EEA trial) were not established. Also, MID in the EoE population is not available for any of the PROs assessed. The clinical

assessment of symptom resolution and patients' HRQoL were based on PROs using a diary recording over a week or questionnaires. Subjective recall biases were highly likely, particularly when such recall was differential between treatment groups, due perhaps to patients' or the assessing physicians' awareness of the treatment assignment as a result of drug-related side effects. In particular, 23% of patients in the budesonide 1 mg group reported at least one AE related to various local fungal infections and, additionally, 8% GERD or nausea, whereas 0% of such events were reported in the placebo group. Moreover, premature withdrawal from the treatment phase due to lack of efficacy occurred in four patients (13.8%) in the placebo group compared to three patients (5.1%) in the budesonide 1 mg group. Together, these could have biased the results in favour of the study drug.

Missing values were accounted for by using an LOCF approach. While the LOCF approach can introduce bias in the results, in the BUL-1/EEA trial, the number of missing values was low and did not raise significant concerns. Also, results did not differ between analysis based on observed data and analysis based on an LOCF approach.

External Validity

Patients enrolled in the BUL-1/EEA trial were deemed to be similar to patients with EoE in Canada, even though no Canadian study site was included in this trial. A considerable proportion of total screened patients (38 out of 126, 30%) were excluded from the trial. Of the EoE diagnosed patients, only those with active symptomatic and histologic EoE who met with pre-specified criteria were enrolled. For instance, this criteria included patients diagnosed not only with EoE but also with dysphagia (trouble swallowing) on at least one day in the last seven days prior to baseline with a severity of at least four points on a NRS of 0 points (no trouble swallowing) to 10 points (the most severe trouble swallowing), or other similar sets of criteria on pain, and peak eosinophils of at least 65 per mm^2 HPF in at least one HPF. An endoscopist assessment of EoE activities showed that, overwhelmingly, the majority of the study patients (> 85%) had moderate or severe EoE. The PGA of EoE activity and PatGA concerning the severity of EoE symptoms also showed a mean score at baseline above 6 (NRS range of 0 to 10) in both treatment groups. First-line therapy, food restriction, or pharmacological therapies (i.e., PPIs and topical corticosteroids) are used to treat the disease. For example, if effective, a PPI is provided at lowest doses to control symptoms. However, in this trial, the use of systemic or topical glucocorticoids, biologics, or immunosuppressants (except for PPI) as concomitant medication or dietary restrictions were prohibited and only 12% of patients used PPIs as concurrent therapy during the study treatment period. Therefore, the study patients would have represented an EoE population who were more likely to respond to the study treatment whereas it is unknown how the drug works in a real-world setting, i.e., as an add-on to those patients on concurrent treatment with dietary restriction or PPI, and whether the drug would have same effect among those patients who were excluded from the trial based on the pre-set criteria on severity.

EoE is a chronic condition where patients experience recurrences of inflammation requiring re-treatment or changes in therapy over time. The BUL-1/EEA trial was designed to demonstrate a superiority over placebo at week 6 and it was unclear how long the remission would be maintained. Also, it is uncertain whether patients who relapse would respond to a subsequent course of treatment with budesonide 1 mg in the same manner as they responded the first time they received budesonide 1 mg.

In order to enrol in the BUL-1/EEA trial, patients had to have undergone a documented trial with PPIs in order to exclude PPI-REE. Health Canada approved budesonide 1 mg for the

induction of clinicopathologic remission in adults with EoE without restrictions on prior PPI use. It is uncertain whether patients who are PPI naive would respond to budesonide 1 mg in the same manner as patients who were included in the trial.

The BUL-1/EEA trial excluded patients with severe strictures, which may limit the interpretations of the efficacy findings to patients who have strictures with a predominant inflammatory component.

Indirect Evidence

No indirect evidence was submitted by the sponsor or identified in our literature search that would match the inclusion and exclusion criteria of this review.

Other Relevant Evidence

This section includes submitted long-term extension studies and additional relevant studies included in the sponsor's submission to CADTH that were considered to address important gaps in the evidence included in the systematic review.

Long-Term Extension Studies

BUL-1/EEA Extension, up to Week 12

One long-term extension study has been summarized to provide evidence regarding budesonide 1 mg twice daily for up to 12 weeks in patients who did not achieve clinicopathologic remission at the end of the double-blind treatment phase (week 6) of the BUL-1/EEA trial.

Methods

In the BUL-1/EEA trial, patients who were not in clinicopathologic remission at completion of the double-blind treatment phase, or who were prematurely withdrawn due to lack of efficacy after at least 4 weeks of treatment and who showed no change or a deterioration in the PatGA concerning the severity of EoE symptoms compared to baseline at their last visit in the double-blind treatment phase, or patients experiencing a food impaction at any time that needed endoscopic intervention were eligible to enrol in the OLI treatment phase of the study. All patients eligible for OLI treatment had the option to enter a six-week OLI treatment with budesonide 1 mg twice daily.

Populations

Study participants who had completed the placebo-controlled double-blind treatment period and were eligible to enrol in the OLI treatment phase had the option to enter in the six-week OLI treatment period.

Interventions

Patients who received budesonide 1 mg twice daily in the six-week placebo-controlled treatment period continued treatment using the same dosing regimen of budesonide 1 mg twice daily (budesonide followed by budesonide). Patients who received placebo in the placebo-controlled treatment period began budesonide 1 mg twice daily in the OLI treatment period (placebo followed by budesonide).

Outcomes

The following exploratory secondary end points were analyzed in the OLI phase:

- the percentage of patients with clinicopathologic remission at week 6 OLI (LOCF)
- the percentage of patients with histologic remission, defined as a peak of fewer than 16 eosinophils per mm^2 HPF at week 6 OLI (LOCF)
- the change in the peak eosinophils per mm^2 HPF from week 6 double-blind (EOT or withdrawal) to week 6 OLI (LOCF)
- the percentage of patients with resolution of symptoms (i.e., no or only minimal problems), defined as a severity of 2 points or less on a NRS of 0 to 10 points for dysphagia *and* a severity of 2 points or less on a NRS of 0 to 10 points for pain during swallowing on each day of the week prior to week 6 OLI (LOCF)
- the percentage of patients with resolution of symptom dysphagia on each day of the week prior to week 6 OLI (LOCF)
- the percentage of patients with resolution of symptom pain during swallowing on each day of the week prior to week 6 OLI (LOCF)
- the change from week 6 double-blind (EOT or withdrawal) to week 6 OLI (LOCF) in modSHS
- the changes from week 6 double-blind (EOT or withdrawal) to week 6 OLI (LOCF) of the total EoE-QoL-A questionnaire and its subscores.

Clinicopathologic remission at week 6 OLI (LOCF) was calculated in a similar manner as was done in the double-blind treatment period.

Harm outcomes including AEs, SAEs, withdrawals due to AEs, and AEs of particular interest were reported at week 12 as well.

Statistical Analysis

Efficacy outcomes in the OLI phase were presented by standard descriptive summary statistics. Two-sided 95% CIs for treatment group differences in means or proportions were presented at OLI week 6 for the modSHS, and the total Eosinophilic Esophagitis Quality of Life Scale for Adults questionnaire.

The calculation of the change in the peak eosinophils per mm^2 HPF from week 6 double-blind (EOT or withdrawal) to OLI week 6 (LOCF) used the EOT or withdrawal double-blind value as week 6 double-blind (EOT or withdrawal) value. In the event the change could not be calculated because no valid OLI week 6 (LOCF) value was available, the change was set to 0 in the FAS analysis. This corresponded to carrying forward the week 6 double-blind EOT or withdrawal value and also ensured that patients without a valid OLI week 6 (LOCF) value for peak eosinophils per mm^2 HPF could be included in the analysis.

Missing values of the efficacy and safety parameters at the EOT or withdrawal visit were replaced by the last measurement (last measured week, if appropriate) obtained during OLI treatment (LOCF). In case of missing diary values (NRS for dysphagia and pain during swallowing, respectively) within a week prior to the respective visit for one or two days, the weekly sum of these values was calculated for valid data only and the sum was divided by the number of days with valid data and multiplied by seven. If data of less than five days were available (> two days missing), the weekly variables were not evaluable for the respective week.

The evaluation of the end points for the OLI phase was performed for the FAS for the OLI phase (FAS-OLI). The SAS for the OLI phase (SAS-OLI) was used for the evaluation of safety during the OLI phase. The FAS-OLI includes all FAS double-blind patients who received at least one dose of budesonide during the OLI phase. The SAS-OLI includes all randomized patients (as treated) who received at least one dose of budesonide during the OLI phase. If the administration of budesonide was not certain, the patient was included in the SAS-OLI.

Patient Disposition

Overall, 51 patients (58.0%) participated in the OLI phase of the study: 28 patients (96.6%) from the double-blind placebo-treated patients and 23 patients (39.0%) from the double-blind budesonide 1 mg twice daily treated patients. Of the 51 patients participating in the OLI phase of the study, one patient (2.0%) discontinued the OLI phase prematurely; this patient was from the double-blind placebo group. The primary reason for premature discontinuation was intolerable AE. The patient experienced two AEs for which the budesonide was withdrawn and that were assessed as probably or likely related to the budesonide.

Table 17: Patient Disposition in the BUL-1/EEA OLI Phase

	BUL-1/EEA	
	Budesonide 1 mg b.i.d. → budesonide 1 mg b.i.d.	**Placebo → budesonide 1 mg b.i.d.**
OLI phase entered and treated, N (%)	23 (39.0)	28 (96.6)
Full OLI phase completed, N (%)	23 (39.0)	27 (93.1)
OLI phase prematurely terminated, N (%)	0 (0.0)	1 (3.4)
FAS-OLI, N (%)	23 (39.0)	28 (96.6)
SAS-OLI, N (%)	23 (39.0)	28 (96.6)

→ = followed by; b.i.d. = twice a day; FAS = full analysis set; OLI = open-label induction; SAS = safety analysis set.

Source: Clinical Study Report of the BUL-1/EEA trial.[9]

Exposure to Study Treatments

Budesonide was administered on average on 43 days (SD = 5.2 days, median = 42 days) in the FAS-OLI. Results were similar in both treatment groups where budesonide was administered on average (SD) on 43 (6.6) days in the placebo followed by budesonide group and 44 (2.9) days in the budesonide followed by budesonide group.

The mean value (SD) for the compliance was 96.9% (7.41%) overall with similar values for both treatment groups. The median value (range) for the compliance was 98.9% (65.2% to108.3%) overall with similar values in both treatment groups.

Efficacy

Seventeen patients (73.9%) in the budesonide followed by budesonide group and 23 patients (82.1%) in the placebo followed by budesonide group achieved resolution of symptoms on each day prior to week 6 OLI (Table 18).

There was no food impaction and there was no need for an endoscopic dilation during the OLI treatment phase in any treatment group (Table 18).

Nineteen patients (82.6%) in the budesonide followed by budesonide group and 25 patients (89.3%) in the placebo followed by budesonide group achieved histologic remission at week 6 OLI (Table 18).

The mean values (SD) of the peak eosinophils per mm^2 HPF at week 6 double-blind (EOT or withdrawal) were 224 (94.5) eosinophils per mm^2 HPF in the placebo followed by budesonide group and 42 (107.2) eosinophils per mm^2 HPF in the budesonide followed by budesonide group. The mean (SD) reduction in the peak eosinophils per mm^2 HPF from week 6 double-blind (EOT or withdrawal) to week 6 OLI for patients in the placebo followed by budesonide group was −205.81 (105.70). Patients in FAS-OLI treated with budesonide 1 mg twice daily during the double-blind phase already had considerably lower values of peak eosinophils per mm^2 HPF at week 6 double-blind (EOT or withdrawal) than patients treated with placebo during the double-blind phase, and therefore only showed a further slight reduction after continued treatment with budesonide 1 mg twice daily during the OLI phase, with a mean (SD) reduction of −12.26 (62.560) (Table 18).

Sixteen patients (69.6%) in the budesonide followed by budesonide group and 22 patients (78.6%) in the placebo followed by budesonide group achieved clinicopathologic remission at week 6 OLI (Table 18).

Table 18: Exploratory Secondary End Points of Eosinophilic Esophagitis Patients Treated With Budesonide Orodispersible Tablets 1 mg Twice Daily in the Optional Six-Week Open-Label Phase of the BUL-1/EEA Trial

	BUL-1/EEA	
	Budesonide 1 mg b.i.d. → budesonide 1 mg b.i.d. (N = 23)[a]	Placebo → budesonide 1 mg b.i.d. (N = 28)[b]
Percentage of patients with resolution of symptoms on each day of the week prior to week 6 OLI (LOCF), n (%)	17 (73.9)	23 (82.1)
Percentage of patients with resolution of symptom dysphagia on each day of the week prior to week 6 OLI (LOCF), n (%)	17 (73.9)	23 (82.1)
Percentage of patients with resolution of symptom pain during swallowing on each day of the week prior to week 6 OLI (LOCF), n (%)	20 (87.0)	25 (89.3)
Food impaction at any time during the OLI treatment phase that needed endoscopic intervention, n (%)	0	0
Endoscopic dilation at any time during the OLI treatment phase full analysis set (OLI phase), n (%)	0	0
Percentage of patients with histologic remission at OLI week 6 (LOCF), n (%)	19 (82.6)	25 (89.3)

	BUL-1/EEA	
	Budesonide 1 mg b.i.d. → budesonide 1 mg b.i.d. (N = 23)[a]	Placebo → budesonide 1 mg b.i.d. (N = 28)[b]
Change in the peak EOS/mm^2 HPF from week 6 double-blind (EOT/withdrawal) to week 6 OLI (LOCF), mean (SD)	−12.26 (62.560)	−205.81 (105.700)
Percentage of patients with clinicopathologic remission at OLI week 6 (LOCF), n (%)	16 (69.6)	22 (78.6)

→ = followed by; b.i.d. = twice a day; EOS = eosinophil; EOT = end of treatment (week 6 [last observation carried forward]); HPF = high-power field; LOCF = last observation carried forward; OLI = open-label induction; SD = standard deviation.

[a] Budesonide 1 mg b.i.d. → budesonide 1 mg b.i.d.: Patients who received budesonide 1 mg twice daily and who were not in clinico-histologic remission at the end of the six-week double-blind phase continued with a six-week open-label treatment with budesonide 1 mg twice daily.

[b] Placebo → budesonide 1 mg b.i.d.: Patients who received placebo and who were not in clinico-histologic remission at the end of the six-week double-blind phase continued with a six-week open-label treatment with budesonide 1 mg twice daily.

Source: Clinical Study Report of the BUL-1/EEA trial.[9]

In both treatment groups, there was improvement from week 6 double-blind (EOT or withdrawal) to week 6 OLI in the four health dimensions of modSHS (symptom burden, social function, disease-related worry, and general well-being). The between-group difference did not favour any treatment group in any of the four health dimensions (Table 19).

In both treatment groups, there was improvement from week 6 double-blind (EOT or withdrawal) to week 6 OLI in the subscales EoE-QoL-A (30 items), EoE-QoL-A (24 items), EoE-QoL-A eating/diet impact (10 items), and EoE-QoL-A eating/diet impact (four items) of the total EoE-QoL-A questionnaire. There was no improvement from week 6 double-blind (EOT or withdrawal) to week 6 OLI in EoE-QoL-A social impact, EoE-QoL-A emotional impact, EoE-QoL-A disease anxiety, or EoE-QoL-A swallowing anxiety in any treatment group. The between-group difference did not favour any treatment group for any subscale measured (Table 20).

Table 19: Changes in HRQoL by Means of the Modified Short Health Scale in Patients With EoE in the Optional Six-Week Open-Label Phase of the BUL-1/EEA Trial

	Total N	Baseline	EOT time point (week 6 OLI)		Treatment group difference vs. control		
		Mean (SD)	Mean (SD)	Mean change from baseline (95% CI)	N	Mean difference (95% CI)	P value
Change from week 6 double-blind (EOT/withdrawal) to week 6 OLI (LOCF) in modSHS[a, b]							
Symptom burden							
Budesonide 1 mg b.i.d. → budesonide 1 mg b.i.d.	23	51.2 (23.8)	23.4 (23.6)	−27.8 (−40.7 to −14.9)	23	−4.3 (−19.3 to 10.7)	NR
Placebo → budesonide 1 mg b.i.d.	28	37.4 (25.5)	13.8 (16.3)	−23.5 (−32.6 to −14.5)	28	Reference	
Social function							
Budesonide 1 mg b.i.d. → budesonide 1 mg b.i.d.	23	51.3 (24.5)	26.4 (25.6)	−25.0 (−35.4 to −14.5)	23	−7.0 (−20.0 to 6.1)	NR

	Total N	Baseline	EOT time point (week 6 OLI)		Treatment group difference vs. control		
		Mean (SD)	Mean (SD)	Mean change from baseline (95% CI)	N	Mean difference (95% CI)	P value
Placebo → budesonide 1 mg b.i.d.	28	32.5 (23.5)	14.5 (16.7)	−18.0 (−26.7 to −9.3)	28	Reference	
Disease-related worry							
Budesonide 1 mg b.i.d. → budesonide 1 mg b.i.d.	23	63.1 (21.2)	51.0 (23.7)	−12.1 (−20.2 to −3.9)	23	1.9 (−10.2 to 13.9)	NR
Placebo → budesonide 1 mg b.i.d.	28	45.3 (28.6)	31.3 (24.4)	−14.0 (−22.9 to −5.0)	28	Reference	
General well-being							
Budesonide 1 mg b.i.d. → budesonide 1 mg b.i.d.	23	44.7 (22.3)	27.0 (23.2)	−17.7 (−26.9 to −8.4)	23	−4.7 (−17.1 to 7.7)	NR
Placebo → budesonide 1 mg b.i.d.	28	27.3 (24.2)	14.3 (15.2)	−12.9 (−21.6 to −4.3)	28	Reference	

→ = followed by; b.i.d. = twice a day; CI = confidence interval; EOT = end of treatment (week 6 [last observation carried forward]); HRQoL = health-related quality of life; LOCF = last observation carried forward; modSHS = modified Short Health Scale; NR = not reported; OLI = open-label induction; SD = standard deviation; vs. = versus.

[a] Range of each score: 0 to 100. Lower numbers indicate higher quality of life.

[b] Two-sided 95% CIs for the mean modSHS: Symptom burden, social function, disease-related worry, and general well-being per group and for the group difference in means, based on t-distribution.

Source: Clinical Study Report of the BUL-1/EEA trial.[9]

Table 20: Changes from Baseline to Week 6 (LOCF) of the Total Eosinophilic Esophagitis Quality of Life Scale for Adults Questionnaire and its Subscores in the Optional Six-Week Open-Label Phase of the BUL-1/EEA Trial

	Total N	Baseline	EOT time point (week 6)		Treatment group difference vs. control		
		Mean (SD)	Mean (SD)	Mean change from baseline (95% CI)	N	Mean difference (95% CI)	P value
Changes from week 6 double-blind (EOT/withdrawal) to week 6 OLI (LOCF) of the total EoE-QoL-A questionnaire and its subscores[a, b]							
EoE-QoL-A, 30 items (weighted average)							
Budesonide 1 mg b.i.d. → budesonide 1 mg b.i.d.	23	2.0 (0.8)	2.2 (0.7)	0.16 (0.003 to 0.327)	23	−0.13 (−0.395 to 0.139)	NR
Placebo → budesonide 1 mg b.i.d.	28	2.5 (0.7)	2.8 (0.6)	0.29 (0.072 to 0.513)	28	Reference	
EoE-QoL-A, 24 items (weighted average)							
Budesonide 1 mg b.i.d.→ budesonide 1 mg b.i.d.	23	2.0 (0.8)	2.1 (0.7)	0.17 (0.017 to 0.324)	23	−0.11 (−0.377 to 0.151)	NR
Placebo → budesonide 1 mg b.i.d.	28	2.5 (0.7)	2.8 (0.6)	0.28 (0.061 to 0.505)	28	Reference	

	Total N	Baseline	EOT time point (week 6)		Treatment group difference vs. control		
		Mean (SD)	Mean (SD)	Mean change from baseline (95% CI)	N	Mean difference (95% CI)	P value
EoE-QoL-A eating/diet impact, 10 items (weighted average)							
Budesonide 1 mg b.i.d.→ budesonide 1 mg b.i.d.	23	2.1 (1.0)	2.4 (1.0)	0.33 (0.085 to 0.580)	23	−0.15 (−0.516 to 0.209)	NR
Placebo → budesonide 1 mg b.i.d.	28	2.5 (0.8)	2.9 (0.7)	0.49 (0.217 to 0.754)	28	Reference	
EoE-QoL-A eating/diet impact, 4 items (weighted average)							
Budesonide 1 mg b.i.d.→ budesonide 1 mg b.i.d.	23	2.0 (0.9)	2.4 (0.9)	0.39 (0.157 to 0.626)	23	−0.06 (−0.441 to 0.313)	NR
Placebo → budesonide 1 mg b.i.d.	28	2.4 (0.8)	2.9 (0.8)	0.46 (0.164 to 0.747)	28	Reference	
EoE-QoL-A social impact (weighted average)							
Budesonide 1 mg b.i.d.→ budesonide 1 mg b.i.d.	23	1.9 (1.2)	1.9 (1.1)	0.04 (−0.213 to 0.299)	23	−0.40 (−0.846 to 0.040)	NR
Placebo → budesonide 1 mg b.i.d.	28	2.5 (0.9)	2.9 (0.8)	0.45 (0.073 to 0.820)	28	Reference	
EoE-QoL-A emotional impact (weighted average)							
Budesonide 1 mg b.i.d.→ budesonide 1 mg b.i.d.	23	2.3 (0.9)	2.5 (0.7)	0.15 (−0.025 to 0.318)	23	−0.07 (−0.351 to 0.213)	NR
Placebo → budesonide 1 mg b.i.d.	28	2.9 (0.7)	3.1 (0.5)	0.22 (−0.005 to 0.436)	28	Reference	
EoE-QoL-A disease anxiety (weighted average)							
Budesonide 1 mg b.i.d.→ budesonide 1 mg b.i.d.	23	1.5 (0.8)	1.7 (0.8)	0.16 (−0.055 to 0.368)	23	−0.002 (−0.320 to 0.316)	NR
Placebo → budesonide 1 mg b.i.d.	28	2.0 (0.9)	2.1 (0.9)	0.16 (−0.080 to 0.397)	28	Reference	
EoE-QoL-A swallowing anxiety (weighted average)							
Budesonide 1 mg b.i.d.→ budesonide 1 mg b.i.d.	23	1.9 (1.1)	2.0 (1.1)	0.13 (−0.077 to 0.338)	23	−0.07 (−0.382 to 0.238)	NR
Placebo → budesonide 1 mg b.i.d.	28	2.7 (0.9)	2.9 (0.8)	0.20 (−0.029 to 0.434)	28	Reference	

→ = followed by; b.i.d. = twice a day; CI = confidence interval; EoE-QoL-A = Adult Eosinophilic Esophagitis Quality of Life; EOT = end of treatment; LOCF = last observation carried forward; NR = not reported; OLI = open-label induction; SD = standard deviation; vs. = versus.

[a] The EoE-QoL-A yields an overall score and five subscale scores. Scores range from 0 to 4. Higher scores indicate better quality of life.

[b] Two-sided 95% CIs for the mean EoE-QoL-A: Overall score (30 items, weighted average), overall score (24 items, weighted average), eating/diet impact (10 items, weighted average), eating/diet impact (four items, weighted average), social impact (weighted average), emotional impact (weighted average), disease anxiety (weighted average), and swallowing anxiety (weighted average). Absolute change from baseline per group and for the group difference in means, based on t-distribution.

Source: Clinical Study Report of the BUL-1/EEA trial.[9]

Harms

In total, 24 TEAEs occurred in 16 patients (57.1%) in the placebo followed by budesonide group and 35 TEAEs occurred in 13 patients (56.5%) in the budesonide followed by budesonide group (Table 21).

The most frequently reported TEAEs were esophageal candidiasis with eight patients (28.6%) affected in the placebo followed by budesonide group, and one patient (4.3%) in the budesonide followed by budesonide group, and headache with one patient (3.6%) in the placebo followed by budesonide group and four patients (17.4%) in the budesonide followed by budesonide group (Table 21).

No deaths or SAEs occurred during the course of the OLI phase (Table 21).

Two AEs in one patient led to discontinuation of budesonide in the placebo followed by budesonide group. The AEs leading to discontinuation of budesonide were lip edema and oral paresthesia, both not serious, of mild intensity, and assessed as probably or likely related to budesonide.

During the OLI phase, a total of 16 suspected candidiasis AEs occurred in 14 patients (27.5%); there were 11 events in 10 patients (35.7%) from the placebo followed by budesonide group and five events in four patients (17.4%) from the budesonide followed by budesonide group. All 16 of the OLI treatment-emergent candidiasis AEs were rated as adverse drug reactions. Nine of these suspected candidiasis AEs in nine patients (17.6%) were histologically confirmed, seven events in seven patients (13.7%) were histologically confirmed and showed endoscopic signs, and none of the events were histologically confirmed and showed endoscopic and clinical signs. For seven of the OLI treatment-emergent suspected candidiasis AEs, the outcome was recovered; for nine events, the outcome was unknown. Unknown outcome was in some cases due to the fact that the candidiasis was confirmed by histology and/or endoscopy without clinical signs and a follow-up histology or endoscopy was not available.

Table 21: Summary of Harms in the BUL-1/EEA OLI Phase

	BUL-1/EEA OLI phase	
	Budesonide 1 mg b.i.d. → budesonide 1 mg b.i.d. (N = 23)[a]	Placebo → budesonide 1 mg b.i.d. (N = 28)[b]
Patients with ≥ 1 adverse event		
n (%)	13 (56.5)	16 (57.1)
Most common events[c]		
Gastroesophageal reflux disease	2 (8.7)	1 (3.6)
Local fungal infection[d]	4 (17.4)	10 (35.7)
Candida infection	2 (8.7)	1 (3.6)
Esophageal candidiasis	1 (4.3)	8 (28.6)
Oral candidiasis	0	1 (3.6)
Oropharyngeal candidiasis	2 (8.7)	1 (3.6)
Headache	4 (17.4)	1 (3.6)
Patients with ≥ 1 SAE		
n (%)	0	0

	BUL-1/EEA OLI phase	
	Budesonide 1 mg b.i.d. → budesonide 1 mg b.i.d. (N = 23)[a]	Placebo → budesonide 1 mg b.i.d. (N = 28) [b]
Patients who stopped treatment due to adverse events		
n (%)	0	1 (3.6)
Most common events		
Lip edema and oral paresthesia	0	1 (3.6)
Deaths		
n (%)	0	0
Notable harms, N (%)		
Local fungal infection	4 (17.4)	10 (35.7)
Candida infection	2 (8.7)	1 (3.6)
Esophageal candidiasis	1 (4.3)	8 (28.6)
Oral candidiasis	0	1 (3.6)
Oropharyngeal candidiasis	2 (8.7)	1 (3.6)
Dysgeusia	0	0
Decreased bone mineral density	0	0
Cataract	0	0
Glaucoma	0	0
Psychiatric disorders	0	1 (3.6)
Sleep disorder	0	1 (3.6)
Symptoms of sore throat (pharyngitis)	0	0
Avascular necrosis of the hip	0	0

→ = followed by; b.i.d. = twice a day; OLI = open-label induction; SAE = serious adverse event.

[a] Budesonide 1 mg twice daily → budesonide 1 mg twice daily: Patients who received budesonide 1 mg twice daily and who were not in clinico-histologic remission at the end of the six-week double-blind phase continued with a six-week open-label treatment with budesonide 1 mg twice daily.

[b] Placebo → budesonide 1 mg twice daily: Patients who received placebo and who were not in clinico-histologic remission at the end of the six-week double-blind phase continued with a six-week open-label treatment with budesonide 1 mg twice daily.

[c] Treatment-emergent adverse events occurring in at least two patients in any treatment group.

[d] Patients with more than one fungal infection event may appear several times in different subcategories, but are counted only once in the “Local fungal infection” category.

Source: Clinical Study Report of the BUL-1/EEA trial.[9]

Critical Appraisal

Internal Validity

The main limitations associated with the OLI phase of the BUL-1/EEA trial arise from the open-label study design, which lacks randomization and the within-group comparisons to week 6 of the double-blind phase in the trial. These may have an impact on the subjective patient-reported questionnaires on dysphagia symptoms, pain during swallowing, and HRQoL where reported improvement to these questionnaires could have been overestimated, given that patients were aware that they were receiving active treatment. Furthermore, the absence of a comparator group makes it challenging to interpret small changes from baseline.

Efficacy results from the OLI phase must be interpreted keeping in mind that the patient population studied during the OLI phase was not a random sample of patients with acute EoE, but a combination of patients with a previous treatment period with placebo of up to six weeks and patients for whom the attempt to induce remission using treatment with

budesonide 1 mg twice daily for up to six weeks was not successful or not yet fully successful.

External Validity

The baseline characteristics of the patients enrolled in the OLI treatment phase was not reported; hence, it is not possible to know whether these patients, especially those enrolled in the budesonide followed by budesonide group, are similar or not to patients with EoE in Canada. On the other hand, patients enrolled in the BUL-1/EEA trial appear to be similar, in general, to patients with EoE in Canada.

Study BUU-2/EEA

Methods

In addition to the BUL-1/EEA trial, the sponsor submitted another trial (Study BUU-2/EEA) that evaluated the efficacy and tolerability of a 14-day treatment with budesonide effervescent tablets versus viscous budesonide suspension and placebo in patients with EoE. Details of the trial characteristics are provided in Table 22.

Table 22: Details of BUU-2/EEA Study

		BUU-2/EEA
Designs and Populations	**Study design**	Phase II, double-blind, multi-centre, placebo-controlled RCT
	Locations	Belgium, Germany, and Switzerland
	Randomized (N)	77
	Inclusion criteria	• Male or female patients, 18 to 75 years of age • Confirmed clinicopathologic diagnosis of EoE according to these established diagnostic criteria: ○ clinical symptoms of esophageal dysfunction ○ peak EOS ≥ 15 in at least 1 HPF • Active symptomatic and histologic EoE fulfilling the following criteria: ○ clinical symptoms of esophageal dysfunction, i.e., Dysphagia Score of ≥ 3 points at screening visit 2 ○ eosinophilic tissue infiltration with a mean cell density ≥ 16 EOS/mm2 HPF, as measured in a total of 30 HPF derived from 6 biopsy specimens, 2 each from the proximal, mid, and distal segment of the esophagus ○ peak EOS ≥ 65/mm2 HPF in at least 1 HPF (corresponding to ≥ 20 EOS/HPF)
	Exclusion criteria	• Clinically and endoscopically suspicion for GERD, achalasia, or scleroderma • History of abnormal pH monitoring of the distal esophagus or clinicopathologic response to a sufficient standard dose and treatment duration (approximately 2 weeks) with PPIs, to exclude GERD and PPI-responsive esophageal eosinophilia • Clinically evident causes other than EoE for esophageal eosinophilia (i.e., Crohn disease, eosinophilic gastroenteritis, connective tissue disease, vasculitis, hypereosinophilic syndrome graft-versus-host disease, drug hypersensitivity response, parasitic infestation) • Any concomitant esophageal disease and relevant gastrointestinal disease (celiac disease, inflammatory bowel disease, oropharyngeal or esophageal bacterial, viral, or fungal infection) • Any relevant systemic disease (e.g., acquired immunodeficiency syndrome, active tuberculosis) • Diseases if careful medical monitoring was not ensured: cardiovascular disease, diabetes mellitus, osteoporosis, active peptic ulcer disease, glaucoma, cataract, or infection • Abnormal hepatic function at screening visit, liver cirrhosis, or portal hypertension • Abnormal renal function at screening • History of cancer in the last 5 years (except for non-metastatic cancers, e.g., basalioma)

		BUU-2/EEA
		• History of esophageal surgery at any time or of esophageal dilation procedures within the last 8 weeks prior to the second screening visit • Upper gastrointestinal bleeding within 8 weeks prior to screening visit concomitant — or within the 4 weeks prior to the second screening visit — treatment with systemic therapies for any reason that may affect assessment of primary and secondary end points, i.e., systemic glucocorticoids, histamine antagonists, mast cell stabilizers, leukotriene receptor antagonists, biologics, or immunosuppressants • Concomitant — or within the 2 weeks prior to the second screening visit — treatment with topical therapies for any reason that may affect assessment of primary and secondary end points, i.e., topical glucocorticoids or inhaled sodium cromoglycate • Installation of dietary restrictions within 4 weeks prior to the second screening visit or during treatment • Intake of food or beverages containing grapefruit during the treatment with study medication
Drugs	**Intervention**	• Budesonide 1 mg effervescent tablet for orodispersible use twice daily plus 5 mL viscous placebo suspension twice daily • Budesonide 2 mg effervescent tablet for orodispersible use twice daily plus 5 mL viscous placebo suspension twice daily • 5 mL viscous budesonide suspension (0.4 mg/mL) twice daily plus Placebo effervescent tablet for orodispersible use twice daily
	Comparator(s)	Placebo effervescent tablet for orodispersible use twice daily plus 5 mL viscous placebo suspension twice daily
Duration	**Phase**	
	Screening	Up to 5 weeks
	Double-blind	2 weeks
	Follow-up	2 weeks
Outcomes	**Primary end point**	• The percentage of patients with histologic remission, defined as a mean of < 16 EOS/mm^2 HPF at week 2 (LOCF) • The co-primary end point was the change in the mean numbers of EOS/mm^2 HPF (EOS load) from baseline to week 2 (LOCF).
	Secondary and exploratory end points	• Percentage of patients with histologic remission defined as a peak of < 16 EOS/mm^2 HPF at week 2 (LOCF) • Change in the peak EOS/mm^2 HPF from baseline to week 2 (LOCF) • Percentage of patients with clinical improvement in the Dysphagia Score at week 2 (LOCF), defined as a decrease of ≥ 3 points from baseline • Change of modSHS in the course of the study
Notes	**Publications**	Miehlke et al.[32]

EoE = eosinophilic esophagitis; EOS = eosinophil; GERD = gastroesophageal reflux disease; HPF = high-power field; LOCF = last observation carried forward; modSHS = modified Short Health Scale; PPI = proton pump inhibitors; RCT = randomized controlled trial.

Source: Miehlke et al. (2016)[32] and Clinical Study Report of the BUU-2/EEA trial.[33]

Description of Studies

Study BUU-2/EEA (N = 77) was a phase II, double-blind, double-dummy, randomized, placebo-controlled trial. Study BUU-2/EEA compared twice daily oral treatment with budesonide 1 mg or 2 mg effervescent tablets for orodispersible use, 5 mL viscous budesonide suspension (0.4 mg/mL) twice daily, or placebo in adult patients with clinico-histologic active EoE. The study was performed according to an adaptive two-stage group sequential design with the possibility for sample size adaptation and treatments group selection at the pre-specified interim analysis. The calculated sample size was about 100

patients (25 patients in each treatment group) who had to be evaluable in the FAS. The interim analysis was scheduled after observation of approximately 60 patients (approximately 15 patients per treatment group) in the FAS. The screening period of up to five weeks was followed by a two-week treatment period and a two-week follow-up period. The patients were assigned to one of the four following treatment groups at a ratio of 1:1:1:1 in conformity with a central randomization list:

- one budesonide 1 mg effervescent tablet (budesonide 1 mg) twice daily plus 5 mL viscous placebo suspension twice daily for 14 days
- one budesonide 2 mg effervescent tablet twice daily plus 5 mL viscous placebo suspension twice daily for 14 days
- 5 mL budesonide viscous suspension (0.4 mg/mL) twice daily plus one placebo effervescent tablet twice daily for 14 days
- one placebo effervescent tablet twice daily plus 5 mL viscous placebo suspension twice daily for 14 days.

Budesonide 2 mg effervescent tablet twice daily is not a dosage approved by Health Canada; hence, results of this treatment group were not further reported.

Populations

Inclusion and Exclusion Criteria

Patients enrolled in the BUU-2/EEA trial were adults (18 to 75 years of age) with a confirmed clinicopathologic diagnosis of EoE. More specifically, patients must have exhibited clinical symptoms of esophageal dysfunction (Dysphagia Score ≥ 3), peak eosinophils of at least 65 per mm^2 HPF in at least one HPF (corresponding to ≥ 20 eosinophils per HPF), and eosinophilic tissue infiltration with a mean cell density of at least 16 eosinophils per mm^2 as measured in a total of 30 HPFs derived from six biopsies (two each from the proximal, mid, and distal segments of the esophagus). Patients were excluded from the BUU-2/EEA trial if they were pregnant or breastfeeding; were responsive to PPI treatment; were intolerant or hypersensitive to the study drug; had a history of abnormal pH monitoring of the distal esophagus; had clinical evidence of any causes other than EoE for eosinophilia of the esophagus; had signs or symptoms of GERD, achalasia, scleroderma, abnormal renal or hepatic function, AIDS, active tuberculosis, a relevant gastrointestinal disease, or relevant systemic disease without proper medical monitoring (cardiovascular disease, diabetes mellitus, osteoporosis, active peptic ulcer disease, glaucoma, cataract, or infection); had a history of topical glucocorticoids or inhaled sodium cromoglycate within two weeks of screening; had a history of systemic glucocorticoids, histamine antagonists, mast cell stabilizers, leukotriene receptor antagonists, biologics, or immunosuppressants within four weeks of screening; previously had esophageal surgery at any time; had undergone dietary restrictive therapy in the preceding four weeks; had experienced esophageal dilation or upper gastrointestinal bleeding in the preceding eight weeks; or had cancer in the preceding five years.

Baseline Characteristics

Almost all patients reported current symptoms of dysphagia (16 patients [84.2%], 19 patients [100.0%], and 17 patients [89.5%] in the budesonide 1 mg group, the budesonide viscous suspension 2 mg group, and the placebo group, respectively). Mean and peak numbers of eosinophils per mm^2 HPF showed that all treatment groups had a substantially eosinophilic inflammation in proofing the histologically active disease status, despite some

variability that was observed between the treatment groups. Details of patients' baseline characteristics are provided in Table 23.

Table 23: Summary of Baseline Characteristics in the BUU-2/EEA Trial

Baseline characteristics	BUU-2/EEA		
	Budesonide 1 mg b.i.d. (N = 19)	Budesonide viscous suspension 2 mg b.i.d. (N = 19)	Placebo (N = 19)
Sex, n (%)			
Male	17 (89.5)	14 (73.7)	16 (84.2)
Female	2 (10.5)	5 (26.3)	3 (15.8)
Age (years)			
Mean (SD)	38.9 (12.6)	46.5 (14.1)	36.3 (9.9)
Median (range)	36 (22 to 61)	47 (26 to 70)	34 (23 to 60)
Race, n (%)			
White	19 (100.0)	19 (100.0)	19 (100.0)
Smoking habits, n (%)			
Current	3 (15.8)	2 (10.5)	0
Former	3 (15.8)	4 (21.1)	1 (5.3)
Never	13 (68.4)	13 (68.4)	18 (94.7)
BMI (kg/m^2)			
Mean (SD)	25.5 (4.41)	25.9 (2.35)	23.7 (3.16)
Median (range)	24.3 (19.2 to 36.7)	25.7 (22.9 to 30.0)	23.8 (19.7 to 31.3)
Concomitant allergic disease, n (%)	14 (73.7)	11 (57.9)	10 (52.6)
Concomitant use of PPIs, n (%)	3 (15.8)	3 (15.8)	3 (15.8)
Time since EoE diagnosis, years			
Mean (SD)	1.9 (3.4)	2.6 (3.3)	2.6 (5.1)
Median (range)	1.0 (0.0 to 14.9)	1.3 (0.1 to 13.2)	0.5 (0.1 to 19.8)
Time since first EoE symptoms, years			
Mean (SD)	8.3 (7.8)	10.8 (9.0)	7.9 (7.5)
Median (range)	4.4 (0.7 to 22.8)	7.8 (0.8 to 32.6)	5.0 (0.2 to 30.1)
Case history, n (%)			
Established disease	12 (63.2)	13 (68.4)	11 (57.9)
New diagnosis	7 (36.8)	6 (31.6)	8 (42.1)
History of esophageal surgery or dilation, n (%)	2 (10.5)	4 (21.1)	1 (5.3)
Number of inflamed segments at baseline, n (%)			
1 segment	1 (5.3)	4 (21.1)	4 (21.1)
2 segments	3 (15.8)	6 (31.6)	6 (31.6)
3 segments	14 (73.7)	7 (36.8)	9 (47.4)
Not calculated	1 (5.3)	2 (10.5)	0
Localization of the inflammation at baseline, n (%)			
Proximal	14 (73.7)	13 (68.4)	13 (68.4)

Baseline characteristics	BUU-2/EEA		
	Budesonide 1 mg b.i.d. (N = 19)	Budesonide viscous suspension 2 mg b.i.d. (N = 19)	Placebo (N = 19)
Mid	18 (94.7)	13 (68.4)	14 (73.7)
Distal	18 (94.7)	14 (73.7)	16 (84.2)
Mean EOS/mm^2 HPF			
Mean (SD)	121 (78.6)	101 (121.0)	153 (153.4)
Median (range)	99 (23 to 303)	45 (20 to 526)	101 (16 to 571)
Peak EOS/mm^2 HPF			
Mean (SD)	242 (144.2)	201 (185.4)	320 (309.0)
Median (range)	206 (78 to 635)	128 (73 to 842)	183 (58 to 977)
Dysphagia, n (%)			
Current	16 (84.2)	19 (100)	17 (89.5)
Previously	2 (10.5)	NR	1 (5.3)
None	1 (5.3)	0	1 (5.3)
Food impaction, n (%)			
Current	4 (21.1)	9 (47.4)	6 (31.6)
Previously	8 (42.2)	2 (10.5)	7 (36.8)
None	7 (36.8)	8 (42.1)	6 (31.6)

b.i.d. = twice a day; BMI = body mass index; EoE = eosinophilic esophagitis; EOS = eosinophil; HPF = high-power field; NR = not reported; PPI = proton pump inhibitor; SD = standard deviation.

[a] Range of each score: 0 to 100. Lower numbers indicate higher quality of life.

Source: Clinical Study Report of the BUU-2/EEA trial.[33]

Interventions

Patients had to take budesonide 1 mg tablets twice daily, 5 mL viscous budesonide suspension (0.4 mg/mL) twice daily, or placebo according to the treatment groups to which they were allocated. Due to the use of two different budesonide formulations, a double-dummy design was used.

Outcomes

The primary efficacy end point in the BUU-2/EEA trial was the percentage of patients with histologic remission, defined as a mean of less than 16 eosinophils per mm^2 HPF at week 2 (LOCF). The co-primary end point was the change in the mean numbers of eosinophils per mm^2 HPF (eosinophil load) from baseline to week 2 (LOCF). The mean numbers of eosinophils per mm^2 HPF were derived from the evaluation of a total of 30 HPFs gleaned from six esophageal biopsies, each to be taken before and after the treatment period. Two biopsy specimens each had to be taken from the proximal, mid, and distal part of the esophagus for the assessment of 30 HPFs.

The main secondary efficacy end points were:

- the percentage of patients with histologic remission defined as a peak of fewer than 16 eosinophils per mm^2 HPF at week 2 (LOCF)
- the change in the peak eosinophils per mm^2 HPF from baseline to week 2 (LOCF)

- the change of the Dysphagia Score within the study; the total Dysphagia Score ranged from 0 to 9 and was based on the frequency of dysphagia ranging from none (0) to several times per day (4), as well as the intensity of dysphagia ranging from unhindered swallowing (0) to long-lasting complete obstruction requiring endoscopic intervention (5) (a clinical response was defined as a decrease in the Dysphagia Score of at least 3 points compared with baseline)
- the change from baseline in modSHS.

Statistical Analysis

Sample sizes of 25 evaluable patients per treatment group ensured a power of at least 95% for the primary end point at the interim analysis, and a power of at least 85% for the co-primary end point at the final analysis. In order to account for 5% of randomized patients dropping out without intake of study medication, 64 patients had to be randomized for the interim analysis and an additional 44 patients had to be randomized for the final analysis. The planned interim analysis was performed on 61 evaluable patients in the FAS. It showed that the primary objective of the study was reached. Recruitment of the study was stopped after the result of the interim analysis was available. However, as recruitment continued while the interim analysis was performed, 16 patients were still in the study. The study was carried on with these patients and the final analysis was performed on a total of 76 evaluable patients in the FAS.

The aim of the BUU-2/EEA trial was to demonstrate superiority of budesonide effervescent tablets (1 mg twice a day) and budesonide viscous suspension (2 mg twice a day) compared to placebo in terms of histologic remission defined as a mean of less than 16 eosinophils per mm^2 HPF at week 2 (LOCF) (primary end point) and in terms of change in mean numbers of eosinophils per mm^2 HPF from baseline to week 2 (LOCF) (co-primary end point).

The analysis consisted of two separate steps. The one-sided significance level for each step was set at 2.5%. Hypothesis testing of the co-primary end point (second step) was performed only if all hypotheses of the primary end point (first step) were rejected. In both steps, each of the active treatment groups was compared to the placebo group. The normal approximation test for the comparison of rates was used to test the three null hypotheses of the primary end point. The three null hypotheses of the co-primary end point were tested with the Wilcoxon-Mann-Whitney test. In order to adjust for multiplicity, a closed testing procedure with the Simes intersection test was employed for hypothesis testing on both steps. Due to the stepwise procedure, tests of the co-primary end point had no impact on the critical values for the tests of the primary end point.

The study was conducted using an adaptive two-stage group sequential design. The interim analysis was planned after observation of 60 patients who were evaluable in the FAS (approximately 15 patients per treatment group). The null hypothesis was planned to be tested and the study was to be stopped at the interim analysis if the test statistic resulting from the inverse normal method exceeded the critical value 2.487. In this case, it had to be determined which of the elementary hypotheses could be rejected by the closed testing procedure. If the null hypothesis could not be rejected, the study could be continued with the pre-specified stage II sample size of 10 further patients per treatment group, or with a recalculated sample size based on the effect size estimation of the interim analysis. Based on the results of the interim analysis, treatments groups could be closed. The critical value at the final analysis was planned to be 2.007. This procedure preserved the overall (experiment-wise) one-sided type I error rate of alpha equal to 0.025.

No comparison between the budesonide 1 mg group and the budesonide viscous suspension 2 mg group was conducted.

Analysis Populations

The FAS included all randomized patients (as randomized) who received at least one dose of study medication. The evaluation of the primary, co-primary, and secondary efficacy variable was performed for the FAS. The SAS included all patients (as treated) who received at least one dose of study medication. If the administration of any study medication was not certain, the patient was included in the SAS. The analysis of safety was based on the SAS.

Results

Patient Disposition

In total, 109 patients were screened. Thirty-two of these patients were not eligible for the study. A total of 77 patients were randomized; of those, 76 patients were treated and 75 patients completed the study. One patient was randomized but did not take at least one dose of study medication and one patient was prematurely withdrawn due to an intolerable AE (swollen lips and skin exanthema).

Details of patient disposition are provided in Table 24.

Table 24: Patient Disposition in the BUU-2/EEA Trial

	BUU-2/EEA		
	Budesonide 1 mg b.i.d.	**Budesonide viscous suspension 2 mg b.i.d.**	**Placebo**
Screened, N	109		
Randomized, N	19	19	20
Treated	19	19	19
Discontinued study	0	1 (5.3)	1 (5.0)
Reason for discontinuation, N (%)			
Intolerable adverse event	0	1 (5.3)	0
Other reasons: Did not meet inclusion/exclusion criteria (coming to light after randomization)	0	0	1 (5.0)
Completed, N (%)			
FAS, N (%)	19	19	19
SAS N (%)	19	19	19
PP, N (%)	19	17	17

b.i.d. = twice a day; FAS = full analysis set; PP = per-protocol; SAS = safety analysis set.

Source: Clinical Study Report of the BUU-2/EEA trial.[33]

Exposure to Study Treatments

Treatment duration was planned to be 14 days. The actual treatment duration was calculated as date of last intake of study medication minus date of first intake of study medication plus one day. The mean (SD) actual treatment duration did not show relevant difference between treatment groups 13.7 (1.2) days, 13.0 (2.4) days, and 14.3 (1.2) days

in the budesonide 1 mg twice daily, budesonide viscous suspension 2 mg twice daily, and placebo groups, respectively. Due to premature study termination, actual treatment duration was only six days in one of the patients in the budesonide viscous suspension 2 mg twice daily

The mean (SD) extent of exposure was 27.2 (2.4) mg in total and 2.0 (0.04) mg/day in the budesonide 1 mg group, and 50.6 (10.6) mg in total and 3.9 (0.3) mg/day in the budesonide viscous suspension 2 mg group.

Efficacy

Ten out of the 19 patients (52.6%) in the budesonide 1 mg group, nine out of the 19 patients (47.4%) in the budesonide viscous suspension 2 mg group, and seven out of the 19 patients (36.8%) in the placebo group experienced clinical improvement (defined as a decrease of at least 3 points in the Dysphagia Score) at week 2. The difference between the budesonide 1 mg and placebo treatment groups was 15.8% (95% CI, −15.4 to 47.0; P = not reported), and the difference between the budesonide viscous suspension 2 mg group and placebo treatment group was 10.5% (95% CI, −20.7% to 41.7%; P = not reported). The between-group difference did not favour any treatment group (Table 25). No comparison between the budesonide 1 mg group and the budesonide viscous suspension 2 mg group was conducted.

Table 25: Clinical Improvement of the Dysphagia Score at Week 2, LOCF, in the BUU-2/EEA Trial

	Total N	n (%)	Difference in proportions: Budesonide vs. placebo (95% CI)	P value
Numbers (%) of patients with clinical improvement (defined as a decrease of ≥ 3 points in the Dysphagia Score) at week 2 (LOCF)				
Budesonide 1 mg b.i.d.	19	10 (52.6)	15.8% (−15.4% to 47.0%)	NR
Budesonide viscous suspension 2 mg b.i.d.	19	9 (47.4)	10.5% (−20.7% to 41.7%)	NR
Placebo	19	7 (36.8)	Reference	Reference

b.i.d. = twice a day; CI = confidence interval; LOCF = last observation carried forward; NR = not reported; vs. = versus.

Source: Clinical Study Report of the BUU-2/EEA trial.[33]

The four scores of the modSHS questionnaire showed a decrease from baseline to the EOT or withdrawal visit in all treatment groups (Table 26). However, due to the large variability of the four scores and due to large differences between treatment groups at baseline, no differences in changes from baseline to the EOT or withdrawal visit of the four scores of the modSHS questionnaire between treatment groups can be concluded.

Table 26: Changes in HRQoL by Means of the Modified Short Health Scale in Patients With EoE in the BUU-2/EEA Trial

	Total N	Baseline	EOT time point (EOT/withdrawal visit)		Treatment group difference vs. control		
		Mean (SD)	Mean (SD)	Mean change from baseline (SD)	N	Mean difference	P value
Changes in the 4 scores of the modSHS questionnaire from baseline to the EOT/withdrawal visit (FAS)							
Symptom burden							
Budesonide 1 mg b.i.d.	19	47.2 (19.4)	22.5 (18.8)	−24.74 (20.87)	19	NR	NR
Budesonide viscous suspension 2 mg b.i.d.	19	55.2 (20.9)	29.9 (22.3)	−23.69 (21.84)	18	NR	
Placebo	19	40.8 (20.9)	20.9 (17.9)	−19.84 (14.32)	19	Reference	
Social function							
Budesonide 1 mg b.i.d.	19	39.9 (23.7)	18.8 (17.5)	−21.16 (16.66)	19	NR	NR
Budesonide viscous suspension 2 mg b.i.d.	19	40.6 (23.9)	24.9 (21.6)	−13.56 (14.14)	18	NR	
Placebo	19	30.8 (21.7)	16.9 (18.0)	−13.95 (15.55)	19	Reference	
Disease-related worry							
Budesonide 1 mg b.i.d.	19	47.3 (18.1)	30.6 (19.4)	−16.68 (18.64)	19	NR	NR
Budesonide viscous suspension 2 mg b.i.d.	19	56.8 (19.0)	40.9 (25.6)	−14.18 (16.53)	18	NR	
Placebo	19	39.1 (29.7)	22.7 (19.9)	−16.42 (16.51)	19	Reference	
General well-being							
Budesonide 1 mg b.i.d.	19	30.7 (19.2)	17.4 (16.3)	−13.26 (17.58)	19	NR	NR
Budesonide viscous suspension 2 mg b.i.d.	19	37.2 (20.5)	26.4 (21.4)	−10.48 (23.90)	18	NR	
Placebo	19	28.9 (19.0)	18.4 (18.6)	−10.47 (17.89)	19	Reference	

b.i.d. = twice a day; EoE = eosinophilic esophagitis; EOT = end of treatment; HRQoL = health-related quality of life; modSHS = Modified Short Health Scale; NR = not reported; SD = standard deviation; vs. = versus.

[a] Range of each score: 0 to 100. Lower numbers indicate higher quality of life.

Source: Clinical Study Report of the BUU-2/EEA trial.[33]

None of the 19 patients (0%) in the placebo group, all of the 19 patients (100%) in the budesonide 1 mg group, and 18 of the 19 patients (94.7%) in the budesonide viscous suspension 2 mg group achieved histologic remission defined as a mean of less than 16 eosinophils per mm^2 HPF at week 2. The difference between the budesonide 1 mg and placebo treatment groups was 100% (95% CI, 64.7 to 100; P = <0.0001), and the difference between the budesonide viscous suspension 2 mg group and placebo treatment group was 94.7% (95% CI, 57.6 to 99.5; P = <0.0001). The between-group difference showed that both budesonide treatment groups were superior to placebo (Table 27). No comparison

between the budesonide 1 mg group and the budesonide viscous suspension 2 mg group was conducted.

The more stringent histologic remission definition by peak count (out of 30 HPFs) of fewer than 16 eosinophils per mm^2 HPF revealed a superiority of all budesonide groups versus placebo (Table 27).

Table 27: Histologic Remission at Week 2, LOCF, in the BUU-2/EEA Trial

	Total N	n (%)	Difference in proportions: Budesonide vs. placebo (95% CI)	P value
Number (%) of patients in histologic remission defined as mean of < 16 EOS/mm^2 HPF at week 2 (LOCF)				
Budesonide 1 mg b.i.d.	19	19 (100)	100% (64.7% to 100%)	< 0.0001
Budesonide viscous suspension 2 mg b.i.d.	19	18 (94.7)	94.7% (57.6% to 99.5%)	< 0.0001
Placebo	19	0 (0)	Reference	Reference
Subgroup analyses: Number (%) of patients in histologic remission defined as mean of < 16 EOS/mm^2 HPF at week 2 (LOCF) stratified by concomitant use of PPIs				
Budesonide 1 mg b.i.d.	3	3 (100)	NR	NR
Budesonide viscous suspension 2 mg b.i.d.	3	3 (100)		
Placebo	3	0 (0)		
Subgroup analyses: Number (%) of patients in histologic remission defined as mean of < 16 EOS/mm^2 HPF at week 2 (LOCF) stratified by no concomitant use of PPIs				
Budesonide 1 mg b.i.d.	16	16 (100)	NR	NR
Budesonide viscous suspension 2 mg b.i.d.	16	15 (93.8)		
Placebo	16	0 (0)		
Number (%) of patients in histologic remission defined as peak of < 16 EOS/mm^2 HPF at week 2 (LOCF)				
Budesonide 1 mg b.i.d.	19	16 out of 19 (84.2)	84.2% (67.8% to 100%)	NR
Budesonide viscous suspension 2 mg b.i.d.	19	14 out of 19 (73.7)	73.7% (53.9% to 93.5%)	NR
Placebo	19	0 (0)	Reference	Reference

b.i.d. = twice a day; CI = confidence interval; EOS = eosinophil; HPF = high-power field; LOCF = last observation carried forward; PPI = proton pump inhibitor; NR = not reported; vs. = versus.

Source: Clinical Study Report of the BUU-2/EEA trial.[33]

The mean change in numbers of eosinophils per mm^2 HPF from baseline to week 2 was −120 (79.3) in the budesonide 1 mg group, −97 (124.3) in the budesonide viscous suspension 2 mg group, and −8 (157.9) in the placebo group. Both budesonide treatment groups were superior to placebo in the mean change in numbers of eosinophils per mm^2 HPF from baseline to week 2 (Table 28).

Similarly, peak numbers of eosinophils per mm^2 HPF showed a decrease from baseline to week 2 in the budesonide groups and no relevant change in the placebo group. Differences in changes of peak numbers of eosinophils per mm^2 HPF were statistically significantly different in favour of the budesonide groups compared to placebo (Table 28).

Table 28: Change in Mean Numbers of Eosinophils per mm^2 HPF in the BUU-2/EEA Trial

	Total N	Baseline	EOT time point (week 6)		Treatment group difference vs. control		
		Mean (SD)	Mean (SD)	Mean change from baseline (SD)	N	Mean difference	P value
Changes in mean numbers of EOS/mm^2 HPF from baseline to week 2 (LOCF)							
Budesonide 1 mg b.i.d.	19	121 (78.6)	NR	−120 (79.3)	19	NR	0.0003[a]
Budesonide viscous suspension 2 mg b.i.d.	19	101 (121.0)	NR	−97 (124.3)	18	NR	0.0020[a]
Placebo	19	153 (153.4)	NR	−8 (157.9)	19	Reference	Reference
Changes in peak numbers of EOS/mm^2 HPF from baseline to week 2 (LOCF)							
Budesonide 1 mg b.i.d.	19	242 (144.2)	NR	−227 (153.3)	19	NR	0.0006[a]
Budesonide viscous suspension 2 mg b.i.d.	19	201 (185.4)	NR	−180 (185.2)	18	NR	0.0037[a]
Placebo	19	320 (309.0)	NR	−30 (241.6)	19	Reference	Reference

b.i.d. = twice a day; EOS = eosinophil; EOT = end of treatment; HPF = high-power field; LOCF = last observation carried forward; NR = not reported; SD = standard deviation; vs. = versus.

[a] P values for the comparison of budesonide 1 mg b.i.d. and budesonide viscous suspension 2 mg b.i.d. versus placebo treatment, two-sample Wilcoxon-Mann-Whitney test.

Source: Clinical Study Report of the BUU-2/EEA trial.[33]

Harms

Proportions of patients with at least one TEAE were larger in the budesonide groups (36.8% and 57.9% in the budesonide 1 mg group and the budesonide viscous suspension 2 mg twice daily treatment group, respectively) than in the placebo group (10.5%) (Table 29).

The most frequently reported TEAEs in the budesonide 1 mg treatment group were suspected cases of esophageal candidiasis, which occurred in two patients (10.5%) in the budesonide 1 mg treatment group, in three patients (15.8%) in the budesonide viscous suspension 2 mg twice daily treatment group, and in none of the patients in the placebo group (Table 29).

Nasopharyngitis was also reported in two patients (10.5%) in the budesonide 1 mg treatment group, and in none of the patients in the other treatment groups. Dyspepsia was reported in two patients (10.5%) in the budesonide viscous suspension 2 mg twice daily treatment group and in none of the patients in the other treatment groups.

No deaths or SAEs occurred during the course of the trial (Table 29).

One patient in the budesonide viscous suspension 2 mg twice daily treatment group experienced an edema of the lips five days after first intake of study medication. The AE was classified as a TEAE. It was assessed as non-serious; intensity was considered moderate and causal relationship with budesonide was rated as possible. Study medication was discontinued immediately and the patient was withdrawn from the study due to the AE. The patient recovered from the AE 2 days after discontinuation of the study medication. No other treatment discontinuation due to AE was reported.

Table 29: Summary of Harms in the BUU-2/EEA Trial

	BUU-2/EEA		
	Budesonide 1 mg b.i.d. (N = 19)	Budesonide viscous suspension 2 mg b.i.d. (N = 19)	Placebo (N = 19)
Patients with ≥ 1 adverse event			
n (%)	7 (36.8)	11 (57.9)	2 (10.5)
Number (%) of patients with at least 1 TEAE			
Esophageal candidiasis[a]	2 (10.5)	3 (15.8)	0
Fungal esophagitis[a]	1 (5.3)	0	0
Nausea	0	0	1 (5.3)
Headache	1 (5.3)	1 (5.3)	0
Nasopharyngitis	2 (10.5)	0	0
Dyspepsia	0	2 (10.5)	0
Hypertension	1 (5.3)	0	0
Pruritus	1 (5.3)	0	0
White blood cell count, increased	1 (5.3)	0	0
Abdominal pain, upper	0	1 (5.3)	0
ALT, increased	0	1 (5.3)	0
Bowel movement irregularity	0	1 (5.3)	0
Deafness	0	1 (5.3)	0
Gastroesophageal reflux disease	0	1 (5.3)	0
Lip edema	0	1 (5.3)	0
Mucous stools	0	1 (5.3)	0
Oropharyngeal pain	0	1 (5.3)	0
Urticaria	0	1 (5.3)	0
Deterioration of eosinophilic esophagitis	0	0	1 (5.3)
Patients with ≥ 1 SAE			
n (%)	0	0	0
Patients who stopped treatment due to adverse events			
n (%)	0	1 (5.3)	0
Most common events[a]			
Edema of the lips	0	1 (5.3)	0
Deaths			
n (%)	0	0	0
Notable harms, N (%)			
Local fungal infection	3 (15.8)	3 (15.8)	0
Esophageal candidiasis[a]	2 (10.5)	3 (15.8)	0
Fungal esophagitis[a]	1 (5.3)	0	0
Dysgeusia	0	0	0
Decreased bone mineral density	0	0	0
Cataract	0	0	0

	BUU-2/EEA		
	Budesonide 1 mg b.i.d. (N = 19)	Budesonide viscous suspension 2 mg b.i.d. (N = 19)	Placebo (N = 19)
Glaucoma	0	0	0
Psychiatric disorders	0	0	0
Symptoms of sore throat (pharyngitis)	0	0	0
Avascular necrosis of the hip	0	0	0

ALT = Alanine aminotransferase; b.i.d. = twice a day; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] Suspected cases based on macroscopic findings, for histologic analysis and confirmation of suspected cases.

Source: Clinical Study Report of the BUU-2/EEA trial.[33]

Critical Appraisal

Internal Validity

The BUU-2/EEA trial used accepted methods to conceal allocation and randomize patients to treatments; in addition, matched placebo was used to maintain blinding.

The sample size per group was relatively small and the baseline characteristics were not always harmoniously distributed across treatment groups. However, these differences were not clearly suggestive of a specific bias toward unduly favouring the active treatments groups.

There was no control from multiplicity among the secondary outcomes analyzed. Hence, results of these end points should be interpreted with consideration of the potential for inflated type I error.

External Validity

The study included a small number of patients. Given the small sample size and the fact that no Canadian study site was included, it is unclear whether the study results can be generalized to the Canadian patient population.

The Health Canada product monograph for budesonide orodispersible tablets indicates that the usual treatment duration is six weeks. Patients enrolled in the BUU-2/EEA trial received budesonide for only two weeks; hence, the generalizability of the study results for the budesonide 1 mg treatment group to the Canadian patient population is unclear.

Budesonide viscous suspension is not indicated for treatment of EoE, and it is used off-label for the treatment of EoE. In the guidelines on EoE put forth by Lucendo et al.,[2] the recommended dosage of budesonide viscous suspension is 2 mg/day to 4 mg/day. The clinical experts indicated that the regular dose used in clinical practice is 1 mg budesonide viscous suspension, which is in the lower recommended range of the guideline. It is worth noting that the guideline referred to was developed in Europe, and no Canadian guideline for recommended doses was identified in the literature. Patients in the BUU-2/EEA trial received budesonide viscous suspension 2 mg twice daily, which is double the dose used in clinical practice. Hence, the generalizability of the study results for the budesonide viscous suspension 2 mg twice daily treatment group to the Canadian patient population is unclear.

Discussion

Summary of Available Evidence

One pivotal phase III, double-blind, randomized, multi-centre, placebo-controlled study met the inclusion criteria. The BUL-1/EEA trial (N = 88) compared the efficacy and safety of a six-week treatment with budesonide effervescent tablets with placebo for the induction of clinicopathologic remission in adult patients with active EoE. The percentage of patients with clinicopathologic remission at week 6 (LOCF) was the primary end point. The percentage of patients with histologic remission, defined as a peak of fewer than 16 eosinophils per mm^2 HPF at week 6 (LOCF), the percentage of patients with resolution of symptoms (i.e., no or only minimal problems), defined as a severity of 2 points or less on a NRS of 0 to 10 points for dysphagia and a severity of 2 points or less on a NRS of 0 to 10 points for pain during swallowing on each day of the week prior to week 6 (LOCF), and the percentage of patients with total weekly EEsAI-PRO score of 20 or less at week 6 (LOCF) were key secondary end points.

In addition to the main trial reviewed, the OLI phase of the BUL-1/EEA trial and the BUU-2/EEA trial were reviewed and critically appraised. The BUU-2/EEA was a phase II, double-blind, double-dummy, randomized, placebo-controlled trial that compared oral treatment with budesonide 1 mg effervescent tablets for orodispersible use twice daily and 5 mL viscous budesonide suspension (0.4 mg/mL) twice daily with placebo in adult patients with clinicohistologic active EoE. Results were reported in the “Other Relevant Evidence” section.

Interpretation of Results

Efficacy

EoE is a chronic, immune-mediated esophageal disease characterized by an eosinophil-predominant inflammation of the esophageal mucosa causing symptoms of esophageal dysfunction, and thus requiring anti-inflammatory treatment to achieve clinicopathologic remission. Otherwise, chronic inflammation with symptoms, including frequent episodes of food impaction, have an unfavourable impact on patients’ quality of life. Endoscopic procedures, including removal of impacted food and dilatation, are often needed. These, coupled with the typical fragility of the mucosa in this disease, have been found to be associated with complications such as mucosal tears, significant pain, and even rare esophageal perforations, which could be serious and life threatening.

The resolution of symptoms is considered an important outcome to patients as reported in the patient input section. The proportion of patients who achieved resolution of symptoms was a key secondary end point and it was one of the two components of the composite primary end point in the BUL-1/EEA trial. The resolution of symptoms was defined as a severity of 2 points or less on a NRS of 0 to 10 points for dysphagia and a severity of 2 points or less on a NRS of 0 to 10 points for pain during swallowing on each day of the week prior to week 6. Patients who met these criteria of symptom resolution were 59.3% in the budesonide 1 mg group versus 13.8% in the placebo group, respectively. The difference between the budesonide 1 mg twice daily and placebo treatment groups was 45.5% (95% CI, 27.8 to 63.3; $P < 0.0001$), which was clinically relevant and statistically significant in favour of budesonide. The clinical experts indicated that using a questionnaire to assess the resolution of symptoms is not common in clinical practice; they also indicated

that the questionnaire employed in the trial is simple to use. However, no studies validating the Dysphagia NRS and Pain During Swallowing NRS in patients with EoE were identified from the literature. It is worth noting that 40.7% of patients in the budesonide 1 mg group had either no change or only mild change in their symptoms, or only achieved histologic remission. Given the short duration of the double-blind period (six weeks), it was unclear how long the remission would be maintained, and it is uncertain whether patients who relapse would respond to a subsequent course of treatment with budesonide 1 mg in the same manner as they responded the first time they received budesonide 1 mg. The clinical experts anticipated repeated use of budesonide 1 mg to treat recurrence of inflammation. A post-hoc analysis of resolution of symptoms used more stringent criteria, defined as a severity of 0 points on a NRS of 0 to 10 points (0 to 10) for dysphagia and a severity of 0 points on a NRS of 0 to 10 points for pain during swallowing on each day of the week prior to week 6 (LOCF). According to this most stringent criterion, none of the 29 patients (0.0%) in the placebo group and 15 of the 59 patients (25.4%) in the budesonide 1 mg group achieved resolution of symptoms at week 6 (LOCF). The difference between the budesonide 1 mg twice daily and placebo treatment groups was 25.4% (95% CI, 14.3 to 36.5) in favour of budesonide. The clinical experts indicated that the post-hoc analysis using the more stringent criteria was very strict, and were comfortable with the definition of resolution of symptoms that was used in the main analysis.

Results from the resolution of symptoms suggested that the treatment benefit was possibly more pronounced for dysphagia (rates of patients with no or minimal dysphagia was 13.8% with placebo as compared to 62.7% with budesonide 1 mg twice daily) than for odynophagia (rates of patients with no or minimal odynophagia was 64.4% with budesonide 1 mg twice daily as compared to 55.2% with placebo).

Food impaction needing endoscopic intervention occurred in only one patient in the placebo group and none in the budesonide 1 mg group, and no endoscopic dilation was needed in either group during the study. It is uncertain if treatment with budesonide 1 mg effervescent tablets would actually decrease the risk of impaction and the need for endoscopic dilation.

It was also clear from the patient group input received for this submission that patients consider improved quality of life to be an important outcome of treatment. In the BUL-1/EEA trial, HRQoL was assessed using the EoE-QoL-A and modSHS instruments. The mean change from baseline to week 6 was higher in the budesonide 1 mg group than in the placebo group for both the EoE-QoL-A (30 items) total scores (mean difference = 0.24; 95% CI, −0.01 to 0.47) and consistently for each of the six subscales (eating/diet impact [10 items], eating/diet impact [four items], social impact, emotional impact, disease anxiety, and swallowing anxiety). Of note, the between-group difference in subscales eating/diet impact (10 items) (0.50; 95% CI, 0.17 to 0.82) and eating/diet impact (four items) (0.49; 95% CI, 0.13 to 0.86) was significantly improved in favour of budesonide 1 mg, whereas these differences were less evident in the other four subscales. Similarly, the modSHS also showed a consistent change from baseline to week 6, with between-group difference significantly improved in favour of budesonide 1 mg for social function and disease-related worry questions of the modSHS, but not for symptom burden and general well-being. An MID for the EoE-QoL-A and modSHS was not identified for patients with EoE. Also, the analysis of modSHS and EoE-QoL-A were not specifically tested for statistical significance with methods adjusted for multiplicity, despite a reporting of 95% CI. It is likely, however, that budesonide 1 mg may have substantially improved a patient's eating and/or diet, whereas the clinical importance of the magnitude of improvement on other outcomes is uncertain.

The clinical experts noted that results of histologic remission achieved in the budesonide 1 mg group were as expected, where none of the 29 patients (0%) in the placebo group and 55 of the 59 patients (93.2%) in the budesonide 1 mg group achieved histologic remission at week 6. The difference between the budesonide 1 mg twice daily and placebo treatment groups was 93.2% (95% CI, 86.8 to 99.6; P < 0.0001) in favour of budesonide. Also, in a post-hoc analysis of histologic remission that used a more stringent criteria, which was defined as peak eosinophils per mm^2 HPF of zero in all biopsies at week 6, the difference between the budesonide 1 mg group and the placebo treatment group was 89.8% (95% CI, 82.1 to 97.5; P < 0.0001) in favour of budesonide. The clinical experts also indicated that histologic testing is invasive and cumbersome, and that in clinical practice, assessment of esophageal inflammation is not conducted on a regular basis.

The primary end point in the BUL-1/EEA trial was the percentage of patients with clinicopathologic remission; this end point encompasses both histologic remission and patient-reported symptom resolution. Thirty-four of 59 patients (57.6%) in the budesonide 1 mg group versus none of the 29 patients (0%) in the placebo group achieved clinicopathologic remission at week 6. The difference between the budesonide 1 mg group and placebo treatment group on this composite outcome was 57.6% (95% CI, 38.2 to 72.0; P < 0.0001) in favour of budesonide. It is noteworthy that post-hoc analyses using a more stringent criteria for severity in symptoms remissions (severity of 0 points for dysphagia and pain during swallowing on each day of the week prior to week 6) and more stringent criteria for clinical remission (a peak of zero eosinophils per mm^2 HPF at week 6) was performed. The results showed that the difference regarding clinicopathologic remission still favoured the budesonide 1 mg group (the between-group difference was 22.0% [95% CI, 11.5% to 32.6%; P = 0.0034]). Results from the primary end point and its main criteria (resolution of symptoms and histologic remission) indicate that almost every patient who achieved resolution of symptoms was also in histologic remission, but not vice versa. The clinical experts indicate that these results underscore the imperfect relationship between esophageal symptoms and the biological activity of EoE.

The EEsAI-PRO score that is used to assess EoE activity was a key secondary end point. Two of the 29 patients (6.9%) in the placebo group and 30 of the 59 patients (50.8%) in the budesonide 1 mg group achieved remission (defined as a total weekly EEsAI-PRO score of ≤ 20) at week 6. The difference between the budesonide 1 mg group and the placebo treatment group was 44.0% (95% CI, 28.2 to 59.7; P < 0.0001) in favour of budesonide. These results were in line with the symptom resolutions as measured by the NRS for dysphagia and pain during swallowing.

While the Health Canada indication does not specify that budesonide 1 mg orodispersible tablets be only used in patients who have previously failed treatment with a PPI, patients who were enrolled in the BUL-1/EEA trial had to be refractory to PPI treatment in order to be eligible to enrol in the trial. It is uncertain whether patients who are PPI naive would respond to budesonide 1 mg in the same manner as patients who were included in the trial. It is worth noting that the diagnostic criteria for EoE have evolved since EoE was first conceptually defined, where one of the diagnostic criteria in prior guidelines was the persistence of mucosal eosinophilia in the esophagus after two months of treatment with a PPI.[1, 4, 17] Current guidelines consider PPIs as one of the treatment options for EoE. The rationale for exclusion of a PPI trial from the EoE diagnostic criteria is that patients with clinical and histologic features compatible with EoE but who respond histologically to a PPI do not appear to be distinct from those with EoE,[1, 17] and the most recent guideline for diagnostic criteria of EoE considered PPI-REE as a subset of EoE rather than a distinct

disease.[1, 4] In addition, the guideline by Lucendo et al.[2] does not recommend that patients try a PPI first, then switch to topical corticosteroids; rather, it recommended that either PPIs or topical corticosteroids be the first line of pharmacological treatment.

The usual treatment duration for budesonide 1 mg orodispersible tablets recommended by Health Canada is six weeks.[8] The usual treatment duration for budesonide 1 mg orodispersible tablets recommended by the European Medicines Agency is six weeks, and treatment with budesonide 1 mg orodispersible tablets could be extended to up to 12 weeks for patients who are not appropriately responding during six weeks of treatment.[34] The panel of clinical experts convened by CADTH indicated that patients would initiate treatment with budesonide 1 mg for six weeks and, if there was no resolution of symptoms (i.e., elimination of the symptom of dysphagia and prevention of food impaction), treatment with budesonide 1 mg should be renewed for an additional six weeks. It is also worth noting that the indication provided for budesonide 1 mg by the European Medicines Agency is for the treatment of EoE in adults,[34] which differs from the Health Canada indication (induction of clinicopathologic remission in adults with EoE).

In the BUL-1/EEA trial, the six-week double-blind treatment period was followed by an optional six-week OLI treatment with budesonide 1 mg twice daily in patients eligible for OLI treatment (clinicopathologic non-remitters). The results suggested that an additional 27% of patients achieved clinicopathologic remission among the 23 patients receiving a total of 12 weeks of treatment with budesonide 1 mg. The sponsor proposed to Health Canada that it recommend patients with no remission after six weeks of treatment continue on an optional additional six weeks. However, Health Canada reviewers indicated that the efficacy of budesonide 1 mg beyond the initial six-week double-blind phase could not be established using the data from the open-label phase, due to the small number of patients (only 23 patients were actually exposed to budesonide 1 mg for 12 weeks), and the lack of randomization and control group.[24]

No indirect evidence was submitted by the sponsor or identified in our literature search that would match the inclusion and exclusion criteria of this review. The sponsor submitted a phase II, double-blind, double-dummy, randomized, placebo-controlled trial (Study BUU-2/EEA) that compared oral treatment with budesonide 1 mg effervescent tablets for orodispersible use twice daily and 5 mL viscous budesonide suspension (0.4 mg/mL) twice daily with placebo in adult patients with clinico-histologic active EoE. While no comparison between the budesonide 1 mg group and the budesonide viscous suspension 2 mg group was conducted for any of the end points assessed in the BUU-2/EEA trial, it is worth noting that both budesonide groups, regardless of formulation, were superior to placebo for induction of histologic remission in active EoE. The differences between the budesonide 1 mg twice daily and placebo treatment groups, and between the budesonide viscous suspension 2 mg group and placebo group, were 100% (95% CI, 64.7 to 100; P = < 0.0001) and 94.7% (95% CI, 57.6 to 99.5; P = < 0.0001), respectively. This indicated that both budesonide treatment groups were effective in achieving histologic remission. The clinical experts indicated that the regular dose used in clinical practice is 1 mg budesonide viscous suspension; however, patients in the BUU-2/EEA trial received budesonide viscous suspension 2 mg twice daily, which is double the dose used in clinical practice. Also, the usual treatment duration for budesonide 1 mg orodispersible tablets recommended by Health Canada is six weeks, whereas patients enrolled in the BUU-2/EEA trial received budesonide 1 mg for only two weeks.

The most recent treatment guidelines identified from the literature were developed by authors participating on behalf of the United European Gastroenterology; the European Society of Pediatric Gastroenterology, Hepatology and Nutrition; the European Academy of Allergy and Clinical Immunology; and the European Society of Eosinophilic Oesophagitis and published by Lucendo et al. in 2017.[2] These guidelines indicated that long-term treatment with topical corticosteroids might be effective in maintaining remission in a proportion of patients who responded to topical corticosteroids as induction treatment. This recommendation is in line with what the panel of clinical experts convened by CADTH suggested about long-term treatment with topical corticosteroids. The panel indicated that some patients might require long-term maintenance therapy with budesonide 1 mg for one year in order to maintain remission. However, budesonide 1 mg is indicated for the induction of clinicopathologic remission and the usual duration of treatment recommended by Health Canada is six weeks; therefore, the use of budesonide 1 mg as a maintenance therapy is not aligned with the usual treatment duration recommended by Health Canada. In the BUL-1/EEA trial, patients without clinical symptoms at the EOT or withdrawal visit double-blind or EOT or withdrawal visit OLI were to remain untreated during this follow-up period or could alternatively participate in a double-blind, randomized, placebo-controlled maintenance of remission trial, if eligible. The maintenance of remission trial was not included in this report as it was ongoing at the time of submission to CADTH. On March 26, 2020, the Committee for Medicinal Products for Human Use of the European Medicines Agency adopted a change to the duration of treatment allowing the use of budesonide 1 mg as maintenance therapy for EoE in adults with a new strength (0.5 mg orodispersible tablet).[35] The recommendations for maintenance therapy were as follows:

- The recommended daily dose is 1 mg budesonide as one 0.5-mg-tablet in the morning and one 0.5-mg-tablet in the evening or 2 mg budesonide as one 1-mg-tablet in the morning and one 1-mg-tablet in the evening, depending on the individual clinical requirement of the patient.
- A maintenance dose of 1 mg budesonide twice daily is recommended for patients with a long-standing disease history and/or high extent of esophageal inflammation in their acute disease state.
- The duration of maintenance therapy is determined by the treating physician.[35]

The patient groups reported that corticosteroids generally resulted in remission; however, they are primarily off-label asthma medications that are swallowed from an inhaler or mixed, and the non-specific nature of drug delivery makes the effectiveness varied and uncertain. Patients expressed a desire for convenience in medication administration as well as clear instructions to maintain compliance. Patients expressed a need for a treatment that improves their day-to-day quality of life (i.e., for eating, working, and socializing) and indicated that an effective therapy that resolves clinicopathologic symptoms and has minimum long-term complications is of high importance. Budesonide 1 mg tablets appear to meet a need expressed in the patient group inputs for a convenient medication with clear instructions to assist adherence.

Harms

In the BUL-1/EEA trial, no deaths or SAEs occurred during the study in any of the treatment groups, and no patient discontinued due to AEs in the budesonide 1 mg group (one patient discontinued placebo due to food impaction).

The clinical experts indicated that the nature and frequency of AEs observed in the budesonide 1 mg group were consistent with the known safety profile of topical budesonide.

The most frequently reported TEAEs in the budesonide 1 mg treatment group during the double-blind treatment phase were 17 suspected AEs of candidiasis, reported either by the investigator based on endoscopic or clinical signs and symptoms, or by the central pathologist based on the assessment of esophageal biopsies, and occurring in 14 patients (23.7%). No such events were reported in the placebo group. It is known that budesonide with its anti-inflammatory and immunosuppressive action can, as an adverse drug reaction, promote candidiasis and other infections. Only four events (three esophageal candidiasis events and one oral candidiasis event) in three patients (5.1%) were histologically confirmed by positive Grocott staining, and showed endoscopic and clinical signs. All four of these events were of mild severity and neither interfered with normal daily activities nor had an impact on the treatment effect in this study.

During the OLI phase, approximately 57% of patients experienced AEs in the group receiving budesonide 1 mg for an additional six weeks (i.e., a total 12 weeks), and in those receiving six weeks but were previously on placebo in the double phase (total of only six weeks). It is noteworthy that Candida infections were reported in 10 patients (35.7%) treated for six weeks (formerly in the placebo group of the double-blind phase) and four patients (17.4%) of those treated for 12 weeks. Health Canada reviewers indicated that the safety of budesonide 1 mg beyond the initial six-week double-blind phase could not be established using the data from the open-label phase, due to the small number of patients (only 23 patients received 12 weeks of treatment with budesonide 1 mg) and the lack of comparison to patients treated with placebo only.[24]

Given the available evidence, the long-term safety of budesonide 1 mg beyond six weeks is unknown. It is also unknown what the safety profile would be if patients use other pharmacological treatment such as PPIs or fluticasone.

Conclusions

The BUL-1/EEA trial provided evidence on the efficacy and safety of budesonide effervescent tablets 1 mg for the induction of clinicopathologic remission in adult patients with active EoE. The BUL-1/EEA trial demonstrated a statistically significant and clinically meaningful improvement of budesonide 1 mg twice daily in inducing clinicopathologic remission in patients with active EoE when compared to placebo, following six weeks of treatment. In addition, budesonide effervescent tablets 1 mg twice daily demonstrated a statistically significant and clinically meaningful improvement on symptomatic remission, following pre-specified criteria that the clinical expert recognized as appropriate. It is uncertain if treatment with budesonide 1 mg effervescent tablets would decrease the risk of impaction and the need for endoscopic dilation. In association with the improvement of patients' symptoms, there were likely consistent improvements of patients' HRQoL, particularly impact on eating and/or diet, even though the assessment of these outcomes may have suffered methodological limitations. The effect of budesonide effervescent tablets 1 mg seemed to be more pronounced on the histologic component and somewhat less so on the symptomatic remission, where 93% achieved histologic remission. The duration of the remission, however, is uncertain. It is also uncertain whether patients who relapse would respond to a subsequent course of treatment with budesonide 1 mg in the same manner as they responded the first time they received budesonide 1 mg. Safety data from the BUL-1/EEA trial did not demonstrate any notable concern. Long-term safety, particularly in combination with other pharmacological therapies, remains unknown.

Appendix 1: Literature Search Strategy

Clinical Literature Search

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	Dec 9, 2019
Alerts:	Weekly search updates until May 20, 2020
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.po	Population group [PsycInfo only]
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
1.	budesonide/
2.	(jorveza* or budesonide* or map-0010 or map0010 or s-1320 or s1320 or Q3OKS62Q6X).ti,ab,rn,nm,kf,ot.
3.	eosinophilic esophagitis/
4.	(eosinophil* adj3 (esophagitis or oesophagitis)).ti,ab,kf.
5.	(eoe or oeoe).ti,ab,kf.
6.	1 or 2
7.	3 or 4 or 5
8.	6 and 7
9.	8 use medall
10.	*budesonide/
11.	(jorveza* or budesonide* jorveza* or budesonide* or map-0010 or map0010 or s-1320 or s1320).ti,ab,kw,dq.
12.	eosinophilic esophagitis/
13.	(eosinophil* adj3 (esophagitis or oesophagitis)).ti,ab,kw,dq.
14.	(eoe or oeoe).ti,ab,kw.
15.	10 or 11
16.	12 or 13 or 14
17.	15 and 16
18.	17 use oemezd
19.	conference abstract.pt.
20.	conference review.pt.
21.	19 or 20
22.	18 not 21
23.	9 or 22
24.	Remove duplicates

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	December 2019
Keywords:	Jorveza (budesonide) AND eosinophilic esophagitis
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search

Appendix 2: Excluded Studies

Table 30: Excluded Studies

Reference	Reason for Exclusion
Dellon ES, Woosley JT, Arrington A, et al. Efficacy of Budesonide vs Fluticasone for Initial Treatment of Eosinophilic Esophagitis in a Randomized Controlled Trial. Gastroenterology. 2019;157(1):65-73.e65. Dellon ES, Woosley JT, Arrington A, et al. Rapid Recurrence of Eosinophilic Esophagitis Activity After Successful Treatment in the Observation Phase of a Randomized, Double-Blind, Double-Dummy Trial. Clin Gastroenterol Hepatol. 2019;06:06. 2. Straumann A, Conus S, Degen L, et al. Budesonide is effective in adolescent and adult patients with active eosinophilic esophagitis. Gastroenterology. 2010;139(5):1526-1537, 1537.e1521. Straumann A, Conus S, Degen L, et al. Long-term budesonide maintenance treatment is partially effective for patients with eosinophilic esophagitis. Clin Gastroenterol Hepatol. 2011;9(5):400-409.e401.	Intervention (inappropriate formulation)
Miehlke S, Hruz P, Vieth M, et al. A randomised, double-blind trial comparing budesonide formulations and dosages for short-term treatment of eosinophilic oesophagitis. Gut. 2016;65(3):390-399.	Study design (not a phase III or phase IV RCT)

Appendix 3: Detailed Outcome Data

Table 31: Change in the Peak Eosinophils per mm^2 HPF From Baseline to Week 6, LOCF, in the BUL-1/EEA Trial

	Total N	Baseline	EOT time point (week 6)		Treatment group difference vs. control		
		Mean (SD)	Mean (SD)	Mean change from baseline (95% CI)	N	Mean difference (95% CI)	P value
Change in the peak EOS/mm^2 HPF from baseline to week 6 (LOCF)[a]							
Budesonide 1 mg b.i.d.	59	242 (140.7)	16.34 (69.15)	−225.5 (−264.7 to −186.4)	59	−221.3 (−287.0 to −155.6)	< 0.0001[b]
Placebo	29	239 (125.0)	224.03 (94.51)	−4.3 (−55.9 to 47.3)	29	Reference	
Subgroup analysis for change in the peak EOS/mm^2 HPF from baseline to week 6 (LOCF) for patients who used concomitant PPI							
Budesonide 1 mg b.i.d.	7	NR	−282.90 (171.277)	NR	NR	NR	NR[c]
Placebo	3	NR	−23.17 (127.583)	NR	NR	Reference	
Subgroup analysis for change in the peak EOS/mm^2 HPF from baseline to week 6 (LOCF) for patients who did not use concomitant PPI							
Budesonide 1 mg b.i.d.	52	NR	−217.82 (147.483)	NR	NR	NR	NR[c]
Placebo	26	NR	−2.10 (138.767)	NR	NR	Reference	

b.i.d. = twice a day; CI = confidence interval; EOS = eosinophil; EOT = end of treatment; HPF = high-power field; LOCF = last observation carried forward; NR = not reported; PPI = proton pump inhibitor; SD = standard deviation; vs. = versus.

[a] In the event the change at week 6 (LOCF) could not be calculated due to no valid week 6 (LOCF) value being available, the change at week 6 (LOCF) was set to 0.

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

Source: Clinical Study Report of the BUL-1/EEA trial.[9]

Table 32: EEsAI-PRO Score, VDQ Score, and AMS Score at Week 6, LOCF, in the BUL-1/EEA Trial

	Total N	n (%)	Difference in proportions: Budesonide vs. placebo (95% CI)	P value
Percentage of patients with total weekly EEsAI-PRO score of ≤ 20 at week 6 (LOCF)				
Budesonide 1 mg b.i.d.	59	30 (50.8)	44.0% (28.2% to 59.7%)	< 0.0001[a]
Placebo	29	2 (6.9)	Reference	
Percentage of patients with an improvement from baseline to week 6 (LOCF) in the weekly VDQ score				
Budesonide 1 mg b.i.d.	59	30 (50.8)	12.9% (−9.9% to 34.7%)	0.1804[a]
Placebo	29	11 (37.9)	Reference	
Percentage of patients with an improvement from baseline to week 6 (LOCF) in the weekly AMS score				
Budesonide 1 mg b.i.d.	59	7 (11.9)	1.5% (−12.3% to 15.3%)	0.5703[a, b]
Placebo	29	3 (10.3)	Reference	

AMS = avoidance, modification, and slow eating; b.i.d. = twice a day; CI = confidence interval; EEsAI-PRO = Eosinophilic Esophagitis Activity Index Patient Reported Outcome; LOCF = last observation carried forward; VDQ = Visual Dysphagia Question; vs. = versus.

[a] Fisher exact test was used for testing.

[b] As the P value for the fifth key secondary end point was not significant, the significance test was considered exploratory in nature.

Source: Clinical Study Report of the BUL-1/EEA trial.[9]

Table 33: Patient's Global Assessment in the BUL-1/EEA Trial

	Total N	n (%)	Difference in proportions: Budesonide vs. placebo (95% CI)	P value
Percentage of patients with overall symptoms resolution defined as PatGA concerning the severity of EoE symptoms (NRS of 0 to 10) ≤ 2 at week 6 (LOCF)				
Budesonide 1 mg b.i.d.	59	38 (64.4)	40.3% (20.5% to 60.1%)	NR
Placebo	29	7 (24.1)	Reference	

b.i.d. = twice a day; CI = confidence interval; EoE = eosinophilic esophagitis; LOCF = last observation carried forward; NR = not reported; NRS = numerical rating scale; PatGA = Patient's Global Assessment; vs. = versus.

Source: Clinical Study Report of the BUL-1/EEA trial.[9]

Table 34: Change From Baseline to Week 6, LOCF, in the Physician's Global Assessment of EoE Activity in the BUL-1/EEA Trial

	Total N	Baseline	EOT time point (week 6 LOCF)		Treatment group difference vs. control		
		Mean (SD)	Mean (SD)	Mean change from baseline (95% CI)	N	Mean difference (95% CI)	P value
Change from baseline to week 6 (LOCF) in the PGA of EoE activity (NRS of 0 to 10)							
Budesonide 1 mg b.i.d.	59	6.1 (1.28)	2.3 (2.45)	−3.8 (−4.40 to −3.19)	59	−3.0 (−4.06 to −2.01)	NR
Placebo	29	6.2 (1.30)	5.5 (2.11)	−0.8 (−1.58 to 0.06)	29	Reference	

b.i.d. = twice a day; CI = confidence interval; EoE = eosinophilic esophagitis; EOT = end of treatment; LOCF = last observation carried forward; NR = not reported; NRS = numerical rating scale; PGA = Physician's Global Assessment; SD = standard deviation; vs. = versus.

Source: Clinical Study Report of the BUL-1/EEA trial.[9]

Appendix 4: Description and Appraisal of Outcome Measures

Aim

To describe the following outcome measures and review their measurement properties (validity, reliability, responsiveness to change, and MID):

- Dysphagia NRS
- Pain During Swallowing NRS
- EEsAI-PRO
- VDQ score
- AMS score
- PGA of EoE activity (NRS of 0 to 10)
- PatGA concerning the severity of EoE symptoms
- modSHS
- EoE-QoL-A questionnaire
- Dysphagia Score

Findings

Table 35: Summary of Outcome Measures and Their Measurement Properties

Outcome measure	Type	Conclusions about measurement properties	MID
Dysphagia Numerical Rating Scale	10-point Likert-type scale concerning the severity of dysphagia symptoms	No evidence found assessing the validity, reliability, and responsiveness of the scale	Not identified from the literature, although a score of ≤ 2 was used in the study as a resolution of symptoms[9]
Pain During Swallowing Numerical Rating Scale	10-point Likert-type scale concerning the severity of pain when swallowing	No evidence found assessing the validity, reliability, and responsiveness of the scale	Not identified from the literature, although a score of ≤ 2 was used in the study as a resolution of symptoms[9]
EEsAI-PRO	5-item scale to assess EoE activity	Construct and content validity was demonstrated;[27] no information on reliability and responsiveness	Not identified from the literature, although a ≥ 20-point decrease from baseline was used in the study as a response to treatment[9]
Visual Dysphagia Question score	A subscale of EEsAI-PRO	VDQ was not validated separately	VDQ-specific MID not identified from the literature
Avoidance, modification, and slow eating score	A subscale of EEsAI-PRO	AMS was not validated separately	AMS-specific MID not identified from the literature
PGA	10-point Likert-type scale for global assessment of patients' EoE activity	No evidence found assessing the validity, reliability, and responsiveness of the scale	Not identified from the literature

Outcome measure	Type	Conclusions about measurement properties	MID
PatGA	10-point Likert-type scale for global assessment of EoE symptoms	No evidence found assessing the validity, reliability, and responsiveness of the scale	Not identified from the literature; a PatGA score of ≤ 2 was used in the study as a resolution of symptoms[9]
Modified Short Health Scale	Generic 4-item HRQoL questionnaire	Validity, reliability, and responsiveness demonstrated in ulcerative colitis[28] and Crohn disease, [29] but not in EoE	Not identified from the literature
Adult Eosinophilic Esophagitis Quality of Life Questionnaire	5-dimension and 37-item questionnaire, refined to a 30-item questionnaire (24-item scale with a 6-question addendum for those on elimination diet therapies)	Validity, reliability, and responsiveness shown for the original version;[30] only construct validity assessed for the shorter version[31]	Not identified from the literature
Dysphagia Score	2-item 9-point questionnaire measuring dysphagia frequency and intensity	Not identified from the literature	Not identified from the literature, although the trial used a decrease of ≥ 3 points from baseline as clinical response[33]

AMS = Avoidance, modification, and slow eating; EoE = eosinophilic esophagitis; EEsAI-PRO = Eosinophilic Esophagitis Activity Index Patient Reported Outcome; HRQoL = health-related quality of life; MID = minimal important difference; PatGA = Patient's Global Assessment; PGA = Physician's Global Assessment; VDQ = Visual Dysphagia Question.

Dysphagia Numerical Rating Scale

The Dysphagia NRS is a 10-point rating scale where patients provide an assessment of the severity of dysphagia symptoms experienced in the past 24 hours or seven days. The scale ranges from 0 to 10 (0 represents no trouble swallowing, 10 represents the most severe trouble swallowing). The Dysphagia NRS captures dysphagia symptoms associated with EoE only and not symptoms associated with cold, e.g., sore throat. Patients in the trial received the scale in the form of a diary, and daily ratings were used to calculate a weekly sum.[9]

No studies validating the Dysphagia NRS in patients with EoE were identified from the literature; neither was an MID found. In the BUL-1/EEA trial, one of the co-primary end points, resolution of symptoms (i.e., no or only minimal problems), was based on a Dysphagia NRS score of 2 points or less.[9]

Pain During Swallowing Numerical Rating Scale

The Pain During Swallowing NRS is a 10-point rating scale where patients provide an assessment of the severity of pain during swallowing experienced in the past 24 hours or seven days. The scale ranges from 0 to 10 (0 represents no pain during swallowing, 10 represents the most severe pain during swallowing).[9]

Evidence regarding the validity, reliability, and MID of the Pain During Swallowing NRS were not found for patients with EoE in the literature. In the BUL-1/EEA trial, one of the co-primary end points, resolution of symptoms (i.e., no or only minimal problems) was based on a Pain During Swallowing NRS score of 2 or less.[9]

The Eosinophilic Esophagitis Activity Index Patient Reported Outcome

The EEsAI-PRO score is used to assess EoE activity over a seven-day recall period in adult patients that consists of five items:

- Frequency of trouble swallowing — Patients are asked the number of times they had trouble swallowing in the past week, and the regularity is scored in four increments ranging from never to daily, with higher frequency associated with a higher score.
- Duration of dysphagia episodes — The duration of dysphagia episodes in the past seven days is scored based on a five-minute cut-off, with longer duration associated with a higher score.
- Pain during swallowing — Patients are asked if they experienced pain when swallowing, and are scored higher when pain was present.
- VDQ — The VDQ score measures the occurrence of dysphagia induced by the virtual ingestion of eight reference foods, each at different consistencies, which are graded on a scale of 0 to 3 (described in detail as follows).
- Behavioural change strategies — This item evaluates the change in patients' behaviour in response to specific foods with eight different consistencies; it also has three sub-items that are scored separately, i.e., AMS (described in detail as follows).

The scores of each item are added to provide an overall score out of 100, with disease severity rated as remission (0 to 20), mild (21 to 40), moderate (41 to 65), and severe (66 to 100).[9]

Assessment of Validity

The EEsAI-PRO score was developed and validated in a clinical trial setting by Schoepfer et al., conducted in three phases.[27] In the first phase, items for the PRO instrument were generated by patient input from a mixed-methods approach using open-ended patient symptom surveys, focus groups, and semi-structured patient interviews. In total, the PRO instrument consisted of 45 items on symptoms severity and behavioural adaptations, which were grouped into five domains: a general domain to assess sociodemographic characteristics, two symptom domains to address symptoms dependent and independent of food intake, a comorbidities domain, and a medication domain. Three different time periods were assessed for the optimum recall period of the PRO instrument, e.g., 24 hours, seven days, and 30 days. For each recall period, patients were asked to provide a PatGA of EoE severity on an 11-point Likert scale, as described previously (where a score of 0 is defined as "no symptoms" and a score of 10 is defined as "most severe symptoms"). This was used as the gold standard and the main outcome parameter in the trial.[27]

During the second phase, the prototype of the PRO instrument was assessed in a test sample of 153 patients with EoE in Switzerland and the US who completed the PatGA at study entry. The data obtained from the VDQ and AMS items were used to create a composite score. Using multivariable linear regression analysis in which the PatGA was used as the outcome, and responses to specific items in the PRO instrument as predictors, seven PRO factors used to assess characteristics of dysphagia, behavioural adaptations to living with dysphagia, and pain while swallowing accounted for 67% of the variation in patients' assessment of disease severity. After grouping the three AMS items, five variables were selected for the final instrument. In terms of recall period, the majority of patients (> 70%) indicated that seven days was the best recall period.[27]

Finally, the PRO instrument and PRO score were tested in an independent validation sample of 120 adult patients with EoE. By comparing the PRO score with the PatGA in the validation sample, it was shown that the EEsAI-PRO score for the seven-day recall period predicted 65% of the variability in PatGA, closely reflecting the results obtained in the test set. The EEsAI-PRO score showed construct validity with the PatGA based on high agreement between the scales. Patients required a median of eight minutes to complete the questionnaire (range of four to 10 minutes), and rated a median difficulty of 1 on an 11-point Likert scale (where 0 stands for "no difficulties at all" and 10 stands for "very difficult") in response to the question, "How difficult was it for you to complete this questionnaire?". Content validity was assessed by asking patients if the scale adequately measured the complaints they had or currently experienced due to EoE, with responses mapped on an 11-point Likert scale (where 10 stands for "perfectly" and 0 stands for "not at all"). The median response from patients was a score of 8 (range of 4 to 10). An assessment of reliability was not done.[27]

MID

A response to treatment was defined by the authors of the BUL-1/EEA trial as a 20-point or more decrease in the EEsAI-PRO score from baseline.[9] However, it is not clear how this MID was established.

Visual Dysphagia Question Score

The VDQ is a subscale in the EEsAI-PRO questionnaire that aims to address the severity of dysphagia when consuming food of eight different consistencies. The types of food consistencies and corresponding examples to illustrate those consistencies are foods that are generally consumed in the US, Europe, and Canada. They included: 1) solid meat (such as steak, chicken, turkey, lamb), 2) soft foods (such as pudding, jelly, apple sauce), 3) dry rice or sticky Asian rice, 4) ground meat (hamburger, meatloaf), 5) fresh white untoasted bread or similar foods (such as doughnuts, muffins, cake), 6) grits, porridge (oatmeal), or rice pudding, 7) raw fibrous foods (such as apples, carrots, celery), and 8) French fries.[9]

Patients are evaluated on the occurrence of dysphagia upon "virtual" consumption of each of these reference foods without any modification such as blending, mashing, cutting in tiny pieces, or dunking into liquid, i.e., the degree of difficulty swallowing the different food types if consumed at that moment. Dysphagia is then rated in the following way:

- Severe difficulties (will not pass at all) (grade 3)
- Moderate difficulties (will need to be washed down with liquid) (grade 2)
- Mild difficulties (will pass with further swallows) (grade 1)
- No difficulties (grade 0)
- "Don't know" for vegetarian patients or patients allergic to wheats when answering questions concerning meat or wheat-based foods, respectively.

The VDQ score is obtained by dividing the summed grades for all foods by the maximum sum of grades that could be attained for each patient; the result of the division is then multiplied by 10. The maximum sum of grades that could be attained for each patient is the multiplication of the number of answered questions not answered with "don't know" by three. The VDQ score is invalid If all questions are unanswered or answered with "don't

know."[9] The VDQ score ranges from 0 to 10 (0 represents no difficulties while 10 represents severe difficulties).

Categorized scores of the VDQ score that were used for calculation of the EEsAI-PRO score were derived as shown in Table 36.

Table 36: Categorization of VDQ Scores

VDQ score intervals for categorization (rounded to 1 decimal)	Categorized VDQ score (contribution to EEsAI-PRO Score)
0	0
0.1 to 2.5	12
2.6 to 5.0	19
5.1 to 7.5	21
7.6 to 10.0	23

EEsAI-PRO = Eosinophilic Esophagitis Activity Index Patient Reported Outcome; VDQ = Visual Dysphagia Question.

Source: Clinical Study Report of the BUL-1/EEA trial.[9]

The VDQ was not validated separately; however, the aforementioned trial by Schoepfer et al. validated the full EEsAI-PRO instrument, which assessed dysphagia caused by eating foods of different consistencies, i.e., the VDQ score.[27] An MID was not reported for the VDQ score.

Avoidance, Modification, and Slow Eating Score

The AMS domain of EEsAI-PRO aims to address the change in eating behaviour due to the symptoms of dysphagia in order for patients to avoid potential food impaction. Patients are asked if the aforementioned eight categories of food resulted in behavioural adaptations, e.g., avoidance of the food altogether, whether the food is eaten, whether any modification is done, or whether the food is eaten more slowly than normal. Similar to the VDQ score, patients who are vegetarian or allergic to wheat answered "no" to questions concerning meat or wheat-based foods, respectively.[9]

Patients are assigned an AMS score of 0 if no behavioural changes are reported, 1 when eating more slowly than others is reported, 2 when modification of a food category is reported, 3 when both eating more slowly than others and modifying food are reported, and 5 if the patient completely avoids the food category due to EoE symptoms. The AMS score is obtained by dividing the summed grades for all avoided or consumed food consistencies by the maximum sum of grades that could be attained by a given patient; the result of the division is then multiplied by 10. The maximum sum of grades that could be attained for each patient is the multiplication of the number of assessed food categories (other than "Did you eat this food = no") multiplied by five. The AMS score ranges from 0 to 10, with 0 corresponding to no behavioural changes and 10 corresponding to completely avoiding all of the assessed food categories. If no question was answered, the eating behaviour score was invalid.[9]

Categorized scores of the AMS score that were used for calculation of the EEsAI-PRO score were derived as shown in Table 37.

Table 37: Categorization of AMS Scores

AMS score intervals for categorization (rounded to 1 decimal)	Categorized AMS score (contribution to EEsAI-PRO score)
0	0
0.1 to 2.5	0
2.6 to 5.0	0
5.1 to 7.5	9
7.6 to 10.0	25

AMS = avoidance, modification, and slow eating; EEsAI-PRO = Eosinophilic Esophagitis Activity Index Patient Reported Outcome.
Source: Clinical Study Report of the BUL-1/EEA trial.[9]

The AMS was not validated separately; however, the aforementioned trial by Schoepfer et al. (2014) validated the full EEsAI-PRO instrument, which took into account behavioural adaptation strategies in response to EoE symptoms, i.e., the AMS score.[27] An MID was not reported for the AMS score.

Physician's Global Assessment of EoE Activity

In this scale, physicians are asked to provide an overall assessment of the patients' EoE activity and severity taking into consideration the symptoms, endoscopy, histology, and laboratory markers. The EoE activity is rated on a 10-point scale, ranging from 0 (inactive EoE) to 10 (most active EoE).[9]

Evidence of validity and reliability as well as MID were not found from the literature.

Patient's Global Assessment Concerning the Severity of EoE Symptoms

The PatGA scale evaluates the severity of EoE symptoms from a patient's perspective. Patients were asked to rate the severity of their EoE symptoms in the past seven days on a scale that ranges from 0 to 10 (0 represents no symptoms and 10 represents the most severe symptoms).[9]

Evidence of validity and reliability as well as MID were not found for the PatGA from the literature. In the BUL-1/EEA trial, resolution of symptoms was defined as having a PatGA score of 2 points or less. Additionally, a decrease of at least 3 points in the PatGA score from baseline was used as an outcome.

Patient's Quality of Life: Modified Short Health Scale

The modSHS is a slightly modified form of the SHS. The SHS demonstrated discrimination validity, reliability (including internal consistency and test-retest reliability), and responsiveness in gastrointestinal conditions such as ulcerative colitis[28] and Crohn disease.[29] To be used in the BUL-1/EEA trial, the SHS was modified by replacing the terms with respect to the underlying disease in questions (1) to (3), i.e., "bowel" replaced by the term "esophageal."[9]

The modSHS is a simplified four-item questionnaire, representing each of four health dimensions: symptom burden, social function, disease-related worry, and general well-being. The patient answers four questions that assess the effects of esophageal disease on the patient's quality of life.[9]

Patients respond to each of the following questions representing the four health dimensions, which is scored on a scale of 0 to 100.

- the severity of the symptoms from esophageal disease (0 represents no symptoms, 100 represents very severe symptoms)
- interference with activities in daily life due to esophageal problems (0 represents not at all, 100 represents interference to a very high degree)
- worry caused by esophageal disease (0 represents no worry, 100 represents constant worry)
- a general feeling of well-being (0 represents very good, 100 represents dreadful).

While the SHS demonstrated discrimination validity, reliability (including internal consistency and test-retest reliability), and responsiveness in gastrointestinal conditions such as ulcerative colitis[28] and Crohn disease,[29] a psychometric analysis of the modified version of the SHS in EoE was not found from the literature. Additionally, an MID was not identified for any of these conditions.

Adult Eosinophilic Esophagitis Quality of Life Questionnaire

The EoE-QoL-A is a self-reported questionnaire that was originally developed as a five-dimension and 37-item symptom inventory for adult patients with EoE, and included symptoms of esophageal dysfunction, disease impact, and anxiety.[30] A refined version with 24 items and a six-question addendum was later developed for those on elimination diet therapies. It met the recommended FDA guideline for PRO development[31] and was used in the BUL-1/EEA trial. The refined 30-item questionnaire (24-item scale with a six-question addendum for those on elimination diet therapies) is categorized according the original five dimensions, listed here:

- impact of the disease on eating patterns and diet (10 items)
- social impact (four items)
- emotional impact (eight items)
- disease anxiety (five items)
- swallowing anxiety (three items).

Patients provide responses based on their life over the past week by checking the responses that best describe their experiences living with EoE. Each question had five answers ranging from 4, which corresponds to “does not describe their experiences at all,” to 0, which corresponds to “extremely describes their experiences.” An overall score and five subscale scores are generated based on the responses. Higher scores indicate better quality of life. Notably, there is a standard version (24 items) and a standard plus dietary restrictions version (30 items) of the EoE-QoL-A questionnaire; the latter is used for patients on elimination diet therapy. Since the dietary restrictions section is not applicable to all patients, a weighted average is calculated for the overall score and the five subscales by adding the value of the response for each item answered, then dividing by the total number of questions answered.[9]

Assessment of Validity and Reliability

The original 37-item version of the EoE-QoL-A version was evaluated for scale reliability, internal consistency, factor structure, and concurrent and convergent validity in 201 adult patients with EoE in the US.[30] Patients were assessed for their current EoE symptoms, illness perceptions, psychological distress, and HRQoL based on the Esophageal Symptoms Questionnaire; the Brief Illness Perception Questionnaire and the Perceived Health Competence Scale; the Brief Symptom Inventory-18; and the Medical Outcomes Study Short Form-12, version 2, and the Centers for Disease Control and Prevention (CDC) Healthy Days Measure, respectively — all previously validated scales for the respective measures. Results from analyses of principal components yielded the 37-item, five-factor structure, which explained 70% of the variance and showed excellent internal consistency (Cronbach's alpha = 0.96, Guttman Split-half = 0.88). Excellent test-retest reliability was shown for the individual items (range of r = 0.54 to 0.88) and for the total scale (r = 0.86). Concurrent validity was supported by a moderate negative relationship with the number of unhealthy days as reported by the CDC-HRQoL-4 (r = −0.41) and moderate positive relationship with HRQoL as measured by the Short Form 12 item (version 2) Health Survey (range of r = 0.43 to 0.52). Participants who were in remission scored statistically significantly higher on the EoE-QoL-A scale than those who were not, supporting evidence for discrimination validity. Finally, convergent validity for the Adult Eosinophilic Oesophagitis Quality of Life instrument was demonstrated by moderate negative relationships with psychological distress and esophageal symptoms as measured by the Esophageal Symptoms Questionnaire and Brief Symptom Inventory 18 (range of r = −0.37 to −0.57) and moderate positive relationships with illness perception measures as measured by the Brief Illness Perception Questionnaire and the Perceived Health Competence Scale (range of r = 0.44 to 0.73).[30]

The shorter and more refined 30-item version of the EoE-QoL-A scale was assessed for validity, usability, and acceptability by the same group of researchers, although the information were published in a conference proceeding.[31] Construct validity and acceptability were confirmed via qualitative cognitive interviews (to assess the clarity, understandability, length, rhetoric, and potential variability in interpretation for each question) of 10 patients and item refinement. Based on interview data, seven questions were deleted due to nearly unanimous agreement in lack of clarity, relevance, and/or repetitiveness with other questions within the survey. Eight questions were rephrased to minimize leading rhetoric and/or ambiguity in wording that resulted in extensive variability in interpretation. Finally, six questions were only reserved for patients on elimination diet therapies as the majority (80%) of patients not on such therapies found these questions to be irrelevant or not applicable. Even though other psychometric properties were not assessed, the authors reported that the final measure met the recommended guidelines for PRO development, allowing for assessment of the impact of EoE across multiple domains in both research and clinical settings.[31]

MID

An MID for the total score or the five domains was not reported by the authors or identified from the literature.

Dysphagia Score

The Dysphagia Score is a nine-point questionnaire with two components: one measuring the frequency of dysphagia events and the second capturing the intensity of dysphagia events. The total Dysphagia Score is calculated by adding the scores of the individual components, ranging from 0 to 9.[33]

The frequency of dysphagia events is scored as:

- 0 = none
- 1 = once per week
- 2 = several times per week
- 3 = once per day
- 4 = several times per day.

The intensity of dysphagia events is assessed the following way:

- 0 = swallowing unhindered
- 1 = slight sensation of resistance
- 2 = slight retching with delayed passage
- 3 = short period of obstruction necessitating intervention (e.g., drinking, breathing)
- 4 = longer-lasting period of obstruction, only removable by vomiting
- 5 = long-lasting complete obstruction, requiring endoscopic intervention.

Evidence for the validity and reliability of the Dysphagia Score was not identified from the literature. The authors cited a randomized, double-blind trial evaluating the efficacy and safety of a 15-day treatment with oral viscous budesonide versus placebo in adolescents and adults with EoE where the scale was used. However, the study did not aim to assess the psychometric properties of the scale.[25, 33]

An MID was not identified from the literature; however, the authors of the BUU-2/EEA trial defined a clinical response as a decrease in the total Dysphagia Score of at least 3 points compared to baseline.

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