NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Budesonide for treating active eosinophilic oesophagitis [ID1202]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Budesonide for treating active eosinophilic oesophagitis [ID1202]

Contents:

The following documents are made available to consultees and commentators:

The **final scope** **and** **final stakeholder list** are available on the NICE website.

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3. Patient group, professional group and NHS organisation submissions **from:**
   a. **British Society of Allergy and Clinical Immunology**
   b. **EOS Network**
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4. Expert personal perspectives **from:**
   a. **Ms Hannah Hunter, Specialist Allergy Dietitian – clinical expert, nominated by** British Society for Allergy and Clinical Immunology (BSACI)
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Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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Document B

Company evidence submission

September 2019

File name	Version	Contains confidential information	Date
ID1202 budesonide NICE STA Document B	1.0 1.01	Yes (AIC only) No	30 September 2019 26 April 2021

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Abbreviations

A&E	accident and emergency
ADR	adverse drug reaction
AE	adverse event
AMS	Avoidance, Modification and Slow-eating score
BID	twice daily
BMI	body mass index
BUL-1/EEA	budesonide pivotal phase III study
BUU-2/EEA	budesonide supportive phase II study
CE	Conformité Européene
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CrI	credible interval
CYP3A	cytochrome P4503A
DB	double blind
DIC	deviation information criterion
DSA	deterministic sensitivity analysis
EEsAI	Eosinophilic Esophagitis Activity Index
EEsAI-PRO	Eosinophilic Esophagitis Activity Index – Patient Reported Outcome
EMA	European Medicines Agency
EoE	eosinophilic oesophagitis
EoE-QoL-A	Eosinophilic Esophagitis Quality of Life Questionnaire – Adults
eos	eosinophil
EoT	end of treatment
EQ-5D	EuroQoL-5 dimensions
EU	European Union
FAS	full analysis set
FE	fixed effects
FU	follow-up
GI	gastrointestinal
GORD	gastro-oesophageal reflux disease
GP	general practitioner
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HCP	healthcare professional
hpf	high-power field
HRQoL	health-related quality of life
HRU	healthcare resource use
ICER	incremental cost-effectiveness ratio
IMC	independent data monitoring committee
ITC	indirect treatment comparison
ITT	intention-to-treat
LOCF	last observation carried forward
mcg	microgram
mg	milligram
ml	millilitre
mm	millimetre
N	number of patients evaluable
n	number of patients in the category
N/A	not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NRS	numerical rating scale
ODT	orodispersible tablet

OLI	open-label induction
OR	odds ratio
OVS	oral viscous suspension
PatGA	patient's global assessment
PGA	physician's global assessment
PP	per-protocol
PPI	proton-pump inhibitor
PSA	probabilistic sensitivity analysis
PSS	Prescribed Specialised Services
Q	quartile
QALY	quality-adjusted life year
QoL	quality of life
RCI	repeated 95% confidence interval
RCT	randomised controlled trial
RE	random effects
SAE	serious adverse events
SAF	safety
SD	standard deviation
SE	standard error
SFED	six-food elimination diet
SHS	Subjective Happiness Scale
SLR	systematic literature review
SmPC	summary of product characteristics
SOC	system organ class
TEAE	treatment-emergent adverse event
UK	United Kingdom
US	United States
VAS	visual analogue scale
VDQ	visual dysphagia question
WTP	willingness-to-pay

B.1. Decision problem, description of the technology and clinical care pathway

Eosinophilic oesophagitis

- Eosinophilic oesophagitis (EoE) is a chronic disorder characterised by eosinophil-predominant inflammation and oesophageal dysfunction[1]
- EoE is a rare disease with estimated prevalence and annual incidence rates in England and Wales of 12.8 and 2.07 per 100,000 population, respectively[2]
- Based on 2018 population estimates,[3] this equates to a prevalence of 5,956 adult patients, with an incidence of 963 cases per year

Burden of EoE

- In adults, symptoms include solid-food dysphagia (difficulty in swallowing), food-bolus impaction and swallowing/non-swallowing-associated chest pain[1]
- Untreated, EoE is associated with persistent symptoms and inflammation, eventually leading to oesophageal remodelling and fibrosis, with possible stricture formation and functional abnormalities[1]
- The symptoms of EoE can be unpleasant, socially embarrassing and restricting,[4, 5] and can have a significant detrimental impact on patients' quality of life (QoL)[4]
- EoE represents a substantial burden on healthcare services; whilst there are no European studies, data from the United States (US) indicate that the cost of EoE is roughly of the same order of magnitude as acute appendicitis ($1.4 billion), gastrointestinal (GI) haemorrhage ($1.1 billion), *Clostridium difficile* infection ($1.1 billion), and inflammatory bowel disease ($1 billion)[6, 7]

Clinical pathway of care

- Awareness of EoE in the UK is generally low and there is no routine clinical practice or UK-specific guidelines
- EoE is frequently misdiagnosed as gastro-oesophageal reflux disease (GORD)[8] and it is estimated that at least 50% of patients currently go undiagnosed[2]
- There is typically a 3–8 year delay between the onset of symptoms and diagnosis of EoE,[9] and patients are typically treated with proton-pump inhibitors (PPIs) prior to receiving a diagnosis[10]
- Following diagnosis, treatment options are limited to off-label topical corticosteroids, such as fluticasone and budesonide (in the form of asthma inhalers, nebulisers and slurries) and elimination diets

Unmet need

- Clinical experts consider EoE to be an area of unmet need,[11] and current treatment options are associated with significant limitations:
    - Off-label corticosteroid formulations are not optimised for oesophageal delivery,[12] leading to undesired lung deposition and variable active drug concentration in the oesophagus[12, 13]

- Patients may be incorrectly instructed on the use of inhalers and nebulisers for EoE and prescriptions may be withheld from non-asthmatic EoE patients, as the need for an asthma inhaler is not widely understood[10]
- Limitations also exist in dietary approaches, including difficulties with adherence, palatability, the requirement of multiple follow-up endoscopies, social limitations and a negative emotional impact[5, 14-16]

- Untreated or inadequately treated patients can suffer food-bolus obstructions and typically attend accident and emergency (A&E) multiple times, eventually requiring endoscopic dilation to resolve oesophageal strictures. This is not a cure and repeated treatment may be necessary

Budesonide orodispersible tablets

- Budesonide orodispersible tablets (ODT) are an immediate-release budesonide formulation specifically designed for the treatment of EoE[17]
- Use of budesonide ODT ensures effective delivery of budesonide to the oesophageal mucosa[18-20] and addresses the unmet need for an effective, convenient and licensed therapy for EoE.

B.1.1 Decision problem

The submission focuses on part of the technology's marketing authorisation – adult patients with EoE who have received prior treatment with a PPI. The proposed population is narrower than the marketing authorisation because:

- This is relevant to NHS clinical practice – according to clinical experts, in typical current UK practice, patients are already treated unsuccessfully with PPIs prior to receiving a diagnosis of EoE (see Section B.1.3.6)[10]
- The evidence base is limited to this population – in the BUL-1/EEA and BUU-2/EEA studies, all patients were refractory to treatment with a PPI used standard or higher dosages (see Section B.2.3)[21, 22]

A summary of the decision problem is presented in Table B.1.1.

Table B.1.1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with active EoE	Adults (>18 years) with EoE who have received prior treatment with a PPI	The population is limited to patients who have received prior treatment with a PPI as: • According to clinical experts, in typical current UK clinical practice, patients are already treated unsuccessfully with PPIs prior to receiving a diagnosis of EoE (see Section B.1.3.6)[10] • The evidence base for budesonide ODT is limited to patients who were refractory to treatment with a PPI used at standard or higher dosages (see Section B.2.3)[21, 22]
Intervention	Budesonide ODT	Budesonide (Jorveza®) 1 mg ODT tablets	N/A
Comparator(s)	Established clinical management without budesonide, which may include PPIs, other corticosteroid formulations and dietary intervention	• Fluticasone (off-label) • SFED	• PPIs are not included as a comparator in the cost-utility analysis, in order to align with the population defined above (all patients are expected to be treated unsuccessfully with PPIs prior to diagnosis of EoE,[10] so would not receive further treatment with PPIs) • Following the failure of PPIs and subsequent diagnosis with EoE, clinical experts indicate that patients in the UK are typically treated with fluticasone (off-label) or SFED, with budesonide slurries used only in exceptional cases. Therefore, the comparators in the cost-utility analysis are fluticasone and SFED
Outcomes	• Disease activity (remission, response, relapse) • Symptoms of oesophagitis	• Disease activity (remission, response) • Symptoms of oesophagitis	• Relapse rates are not included as a measure of disease activity as data

	• Complications such as stricture formation • Mortality • Adverse effects of treatment • HRQoL	• Complications such as stricture formation • Adverse effects of treatment • HRQoL	were not collected in the BUL-1/EEA or BUU-2/EEA studies • EoE is not a life-threatening disease and life expectancy does not appear to be affected by EoE.[23] Therefore, mortality is not addressed in this submission
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective	Cost-utility analysis with full incremental analysis	N/A

Abbreviations: EoE = eosinophilic oesophagitis; HRQoL = health-related quality of life; mg = milligram; N/A = not applicable; ODT = orodispersible tablet; PPI = proton-pump inhibitor; SFED = six-food elimination diet

B.1.2 Description of the technology being appraised

A summary of budesonide (Jorveza) 1 mg ODT is presented in Table B.1.2. The summary of product characteristics and European public assessment report are included in Appendix C.

Budesonide ODT is an immediate-release tablet specifically designed for the treatment of EoE.[17] It is an orphan medicinal product (EU/3/13/1181) and is the first licensed medical treatment for the treatment of EoE in adults (older than 18 years of age). When placed on the tongue, the orodispersible formulation begins to effervesce, stimulating the production of saliva. As the saliva is swallowed, the mucins it contains help coat the oesophagus, effectively delivering high concentrations of budesonide to the site of inflammation.[18-20]

Table B.1.2. Technology being appraised

UK approved name and brand name	Budesonide (Jorveza) 1 mg ODT
Mechanism of action	Budesonide is a non-halogenated glucocorticosteroid, which acts primarily as an anti-inflammatory via binding to the glucocorticoid receptor.[18] It is a potent corticosteroid with a high topical anti-inflammatory activity and low systemic effects[23] In the treatment of EoE, budesonide inhibits antigen-stimulated secretion of many pro-inflammatory signal molecules such as thymic stromal lymphopoietin, interleukin-13 and eotaxin-3 in the oesophageal epithelium, which results in a significant reduction of the oesophageal eosinophilic inflammatory infiltrate[18]
Marketing authorisation/CE mark status	Budesonide ODT received approval in the EU for the indication in this submission through the centralised procedure on 8 January 2018 (EU/1/17/1254/001-5)[24]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Budesonide ODT is indicated for the treatment of EoE in adults (older than 18 years of age)[18]
Method of administration and dosage	The recommended dose of budesonide ODT is 1 mg BID, taken orally[18] The usual duration of treatment is 6 weeks, which may be extended to 12 weeks for patients who do not respond completely.[18] Budesonide ODT 1 mg BID is currently not licensed for maintenance use
Additional tests or investigations	None
List price and average cost of a course of treatment	List price: £323 (pack of 90 tablets) Cost for 6 weeks treatment: £323 (including wastage) Cost for 12 weeks treatment: £646 (including wastage)
Patient access scheme (if applicable)	N/A

Abbreviations: BID = twice daily; CE = Conformité Européene; EoE = eosinophilic oesophagitis; EU = European Union; mg = milligram; N/A = not applicable; ODT = orodispersible tablet

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease overview

EoE is a chronic disorder first identified in 1989,[25] in which eosinophils infiltrate the oesophageal epithelium.[1] It is characterised clinically by symptoms related to oesophageal dysfunction, and histologically by eosinophil-predominant inflammation.[1] EoE is triggered by allergen exposure, typically food allergens. The foods most commonly implicated in EoE are milk, egg, wheat, soy, peanuts, beans, rye and beef.[26]

B.1.3.2 Epidemiology

EoE is a rare disease, with a recent meta-analysis reporting a prevalence rate of 16.1 per 100,000 population, based on five European studies.[27] While children and adults from all continents have been affected, cases are more frequently reported in white people compared with other races and ethnicities.[28, 29] Males are 3–4 times more commonly affected than females.[30]

The estimated prevalence and annual incidence rates in England and Wales are 12.8 and 2.07 per 100,000 population, respectively.[2] In the absence of UK-specific data, these estimates are derived from an extensive study in the Netherlands[2] and confirmed by a similar study in Denmark.[31] Although these estimates are not specific to England or Wales, they are considered to be more representative of Western European countries than the above European estimate,[2] which was based on studies from Northern, Central and Southern Europe.[27] Based on 2018 population estimates (46,531,406 adults [18–90 years]),[3] this equates to a prevalence estimate of 5,956 adult patients with EoE in England and Wales, with an incidence of 963 cases per year.

B.1.3.3 Symptomatology and clinical presentation

EoE has been reported throughout the life span, but most cases occur in children, adolescents and adults younger than 50 years[29] (the current licensed indication for budesonide ODT and the scope of this appraisal is for adults [≥18 years], with a study ongoing in children and adolescents[32]). The majority of patients have a personal history of allergic disorders such as bronchial asthma, allergic rhinitis, allergic conjunctivitis and food allergy.[26]

In adults, symptoms related to oesophageal dysfunction include solid-food dysphagia (difficulty in swallowing), food-bolus impaction and swallowing/non-swallowing-associated chest pain.[1] Although EoE is distinct from GORD, the two conditions may co-exist in some patients.[33]

Patients with EoE typically experience symptoms for a number of years prior to diagnosis.[1] As such, they can become used to the sensation of being aware of food travelling down the oesophagus and may adapt their eating in order to avoid these sensations (e.g., drinking large amounts of water or only eating foods that are known to travel smoothly down the oesophagus). In addition, they may be slow to eat and chew food for a prolonged period.[8]

B.1.3.4 Burden to patients, carers and society

As EoE is a relatively new disease,[25] uncertainties remain about its progression and long-term consequences.[29] Untreated, EoE is usually associated with persistent symptoms and

inflammation, eventually leading to oesophageal remodelling, resulting in fibrosis with possible stricture formation and functional abnormalities.[1] There is no evidence that EoE is a pre-malignant condition,[1] and mortality due to EoE has not been reported.

The symptoms of EoE can be unpleasant, socially embarrassing and restricting,[4, 5] and those associated with oesophageal dysfunction (solid-food dysphagia, reflux, food-bolus impaction and chest pain) can have a significant detrimental impact on patients' QoL. In a UK study, patients with EoE had reduced general energy/vitality levels and the condition had a negative impact on their mental health.[4] Perhaps the most striking EoE symptom is food-bolus impaction – choking sensations can cause a sense of panic[4] and emergency endoscopic removal of the food bolus may be required.

B.1.3.5 Economic burden

EoE represents a substantial burden on healthcare services. Whilst there is a paucity of European published data, a recent systematic literature review published in 2018 identified seven US studies, reporting costs associated with EoE in children and adults.[34] The most comprehensive of these seven studies (Jensen et al., 2015), identified 8,135 patients with EoE and 32,540 sex- and age-matched controls.[6] Overall medical resource utilisation costs associated with EoE were $2,302/patient/year with total costs ranging from $503 million to $1.36 billion (depending on the prevalence estimate). Based on a recent analysis of the burden of all GI illnesses in the US, the costs attributable to EoE are roughly of the same order of magnitude as hospital-related costs for acute appendicitis ($1.4 billion), GI haemorrhage ($1.1 billion), *Clostridium difficile* infection ($1.1 billion), and inflammatory bowel disease ($1 billion).[6, 7]

B.1.3.6 Clinical pathway of care

The natural history of EoE is not well-documented and few clinicians outside of tertiary centres have diagnosed a case of EoE or received training in diagnosis and management. Therefore, awareness is generally low and there is no routine clinical practice for EoE in the UK.

At present, there is no UK-specific clinical practice guideline for EoE, although British Society of Gastroenterology guidelines are in development. The only international guidelines for the diagnosis and management of EoE were published in 2017 by Lucendo et al.[1]

B.1.3.6.1 Diagnostic pathway

Diagnosis of EoE requires endoscopy and serial biopsies, and cannot be based on symptoms alone.[35] Oesophageal features of EoE include fixed (also referred to as concentric or corrugated) rings, exudates, furrows (vertical lines), oedema and 'crepe paper' oesophagus (mucosal fragility or tearing upon passage of the endoscope).[8, 36, 37] However, since endoscopic findings are frequently subtle and unspecific,[8] at least six biopsies are required from the proximal, mid and distal sections of the oesophagus, focusing on areas with endoscopic mucosal abnormalities, for accurate diagnosis.[1, 38] The accepted threshold for eosinophil density for the diagnosis of EoE is ≥15 eosinophils (eos) per high-power field (hpf; standard size of ~0.3 mm^2, equivalent to 50 eos/mm^2) in the oesophageal mucosa.[1]

It is estimated that at least 50% of patients with EoE currently go undiagnosed,[2] and there is typically a 3–8 year delay between the onset of symptoms and diagnosis.[9] In addition, as patients may have difficulty in describing their symptoms to general practitioners (GPs), EoE is frequently misdiagnosed as GORD.[8] Typically, patients present to their GP with

oesophageal symptoms and are initially prescribed a PPI. For patients with EoE rather than GORD, there will be little or no response to PPIs; therefore, symptoms continue and patients may be referred to a gastroenterologist for further investigations. Patients who experience food-bolus obstruction may revisit their GP and/or attend an A&E department, before being referred to either an ear, nose and throat specialist or gastroenterologist. Depending on symptoms and knowledge/awareness of EoE, gastroenterologists may conduct an endoscopy with or without biopsy and eosinophil count.

For patients with co-existing GORD and EoE,[33] there may be a partial response to PPI therapy and patients may learn to live with the symptoms and reduced QoL and not immediately progress towards a diagnosis of EoE. Eventually, after repeated food-bolus obstructions and the need for dilation of strictures, a diagnosis of EoE may be made.

B.1.3.6.2 Treatment pathway

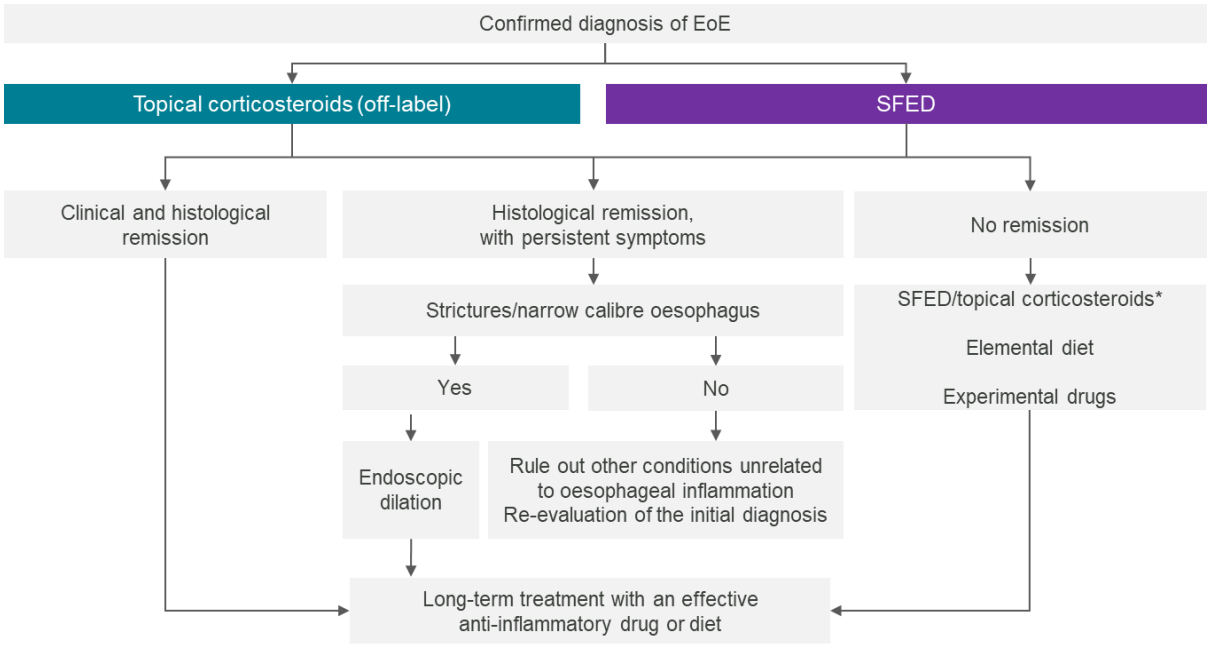
The treatment of EoE is based on its pathogenesis, with drugs and dietary modifications used to target the inflammation associated with EoE while endoscopic dilation is used to treat oesophageal remodelling and fibrotic complications.[1, 39] Although the most common aim of treatment is a reduced number of eosinophils in biopsies, changes in symptoms and endoscopic features are becoming important targets of therapy.[40]

Following a diagnosis of EoE, international guidelines recommend treatment with dietary elimination, off-label PPIs or off-label topical corticosteroids.[1] However, according to clinical experts, in typical current UK clinical practice, patients are already treated unsuccessfully with PPIs prior to receiving a diagnosis of EoE.[10] Treatment options are therefore limited to off-label topical corticosteroids, such as fluticasone and budesonide (in the form of asthma inhalers, nebulisers and slurries) and elimination diets. Off-label topical corticosteroids must be swallowed rather than inhaled, patients are required to administer asthma preparations into the mouth using metered-dose inhalers, or mix aqueous forms into slurries.[12, 13] Given the link between EoE and food allergens, dietary avoidance is also a logical treatment option,[14] and approaches include:

- Elemental diet – an amino acid-based allergen-free formula, followed by slow reintroduction of foods
- Testing-directed elimination diet, which eliminates food groups based on allergy testing
- Empiric elimination diet (six-food elimination diet [SFED]), which requires the avoidance of the six food types that are most commonly associated with allergy (typically milk, wheat, eggs, soy, nuts and seafood)[14-16]

Following the failure of PPIs and diagnosis with EoE, clinical experts indicate that patients in the UK are typically treated with either fluticasone (swallowed rather than inhaled) or SFED, with budesonide slurries being used in exceptional cases.[10] However, clinical practice is not uniform and there is no agreement or guideline on the optimal sequence of therapy, even among centres with an interest in EoE. The current therapeutic algorithm following a confirmed diagnosis in UK clinical practice is presented in Figure B.1.1.

Figure B.1.1. EoE treatment pathway



Abbreviations: EoE = eosinophilic oesophagitis; SFED = six-food elimination diet
*Choice dependent on previous therapy
Adapted from Lucendo et al., 2017[1]

B.1.3.7 Unmet need

The National Institute for Health and Care Excellence (NICE) scoping document states, 'clinical experts considered this to be an area of unmet need and would welcome guidance on the use of this drug' (budesonide ODT).[11] In practice, only a few specialist centres have knowledge or experience of EoE, and guidance is required at all levels, from primary care to tertiary centres.

Current treatment options for EoE are associated with significant limitations. The treatment effect of topical corticosteroids is localised, and response is dependent on the concentration at the site of inflammation. Therefore, in order to provide symptomatic and histological remission of EoE, drugs must target the oesophagus. However, aside from budesonide ODT, corticosteroid formulations are limited to asthma inhalers and nebulisers used off-label, which are not optimised for oesophageal delivery.[12] Patients using fluticasone must swallow, rather than inhale, the medication,[41] whilst those using budesonide must swallow the nebulised medicine or open the respules and use the contents to make a slurry with a carrier, such as sucrose. Undesired lung deposition can result from medication administered into the mouth using metered-dose inhalers, and while greater oesophageal deposition is possible with topical viscous steroids, active drug concentrations may be variable when patients mix aqueous forms into slurries.[12, 13] As such, off-label corticosteroids do not adequately target the inflamed areas and there are no data available to demonstrate that patients receive a consistent dose at each administration.

In addition to inadequate targeting and inconsistent dosing, evidence from clinical experts suggests that there is confusion in primary care surrounding the prescription of asthma medications for EoE. Experts report that prescriptions may be withheld from non-asthmatic patients with EoE because the need for an asthma inhaler is not understood. Disease control may also be poor because EoE patients receive incorrect instructions on the use of inhalers and nebulisers for EoE.[10]

Limitations also exist in dietary approaches to the management of EoE. As such, only 10% of patients attempt dietary therapy. Resources must be readily available, such as specialist GI dietitians, and patients need a high level of commitment to endure the diet and associated repeated endoscopies (≥6). Dietary restrictions can also lead to a significantly worse emotional impact compared to patients receiving pharmacological intervention,[5] and all three dietary approaches are associated with specific limitations:

- The elemental diet is the most effective but also the strictest diet. The need to forgo all food has significant social limitations and patients often have difficulties with adherence and palatability
- The testing-directed elimination diet is appealing to patients due to the need for avoidance of only one or two foods. However, it can be time-consuming, expensive, and is limited by false-positives rates. It is associated with overall poor efficacy and is the least favoured of the three dietary regimens
- SFED is generally the preferred diet but requires strict adherence and involves a cumbersome process of stepwise reintroduction of foods with multiple follow-up endoscopies.[14-16]

In addition to the clinical effects of inadequate treatment, limitations in current treatment approaches result in increased healthcare resource use (HRU). Untreated or inadequately treated patients can suffer food-bolus obstructions and typically attend A&E multiple times, eventually requiring endoscopic dilation to resolve oesophageal strictures. As dilation is not a cure for EoE, procedures must be repeated over time.

In conclusion, current approaches to the management of EoE are associated with significant limitations which limit their efficacy and result in increased HRU. Therefore, despite the availability of dietary and current pharmacological approaches to the management of EoE, a significant unmet need exists for a licensed treatment with improved efficacy and convenience.

B.1.3.8 Place of budesonide ODT in the treatment pathway

Budesonide ODT is the only licensed pharmacotherapy for EoE, and addresses the unmet need for an effective, convenient and approved treatment option. It is expected to become the preferred 1st-line treatment following a confirmed diagnosis of EoE, replacing off-label corticosteroids and SFED. It is expected that patients will be prescribed PPIs prior to a confirmed diagnosis of EoE and may continue PPI therapy concomitantly with budesonide ODT.

In the budesonide pivotal phase III study (BUL-1/EEA; see Section B.2), 57.6% of patients showed both clinical (i.e. no or minimal symptoms of dysphagia and odynophagia [painful swallowing]) and histological remission (referred to throughout this submission as clinico-histological remission)* at week 6. Non-responders received a further 6 weeks' treatment, resulting in an overall cumulative clinico-histological remission rate of 84.7%. If all theoretical 5,956 patients in England and Wales (see Section B.1.3.2) were treated, 3,431 might respond at 6 weeks, leaving 2,525 to go into a further 6 weeks of treatment. With 5% of patients treated (estimated first-year uptake; 298 patients) 172 patients would be expected to respond at 6 weeks, leaving 126 patients to receive a further 6 weeks' treatment. With 25% treated

* Note: clinico-histological and clinico-pathological are used interchangeably throughout the budesonide ODT study publications and the clinical study reports

(estimated fifth-year uptake; 1,489 patients) 858 patients would be expected to respond, leaving 631 patients to receive a further 6 weeks' treatment.*

For patients who do not respond to budesonide ODT, dietary approaches (predominantly SFED) would be expected to become the preferred 2nd-line therapy. Off-label corticosteroids are not expected to be used following budesonide ODT – the efficacy of corticosteroid therapy is determined by the amount of steroid coming into direct contact with the inflamed area of the oesophagus.[42-44] Therefore, as current treatment options are designed to deliver drug to the airways and are not optimised for oesophageal delivery, efficacy would not be expected to be improved compared with budesonide ODT, which is specifically designed to deliver therapeutic levels of budesonide to the oesophagus. As such, if budesonide ODT was not effective, it is unlikely that a clinician would then prescribe a delivery system appropriate for asthma but not for EoE, with an essentially similar active ingredient.

B.1.4 Equality considerations

There are no known equality issues relating to the use of budesonide for the treatment of adults with EoE.

* Uptake of budesonide ODT is expected to be low due to the lack of awareness of EoE in the UK and the significant amount of HCP education required

B.2. Clinical effectiveness

BUL-1/EEA study (pivotal phase III study):

Budesonide ODT 1 mg twice daily (BID) was highly effective with up to 12 weeks of treatment for EoE

- The primary efficacy outcome, rate of clinico-histological remission at week 6 (double-blind [DB] phase) was achieved in 57.6% (n=34) patients receiving budesonide ODT 1 mg BID and in no patients receiving placebo (p<0.0001)
    - The overall cumulative rate of clinico-histological remission at week 12 (open-label induction [OLI] phase – up to 12 weeks of treatment) in the budesonide-budesonide group was 84.7% (n=50), providing evidence that with a prolonged treatment, an additional 27.1% of patients were able to achieve clinico-histological remission
- All pre-specified subgroup analyses of the primary outcome (Appendix E) were in line with the primary outcome and showed the robustness of the observed superiority of budesonide ODT 1 mg BID over placebo
    - Treatment with budesonide ODT 1 mg BID was even successful in 43% (n=12) of difficult-to-treat patients who were refractory to previous dietary approaches to treat EoE (Appendix E)
- All but three patients in the budesonide group showed a dramatic decrease from baseline in peak eosinophil count, demonstrating that budesonide ODT 1 mg BID was able to induce remission, even in cases of severe inflammation
- Histological remission in the budesonide ODT 1 mg BID group was independently achieved in all oesophageal segments (proximal, mid, distant) and irrespective of the extent of the inflamed area
    - Even patients with a pan-oesophageal inflammation where all three segments of the oesophagus were affected, achieved histological remission rates of 95.3% (p<0.0001 for each comparison, indicating that the budesonide ODT formulation offers optimal oesophageal targeting
- Further exploratory clinical and endoscopic secondary outcomes, were all significantly in favour of budesonide ODT 1 mg BID, demonstrating a high consistency of the results across a wide variety of symptomatic and endoscopic outcomes
- Patient QoL improved much more with budesonide ODT 1 mg BID versus placebo, clear differences were observed with respect to changes in the patients' QoL measured by the Eosinophilic Esophagitis Quality of Life Questionnaire – Adults (EoE-QoL-A) questionnaire and Subjective Happiness Scale (SHS) during the DB phase of the study
    - With respect to the SHS results, the superiority of budesonide ODT 1 mg BID versus placebo was demonstrated in the areas of 'social function' and 'disease-related worry'

Budesonide ODT 1 mg BID was well tolerated with up to 12 weeks of treatment for EoE

- The nature and frequency of treatment-emergent adverse events (TEAEs) observed in the budesonide ODT 1 mg BID treatment group were consistent with the known safety profile of topical budesonide
- The majority of TEAEs were of mild or moderate severity
- The most frequently reported adverse drug reactions (ADRs) in the budesonide group during the DB treatment phase were suspected TEAEs of candidiasis, known ADRs caused by the anti-inflammatory and immunosuppressive action of budesonide
- No deaths and no serious adverse events (SAEs) occurred during the study in any of the treatment groups
- Safety results from the 6-week OLI phase did not reveal any new safety signals

BUU-2/EEA study (supportive phase IIa study):

Budesonide ODT 1 mg BID was highly effective with 2 weeks of treatment for EoE

- All patients (n=19) in the budesonide 1 mg BID group achieved histological remission at week 2 (primary efficacy outcome) while no histological remission was observed in the placebo group (p<0.0001)
- The co-primary efficacy outcome (change in the mean numbers of eos/mm^2 hpf from baseline to week 2) also showed statistically significant superiority for the budesonide ODT 1 mg BID group (–120) versus placebo (–8; p=0.0003)
- All prespecified subgroup analyses of the primary outcome (Appendix E) were in line with the primary outcome and showed the robustness of the observed superiority of budesonide ODT 1 mg BID over placebo
- The mean peak number of eos/mm^2 hpf decreased significantly from baseline to end of treatment (EoT) in the budesonide ODT 1 mg BID group (–227, p=0.0006), while no significant decrease was observed in the placebo group (–30)
    - The corresponding histological remission rates (defined as peak of <16 eos/mm^2 hpf) were 84.2% (n=16) and 0% for the budesonide ODT 1 mg group and placebo group, respectively
- The findings of the histological outcomes were supported by the data on the secondary endoscopic and clinical outcomes
- Improvement in patients' QoL were similar between the treatment groups

Budesonide ODT 1 mg BID was well tolerated with 2 weeks of treatment for EoE

- All TEAEs were non-serious and assessed as mild or moderate in severity[21]
- The most frequent suspected ADRs were suspected local fungal infections, confirmed by positive Grocott stain in two patients in the budesonide ODT 1 mg BID group (10.5%)
- No deaths and no SAEs occurred during the study in any of the treatment groups
- Tolerability and acceptance of the budesonide ODT formulation was high among patients

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify the evidence for efficacy and safety of treatments for EoE. Full details of the methodology and the results of the SLR are provided in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

This submission is supported by data from the pivotal phase III BUL-1/EEA study (Lucendo et al., 2019; EOS-1; NCT02434029; EudraCT 2014-001484-12)[17, 19, 22, 45] and a supportive phase IIa BUU-2/EEA study (Miehlke et al., 2016; NCT02280616; EudraCT 2009-016692-29)[20, 21].

BUL-1/EEA was a European, multicentre, randomised, DB, placebo-controlled study of budesonide ODT 1 mg BID in adult patients with clinico-histological active EoE.[22]. BUU-2/EEA was a European multicentre, randomised, DB, double-dummy, dose-finding study of budesonide ODT 1 mg and 2 mg BID versus budesonide oral viscous suspension (OVS) 0.5 ml BID versus placebo in adult patients with clinico-histological active EoE.[21] An overview of BUL-1/EEA and BUU-2/EEA is provided in Table B.2.1.

Table B.2.1. Clinical effectiveness evidence – BUL-1/EEA

Study	BUL-1/EEA (Lucendo et al., 2019; EOS-1; NCT02434029; EudraCT 2014-001484-12)[17, 22, 45]				
Study design	DB, randomised, placebo-controlled, phase III study				
Population	Adult patients with clinico-histological active EoE (N=88)				
Intervention(s)	Budesonide ODT 1 mg BID				
Comparator(s)	Placebo				
Indicate if trial supports application for marketing authorisation	Yes	✓	**Indicate if trial used in the economic model**	Yes	✓
	No			No	
Rationale for use/non-use in the model	Pivotal phase III trial supporting this indication				
Reported outcomes specified in the decision problem	• Disease activity (**remission**, response) • Symptoms of oesophagitis • Complications such as stricture formation • Mortality • Adverse effects of treatment • HRQoL				
All other reported outcomes	None				

Abbreviations: BID = twice daily; DB = double blind; EoE = eosinophilic oesophagitis; HRQoL = health-related quality of life; mg = milligram; ODT = orodispersible tablet

Table B.2.2. Clinical effectiveness evidence – BUU-2/EEA

Study	BUU-2/EEA (Miehlke et al., 2016; NCT02280616; EudraCT 2009-016692-29)[20, 21]				
Study design	DB, double-dummy, randomised, placebo-controlled, parallel multicentre phase II dose-finding study				
Population	Adult patients with clinico-histological active EoE (N=76)				
Intervention(s)	Budesonide ODT 1 mg BID Budesonide ODT 2 mg BID Budesonide OVS 5 ml (0.4 mg/ml) BID				
Comparator(s)	Placebo				
Indicate if trial supports application for marketing authorisation	Yes	✓	**Indicate if trial used in the economic model**	Yes	✓
	No			No	
Rationale for use/non-use in the model	Study included in the NMA used to populate the economic model				
Reported outcomes specified in the decision problem	• Disease activity (**remissio**n, response) • Symptoms of oesophagitis • Complications such as stricture formation • Mortality • Adverse effects of treatment • HRQoL				
All other reported outcomes	None				

Abbreviations: BID = twice daily; EoE = eosinophilic oesophagitis; HRQoL = health-related quality of life; mg = milligram; ml = millilitre; NMA = network meta-analysis; ODT = orodispersible tablet; OVS = oral viscous suspension

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

A comparative summary of the methodology for BUL-1/EEA and BUU-2/EEA is provided in Table B.2.3. Further methodological details are provided in Section B.2.3.1 and Section B.2.3.2, respectively.

Table B.2.3 Summary of the methodology for the BUL-1/EEA and BUU-2/EEA studies

	BUL-1/EEA	**BUU-2/EEA**
Location	19 centres in Europe: Germany (n=10), Spain (n=6), Switzerland (n=2), and The Netherlands (n=1)	21 centres in Europe: Germany (n=16), Switzerland (n=3), and Belgium (n=2)
Study design	6-week, multicentre, DB, randomised, placebo-controlled, phase III study (N=88)	2-week, multicentre, DB, double-dummy, randomised, placebo-controlled, phase IIa dose-finding study (N=76)
Eligibility criteria	• Male and female aged 18–75 years • Clinico-histological active EoE • Refractory to treatment with a PPI used at standard or higher dosages (e.g. omeprazole ≥20 mg/day, pantoprazole ≥40 mg/day, esomeprazole ≥40 mg/day, lansoprazole ≥30 mg/day or rabeprazole ≥20 mg/day) for a 4-week period	• Male and female aged 18–75 years • Clinico-histological active EoE according to the following diagnostic criteria: ○ Clinical symptoms of oesophageal dysfunction (dysphagia score ≥3) ○ Peak eos ≥65/mm^2 hpf in at least 1 hpf (corresponding to ≥20 eos/hpf)

	• Severity of ≥4 points on a 0–10 NRS for either dysphagia OR odynophagia for ≥1 day in the week before randomisation AND PatGA of EoE activity ≥4 points on a 0–10 NRS AND histologic activity with peak eos ≥65/mm^2 hpf in at least 1 hpf (corresponding to ≥20 eos/hpf), as measured in a total of 6 hpfs derived from 6 biopsies, 2 each from the proximal, mid, and distal segments of the oesophagus	○ Eosinophilic tissue infiltration with a mean cell density ≥16 eos/mm^2, as measured in a total of 30 hpf derived from six biopsy specimens, two each from the proximal, mid, and distal segment of the oesophagus
Setting	Outpatient	Outpatient
Study drugs	Budesonide ODT 1mg BID or placebo	Budesonide ODT 1 mg BID, budesonide ODT 2 mg BID, budesonide OVS 5 ml BID or placebo
Permitted and disallowed concomitant medications	The following were not permitted: • The use of other concomitant anti-inflammatory drugs systemic (i.e. systemic glucocorticoids, biologics, or immunosuppressants) or topical (i.e. glucocorticoids) • Drugs which could influence hepatic biotransformation (CYP3A inducers/inhibitors) • Concomitant treatment with ethinylestradiol in a dose of more than 30 µg/day, • Installation of dietary restrictions • Intake of grapefruit containing food or beverages Existing, concomitant treatments (e.g. PPIs) were not to be changed during the course of the study	The following were not permitted: • The use of other concomitant anti-inflammatory drugs systemic (i.e. systemic glucocorticoids, biologics, or immunosuppressants) or topical (i.e. glucocorticoids) • Drugs which could influence hepatic biotransformation (CYP3A inducers/inhibitors) • Installation of dietary restrictions • Intake of grapefruit containing food or beverages Existing, permitted concomitant treatments (e.g. PPIs) were not to be changed during the course of the study
Primary outcomes (including scoring methods and timing of assessments)	• Rate of clinico-histological remission at week 6, defined as fulfilling both of the following criteria: ○ Histologic remission at EoT (peak eosinophil count <16 eos/mm^2 hpf) ○ Clinical remission i.e. no or minimal problems, defined as symptom severity of ≤2 points on each 0–10 NRS, for dysphagia and odynophagia, respectively on each day in the week before EoT	• The rate of histological remission at week 2 (peak eosinophil count <16 eos/mm^2 hpf) ○ The co-primary efficacy outcome was change in the mean numbers of eos/mm^2 hpf (eosinophil load) from baseline to week 2
Other outcomes used in the economic model specified in the scope	• Rate of patients with histological remission, defined as a peak of <16 eos/mm^2 hpf at week 6	• Rate of histological remission defined as peak of <16 eos/mm^2 hpf at week 2
Pre-planned subgroups	The primary and key secondary efficacy outcomes were analysed	The primary and co-primary efficacy outcomes were analysed

	descriptively with respect to the following subgroups (pre-planned):
	• Stage 1 and overrun patients, respectively
	• Localisation of the inflammation at baseline (unique categories):
	  ○ Proximal, median, and distal oesophagus, respectively
	  ○ One, two, or three oesophageal segments affected
	A post-hoc analysis on history of any dietary approach to treat EoE (yes/no) was also performed for the primary outcome for the FAS-DB
		descriptively with respect to the following subgroups (pre-planned):
		• Localisation of the inflammation at baseline (unique categories) (proximal/mid/distal oesophagus)
		• Number of inflamed segments at baseline (one segment/two segments/three segments)
		• Concomitant use of PPIs (yes/no)
		• Concomitant allergic diseases (yes/no)
		• Duration of disease (time from first symptoms to baseline [years]) (< median [years] and ≥ median [years])
		• 30 hpfs each at baseline and at EOT available (yes/no)
		• At least one biopsy for all three segments at baseline and EOT available (yes/no)

Abbreviations: AMS = Avoidance, Modification and Slow-eating score; BID = twice daily; CYP3A = cytochrome P4503A; DB = double blind; EEsAI-PRO = Eosinophilic Esophagitis Activity Index – Patient Reported Outcome; EoE = eosinophilic oesophagitis; eos = eosinophils; EoT = end of treatment; hpf = high-power field; mm = millimetre; n = number of patients in the category; NRS = numerical rating scale; ODT = orodispersible tablet; OVS = oral viscous suspension; PatGA = patient's global assessment; PGA = physician's global assessment; PPI = proton-pump inhibitor; SHS = subjective happiness scale; VDQ = visual dysphagia question
Source: Miehlke et al., 2016[20]; Lucendo et al., 2019[19]; Dr Falk Pharma, data on file[21, 22]

B.2.3.1 Pivotal study BUL-1/EEA

B.2.3.1.1 Study design and objectives

BUL-1/EEA was a 6-week, multicentre, (DB, randomised, placebo-controlled, phase III study (N=88).[19]

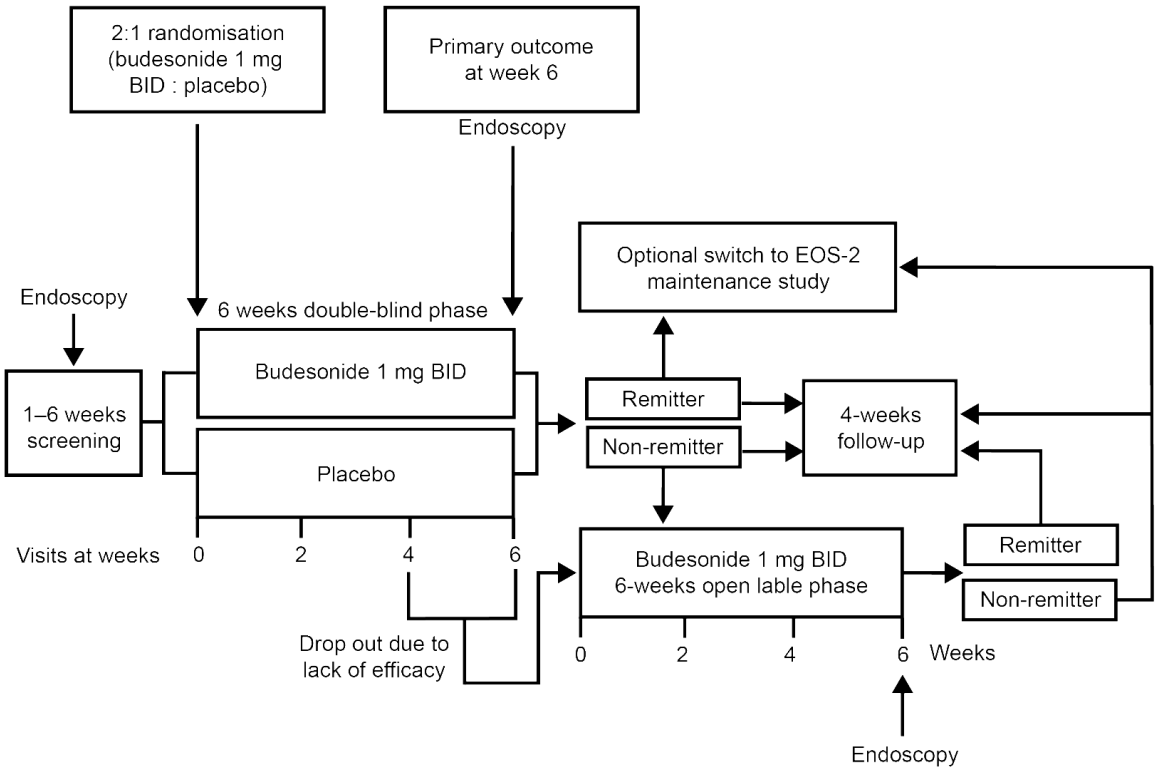
The primary objective was to assess the efficacy of budesonide ODT 1 mg BID versus placebo for the induction treatment of EoE. Secondary objectives included the assessment of safety and tolerability in the form of adverse events (AEs) and laboratory parameters, and patient's QoL. The exploratory objective was to study biomarkers in EoE.[22]

The study was conducted in the outpatient setting, across 19 European centres (Germany [n=10], Spain [n=6], Switzerland [n=2], and the Netherlands [n=1]).[22] Although there were no UK centres, the study was considered to be generalisable to UK clinical practice (see Section B.2.13.1.3.2). A study schematic is provided in Figure B.2.1. The study included the following phases:

- Screening phase: 1–6 weeks prior to baseline visit
- DB, randomised (2:1) treatment phase (6 weeks)
- OLI phase:
  - Patients not achieving clinico-histological remission at the end of the DB treatment phase, or who dropped out after at least 4 weeks of DB treatment due to lack of efficacy, were offered an additional 6 weeks of OLI treatment with budesonide ODT 1 mg BID[19]
- Follow-up phase:

- All patients in clinico-histological remission (either after DB- or OLI-treatment phase) of BUL-1/EEA, had the option to enter a DB, randomised, placebo-controlled maintenance of clinico-histological remission study (BUL-2/EER; EOS-2; EudraCT 2014-001485-99)* for treatment with budesonide ODT 1 mg BID or placebo for up to 48 weeks. Otherwise, patients were followed-up 4 weeks after their last visit of the DB- or OLI-treatment phase, respectively[22]

Figure B.2.1. Study schematic



Abbreviations: BID = twice daily; DB = double blind
Note: EOS-2 (BUL-2/EER) is a phase III maintenance study for patients achieving clinico-histological remission either at the end of the DB or OLI phase
Source: Lucendo et al., 2019 (supplementary appendix)[19]

B.2.3.1.2 Study visits

Post-randomisation visits took place every 2 weeks during the DB and the optional OLI phase, and at the 4-week follow-up visit if the patient did not switch to the maintenance of remission study. Clinical symptoms were assessed daily during the 7 days before baseline and throughout the study using 0–10 points on a numerical rating sale (NRS) with obvious face validity for dysphagia and odynophagia (painful swallowing), respectively.[19]

B.2.3.1.3 Eligibility criteria

Key inclusion and exclusion criteria are provided in Table B.2.4.

* This maintenance study is not reported in the submission as the current licensed indication for budesonide does not include maintenance treatment, as such this study is not relevant to this submission.

Table B.2.4. Key inclusion and exclusion criteria

Key inclusion criteria	Key exclusion criteria
• Male and female aged 18–75 years • Clinico-histological active EoE • Refractory to treatment with a PPI used at standard or higher dosages (e.g. omeprazole ≥20 mg/day, pantoprazole ≥40 mg/day, esomeprazole ≥40 mg/day, lansoprazole ≥30 mg/day or rabeprazole ≥20 mg/day) for a 4-week period • Severity of ≥4 points on a 0–10 NRS for either dysphagia or odynophagia for ≥1 day in the week before randomisation • PatGA of EoE activity ≥4 points on a 0–10 NRS • Histological activity with peak eos ≥65/mm^2 hpf in at least 1 hpf (corresponding to ≥20 eos/hpf), as measured in a total of 6 hpfs derived from 6 biopsies, 2 each from the proximal, mid, and distal segments of the oesophagus	• Clinical and endoscopic suspicion for gastroesophageal reflux disease (at least Los Angeles Classification of Esophagitis Grade A), achalasia or scleroderma • Evidence of causes other than EoE for oesophageal eosinophilia; pathological eosinophilic infiltration in gastric and duodenal biopsies • History of oesophageal surgery at any time OR of oesophageal dilation procedures within the last 8 weeks before screening • Any relevant systemic therapies; systemic glucocorticosteroids, immunosuppressants, biological drugs within 4 weeks before screening, OR topical glucocorticosteroids within 2 weeks before screening • Onset of dietary restrictions within 4 weeks before screening

Abbreviations: EoE = eosinophilic oesophagitis; eos = eosinophils; hpf = high-power field; NRS = numerical rating scale; PatGA = patient's global assessment; PPI = proton-pump inhibitor
Source: Lucendo et al., 2019[19]

B.2.3.1.4 Study treatments

B.2.3.1.4.1 Treatments administered

At baseline, eligible patients were centrally randomised in a 2:1 ratio (budesonide ODT 1 mg BID to matching placebo 1 mg BID).[19]

Budesonide ODT and corresponding placebo were identical in physical appearance and were administered BID (one ODT in the morning and one in the evening both after food). The ODT was placed on the tip of the tongue and pressed gently against the hard palate until it had completely disintegrated by contact with saliva, the production of which was stimulated by the slight effervescence of the study medication. The components dissolved in saliva were then to be swallowed (approximately 5–10 swallows within a few minutes). Patients were instructed to avoid eating, drinking, or oral hygiene procedures for 30 minutes after study drug administration. Compliance was assessed by pill count.[19]

Patients, investigators and their study team, the sponsor, monitoring staff, central laboratory, and central pathologist were all kept blinded to the randomisation sequence, the block size, and patient's treatment, until all patients had completed the study and the database was clean and locked. No individual unblinding was needed or performed.[19]

B.2.3.1.4.2 Concomitant therapies

The following were not permitted:

- The use of other concomitant anti-inflammatory drugs systemic (i.e. systemic glucocorticoids, biologicals, or immunosuppressants) or topical (i.e. glucocorticoids)

- Drugs which could influence hepatic biotransformation (cytochrome P4503A [CYP3A] inducers/inhibitors)
- Concomitant treatment with ethinylestradiol in a dose of more than 30 µg/day,
- Installation of dietary restrictions
- Intake of grapefruit-containing food or beverages

Existing, concomitant treatments (e.g. PPIs) were not to be changed during the course of this study.[22]

B.2.3.1.5 Assessments and outcomes

B.2.3.1.5.1 Efficacy outcomes

Primary outcome:

- Rate of clinico-histological remission at week 6, defined as fulfilling both of the following criteria:
  - Histological remission at EoT (peak eosinophil count <16 eos/mm^2 hpf)*
  - Clinical remission† i.e. no or minimal problems, defined as symptom severity of ≤2 points on each 0–10 NRS, for dysphagia and odynophagia, respectively on each day in the week before EoT[19]

The occurrence of food impaction, need for endoscopic intervention or dilation, or premature withdrawal was assessed as treatment failure.[19]

The European Medicines Agency (EMA) agreed that the proposed cut-off of <16 eos/mm^2 hpf (corresponding to <5 eos/hpf) for defining histological remission was acceptable, as this criterion was used in most of the previous studies in the field.

To assess clinical response, the EMA proposed to cover the main parts of the EoE symptoms (dysphagia and odynophagia) with 'simple' questionnaires, e.g., 11-point NRS, or 5–7-point Likert scales, asking for the severity of these symptoms, in comparison to the time before the start of the study, because such scales are well-known and have, as agreed with the EMA, an obvious face validity. A patient in remission was then to be defined on the most obvious state of freedom from (relevant) symptoms from these domains (i.e. having only minimal or no problems). The EMA recommended to record these simple symptom questionnaires on a daily basis to avoid recall bias. The chosen composite primary outcome consisting of histological findings and a simplified patient symptom questionnaire with obvious face validity was therefore in line with this recommendation.

The expected difference of approximately 40% in the clinico-histological remission rates between budesonide ODT and placebo was also agreed by the EMA to represent a clinically meaningful difference between treatments, assuming that the safety profile of budesonide 1 mg is not relevantly different from previously licensed formulations to be administered within the GI tract.

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* Histological remission (not clinical remission) is used to determine clinical efficacy in the NMA and cost-utility analysis.

† Note remission and resolution of symptoms are used interchangeably throughout the budesonide study publications and the clinical study reports.

Key secondary outcomes (*A priori* ordered [confirmatory] DB phase):

- Rate of patients with histological remission, defined as a peak of <16 eos/mm^2 hpf at week 6
- Change in the peak eos/mm^2 hpf from baseline to week 6
- Rate of patients with clinical remission defined as a severity of ≤2 points on 0–10 NRS for dysphagia AND a severity of ≤2 points on 0–10 NRS for pain during swallowing on each day in the week prior to week 6
- Rate of patients in clinical remission total weekly Eosinophilic Esophagitis Activity Index – Patient Reported Outcome (EEsAI-PRO) score of ≤20 at week 6[19]
- Rate of patients with an improvement from baseline to week 6 in the weekly Visual Dysphagia Question (VDQ) score
- Rate of patients with an improvement from baseline to week 6 in the weekly 'Avoidance, Modification, and Slow-eating' (AMS) score[22]

Further clinical exploratory secondary efficacy outcomes DB phase:

- Mean change from baseline to week 6 in patient's global assessment (PatGA) – severity of EoE symptoms (NRS 0–10)
- Number (%) of patients with overall symptoms resolution (PatGA ≤2) at week 6
- Mean change from baseline to week 6 in PatGA of EoE activity (NRS 0–10)
- Median time (days) to first symptom resolution (dysphagia and pain during swallowing)
- Mean change from baseline to week 6 in blood eos/cm^3 [22]

Further endoscopy exploratory secondary efficacy outcomes DB phase:

- Number (%) of patients with 'no endoscopic findings' at week 6
- Mean change from baseline to week 6 in total modified EEsAI endoscopic score (0–9)
- Mean change from baseline to week 6 in 'inflammatory signs' sub-score of modified EEsAI endoscopic score (0–4)
- Mean change from baseline to week 6 in 'fibrotic signs' sub-score (consisting of 'fixed rings' and 'stricture') of modified EEsAI endoscopic score (0–4)[22]

Further health-related quality of life (HRQoL) exploratory secondary efficacy outcomes DB phase:

- Mean changes from baseline at week 6 in the modified SHS score
- Mean changes from baseline at week 6 in the disease-specific EoE-QoL-A questionnaire and its sub-scores[22]

B.2.3.1.5.2 Safety outcomes

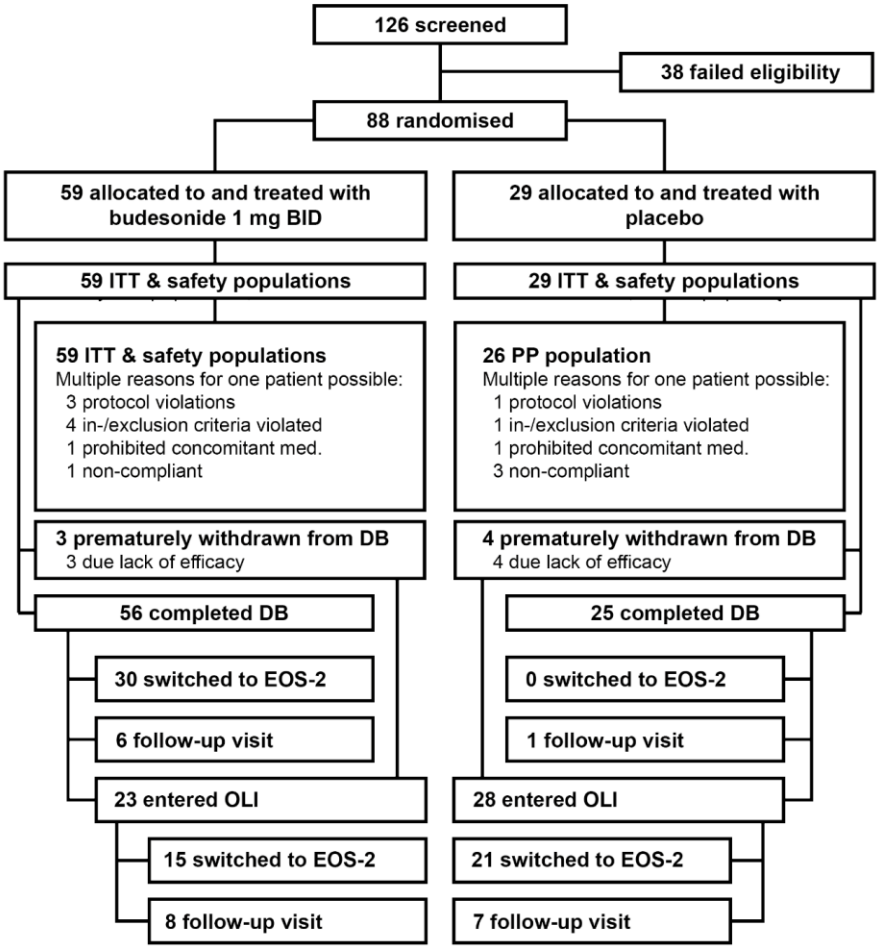
Safety was assessed on the basis of AEs, vital signs and body weight, physical examination, laboratory parameters including morning serum cortisol, and assessment of tolerability by the investigator and the patient.[19]

B.2.3.1.6 Study population

B.2.3.1.6.1 Patient disposition

In total, 126 patients were screened, 88 met the inclusion criteria and were randomised and treated. In total, 81* patients completed the DB phase (92.0%), but all 88 patients were evaluable for the primary analysis (Figure B.2.2).[19]

Figure B.2.2: Patient disposition



Abbreviations: BID = twice daily; DB = double-blind; ITT = intention-to-treat; OLI = open-label induction; PP = per-protocol
Note: EOS-2 (BUL-2/EER) is a phase III maintenance study for patients achieving clinico-histological remission either at the end of the DB or OLI phase
Source: Lucendo et al., 2019 (supplementary appendix)[19]

B.2.3.1.6.2 Demographics and baseline characteristics

A summary of demographics and baseline characteristics is presented in Table B.2.5. Both treatment groups had similar baseline characteristics, being typical for an adult patient population with EoE.[19]

* In the results section of Lucendo et al., 2019 the authors report 82 patients, this is a typographical error 81 patients completed the DB phase.

Table B.2.5. Demographics and baseline characteristics – BUL-1/EEA

	Budesonide ODT 1 mg BID (N=59)	Placebo (N=29)	Total (N=88)
Sex, n (%)			
Male	48 (81.4)	25 (86.2)	73 (83.0)
Female	11 (18.6)	4 (13.8)	15 (17.0)
Race, n (%)			
White	59 (100.0)	29 (100.0)	88 (100)
Mean (SD) age, years	37.0 (11.47)	36.9 (9.20)	37.0 (10.72)
Mean (SD) BMI, kg/m^2	24.4 (2.86)	25.6 (4.08)	24.8 (3.34)
Smoking status, n (%)			
Current	3 (5.1)	0 (0)	3 (3.4)
Former	5 (8.5)	3 (10.3)	8 (9.1)
Never	51 (86.4)	26 (89.7)	77 (87.5)
Concomitant allergic disease, n (%)	47 (80)	23 (79)	70 (79.5)
Concomitant PPI use, n (%)	7 (11.9)	3 (10.3)	10 (11.4)
Mean (SD) duration since first symptoms, months	134.2 (104.6)	139.0 (98.8)	135.8 (102.2)
Mean (SD) duration since diagnosis, months	48.8 (44.3)	57.6 (49.3)	51.7 (45.9)
Diagnosis of EoE, n (%)			
Established	58 (98.3)	27 (93.1)	85 (96.6)
New	1 (1.7)	2 (6.9)	3 (3.4)
Number of inflamed segments, n (%)			
1	6 (10.2)	2 (6.9)	8 (9.1)
2	10 (16.9)	4 (13.8)	14 (15.9)
3	43 (72.9)	23 (79.3)	66 (75.0)
Localisation of inflammation, n (%)			
Proximal	47 (79.7)	25 (86.2)	72 (81.8)
Mid	52 (88.1)	26 (86.7)	78 (88.6)
Distal	56 (94.9)	28 (96.6)	84 (95.5)
Peak eos/mm^2 hpf			
Mean (SD)	242 (140.7)	239 (125.0)	-
Median (range)	205 (56–611)	197 (99–620)	-
Mean (SD) blood eos/mm^3	427 (255.4)	455 (255.5)	-

Abbreviations: BID = twice daily; BMI = body mass index; EoE = eosinophilic oesophagitis; eos = eosinophils; hpf = high-power field; mg = milligram; mm = millimetre; n = number of patients in the category; N = number of patients evaluable; ODT = orodispersible tablet; PPI = proton-pump inhibitor; SD = standard deviation
Source: Dr Falk Pharma, data on file[22]

B.2.3.2 Supportive study BUU-2/EEA

B.2.3.2.1 Study design and objectives

BUU-2/EEA was a 2-week, multicentre, DB, double-dummy, randomised, placebo-controlled, phase IIa dose-finding study (N=76).[20]

The primary objective was to assess the efficacy of two different budesonide formulations; budesonide ODT (1 mg BID and 2 mg BID) and OVS versus placebo for the induction treatment of EoE.[20] Secondary objectives included identification of the optimum dose for induction of remission in EoE, the assessment of safety and tolerability in the form of AEs and laboratory parameters and patient's QoL.[22]

The study was conducted in the outpatient setting, across 21 European centres (Germany [n=16], Switzerland [n=3], and Belgium [n=2]).[20] As with BUL-1/EEA, the study was considered

to be generalisable to UK clinical practice despite the lack of UK centres (see Section B.2.13.1.3.2). The screening phase (up to 5 weeks), was followed by a 2-week treatment phase and a 2-week follow-up phase.[21]

B.2.3.2.2 Study visits

The following study visits were conducted:

- Screening visit 1, which took place within 4 weeks prior to screening visit 2 at which the first screening examinations were performed
- Screening visit 2 (up to 1 week prior to baseline), further in-/exclusion criteria were checked, an upper endoscopy was performed and biopsies were taken
- At baseline (visit 1), only patients suffering from clinically and histologically active EoE could be enrolled and received randomised treatment in this study
- The EoT visit (visit 2) took place at day 15 ± 4. If a patient was prematurely withdrawn from the study, the corresponding examinations of the EoT visit had to be performed
- A follow-up visit (visit 3) took place 14 days ± 4 after the EoT/withdrawal visit[21]

B.2.3.2.3 Eligibility criteria

Key inclusion/exclusion criteria are provided in Table B.2.6.

Table B.2.6. Key inclusion/exclusion criteria

Key inclusion criteria	Key exclusion criteria

• Male and female aged 18–75 years
• Clinico-histological active EoE according to the following diagnostic criteria:
  ○ Clinical symptoms of oesophageal dysfunction (dysphagia score ≥3)
  ○ Peak eos ≥65/mm^2 hpf in at least 1 hpf (corresponding to ≥20 eos/hpf)
  ○ Eosinophilic tissue infiltration with a mean cell density ≥16 eos/mm^2, as measured in a total of 30 hpf derived from six biopsy specimens, two each from the proximal, mid, and distal segment of the oesophagus
	• Clinical and endoscopic suspicion for GORD, achalasia or scleroderma
	• History of abnormal pH monitoring of the distal oesophagus or clinico-histological response to a treatment with PPIs at a standard dose with a treatment duration of at least 2 weeks
	• Other clinical evidence of causes other than EoE for oesophageal eosinophilia
	• Any concomitant oesophageal disease and relevant GI disease
	• History of oesophageal surgery at any time OR of oesophageal dilation procedures within the last 8 weeks prior to screening
	• Any relevant systemic disease if careful medical monitoring was not ensured
	• Abnormal hepatic function, liver cirrhosis, OR portal hypertension
	• Abnormal renal function
	• History of cancer in the last 5 years
	• Upper GI bleeding within 8 weeks prior to screening
	• Any relevant systemic therapies; systemic glucocorticosteroids, immunosuppressants, within 4 weeks before screening, or topical glucocorticosteroids within 2 weeks before screening
	• Onset of dietary restrictions within 4 weeks before screening

Abbreviations: EoE = eosinophilic oesophagitis; eos = eosinophils; GI = gastrointestinal; GORD = gastro-oesophageal reflux disease; hpf = high-power field; PPI = proton-pump inhibitor
Source: Miehlke et al., 2016[20]

B.2.3.2.4 Study treatments

B.2.3.2.4.1 Treatments administered

Patients were assigned to a DB, double-dummy treatment in one of the four following treatment groups at a rate of 1:1:1:1; budesonide ODT 1 mg BID, budesonide ODT 2 mg BID, OVS 5 ml BID or placebo. In order to maintain the study blinding when using different pharmaceutical preparations, a double-dummy design was used. Therefore, both formulations, that is, ODTs (containing budesonide or placebo) as well as OVS (containing budesonide or placebo) were taken by all patients in divided doses BID. Depending on the treatment group, either the ODT or the OVS contained budesonide or placebo, respectively.[20]

Patients were instructed to take budesonide ODT as per BUL-1/EEA (section B.2.3.1.4.1). At least 15 minutes after ingestion of each ODT, 5 ml of the viscous suspension were swallowed. Compliance was assessed by counting (blister and tablets) or weighing (bottles) of the study medication returned at the EoT/withdrawal visit.[20]

B.2.3.2.5 Concomitant therapies

The following were not permitted:

- The use of other concomitant anti-inflammatory drugs systemic (i.e. systemic glucocorticoids, biologicals, or immunosuppressants) or topical (i.e. glucocorticoids)
- Drugs which could influence hepatic biotransformation (CYP3A inducers/inhibitors)
- Installation of dietary restrictions
- Intake of grapefruit-containing food or beverages[22]

Existing, permitted concomitant treatments (e.g. PPIs) were not to be changed during the course of the study.[22]

B.2.3.2.6 Assessments and outcomes

B.2.3.2.6.1 Efficacy outcomes

Primary outcome:

- The rate of histological remission at week 2 (mean of <16 eos/mm^2 hpf)
    - The co-primary efficacy outcome was change in the mean numbers of eos/mm^2 hpf (eosinophil load) from baseline to week 2[20]

Key secondary outcomes:

- Rate of histological remission defined as (mean of <16 eos/mm^2 hpf at week 2)
- Change in the peak eos/mm^2 hpf from baseline to week 2
- Change in the total endoscopic intensity score and its sub-scores
- Change in blood eosinophil counts from screening visit 2 to week 2
- Course and change of the dysphagia score within the study
- Physician's global assessment
- Change of modified SHS in the course of the study[21]

B.2.3.2.6.2 Safety outcomes

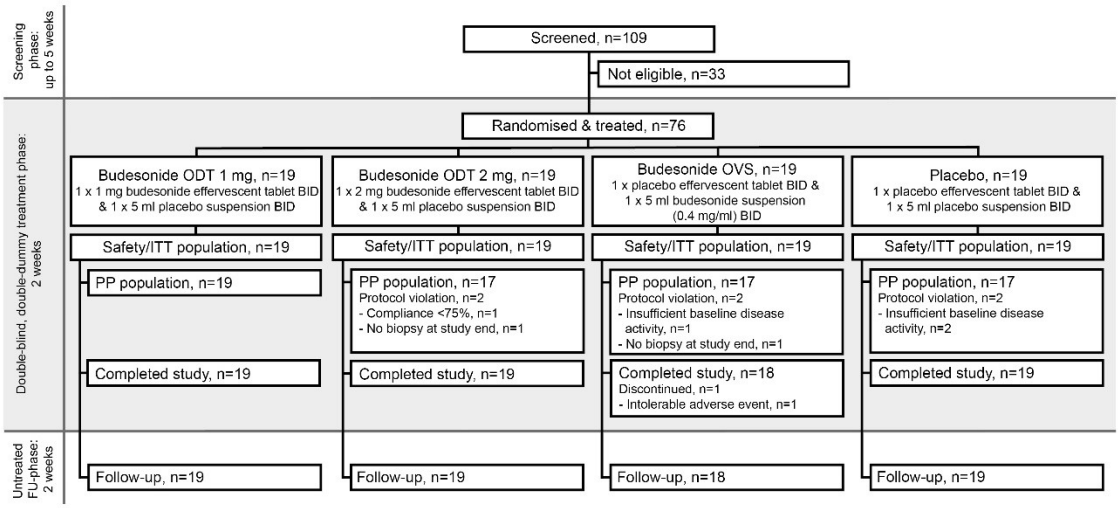
Safety was assessed on the basis of AEs, vital signs and body weight, laboratory parameters including morning serum cortisol, and assessment of tolerability by the investigator and the patient.[20, 22]

B.2.3.2.7 Study population

B.2.3.2.7.1 Patient disposition

In total, 109 patients were screened, 77 met the inclusion criteria and were randomised and treated. One randomised patient did not take at least one dose of study medication and was excluded from all analysis sets. Based on the results of the interim analysis of 61 observed patients (16 patients in the budesonide ODT 2 mg BID group and 15 patients each of the other three treatment groups) which revealed significant differences in the primary and co-primary outcome for all three budesonide groups versus placebo, the independent data monitoring committee (IMC) recommended termination of the study. Since recruitment continued during the interim analysis, 16 patients were still in the study resulting in a total of 76 evaluable patients for the final analysis set (19 patients per treatment group) (Figure B.2.3).[20]

Figure B.2.3: Patient disposition



Abbreviations: BID = twice daily; FU = follow-up; ITT = intention-to-treat; ODT = orodispersible tablet; OVS = oral viscous suspension; PP = per-protocol
Source: Miehlke et al., 2016 (supplementary figure)[20]

B.2.3.2.7.2 Demographics and baseline characteristics

A summary of demographics and baseline characteristics is presented in Table B.2.7. From this point onwards in the submission only results for the budesonide ODT 1 mg BID group are reported, as this is the licensed dose for budesonide ODT.

Table B.2.7. Demographics and baseline characteristics – BUU-2/EEA

	Budesonide ODT 1 mg BID (N=19)	Placebo (N=19)	Total (N=76)
Sex, n (%)			
Male	17 (89.5)	16 (84.2)	63 (82.9)
Female	2 (10.5)	3 (15.8)	13 (17.1)
Race, n (%)			
White	19 (100.0)	19 (100.0)	75 (98.7)
Mean (SD) age, years	38.9 (12.6)	36.3 (9.9)	39.7 (13.1)
Mean (SD) BMI, kg/m^2	25.5 (4.41)	23.7 (3.16)	24.8 (3.34)
Smoking status, n (%)			
Current	3 (15.8)	0 (0.0)	6 (7.9)
Former	3 (15.8)	1 (5.3)	9 (11.8)
Never	13 (68.4)	18 (94.7)	61 (80.3)
Concomitant allergic disease, n (%)	14 (73.7)	10 (52.6)	49 (64.5)
Concomitant PPI use, n (%)	3 (15.8)	3 (15.8)	10 (13.2)
Mean (SD) duration since first symptoms, years	8.3 (7.8)	7.9 (7.5)	8.5 (7.9)
Mean (SD) duration since diagnosis, years	1.9 (3.4)	2.6 (5.1)	2.2 (3.6)
Diagnosis of EoE, n (%)			
Established	12 (63.2)	11 (57.9)	49 (64.5)
New	7 (36.8)	8 (42.1)	27 (35.5)
Number of inflamed segments, n (%)			
1	1 (5.3)	4 (21.1)	10 (13.2)
2	3 (15.8)	6 (31.6)	21 (27.6)
3	14 (73.7)	9 (47.4)	42 (55.3)
Localisation of inflammation, n (%)			
Proximal	14 (73.7)	13 (68.4)	54 (71.1)
Mid	18 (94.7)	14 (73.7)	62 (81.6)
Distal	18 (94.7)	16 (84.2)	66 (86.8)
Peak eos/mm^2 hpf			
Mean (SD)	242 (144.2)	320 (309.0)	263 (216.3)
Median (range)	206 (78–635)	183 (58–977)	196 (58–977)
Mean (SD) blood eos/mm^3	470 (453.3)	372 (224.7)	390 (310.5)

Abbreviations: BID = twice daily; BMI = body mass index; EoE = eosinophilic oesophagitis; eos = eosinophils; hpf = high-power field; mm = millimetre; n = number of patients in the category; N = number of patients evaluable; ODT = orodispersible tablet; PPI = proton-pump inhibitor; SD = standard deviation
Source: Dr Falk Pharma, data on file[21]

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1.1 BUL-1/EEA

B.2.4.1.2 Hypothesis objective

The hypothesis objective was H0: πPla ≥ πEff against H1: πPla < πEff, where πPla and πEff denote the rate of clinico-histological remission in the placebo and budesonide 1 mg group, respectively.[22]

B.2.4.1.3 Sample size, and power calculation

The remission rate assumptions of 10% for placebo and 50% for the budesonide 1 mg group showed that a total of 81 full analysis set (FAS) patients using 2:1 randomisation, were needed

to detect the difference of 40% using Fisher's exact test (1-sided α=.025) with a statistical power of at least 90%. This sample size was increased to account for 10% of randomised patients who did not take at least one dose of study drug.[19]

B.2.4.1.4 Statistical analysis

The primary efficacy outcome was compared between treatment groups using Fisher's exact test (1-sided α=.025). Efficacy significance testing continued in a hierarchical fashion for the *a priori* ordered key secondary efficacy outcomes. Once a 1-sided non-significant p value (>.025) occurred, subsequent significant tests were considered exploratory. Dichotomous key secondary efficacy outcomes were analysed using Fischer's exact test. Change in the peak eos/mm^2 hpf was analysed by fitting a linear least squares model with treatment effect and baseline value as covariate. Exploratory comparisons of further outcomes between treatment groups or between baseline and EoT were performed using 2-side *t* tests or Wilcoxon rank sum tests, as appropriate, in case of continuous data. Two-sided Fischer's exact test was applied to dichotomous data. Descriptive statistics were used to summarise data, including incidence of AEs.

B.2.4.1.5 Data management

The interim analysis was performed based on 54 FAS patients as planned. Recruitment of the study was stopped after the results of the interim analysis were available due to proven superiority of budesonide ODT versus placebo. All patients who were randomised before this decision and were still receiving treatment were to complete the study. Missing data at week 6 were replaced using the last observation carried forward (LOCF) method.[22]

B.2.4.1.6 Study population

The study population for final analyses is outlined in Table B.2.8.

Table B.2.8. Study population for the final analyses

	Budesonide ODT 1 mg BID	Placebo	Total
FAS-DB, n	59	29	88
PP, n	51	26	77
SAF-DB, n	59	29	88
FAS-OLI, n	23	28	51
SAF-OLI, n	23	28	51
FAS-FU, n	14	8	22

Abbreviations: BID = twice daily; FAS = full analysis set; FU = follow-up; ODT = orodispersible tablet; OLI = open-label induction; PP = per protocol; SAF = safety
Source: Dr Falk Pharma, data on file[22]

B.2.4.2 BUU-2/EEA

B.2.4.2.1 Hypothesis objective

The hypothesis objective was superiority of budesonide ODT and OVS compared with placebo in terms of histological remission[21]

B.2.4.2.2 Sample size and power calculation

The initial sample size calculation was based on the histological remission rates of Straumann et al,[46] the initial sample size calculation with a Bonferroni adjusted α=0.025/3 yielded that 15.3 evaluable patients per treatment group were needed to achieve 80% power. A sample size of 15 + 10 evaluable patients per group was justified by ensuring a power of more than 80%.[20]

B.2.4.2.3 Statistical analyses

The primary efficacy outcome was subjected to a (α=0.025, one-sided testing) in the context of the adaptive two-stage group sequential design with a one-sided significance level of 2.5% for each step. The normal approximation test for the comparison of the rates was used for the primary efficacy outcome. The co-primary outcomes were only subjected to a confirmatory analysis (using the Mann-Whitney test) if the primary efficacy outcome showed statistically significant results for all three budesonide groups versus placebo. The primary and co-primary efficacy outcomes were evaluated by ITT and PP analyses. Evaluations of secondary efficacy outcomes and safety variables were performed in an exploratory sense.[20]

B.2.4.2.4 Data management

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 during the time the interim analysis was performed, 16 patients were still in the study, resulting in a total of 76 evaluable patients. The final analysis was planned after observation of additional 40 patients who were evaluable in the FAS.[20] Missing data at week 2 were replaced using the LOCF method. For the follow-up phase, no general LOCF approach was applied in order to follow a conservative approach of statistical analysis.[21]

B.2.4.2.5 Study population

The study population for the final analyses is outlined in Table B.2.9.

Table B.2.9. Study population for the final analyses

	Budesonide ODT 1 mg BID	Placebo	Total
SAF, n	19	19	76
FAS, n	19	19	76
PP, n	19	17	70

Abbreviations: BID = twice daily; FAS = full analysis set; ODT = orodispersible tablet; PP = per protocol; SAF = safety
Source: Dr Falk Pharma, data on file[21]

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

B.2.5.1 Methods

The quality of the studies included in the network meta-analysis (NMA) were assessed with respect to the outcome of histological remission, defined as <5 eos/hpf. As the quality assessment was performed as part of the development of a health economic model to be

adapted to several countries, the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach was chosen. This represents a stringent approach to assess study quality and the one which appears to be most portable and widely understood as a reference point across different countries.[47]

The quality assessment was performed by two reviewers independently. Disagreements were resolved by finding consensus between the two reviewers. The results of the quality assessment are presented in Appendix D.

B.2.6 Clinical effectiveness results of the relevant trials

B.2.6.1 Pivotal study BUL-1/EEA

B.2.6.1.1 Primary efficacy outcome

The primary efficacy outcome of rate of clinico-histological remission at week 6 was achieved in 34 (57.6%) patients receiving budesonide ODT, but in none of the 29 patients receiving placebo (p<0.0001) (Table B.2.10).[19]

Table B.2.10. Primary efficacy outcome (FAS-DB)

Outcome	Budesonide ODT 1 mg BID (N=59)	Placebo (N=29)
Clinico-histological remission at week 6, n (%)	34 (57.6)	0 (0.0)
	p<0.0001	

Abbreviations: BID = twice daily; DB = double blind; FAS = full analysis set; N = number of patients evaluable
ODT = orodispersible tablet
Source: Lucendo et al., 2019[19]

A further 6-week OLI therapy with budesonide ODT 1 mg BID was offered to clinical or histological non-responders at EoT of the DB phase and was chosen by 23 patients from the budesonide ODT group (budesonide-budesonide) and all 28* patients from the placebo group (placebo-budesonide).[19]

As achievement of clinical remission takes longer than achievement of histological remission with budesonide, the majority of budesonide ODT (budesonide-budesonide) patients were already in histological remission at EoT of the DB phase (93.2%) but benefited clinically from prolonged treatment with budesonide ODT. The overall cumulative clinico-histological remission rate after up to 12 weeks of treatment in the budesonide-budesonide group was 84.7% (n=50)[19], providing evidence that with a prolonged treatment of up to 12 weeks, an additional 27.1% of patients were able to achieve clinico-histological remission.[22]

The rates of patients in clinico-histological remission at OLI week 6 (further exploratory secondary outcome OLI phase) were comparable between patients formerly treated with budesonide ODT in the DB phase (budesonide-budesonide; n=16 [69.6%]) and patients formerly treated with placebo in the DB phase (placebo-budesonide; n=22 [78.6%]), and support the results obtained for patients in the budesonide ODT group in the DB phase.[22]

* In the results (clinical efficacy) section of Lucendo et al., 2019 the authors report 29 patients; this is a typographical error – 28 patients from the placebo group entered the OLI phase.

Patients in clinico-pathological remission after either the DB or OLI phase of BUL-1/EEA were eligible to enter the EOS-2 (BUL-2/EER) study. In the OLI phase of EOS-2, findings were similar and confirm in a larger number of patients with active EoE (N=181) the results obtained in the DB phase of the BUL-1/EEA study. After 6 weeks of treatment with budesonide ODT 1 mg BID, clinico-histological remission and histological remission (both defined as per the BUL-1/EEA study) were achieved by 126 (69.6%) and 163 (90.1%) patients, respectively.[48]

B.2.6.1.2 Key secondary outcomes (a priori ordered [confirmatory] DB phase)

Results for the key secondary efficacy outcomes (DB-phase) are outlined in Table B.2.11. The first four of the six *a priori*-ordered outcomes points proved superiority of budesonide ODT versus placebo in a confirmatory manner.[22]

All but three patients in the budesonide ODT group showed a dramatic decrease from baseline in peak eosinophil count, independently of the eosinophil load, demonstrating that budesonide ODT was able to induce remission, even in severely inflamed cases.

Histological remission in the budesonide ODT group was independently achieved in all oesophageal segments (proximal, mid, distant) and irrespective of the extent of the inflamed area, as even patients with a pan-oesophageal inflammation, where all three segments of the oesophagus were affected, achieved histological remission rates of 95.3% (p<0.0001 for each comparison).[19]

Table B.2.11. *A priori*-ordered key secondary endpoints (confirmatory testing; FAS-DB)

Outcome	Budesonide ODT 1 mg BID (N=59)	Placebo (N=29)
Histological remission* at week 6, n (%)	55 (93.2)	0 (0.0)
	p<0.0001	
Change in peak eos/mm^2 hpf from baseline to week 6, mean (SD)	–226 (150.4)	–4.3 (135.6)
	p<0.0001	
Clinical remission* on each day in the week prior to week 6, n (%)	35 (59.3)	4 (13.8)
	p<0.0001	
Total weekly EEsAI-PRO score ≤20 at week 6, n (%)	30 (50.8)	2 (6.9)
	p<0.0001	
Improvement from baseline to week 6 in weekly VDQ score, n (%)	30 (50.8)	11 (37.9)
	p=0.1804	
Improvement from baseline to week 6 in weekly AMS score, n %	7 (11.9)	3 (10.3)
	p=0.5703	

Abbreviations: AMS = Avoidance, Modification, and Slow-eating; BID = twice daily; DB = double blind; EEsAI-PRO = Eosinophilic Esophagitis Activity Index – Patient-Reported Outcome; eos = eosinophils; FAS = full analysis set; hpf = high-power field; mm = millimetre; n = number of patients in the category; N = number of patients evaluable; ODT = orodispersible tablet; SD = standard deviation; VDQ = Visual Dysphagia Question
*As defined in the primary efficacy outcome
Source: Lucendo et al., 2019[19]; Dr Falk Pharma, data on file[22]

B.2.6.1.3 Further exploratory secondary efficacy outcomes (DB-phase)

The further exploratory clinical and endoscopic secondary outcomes, were all significantly in favour of budesonide ODT, demonstrating a high consistency of the results across a wide variety of symptomatic and endoscopic outcomes.

B.2.6.1.3.1 Further exploratory clinical secondary efficacy outcomes (DB-phase)

Results for further exploratory clinical secondary efficacy outcomes (DB-phase) are outlined in Table B.2.12. All outcome points demonstrated the statistically significant superiority of budesonide ODT versus placebo.

Table B.2.12. Further exploratory clinical secondary efficacy outcomes (FAS-DB)

Outcome	Budesonide ODT 1 mg BID (N=59)	Placebo (N=29)
Change from baseline to week 6 in PatGA – severity of EoE symptoms (NRS 0–10)*, mean (95% CI)	–3.6 (-4.3; -2.9)	–1.9 (–3.0; –0.9)
	p=0.0073	
Overall symptoms resolution (PatGA ≤2) at week 6, n (%)	38 (64.4)	7 (24.1)
	p=0.0006	
Change from baseline to week 6 in PatGA of EoE activity (NRS 0–10)*, mean (95% CI)	–3.8 (–4.4; –3.2)	–0.8 (–1.6; 0.1)
	p<0.0001	
Time (days) to first symptom resolution (dysphagia and pain during swallowing), median [Q25%; Q75%]	19 [7; 34]	35 [24; 36]
	p<0.0001	
Change from baseline to week 6 in blood eos/cm^3, mean (95% CI)	–219 (–288; –150)	–28 (–124; 68)
	p=0.0016	

Abbreviations: BID = twice daily; CI = confidence interval; DB = double blind; EoE = eosinophilic oesophagitis; FAS = full analysis set; mg = milligram; n = number of patients in the category; N = number of patients evaluable; NRS = numerical rating scale; ODT = orodispersible tablet; PatGA = patient's global assessment; Q = quartile

*0: no EoE activity, 10: most severe EoE activity.

Source: Lucendo et al., 2019[19]; Dr Falk Pharma, data on file[22]

B.2.6.1.3.2 Further exploratory endoscopy secondary efficacy outcomes

Results for further exploratory endoscopy secondary efficacy outcomes (DB-phase) are outlined in Table B.2.13. All outcomes demonstrated the statistically significant superiority of budesonide ODT versus placebo.

Table B.2.13. Further exploratory endoscopy secondary efficacy outcomes (DB-phase)

Outcome	Budesonide ODT 1 mg BID (N=59)	Placebo (N=29)
'No endoscopic findings' at week 6, n (%)	36 (61.0)	0 (0)
	p<0.0001	
Change from baseline to week 6 in total modified EEsAI endoscopic score (0–9), mean [95% CI]	–2.6 [–3.1, –2.1].	–0.1 [–0.8, 0.5]
	p<0.0001	
Change from baseline to week 6 in 'inflammatory signs' sub-score of modified EEsAI endoscopic score (0–4), mean [95% CI]	–2.1 [–2.5, –1.7]	0.0 [–0.4, 0.3]
	p<0.0001	
Change from baseline to week 6 in 'fibrotic signs' sub-score of modified EEsAI endoscopic score (0–4), mean [95% CI]	–0.4 [–0.6, –0.2]	–0.1 [–0.5, 0.4]
	p<0.0001	

Abbreviations: BID = twice daily; CI = confidence interval; DB = double blind; EoE = eosinophilic oesophagitis; EEsAI = Eosinophilic Esophagitis Activity Index; mg = milligram; n = number of patients in the category; N = number of patients evaluable; ODT = orodispersible tablet
Source: Lucendo et al., 2019[19]

B.2.6.1.3.3 Further exploratory HRQoL secondary efficacy outcomes (DB-phase)

Mean changes from baseline at week 6 in the modified SHS (DB-phase) are outlined in Table B.2.14. All dimensions of the generic modified SHS (symptom burden, social function, disease-related worry, and general well-being) improved significantly from baseline to week 6 with budesonide ODT (lower scores indication better QoL). The intragroup differences (budesonide–placebo) in mean absolute changes (95% CI) from baseline to week 6 for 'symptom burden', 'social function', 'disease-related worry', and 'general well-being', respectively were: –14.02 (–28.086, 0.052), –14.79 (–27.393, –2.194), –12.79 (–24.427, –1.159), and –7.90 (–17.424, 1.630), respectively, indicating a statistically significant superiority of budesonide ODT versus placebo in the fields of 'social function' and 'disease-related worry'.[22]

Table B.2.14. Mean change from baseline at week 6 in the modified SHS (FAS-DB)

Outcome	Budesonide ODT 1 mg BID (N=59)	Placebo (N=29)
Symptom burden (0–100 VAS)		
Baseline, mean (SD)	58 (23.5) [n=58]	55 (18.1)
Week 6, mean (SD)	27 (27.1)	38 (25.1)
Change from baseline to week 6, mean (95% CI)	–32 (40.2, 23.1) p<0.0001	–18 (–28.3, –6.9) p=0.0022
Social function (0–100 VAS)		
Baseline, mean (SD)	55 (29.0)	46 (24.3)
Week 6, mean (SD)	26 (27.2)	32 (23.1)
Change from baseline to week 6, mean (95% CI)	–29 (–36.8, –21.0) p<0.0001	–14 (–22.8, –5.4) p=0.0052
Disease-related worry (0–100 VAS)		
Baseline, mean (SD)	57 (26.4)	52 (26.8)
Week 6, mean (SD)	37 (29.6)	44 (28.6)
Change from baseline to week 6, mean (95% CI)	–21 (–27.8, –13.4) p<0.0001	–8 (16.3, 0.6) p=0.0673
General well-being burden (0–100 VAS)		
Baseline, mean (SD)	40 (23.3)	35 (29)
Week 6, mean (SD)	24 (22.9)	26 (24.3)
Change from baseline to week 6, mean (95% CI)	–16 (–21.4, –11.5) p<0.0001	–9 (–18.0, 0.9) p=0.0751

Abbreviations: BID = twice daily; CI = confidence interval; DB = double blind; FAS = full analysis set; mg = milligram; N = number of patients evaluable; ODT = orodispersible tablet; SD = standard deviation; VAS = visual analogue scale
Source: Lucendo et al., 2019[19]

Mean changes from baseline at week 6 in the disease-specific EoE-QoL-A questionnaire and its sub-scores, are outlined in Table B.2.15. The improvements from baseline to EoT in HRQoL were all significant for the budesonide ODT group. The intra-group comparison of the mean changes from baseline to EoT were statistically significant for budesonide ODT versus placebo for the sub-scores ‘eating/diet impact 10 items’ (mean difference 0.50 [95% CI: 0.174, 0.817]; p=0.0030) and for ‘eating/diet impact 4 items’ (mean difference 0.49 [95% CI: 0.131, 0.858]; p=0.0082).[19]

Table B.2.15. Mean change from baseline to week 6 in the EoE-QoL-A questionnaire (FAS-DB)

Outcome	Budesonide ODT 1 mg BID (N=59)	Placebo (N=29)
EoE-QoL-A 30-items (weighted average)		
Baseline, mean (SD)	2.3 (0.8)	2.3 (0.8)
Week 6, mean (SD)	2.8 (0.9)	2.6 (0.7)
Change from baseline to week 6, mean (95% CI)	0.5 (0.32, 0.62) p<0.0001	0.2 (0.06, 0.42) p=0.0115
EoE-QoL-A 24-items (weighted average)		
Baseline, mean (SD)	2.2 (0.8)	2.3 (0.8)
Week 6, mean (SD)	2.7 (0.9)	2.6 (0.7)
Change from baseline to week 6, mean (95% CI)	0.5 (0.33, 0.63) p<0.0001	0.2 (0.07, 0.42) p=0.0093
EoE-QoL-A eating/diet impact 10 items (weighted average)		
Baseline, mean (SD)	2.2 (1.0)	2.3 (0.8)
Week 6, mean (SD)	2.9 (1.0)	2.5 (0.7)
Change from baseline to week 6, mean (95% CI)	0.7 (0.41, 0.88) p<0.0001	0.2 (–0.08, 0.38) p=0.1848
EoE-QoL-A eating/diet impact 4 items (weighted average)		
Baseline, mean (SD)	2.1 (1.0)	2.2 (0.9)
Week 6, mean (SD)	2.8 (1.0)	2.4 (0.8)
Change from baseline to week 6, mean (95% CI)	0.7 (0.46, 0.92) p<0.0001	0.2 (-0.04, 0.44) p=0.1039
EoE-QoL-A social impact (weighted average)		
Baseline, mean (SD)	2.1 (1.0)	2.2 (1.0)
Week 6, mean (SD)	2.6 (1.1)	2.5 (0.9)
Change from baseline to week 6, mean (95% CI)	0.5 (0.27, 0.65) p<0.0001	0.3 (0.02, 0.58) p=0.0364
EoE-QoL-A emotional impact (weighted average)		
Baseline, mean (SD)	2.6 (0.9)	2.7 (0.8)
Week 6, mean (SD)	3.0 (0.9)	2.9 (0.7)
Change from baseline to week 6, mean (95% CI)	0.4 (0.28, 0.60) p<0.0001	0.2 90.04, 0.43) p=0.0186
EoE-QoL-A disease anxiety (weighted average)		
Baseline, mean (SD)	2.0 (0.9)	1.8 (0.9)
Week 6, mean (SD)	2.3 (1.0)	2.0 (0.9)
Change from baseline to week 6, mean (95% CI)	0.3 (0.17, 0.45) p<0.0001	0.2 (–0.04, 0.34) p=0.1078
EoE-QoL-A swallowing anxiety (weighted average)		
Baseline, mean (SD)	2.1 (1.0)	2.3 (1.1)
Week 6, mean (SD)	2.7 (1.1)	2.8 (0.9)
Change from baseline to week 6, mean (95% CI)	0.6 (0.39, 0.80) p<0.0001	0.4 (0.13, 0.68) p=0.0055

Abbreviations: BID = twice daily; CI = confidence interval; DB = double blind; EoE-QoL-A = Eosinophilic Esophagitis Quality of Life Questionnaire – Adults; FAS = full analysis set; mg = milligram; N = number of patients evaluable; ODT = orodispersible tablet; SD = standard deviation; VAS = visual analogue scale
Source: Lucendo et al., 2019[19]

Table B.2.16 shows the analysis of the OLI for some of the outcomes that were also part of the evaluations in the DB phase. The rates of patients in clinico-histological remission at OLI week 6 were comparable between patients formerly treated with placebo in the DB phase and patients formerly treated with budesonide ODT in the DB phase, and support the results obtained for patients in the budesonide ODT group in the DB phase.

Table B.2.16. Further exploratory secondary efficacy outcomes (OLI-phase)

Outcome	Budesonide-budesonide 1 mg BID (N=23)	Placebo-budesonide (N=28)
Clinico-histological remission at OLI week 6, n (%)	16 (69.6)	22 (78.6)
Histological remission at OLI week 6*, n (%)	19 (82.6)	25 (89.3)
Clinical remission at OLI week 6*, n (%)	17 (73.9)	23 (82.1)
Change in peak eos/mm^2 hpf from week 6 DB to week 6 OLI, mean (95% CI)	–12 (–39, 15)	–206 (–247, –165)†

Abbreviations: BID = twice daily; CI = confidence interval; eos = eosinophils; hpf = high-power field; mm = millimetre; n = number of patients in the category; N = number of patients evaluable; OLI = open-label induction
*As defined in the primary efficacy outcome
†Significant changes from the end of treatment (EoT) double-blind phase to EoT OLI, as 0 was excluded from the 95% CI
Source: Lucendo et al., 2019[19]

B.2.6.1.4 Efficacy conclusions

The pivotal phase III BUL-1/EEA study demonstrated overall highly significant results with regard to the superiority of budesonide ODT 1 mg BID over placebo.

Treatment with budesonide ODT was highly superior to placebo for the induction of clinico-histological remission at week 6 (DB phase) in adult patients with active EoE (57.6% budesonide ODT versus 0% placebo; p<0.0001).[45] Prolonged treatment with budesonide ODT for a further 6 weeks in 23 patients from the budesonide ODT group and all 28 patients from the placebo group at week 6 (OLI phase) was beneficial, with an additional 27.1% of patients achieving clinico-histological remission. The overall cumulative clinico-histological remission rate in the budesonide-budesonide group after a total of up to 12 weeks of treatment with budesonide ODT was 84.7% (50 of 59 patients).[45, 49]

The rates of patients in clinico-histological remission at OLI week 6 were comparable between patients formerly treated with placebo in the DB phase and patients formerly treated with budesonide ODT in the DB phase, and support the results obtained for patients in the budesonide ODT group in the DB phase.

All but three patients in the budesonide ODT group showed a dramatic decrease from baseline in peak eosinophil count, independently of the eosinophil load, demonstrating that budesonide ODT was able to induce remission, even in severely inflamed cases.[19]

Histological remission in the budesonide ODT group was independently achieved in all oesophageal segments (proximal, mid, distant) and irrespective of the extent of the inflamed area, as even patients with a pan-oesophageal inflammation, where all three segments of the oesophagus were affected, achieved histological remission rates of 95.3% (p<0.0001 for each comparison),[19] indicating that the budesonide ODT formulation offers optimal oesophageal targeting.

Further exploratory clinical and endoscopic secondary outcomes were all significantly in favour of the active treatment group, demonstrating a high consistency of the results across a wide variety of symptomatic and endoscopic outcomes.

Patient QoL improved much more with budesonide ODT versus placebo; clear differences were observed with respect to changes in the patients' QoL measured by the EoE-QoL-A questionnaire and SHS during the DB phase of the study.[19]

With respect to the SHS results, budesonide ODT demonstrated superiority of budesonide ODT versus placebo in the areas of 'social function' and 'disease-related worry'.[19]

For both EoE-QoL-A overall scores (standard and extended), as well as for all five sub-scores the improvement in the budesonide ODT group were numerically higher than in the placebo group.[19]

B.2.6.2 Supportive study BUU-2/EEA

B.2.6.2.1 Primary efficacy outcomes

All patients in the budesonide ODT 1 mg BID group achieved histological remission at week 2 (primary efficacy outcome) while no histological remission was observed in the placebo group. The co-primary efficacy outcome also showed superiority for the budesonide ODT group versus placebo (Table B.2.17).[20]

Table B.2.17. Primary and co-primary efficacy outcomes (FAS-DB)

Outcome	Budesonide ODT 1 mg BID (N=19)	Placebo (N=19)
Primary: histological remission (mean of <16 eos/mm^2 hpf) from baseline to week 2, n (%)	19 (100.0)	0 (0.0)
	p<0.0001	
Co-primary: mean change in eos/mm^2 hpf from baseline to week 2	–120	–8
	p=0.0003	

Abbreviations: BID = twice daily; DB = double blind; eos = eosinophils; FAS = full analysis set; hpf = high-power field; mg = milligram; mm = millimetre; N = number of patients evaluable
Source: Miehlke et al., 2016[20]

The mean peak number of eos/mm^2 hpf (secondary efficacy outcome) decreased significantly from baseline to EoT in the budesonide ODT group (–227, p=0.0006), while no significant decrease was observed in the placebo group (–30). The corresponding histological remission rates (defined as peak of <16 eos/mm^2 hpf) were 84.2% (n=16) and 0% for the budesonide ODT group and placebo group, respectively.[20]

B.2.6.2.2 Key secondary efficacy outcomes

B.2.6.2.2.1 Endoscopy

The following endoscopic abnormalities were recorded and classified as absent (0), mild (1), moderate (2) or severe (3); white exudates (distinct white spots or plaques, these micro-abscesses occur when eosinophils burst in clumps from the mucosa), furrows (vertical lines, longitudinal furrows, tram-track lesions), oedema (decreased vascular markings, mucosal pallor), fixed rings (concentric rings, corrugated oesophagus, corrugated rings, ringed oesophagus, trachealisation), crepe-paper sign (mucosal fragility/tearing upon passage of the endoscope), short-segment stenosis, long-distance stenosis. The mean change from baseline to EoT in the total endoscopic intensity score (0−21) was significantly superior in the budesonide ODT (–4.1, p=0.0001) group compared with the placebo group, that only showed a decrease of –0.7 points.[20]

The endoscopic intensity sub-scores decreased significantly from the screening visit 2 to the EoT visit for mainly inflammatory signs 'white exudates' (–1.0 [SD: 0.9], p=0.0339), 'furrows' (–1.0 [SD: 0.9], p=0.0034), 'oedema' (–0.8 [SD: 0.6], p=0.0367), and 'crepe-paper signs' (–-0.6 [SD 1.0], p=0.0049) in the budesonide ODT group compared with placebo (–0.2 [SD: 0.7]), (–

0.1 [SD: 0.8]), (–0.4 [SD: 0.5]) and (0.1 [SD: 0.3]), respectively. In the placebo group none of the endoscopic intensity scores changed significantly.[21]

The proportion of patients with improvement of the endoscopic abnormality score was higher in the budesonide ODT (73.7%) group compared with the placebo group (26.3%). Accordingly, the mean endoscopic VAS score improved in the budesonide ODT group (–37.4) and changed only slightly in the placebo group (–9.6).[20]

B.2.6.2.2.2 Clinical

The mean dysphagia score, which was used as a primary metric of symptom response, decreased significantly from baseline to EoT in in the budesonide ODT (–2.7, p=0.0001); placebo: –2.0, p=0.0001) without statistically significant differences between the groups. Sustained improvement 2 weeks after EoT budesonide ODT was statistically significantly superior versus placebo (p=0.0196).[20]

Mean change in blood eosinophil counts from screening visit 2 to week 2 showed clear and clinically relevant decreases in the budesonide ODT group (–227 [SD: 313.1]) and no relevant change in the placebo group (10 [SD: 202.2]).

The budesonide ODT group showed clinically relevant higher proportions of patients with therapeutic success and therapeutic benefit, respectively compared with the placebo group (Table B.2.18).

Table B.2.18. PGA at week 2 (FAS-DB)

	Budesonide ODT 1 mg BID (N=19)	**Placebo (N=19)**
Therapeutic success,* n (%)	11 (57.9)	6 (31.6)
Therapeutic benefit,† n (%)	18 (94.7)	11 (42.1)

Abbreviations: BID = twice daily; DB = double blind; FAS = full analysis set; mg = milligram; n = number of patients in the category; N = number of patients evaluable; ODT = orodispersible tablet; PGA = physician's global assessment
*At least marked improvement of symptoms
†At least slight improvement of symptoms
Source: Dr Falk Pharma, data on file[21]

B.2.6.2.2.3 HRQoL (SHS)

The four scores of the modified SHS questionnaire showed a decrease from baseline to week 2 in the budesonide ODT group. 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 between treatment groups could be concluded.

B.2.6.2.3 Efficacy conclusions

The supportive phase IIa BUU-2/EEA study demonstrated overall statistically significant results with regard to the superiority of budesonide ODT 1 mg BID over placebo. All patients in the budesonide ODT group (n=19) achieved histological remission at week 2 (primary efficacy outcome) while no histological remission was observed in the placebo group (p<0.0001). The co-primary efficacy outcome (change in the mean numbers of eos/mm^2 hpf from baseline to week 2) also showed statistically significant superiority for the budesonide ODT group versus placebo (p=0.0003).[20]

The induction of histological remission was independent of the localisation or extent of oesophageal inflammation, indicating that the budesonide ODT formulation offers optimal oesophageal targeting.[20]

The findings of the histological outcomes were supported by the data on the secondary endoscopic and clinical outcomes. Improvement in patients' QoL were similar between the treatment groups.[21]

B.2.7 Subgroup analysis

B.2.7.1 Pivotal study BUL-1/EEA

The primary and key secondary efficacy outcomes were analysed descriptively with respect to the following subgroups (pre-planned):

- Stage 1 and overrun patients, respectively
- Localisation of the inflammation at baseline (unique categories):
  - Proximal, median, and distal oesophagus, respectively
  - One, two, or three oesophageal segments affected (defined as peak eos/mm² hpf ≥16)
- Concomitant use of PPIs (yes/no) during the DB phase
- History of allergic diseases (yes/no)
- Baseline PatGA
- Duration of disease (i.e. time from first symptoms to baseline [years]): < median (years) and ≥ median (years)

A post-hoc analysis on history of any dietary approach to treat EoE (yes/no) was also performed for the primary outcome for the FAS-DB.[22]

Results are provided in Appendix E for the primary outcome. A high level of consistency was observed between relevant subgroups of the patient population – all prespecified subgroup analyses of the primary outcome (e.g. localisation and extent of inflammation, concomitant PPI use, or time since first symptoms) were in line with the primary outcome and showed the robustness of the observed superiority of budesonide ODT versus placebo. Treatment with budesonide ODT was even successful in 43% (n=12) of difficult-to-treat patients who were refractory to previous dietary approaches to treat EoE.[22]

B.2.7.2 Supportive study BUU-2/EEA

The primary and co-primary efficacy outcomes were analysed descriptively with respect to the following subgroups (pre-planned):

- Localisation of the inflammation at baseline (unique categories) (proximal/mid/distal oesophagus)
- Number of inflamed segments at baseline (one segment/two segments/three segments),
- Concomitant use of PPIs (yes/no)
- Concomitant allergic diseases (yes/no)
- Duration of disease (time from first symptoms to baseline (years)) (< median [years] and ≥ median [years])
- 30 hpfs each at baseline and at EoT available (yes/no)
- At least one biopsy for all three segments at baseline and EOT available (yes/no)[21]

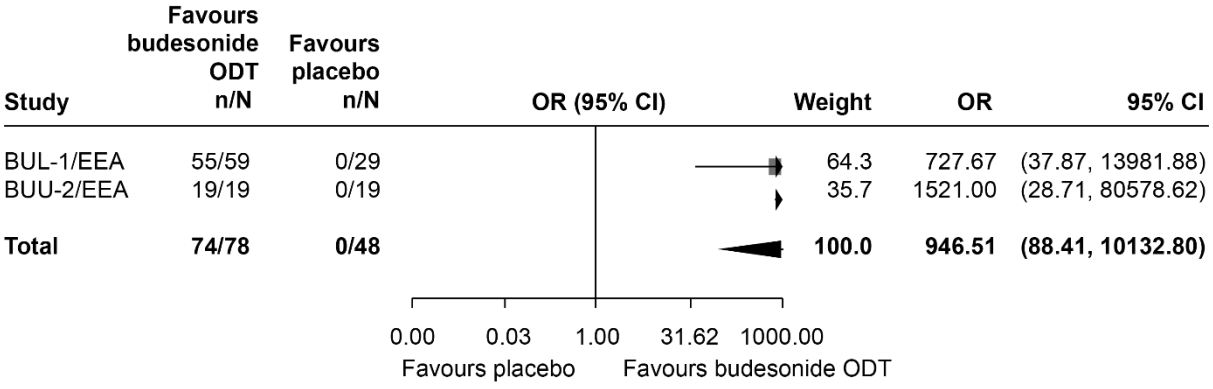
Results are provided in Appendix E for the primary outcome. A high level of consistency was observed for relevant subgroups of the patient population – all pre-specified subgroup analyses of the primary outcome were in line with the primary outcome and showed the robustness of the observed superiority of budesonide ODT versus placebo.[21]

B.2.8 Meta-analysis

The budesonide ODT pivotal phase III study (BUL-1/EEA)[19] and the supportive phase IIa study (BUU-2/EEA)[20] were included in an inverse variance weighted meta-analysis. Whilst these two studies differed with respect to study duration (6 weeks versus 2 weeks respectively) and the number of patients in the budesonide ODT 1 mg BID arms (N=59 versus N=19 respectively), the characteristics of patients included, as well as the intervention received in the two studies were very similar with respect to geographic distribution, age, sex, race, body mass index (BMI), history of endoscopic dilation and proportion of patients receiving concomitant PPI treatment. BUU-2/EEA included more patients with a new EoE diagnosis than BUL-1/EEA (35.5% vs 3% respectively), which was reflected in differing proportions of patients included with a history of PPI use (100% versus 38.2% respectively).

The results of the inverse weighted meta-analysis for these two studies are shown in Figure B.2.4. Patients treated with budesonide ODT 1 mg BID had a 946.51 times higher chance of achieving histological remission (defined as <16 eos/mm^2 hpf, corresponding to <5 eos/hpf), than patients treated with placebo. The CI shows this difference to be statistically significant.

Figure B.2.4. Results of pairwise meta-analysis of budesonide ODT 1 mg BID versus placebo for rate of histological remission (<16 eos/mm^2 hpf, corresponding to <5 eos/hpf)
Fixed effect model (inverse variance)



Heterogeneity: Q=0.09, df=1, p=0.770, I^2=0%
Overall effect: Z Score=5.67, p<0.001
Abbreviations: CI = confidence interval; eos = eosinophil; hpf = high-power field; mm = millimetre; ODT = orodispersible tablet; OR = odds ratio

B.2.9 Indirect and mixed treatment comparisons

B.2.9.1.1 Overview of available studies

An SLR was conducted to identify the evidence for efficacy and safety of budesonide ODT and comparator treatments for EoE. Full details of the methodology and the results of the SLR are provided in Appendix D.

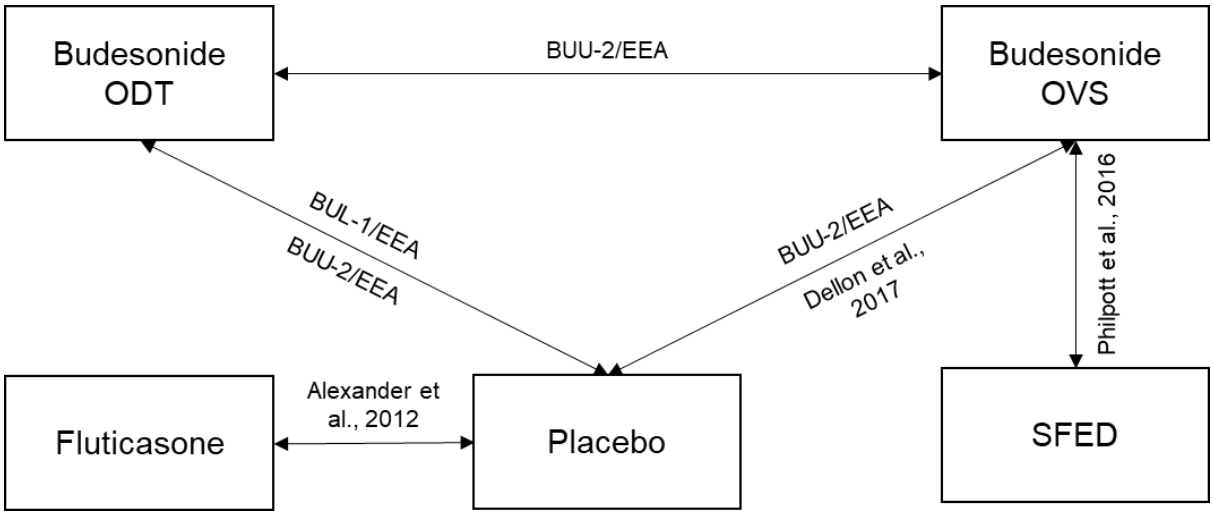
In order to generate efficacy estimates against all comparators which play a role in routine clinical practice in the UK, a network meta-analysis (NMA) was conducted, using the methods described in Appendix D. Table B.2.19 provides an overview of studies used to compare the efficacy of budesonide ODT with the comparators (fluticasone and SFED) for the outcome of histological remission (defined as <16 eos/mm^2 hpf). The network consisted of five studies; four RCTs[12, 20, 37, 42] and one controlled trial.[50] A network diagram is provided in Figure B.2.5.

Table B.2.19. Summary of studies included in the NMA

Study	Budesonide ODT	Fluticasone	Budesonide OVS*	SFED	Placebo*
BUL-1/EEA (Lucendo et al., 2019)†[19]	Yes				Yes
BUU-2/EEA (Miehlke et al., 2016)[20]	Yes		Yes		Yes
Alexander et al., 2012[42]		Yes			Yes
Dellon et al., 2017[12]			Yes		Yes
Philpott et al., 2016[50]			Yes	Yes	

Abbreviations: NMA = network meta-analysis; ODT = orodispersible tablet; OVS = oral viscous suspension; SFED = six-food elimination diet; SLR = systematic literature review
*Results not presented as comparator is not relevant to the decision problem
†When the SLR was conducted the BUL-1/EEA study was unpublished (this has since been published by Lucendo et al., 2019)[19]

Figure B.2.5. Network diagram



Abbreviations: ODT = orodispersible tablet; OVS = oral viscous suspension; SFED = six-food elimination diet

B.2.9.1.2 Assessment of clinical heterogeneity in available study pool

Data were extracted for the five studies included in the NMA on key aspects of study participants' characteristics, study interventions and outcomes measurement (see Appendix D).

Potential clinical heterogeneity was considered at the stage of identifying relevant evidence to assess efficacy and safety of the different treatment options. It was also considered during the process of data extraction and inclusion into the NMA, and was further considered when interpreting the results of the NMA. Since EoE was first identified, scientific knowledge of the disease processes has evolved steadily. This is reflected in characteristics of the studies available to assess the efficacy and safety of different treatment options.

Studies differed with respect to participants, interventions and outcomes assessed. However, an examination of clinical heterogeneity did not show substantial variations between comparisons with respect to known effect modifiers. Hence, the available study pool was considered suitable for conducting an NMA.

B.2.9.1.2.1 Study and study participants' characteristics

There were four RCTs and one prospective observational study available. There was no RCT evidence available for dietary approaches. The number of study participants ranged between 42 and 93, with four of the five studies being clustered at the higher end of that range.[12, 19, 20, 42, 50]

The study pool included three multicentre and two single-centre studies. Two of the multicentre studies were the international RCTs conducted for budesonide ODT (BUL-1/EEA and BUU-2/EEA), covering several North-Western European countries.[19, 20] The third multicentre study was conducted in the US (Dellon et al., 2017).[12] Of the two single-centre studies, one was conducted in Australia (Philpott et al., 2016) and one in the US (Alexander et al., 2012).[42] There was no discernible focus that evidence for any one comparator came from a specific country only.

On average, patients included in the studies were in their 30s. Only the study by Dellon et al., 2017, comparing two different formulations of budesonide included mainly younger patients (mean age 21–22 years).[12] All studies included a higher proportion of men than women. The studies were conducted mainly in a Caucasian patient population, with the exception of Dellon et al., 2017, in which approximately half of study participants were Caucasian/White.[12] BMI was also comparable among the three studies which reported BMI or height and weight, with BMI values in the mid-20s. Studies were also comparable in terms of the percentage of patients with a history of concomitant allergic or atopic disease, as far as this can be discerned from the way this was reported differently between the studies (total percentage or percentage of patients with different types of atopic/allergic diseases summing to >100%) with the BUL-1/EEA study including the highest percentage of patients with a history of concomitant allergic or atopic disease. Mean symptom duration and mean time since diagnosis ranged between 1–8 years and 0–4 years, respectively, in the studies reporting this. The only study which included only newly-diagnosed patients with a shorter symptom duration was Alexander et al., 2012, which compared fluticasone with placebo. The majority of studies included a patient population mostly pre-treated with PPIs (SFED: 100% pre-treated;[50] budesonide ODT: 100% for the BUL-1/EEA study contributing the majority of patients to the NMA,[19] and 38% for the BUU-2/EEA study;[20] fluticasone: approximately 50% pre-treated;[42] budesonide OVS: 32%[20] and 69%[12] pre-treated. Three studies reported on whether patients had been dilated before or were dilated at baseline, ranging between 0% (Alexander et al., 2012) and 13–16% (BUL-1/EEA and BUU-2/EEA).[19, 20, 42] The way disease severity was reported in terms of various measures of the number of eos/hpf or the percentage of patients with stenosis or oesophageal rings did not allow for a comparison between patients in this respect. However, what was

reported did not suggest that there were systematic differences in the patient population with respect disease severity.

In conclusion, the analysis of patient characteristics included in the pool of evidence available for the different comparators did not suggest substantial variation with respect to potential effect modifiers between comparisons.

B.2.9.1.2.2 Interventions

The dosing among studies investigating budesonide ODT was the same.[19, 20] Budesonide OVS doses were similar.[12, 20, 50]

Concomitant treatment with PPI differed. In the budesonide ODT studies, 12–16% of patients receiving the licensed dose of budesonide ODT (1 mg BID) received concomitant treatment with PPIs.[19, 20] In studies investigating budesonide OVS, concomitant treatment with PPI differed (0% of patients in Philpott et al., 2016, 16% in BUU-2/EEA and 71% in Dellon et al., 2017).[12, 20, 50] In Alexander et al., 2012, 26% of patients receiving fluticasone also received concomitant PPIs.[42] The data included in the NMA from Philpott et al., 2016 (SFED and budesonide OVS) only included patients who were non-responders to PPI treatment.[50]

Although treatment duration differed between studies from 2–12 weeks, the majority of patients for all treatments were treated for 6–12 weeks and there was no systematic difference in the evidence available for different treatments, in that only short-term data were available for a particular treatment but not for others.[12, 19, 20, 42, 50]

B.2.9.1.2.3 Outcomes

There were no systematic differences between the evidence available for different treatments regarding the eos/hpf threshold used as a cut-off for histological remission or the way it was measured, with the majority of studies assessing peak eosinophil count.

B.2.9.2 Results

Table B.2.20 shows the results of the random-effects NMA comparing budesonide ODT 1 mg BID with the EoE treatments used in routine clinical practice in the UK (fluticasone and SFED), for the outcome of histological remission (defined as <16 eos/mm^2 hpf). The NMA demonstrated that patients treated with budesonide ODT had odds ratios (ORs) for achieving remission of 8.7 and 81.8, compared with fluticasone and SFED, respectively. Therefore, budesonide ODT has greater efficacy than both comparator treatments, although the wide CIs indicate substantial uncertainty.

Table B.2.20. Random-effects NMA based on analysis of rates of remission (defined as <16 eos/mm^2 hpf)

Budesonide ODT 1 mg BID versus:	OR	95% CrI
Fluticasone	8.657	0.009, 7,508.000
SFED	81.840	0.109, 63,620.000

Abbreviations: BID = twice daily; CrI = credible interval; eos = eosinophil; hpf = high-power field; mg = milligram; mm = millimetre; NMA = network meta-analysis; ODT = orodispersible tablet; OR = odds ratio; SFED = six-food elimination diet

Several sensitivity analyses were conducted to examine whether the results of the NMA would change if only studies of a certain design or differences in endpoint definitions were considered

in the analysis. Results of the sensitivity analyses were derived from the random-effects models to allow better comparison with the main analysis. Sensitivity analyses included:

- eos/hpf (analysis not standardised by mm^2 hpf but based on the rates of remission reported in the respective publications) (Table B.2.21)
- Alternative outcome definition in BUU-2/EEA (peak eos/hpf instead of mean eos/hpf)[20] (Table B.2.22)
- Including only the available RCTs in the analysis (Table B.2.23).

These sensitivity analyses confirmed the superior efficacy of budesonide ODT compared with fluticasone and SFED (Table B.2.21, Table B.2.22 and Table B.2.23).

Table B.2.21. Random-effects NMA based on analysis of eos/hpf

Budesonide ODT 1 mg BID versus:	OR	95% CrI
Fluticasone	9.734	0.009, 8,372.000
SFED	156.700	0.177, 113,200.000

Abbreviations: BID = twice daily; CrI = credible interval; eos = eosinophil; hpf = high-power field; mg = milligram; NMA = network meta-analysis; ODT = orodispersible tablet; OR = odds ratio; SFED = six-food elimination diet

Table B.2.22. Random-effects NMA based on alternative outcome definition in BUU-2/EEA (peak eos/hpf)

Budesonide ODT 1 mg BID versus:	OR	95% CrI
Fluticasone	2.302	0.004, 999.800
SFED	23.590	0.066, 9,405.000

Abbreviations: BID = twice daily; CrI = credible interval; eos = eosinophil; hpf = high-power field; mg = milligram; NMA = network meta-analysis; ODT = orodispersible tablet; OR = odds ratio; SFED = six-food elimination diet

Table B.2.23. Random-effects NMA based on analysis of RCTs only

Budesonide ODT 1 mg BID versus:	OR	95% CrI
Fluticasone	9.277	0.009, 7,625.000
SFED	No data available	

Abbreviations: BID = twice daily; CrI = credible interval; mg = milligram; NMA = network meta-analysis; ODT = orodispersible tablet; OR = odds ratio; RCT = randomised controlled trial; SFED = six-food elimination diet

B.2.9.3 Uncertainties in the indirect and mixed treatment comparisons

Comparison of efficacy estimates between available studies was hampered by the following issues:

- Studies had different patient numbers and observation periods
- Rates of previous and/or concomitant PPI treatment differed between studies
- Not all studies were randomised.

Although a formal quality assessment of the included studies was carried out as described in Section B.2.5 and Appendix D, the results of this assessment were not used to conduct sensitivity analyses to explore the uncertainties in the results of the NMA. Removing studies from the analysis based on the results of the quality assessment would not have allowed estimates of the treatment effect of budesonide ODT relative to the comparators used in routine clinical practice in the UK to be derived.

B.2.10 Adverse reactions

B.2.10.1 Pivotal study BUL-1/EEA

B.2.10.1.1 Incidence of treatment-emergent adverse events

In the SAF-DB analysis set, TEAEs occurred in 37 patients (62.7%) and 12 patients (41.4%) in the budesonide ODT 1 mg BID and placebo groups, respectively (Table B.2.24).[19] No severe TEAEs occurred in the budesonide ODT group and one severe TEAE occurred in the placebo group (food impaction requiring endoscopic surgery), that led to study withdrawal.[19] No TEAE led to withdrawal in the budesonide ODT group.[19] No deaths or SAEs were reported in BUL-1/EEA.[19, 22]

Table B.2.24. Treatment-emergent adverse events (SAF-DB)

	Budesonide ODT 1 mg BID (N=59)	Placebo (N=29)
Total TEAEs, n (%)	37 (62.7)	12 (41.1)
TEAEs related to study drug, n (%)	23 (39.0)	1 (3.4)
Severe TEAE, n (%)	0 (0.0)	0 (0.0)
TEAEs leading to withdrawal, n (%)	0 (0.0)	1 (3.4)
TEAEs occurring in ≥2 patients in any treatment group, n (%)		
GORD	3 (5.1)	0 (0.0)
Nausea	2 (3.4)	0 (0.0)
Infections and infestations	21 (35.6)	6 (20.7)
Suspected local fungal infection*	14 (23.7)	0 (0.0)
Histologically confirmed	10 (16.9)	0 (0.0)
Histologically confirmed with suspected endoscopic signs	8 (13.6)	0 (0.0)
Histologically confirmed with suspected endoscopic signs and clinical systems	3 (5.1)	0 (0.0)
Nasopharyngitis	2 (3.4)	1 (3.4)
Pharyngitis	1 (1.7)	2 (6.9)
Blood cortisol decreased	3 (5.1)	0 (0.0)
Nervous system disorders	5 (8.5)	1 (3.4)
Headache	4 (6.8)	1 (3.4)
Asthma	0 (0.0)	2 (6.9)
Hypertension	2 (3.4)	0 (0.0)

Abbreviations: BID = twice daily; DB = double-blind; GORD = gastro-oesophageal reflux disease; mg = milligram; n = number of patients in the category; N = number of patients evaluable; ODT = orodispersible tablet; SAF = safety; TEAE = treatment-emergent adverse event.
*Included suspected cases of candida infection, oesophageal candidiasis, oral candidiasis and oropharyngeal candidiasis
Source: Lucendo et al., 2019[19]

No important differences were observed among the study groups in the most commonly reported TEAEs.[19] The nature and frequency of AEs observed in the budesonide ODT group were consistent with the known safety profile of topical budesonide. The vast majority of TEAEs were mild or moderate in severity.[22]

Infections and infestations was the system organ class (SOC) with the highest frequency of TEAEs in both treatment groups and also with the biggest difference between treatment groups. The TEAEs with the highest frequency of patients in the infections and infestations SOC were suspected candidiasis (candida infection [n=2], oesophageal candidiasis [n=10], oral candidiasis [n=2] and oropharyngeal candidiasis [n=3]), these are known ADRs caused by the anti-inflammatory and immunosuppressive action of budesonide.[22] Suspected candidiasis in endoscopy carried out per protocol at the EoT visit was confirmed histologically in only 10 of 59 (16.9%) patients.[19] Finally, and clinically most important, only 3 (5.1%) of these patients presented with clinical symptoms (two patients with oesophageal symptoms and one with oral and oesophageal symptoms), all of mild intensity, with no impact on daily life activities, and which recovered after medical treatment.[19]

There were no significant differences between treatment groups in cortisol levels at the EoT assessment.[19] A decrease in serum morning cortisol from normal at screening to a value below the lower limit of normal (6.2 µg/dl) was recorded in only three patients (5.1%) in the budesonide ODT group.[19] All three events were assessed as possibly related to study drug.[22] No patient had to prematurely stop administration of study medication.[19]

Three patients (5.1%) in the budesonide ODT group experienced GORD.[19] Two of these events were assessed as possibly related to study drug, one as unlikely.[22] More patients were affected by asthma in the placebo group than in the budesonide ODT group (no patients).[19] One patient (3.4%) in the placebo group versus four patients (6.8%) in the budesonide ODT group experienced headache.[19] All headache AEs were assessed as either unlikely related or not related to study drug.[22]

Apart from the changes seen in the eosinophil count (which showed a reduction), there were no fully consistent and clinically relevant changes in any of the laboratory parameters, or vital signs and physical examinations.[23]

Safety results from the 6-week OLI phase did not reveal any new safety signals[19] (Table B.2.25).

Table B.2.25. Treatment-emergent adverse events (SAF-OLI)

	Budesonide-budesonide BID 1 mg (N=23)	**Placebo-budesonide (N=28)**
Total TEAEs, n (%)	13 (56.5)	16 (57.1)
TEAEs related to study drug, n (%)	6 (26.1)	13 (46.4)
Serious adverse event, n (%)	0 (0)	0 (0)
TEAEs leading to withdrawal, n (%)	0 (0)	1 (3.6)
TEAEs occurring in ≥2 patients in any treatment group, n (%)		
GORD	3 (13.0)	2 (7.1)
Infections and infestations	4 (17.4)	12 (42.9)
Suspected local fungal infection	4 (17.4)	10 (35.7)
Histologically confirmed	2 (8.7)	7 (25.0)
Histologically confirmed with suspected endoscopic signs	1 (4.3)	6 (21.4)
Histologically confirmed with suspected endoscopic signs and clinical systems	0 (0)	0 (0)
Nervous system disorders	4 (17.4)	1 (3.6)
Headache	4 (17.4)	1 (3.6)

Abbreviations: BID = twice daily; GORD = gastro-oesophageal reflux disease; mg = milligram; n = number of patients in the category; N = number of patients evaluable; OLI = open=label induction; SAF = safety; TEAE = treatment-emergent adverse event
Source: Lucendo et al., 2019 (supplementary appendix)[19]

B.2.10.1.2 Safety conclusions

Overall, budesonide ODT 1 mg BID was well tolerated with up to 12 weeks of treatment (6-week treatment [DB phase] and a subsequent optional 6-week OLI phase) in patients with active EoE.

Proportions of patients in the DB phase with TEAEs were larger in the budesonide ODT group (62.7% of patients) than in the placebo group (41.4% of patients).[19] During the DB treatment phase, a total of 23 patients (39.0%) taking budesonide ODT and one patient (3.4%) receiving placebo had TEAEs that were related to study drug.[19] The nature and frequency of TEAEs observed in the budesonide ODT group were consistent with the known safety profile of topical budesonide.[22] The vast majority of TEAEs were of mild or moderate severity.[22] The most frequently reported ADRs in the budesonide ODT group during the DB treatment phase were suspected TEAEs of candidiasis. These are known ADRs caused by the anti-inflammatory and immunosuppressive action of budesonide.[22] TEAEs of candidiasis occurred in 14 patients (23.7%) compared with no patients in the placebo group.[19] However, suspected candidiasis in

endoscopy carried out per protocol at the EoT visit was confirmed histologically in only 10 of 59 (16.9%) patients.[19]

No deaths and no SAEs occurred during the study in any of the treatment groups.[19, 22]

Safety results from the 6-week OLI phase did not reveal any new safety signals.[19]

B.2.10.2 Supportive study BUU-2/EEA

B.2.10.2.1 Incidence of treatment-emergent adverse events

In the SAF analysis set, TEAEs occurred in seven patients (36.8%) and two patients (10.5%) in the budesonide ODT 1 mg BID and placebo group, respectively.[21] The majority of AEs were mild or moderate in severity. No severe TEAEs, SAEs or deaths were reported in BUU-2/EEA.[21]

Presentations by preferred term showed an overall accumulation of TEAEs in the budesonide ODT group. However, numbers of patients with TEAEs were too small to conclude any differences between treatment groups (Table B.2.26).[21]

Table B.2.26. Treatment-emergent adverse events (SAF)

	Budesonide ODT 1 mg BID (N=19)	Placebo (N=19)
Oesophageal candidiasis, n (%)	2 (10.5)	0 (0.0)
Fungal oesophagitis, n (%)	1 (5.3)	0 (0.0)
Nausea, n (%)	0 (0.0)	1 (5.3)
Headache, n (%)	1 (5.3)	0 (0.0)
Nasopharyngitis, n (%)	2 (10.5)	0 (0.0)
Dyspepsia, n (%)	0 (0.0)	0 (0.0)
Hypertension, n (%)	1 (5.3)	0 (0.0)
Pruritus, n (%)	1 (5.3)	0 (0.0)

Abbreviations: BID = twice daily; n = number of patients in the category; N = number of patients evaluable; ODT = orodispersible tablet; SAF = safety
Source: Dr Falk Pharma, data on file[21]

Infections and infestations was the SOC with the highest frequency of TEAEs (4/19, 21.1%) in the budesonide ODT group.

Five TEAEs in four patients (21.1%) in the budesonide ODT group were rated as ADRs, as causal relationship with budesonide ODT were considered at least possible by the investigator. The most frequent suspected ADRs were suspected local fungal infections, confirmed by positive Grocott stain in two patients in the budesonide ODT group (10.5%).[20]

There were no statistically significant changes in mean serum morning cortisol levels (screening versus EoT) in any treatment groups. No decrease in serum morning cortisol from normal at screening to a value below the lower limit of normal (4.3 mg/dl) was recorded in the budesonide ODT group.[20]

Laboratory parameters in general did not provide evidence for safety concerns. Two patients in the budesonide ODT group showed abnormal laboratory values assessed as clinically significant by the investigator. In one patient in the budesonide ODT group, an increase in leukocytes was assessed as causally related to study medication. Vital signs did not show any meaningful changes from screening visit 1/2 to the EoT/withdrawal visit in the budesonide ODT group.[21]

Tolerability and acceptance of the budesonide ODT formulation was high among patients. Eighty per cent of patients preferred the ODT, while 17% preferred the OVS.[20]

B.2.10.2.2 Safety conclusions

Overall, budesonide ODT was well tolerated with 2 weeks of treatment in patients with active EoE.

Proportions of patients with TEAEs were larger in the budesonide ODT group (36.8% of patients) than in the placebo group (10.5% of patients).[21] A total of five TEAEs in four patients (21.1%) receiving budesonide ODT were rated as ADRs, as a causal relationship with budesonide ODT was considered at least possible by the investigator. No ADRs were observed in the placebo group. All TEAEs were non-serious and assessed as mild or moderate in severity.[21]

No deaths and no SAEs occurred during the study in any of the treatment groups.[21]

Tolerability and acceptance of the budesonide ODT formulation was high among patients.[20]

B.2.11 Ongoing studies

EOS-2 (BUL-2/EER; NCT02493335; EudraCT 2014-001485-99) is an ongoing study to prove the superiority of a 48-weeks treatment with budesonide ODT versus placebo for the maintenance of clinico-histological remission in patients with EoE. The estimated study completion date is December 2020.

As budesonide ODT is currently not licensed for maintenance treatment, this study is not relevant to the submission.

B.2.12 Innovation

The innovation of budesonide ODT lies in its licensed status and unique mode of delivery; globally budesonide ODT is the first and only licensed treatment option for adult patients with EoE and is specifically designed to directly target the area of inflammation within the oesophageal mucosa.

Current treatment options for EoE are off-label, are impractical for patients and are associated with significant limitations. Patients using off-label fluticasone must swallow, rather than inhale, the medication,[41] whilst those using off-label budesonide must swallow the nebulised medicine or open the respules and use the contents to make a slurry with a carrier, such as sucrose. Limitations also exist in dietary approaches to the management of EoE, including difficulties with adherence, palatability, the requirement of multiple follow-up endoscopies, social limitations and a negative emotional impact.[5, 14-16]

Clinical studies have demonstrated that budesonide ODT is highly effective with few side effects compared with placebo.[19, 20] Ease of administration with budesonide ODT may favourably impact on patient compliance and in turn, effectiveness, resulting in improved response to treatment.

B.2.13 Interpretation of clinical effectiveness and safety evidence

B.2.13.1 Summary of the principle findings of the clinical evidence base

B.2.13.1.1 Clinical evidence

Budesonide ODT 1 mg BID is the first and only licensed therapy for the treatment of adults with EoE and the pivotal phase III study (BUL-1/EEA) has shown overall highly significant and clinically convincing results with regard to the superiority of the active medication compared with placebo. Budesonide ODT was highly effective in bringing patients with active EoE into clinical and histologic remission. At 6 weeks, 57.6% of patients receiving budesonide ODT were in complete clinico-histological remission compared with no patients in the placebo group ($p<0.0001$).[19] After a further 6 weeks of treatment 84.7% of patients were in clinico-histological remission.[19] The majority of patients (93.2%) were in histological remission at the end of 6 weeks of treatment (secondary outcome) compared with no patients in the placebo group.[19] The resolution of symptoms was achieved by only 13.8% in the placebo group, and by almost 60% in the budesonide ODT group.[19]

Further exploratory clinical and endoscopic secondary outcomes were all significantly in favour of the active treatment group, demonstrating a high consistency of the results across a wide variety of symptomatic and endoscopic outcomes.

Patient QoL was improved with budesonide ODT compared with placebo, clear differences were observed with respect to changes in the patients' QoL measured by the EoE-QoL-A questionnaire and SHS during the DB phase of the study.[19] For both EoE-QoL-A overall scores (standard and extended) as well as for all five sub-scores the improvement in the budesonide ODT group were numerically higher than in the placebo group.[19] With respect to the SHS results, the improvement from baseline to DB week 6 was much greater and clinically relevant in the budesonide ODT group than in the placebo group for all four questions of the scale.[19] With a superiority of budesonide ODT compared with placebo in the areas of 'social function' and 'disease-related worry'.[19]

High consistency was seen for relevant subgroups of the patient population. All pre-specified subgroup analyses of the primary outcome (Appendix E) (e.g. localisation and extent of inflammation, concomitant PPI use, or time since first symptoms) were in line with the primary outcome and showed the robustness of the observed superiority of budesonide ODT over placebo.[22] The induction of clinico-histological remission, independently of the localisation, extent, or severity of oesophageal inflammation, indicates that the budesonide ODT formulation offers optimal oesophageal targeting. Treatment with budesonide ODT was even successful in 43% (12 of 28) of difficult-to-treat patients who were refractory to previous dietary approaches to treat EoE (Appendix E).[22]

The results of the OLI phase support the licensed indication (treatment duration of 6 weeks, plus 6 weeks extension, if a sufficient response to treatment has not been achieved).

The data from this study confirmed the results of the supportive phase IIa dose-finding study (BUU-2/EEA), which reported a 100% histological remission rate and showed that budesonide ODT had similar anti-inflammatory effects in the entire oesophagus, independent of severity, localisation, or extent of inflammation, indicating optimal oesophageal targeting with budesonide ODT.

B.2.13.1.2 Safety evidence

In BUL-1/EEA and BUU-2/EEA, budesonide ODT 1 mg BID was well tolerated and there were no deaths or SAEs. Numbers of TEAEs and proportions of patients with TEAEs were larger in the budesonide ODT group than in the placebo group in both studies.[19, 20]

The nature and frequency of AEs observed with budesonide ODT were consistent with the known safety profile of topical budesonide ODT.[22] The majority of AEs were of mild or moderate severity.[21, 22] The most frequently reported treatment-emergent ADRs in both studies were suspected local fungal infections.[19, 20] These are known ADRs caused by the anti-inflammatory and immunosuppressive action of budesonide.[22]

Two periodic safety update reports (PSUR) have been prepared since grant of the product licence in January 2018, with both concluding no change to the benefit/risk profile.

B.2.13.1.3 Strengths and limitations of the clinical evidence base

The main strengths of the clinical efficacy studies lie in their rigorous design and multicentre conduct. Both budesonide ODT studies were RCTs and hence provide the highest level of evidence.

B.2.13.1.3.1 Internal validity

Randomisation and allocation concealment were adequate in each RCT. Homogeneity of baseline characteristics was ensured. In both RCTs, patients and investigators were blinded to the study treatment; in BUU-2/EEA comparing different formulations of budesonide, a double-dummy procedure was performed to further ensure blinding.[20] Application of the study medication was standardised in both studies and outcomes were evaluated as pre-specified. Multiple microscopic hpfs of several different biopsy locations per patient were analysed and averaged. Thus, sample selection bias was minimised.

Elevated eosinophil counts in the oesophagus are the pathognomonic feature of EoE and the reduction of eosinophil counts indicates alleviation of inflammation. The established threshold of <16 eos/mm^2 hpf for complete remission was chosen as the most robust outcome with which to assess histological disease activity in addition to clinical remission (symptom severity of ≤2 points on each 0–10 NRS for dysphagia and odynophagia, respectively on each day of the week before EoT), in the pivotal phase III study.

B.2.13.1.3.2 External validity

External validity of the studies is also fulfilled. The studies are generally transferrable to the standard of care in England and Wales. Each of the studies were conducted in Western Europe and the vast majority of patients were Caucasian.

The cohorts can be considered representative for the target population of budesonide ODT in clinical practice in England and Wales. First, the demographics at baseline reflect the epidemiology of EoE.[51] The mean age of patients was 37 and 40 years in the BUL-1/EEA and BUU-2/EEA studies, respectively.[19, 20] The majority of patients were male in each of the studies.[19, 20] Further, the inclusion/exclusion criteria of each study basically mirror the consensus criteria for EoE.[19, 20] The study subjects thus represent EoE patients suitable for treatment with budesonide ODT. GORD, typically defined by PPI-responsiveness, was an exclusion criterion in both studies. Patients selected for the pivotal phase III study were all PPI-resistant.[19]

The studies provide evidence for the use of budesonide ODT 1 mg BID as per the licensed indication in clinical practice.[18]

In conclusion, the best available evidence with sufficient internal and external validity is presented in this clinical evidence case. The studies demonstrate the effectiveness of budesonide ODT 1 mg BID, which is specifically licensed for EoE. The majority of patients are likely to respond to treatment.

There are some limitations to the clinical evidence base, specifically with regard to the pivotal phase III study:

- Patients were excluded at screening with severe strictures unable to be passed with a standard gastroscope ruling out the possibility that some strictures with a pre-dominant inflammatory component may have responded to budesonide ODT
- The study was not able to answer the question whether the resolution of symptoms, and more so, the resolution of the inflammation does indeed bring about the prevention of the fibrosis and stenosis development, and food impaction events[19]

B.2.13.2 End-of-life criteria

End-of-life criteria do not apply since EoE is not a life-threatening disease and life expectancy does not appear to be affected by EoE.[23]

B.3. Cost effectiveness

Methods

- A *de novo* economic model was developed to evaluate the cost-utility of budesonide ODT for adult patients (>18 years) with EoE in the UK, compared with fluticasone and SFED
- The cost-utility analysis utilised a Markov state transition model with six disease health states, (three representing active EoE and three remission health states), and an additional health state for death
- Response rates for budesonide ODT, fluticasone and SFED were calculated based on ORs derived from the NMA detailed in Section B.2.9 and Appendix D
    - In the base-case analysis, response rates were 95%, 68% and 18% per 12-week cycle for budesonide ODT, fluticasone and SFED, respectively
- Relapse rates were derived the placebo arm of the BUL-2/EEA study (88% relapse after 1 year)[20] and applied to all treatments at a rate of 22% per 12-week cycle
- Safety data were derived from the five studies identified by an SLR (see Appendix D), which included the two RCTs of budesonide ODT/budesonide OVS versus placebo (BUL-1/EEA and BUU-2/EEA),[19, 20] two further RCTs of fluticasone/budesonide OVS versus placebo[12, 42] and a prospective observational study of budesonide OVS versus SFED[50]
- No HRQoL data were available in either of the budesonide ODT clinical studies (BUL-1/AA and BUU-2/EEA)[19, 20] which could be used directly or indirectly to infer utility values for the different health states. Therefore, following structured searches, utilities were derived from a study assessing HRQoL in patients with GORD with heartburn[52]
- No studies reporting relevant resource use or unit cost were identified. Therefore, seven UK clinical experts were interviewed to obtain information about current treatment patterns and the associated resource. Unit costs were obtained from national tariffs

Base-case results

- In the base-case analysis, budesonide dominates both fluticasone and SFED. Therefore, budesonide ODT is associated with improved outcomes and lower costs compared with both fluticasone and SFED
    - Over a 40-year time horizon, total costs were £24,020 for budesonide ODT, £27,122 for fluticasone and £27,657 for SFED
    - Total QALYs were 16.12, 15.30 and 15.14 for budesonide ODT, fluticasone and SFED, respectively
- The base-case analysis indicated a 77% probability of budesonide ODT being cost effective at a willingness-to-pay (WTP) threshold of £30,000/QALY, compared with 0% for both fluticasone and SFED

Sensitivity and scenario analyses

- Probabilistic sensitivity analyses (PSA) resulted in similar ICERs to the base-case analysis, with budesonide ODT continuing to dominate both fluticasone and SFED

- Deterministic sensitivity analyses (DSA) showed that the results are most sensitive to the mean utility values
- Budesonide ODT continues to dominate both fluticasone and SFED in all scenario analyses, including a duration of budesonide ODT treatment of 12 weeks for all patients

B.3.1 Published cost-effectiveness studies

A systematic review was undertaken to identify resource use, cost and cost-effectiveness studies associated with EoE to identify values to populate the economic model. The review was undertaken to: (i) identify published cost-effectiveness studies to inform the economic model; and (ii) identify potential data inputs for the economic model. The eligibility criteria implemented, search strategy details, selection process and quality assessment are provided in Appendix G. The searches were undertaken in the Centre for Reviews and Dissemination database on 21st January 2019 and in PubMed on 25th January 2019.

Out of 82 unique records, five studies were deemed eligible for inclusion. The PRISMA flow chart is provided in Appendix G. Of the five studies identified, four studies were cost analyses or estimations of resource utilisation. Only one was a cost-effectiveness analysis.[53] However, this estimated the cost-effectiveness of endoscopic biopsy for the diagnosis of EoE in patients with refractory GORD without dysphagia, and was therefore not directly relevant to the decision problem. Thus, no relevant cost-effectiveness studies were identified.

B.3.2 Economic analysis

B.3.2.1 Cost-effectiveness studies

No suitable published cost-effectiveness studies were identified for EoE (see Appendix G). Therefore, it was necessary to develop a *de novo* economic model to evaluate the cost-utility of budesonide ODT compared with existing treatments for adult patients with EoE in the UK, in accordance with the NICE reference case specifications.

B.3.2.2 Patient population

The economic evaluation addresses the decision problem (Section B.1.1) and seeks to explore the cost-effectiveness of budesonide ODT in adults (>18 years) with EoE. According to UK clinical experts, in typical current UK clinical practice, patients are pre-treated with PPIs prior to receiving a diagnosis of EoE, hence prior to receiving budesonide ODT (see Section B.1.3.6). Thus, the patient population included in the economic analysis is adult patients with confirmed EoE (>15 eos/hpf[1]), who have received prior treatment with PPIs.

B.3.2.3 Input from UK expert clinicians

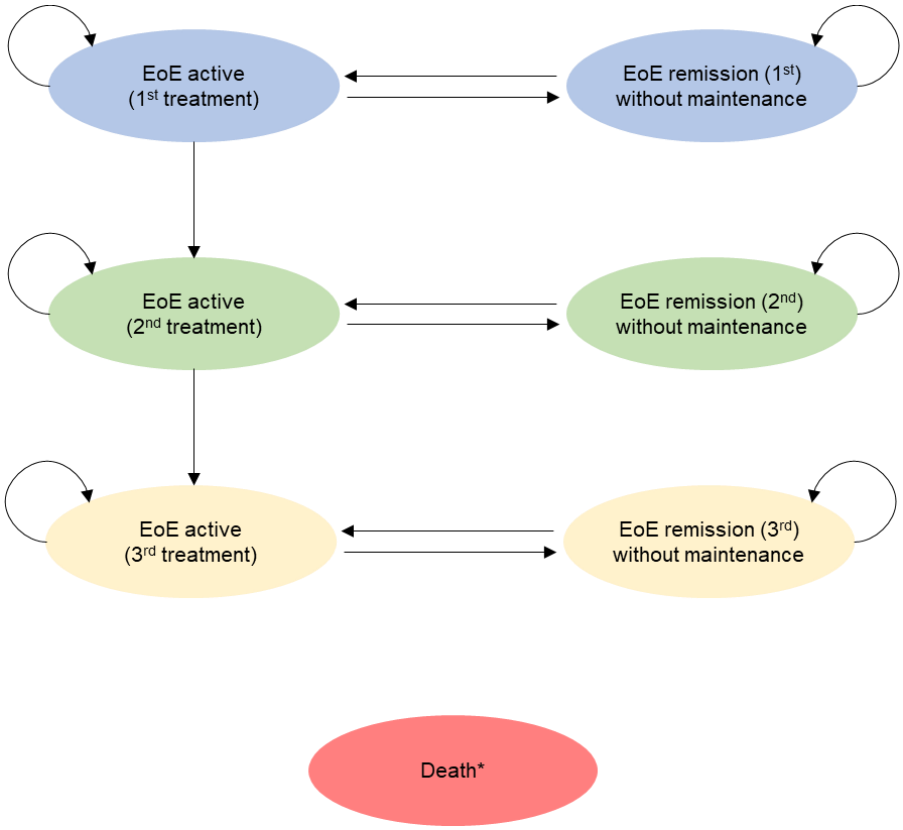
Given a lack of data on the management of EoE in the UK, seven UK clinicians with expertise in EoE were approached regarding the NICE review/appraisal and all agreed to participate in this submission. The seven UK clinical experts were consulted in a telephone interview, conducted by external consultants, lasting approximately one hour per expert. The interviews took place in January and February 2019. The main aim of the expert interviews was to gain a deeper insight into typical treatment patterns of EoE in the UK at present and to bridge gaps in the evidence available regarding resource use to populate the economic model. In addition,

the experts were consulted regarding key assumptions used in the model. The questionnaire used is provided in Appendix L. Further information about the UK clinical experts interviewed is provided in Appendix M. In addition, the UK experts were consulted with some additional questions in September 2019.

B.3.2.4 Model structure

The cost-utility analysis utilised a Markov state transition model with six disease health states and an additional health state for death. The model is programmed in Microsoft Excel® using standard Excel® functions and visual basic for applications (Microsoft, Redmont, WA). The model structure diagram is shown in Figure B.3.1.

Figure B.3.1. Cost-utility model - Markov model structure



Abbreviations: EoE = eosinophilic oesophagitis
*Patients can transition to the death health state from any other health state

Patients enter the cost-utility model with the diagnosis of EoE. The model consists of six disease health states which are shown in Figure B.3.1. Three of these disease health states are active disease health states which define day-to-day symptoms for patients with EoE. The other three disease health states are remission health states in which patients do not experience active disease (or symptoms). The final health state is a death health state, which is an absorbing health state. Patients can transition to the death health state from any other health state. As EoE has no impact on mortality, this health state reflects the general population mortality only.

B.3.2.5 Health states

The model consists of seven health states listed below:

- Health state 'a' is named '*EoE Active - 1st treatment'*: This represents patients who are 'unwell' and actively consult with a healthcare professional (HCP) and are seeking treatment. Patients in health state 'a' are eligible for 1st treatment for EoE. These patients may also have relapsed from the *'EoE in remission (1st)'* health state.
- Health state 'b' is named '*EoE in remission (1st)*': This represents patients who have responded to 1st treatment and are 'better/well'. In this health state patients are not treated with maintenance therapy.
- Health state 'c' is named '*EoE Active - 2nd treatment'*: This represents patients who are 'unwell' and actively consult with an HCP and are seeking treatment (if available). Patients in health state 'c' have failed 1st treatment and are eligible for 2nd treatment for EoE. These patients may also have relapsed from the *'EoE in remission (2nd)'* health state.
- Health state 'd' is named '*EoE in remission (2nd)'*: This represents patients who have responded to 2nd treatment and are 'better/well'. In this health state patients are not treated with maintenance therapy.
- Health state 'e' is named 'EoE *active - 3rd treatment'*: This represents patients who are 'unwell' and actively consult with an HCP and are seeking treatment (if available). Patients in health state 'e' have failed both 1st treatment and 2nd treatment and are eligible for 3rd treatment for EoE. These patients may also have relapsed from the *'EoE in remission (3rd)'* health state.
- Health state 'f' is named '*EoE in remission (3rd)*': This represents patients who have responded to 3rd treatment and are 'better/well'. In this health state patients are not treated with maintenance therapy.
- Health state 'g' is the 'death' health state. As EoE does not impact mortality, this health state represents the general population mortality.

B.3.2.6 Model description

Patients enter the model in health state 'a', i.e. 'Active EoE – 1st treatment' and receive either budesonide ODT or one of the comparator treatments. In the absence of UK data for adult EoE patients, the starting age of the cohort in the model is 30 years, based on a recent systematic review of the international epidemiological literature.[9] Patients progress through the model according to transition probabilities applied every cycle (12 weeks) for the duration of the 40-year time horizon considered in the base-case analysis.

Patients may or may not respond to the 1st treatment option after the 12-week cycle. Patients in health state 'a' who respond (i.e. achieve histological response) to 1st treatment transition to health state 'b'. Patients in health state 'b' are in remission and do not receive maintenance therapy, as neither budesonide ODT nor fluticasone are licensed for maintenance therapy.

Patients in health state 'b' may move back to health state 'a' at any time if their EoE becomes active again, according to treatment specific relapse rates which are applied at the end of every cycle (12 weekly). Patients who relapse are treated with the same treatment. If patients do not relapse, they remain in EoE remission health state 'b'.

Patients who do not respond to a 1st treatment option (before or after relapse) after 12 weeks' treatment move to health state 'c' where the assumption is made that the clinician will prescribe an alternate treatment option (2nd treatment). If patients respond to 2nd treatment, they move to health state 'd' and again do not receive maintenance therapy. Patients in health state 'd' can relapse and return to health state 'c'.

Patients who do not respond to a 2nd treatment option move to health state 'e' where the assumption is made that the clinician will prescribe an alternative treatment option (3rd treatment). If patients respond to 3rd treatment, they move to health state 'f' and do not receive maintenance therapy. Patients in health state 'f' can relapse and return to health state 'e'.

The model only includes the possibility of three different treatments. Patients who do not respond to 3rd treatment will remain in health state 'e', receiving no treatment (which is what they were already receiving [as per the base-case analysis]).

Whilst EoE does not have an impact on mortality, in the model, patients can die of all causes at any time. The death health state thus represents the general population mortality.

To capture time dependency in the model, tunnel states have been added. Tunnel states are states used to add memory to a Markov model. Tunnel states are required in the model to count the number of cycles a patient is in an EoE remitting health state. This is to model the assumption that if a patient enters a remitting EoE health state and remains in it for four cycles (48 weeks), that patient is to remain in that health state for the remaining duration of the model. In other words, if a patient remains in a remitting EoE state for four cycles, that patient will transition to a permanent version of that state in the base-case analysis. Once in the permanent version of the state, a patient cannot transition to an active EoE health state in the base-case analysis. Tunnel states are implemented for the 1st, 2nd and 3rd treatment lines of the model meaning that a patient can enter a permanent EoE remitting state on a 1st, 2nd or 3rd line treatment. Hence the assumption in the model is that patients who do not relapse within a year of responding to treatment, will not relapse. Further detail about relapse is provided in Appendix M.

The Markov model cycle length of 12 weeks is in line with the maximum treatment period for budesonide ODT. It is also in line with the treatment period for fluticasone, as highlighted by the UK expert clinicians. The model estimates the cost-effectiveness of budesonide ODT over a 40-year time horizon, as EoE is a chronic relapsing and remitting disease.

Further details about the model and its development are provided in Appendix M. A summary of the features of the economic evaluation and justification for chosen values is provided in Table B.3.1.

Table B.3.1. Features of the economic analysis

Factor	Current appraisal – chosen value/factor	Justification	NICE scope or reference case (where applicable)
Intervention	Budesonide ODT	As per NICE scope	Budesonide ODT
Comparator(s)	• Topical corticosteroid: swallowed fluticasone (Flixotide 500 mcg Evohaler) • SFED	Comparators are those used in routine clinical practice in the UK	Established clinical management without budesonide, which may include PPI, other corticosteroid formulations and dietary intervention
Symptoms of oesophagitis	Not included – i.e., not used to transition through the model. Instead, histological remission is used as a proxy for symptoms	Evidence suggests that it is difficult to use clinical symptoms to evaluate EoE*	Symptoms of oesophagitis
Complications e.g., stricture formation	Included in the model. For complications, patients will receive treatment with endoscopic dilation and/or emergency food bolus removal	In the model, dilation is not considered as a comparator, but as a supplementary (optional add-on) treatment for patients depending on the underlying severity of EoE and its impact on the anatomy and physiology of the oesophagus (for example, extent of oesophageal remodelling, presence of strictures etc)†	Complications such as stricture formation
Mortality	General population mortality included	EoE does not influence the mortality of patients.[54] Hence, only general population mortality is included	Mortality
Adverse effects of treatment	Included	As per NICE scope	Adverse effects of treatment
HRQoL	Included as QALY measured by EQ-5D in patients	As per NICE scope	HRQoL
Perspective on outcomes	Direct health effects	As per NICE scope	Direct health effects
Perspective on costs	NHS and PSS	As per NICE scope	NHS and PSS
Health related quality of life	Included as QALY measured by EQ-5D in patients with GORD with heartburn (as a proxy for EoE)	As per NICE scope	Health related quality of life
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	As per NICE scope	Cost-utility analysis with fully incremental analysis

Time horizon	40 years in base-case analysis	Long enough to reflect important differences in costs or outcomes between technologies being compared	Long enough to reflect all important differences in costs or outcomes between the technologies being compared
Synthesis of evidence on health effects	Systematic review, including ITC/NMA	As per NICE scope	Systematic review
Measuring and valuing health effects	QALYs, measured by EQ-5D	As per NICE scope	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure
Source of data for measurement of health-related quality of life	Patient reported	As per NICE scope	Reported directly by patients and/or carers
Source of preference data for valuation of changes in health-related quality of life	General UK population utility[55]	As per NICE scope	Representative sample of the UK population
Evidence on resource use and costs	NHS and PSS	As per NICE scope	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS
Discounting	• Costs: 3.5% • Health effects: 3.5%	As per NICE scope	Costs and health effects (currently 3.5%)
Treatment waning effect	Not applicable	Not applicable	Not applicable
Source of utilities	Systematic review	As per NICE scope	Systematic review
Source of costs	Unit costs based on national tariffs	As per NICE requirements	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS

Abbreviations: EoE = eosinophilic oesophagitis; EQ-5D = EuroQoL-5 dimensions; HRQoL = health-related quality of life; ITC = indirect treatment comparison; mcg = microgram; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; ODT = orodispersible tablet; PPI = proton-pump inhibitor; PSS = Prescribed Specialised Services; QALY = quality-adjusted life year; SFED = six-food elimination diet; UK = United Kingdom

*Symptom assessment can be challenging because most patients have chronic progressive symptoms and may have developed adaptive behaviours such as avoidance of specific food textures, excessive mastication, or increased meal times to avoid dysphagia and food impaction. In addition, dysphagia and food impaction may occur as sporadic events in many patients and may not be captured in therapeutic studies of short duration'. The authors caution that assessment of disease activity on the basis of symptoms alone is probably 'inadequate.'[56] To compound this difficulty, there is no clear correlation between symptoms and histology.[1, 57] 'Symptoms do not correlate accurately with histologic disease activity, so histology currently continues to be necessary to monitor the disease'.[1, 58] Biomarkers are promising for the future but currently have no place in accurately assessing EoE. 'Currently, non-invasive biomarkers are not accurate to diagnose or monitor EoE. Some minimal invasive diagnostic tools show promise and merit further evaluation'.[1]

The available clinical studies reviewed for the purpose of this work, confirmed that a range of different instruments have been used to assess clinical response making comparison of studies difficult with respect to the outcome of clinical symptoms. In comparison, more clinical studies have used histological response as a measure of efficacy of treatment for EoE. As a result, histological thresholds are included in the model as a measure of treatment efficacy and treatment response. Therefore, the intrinsic assumption made in the model is that histological remission (measurable) equates to clinical symptoms. By implication, patients above the threshold for histological remission are asymptomatic and patients below the threshold for histological remission are symptomatic. Assuming a normal distribution of clinical symptoms across the cohort, the average patient is represented in the model

[†]According to the literature, dilation provides symptom relief especially in strictures without affecting the underlying inflammation and is recommended only for patients with dysphagia/food impaction unresponsive to anti-inflammatory treatment.[1] 'Endoscopic dilation improves dysphagia in up to three quarters of adult EoE patients with reduced oesophageal calibre, without having an effect on the underlying oesophageal inflammation'[1]

B.3.2.7 Intervention technology and comparators

The intervention and comparators included in this appraisal are detailed in Table B.3.2. Comparators are based on the latest available international clinical treatment guideline (Lucendo et al., 2017)[1] and validated by the UK expert clinicians (see Appendix M). In line with Lucendo et al., 2017, off-label products are included in the model.[1]

Table B.3.2. Intervention and comparators

Intervention/ comparator	Name	Description
Intervention	Budesonide ODT (Jorveza)	Budesonide ODT is an immediate-release tablet specifically designed for the treatment of EoE.[17] The recommended dose of budesonide ODT is 1 mg BID, taken orally.[18] The usual duration of treatment is 6 weeks, which may be extended to 12 weeks for patients who do not respond completely.[18] In the pivotal phase III BUL-1/EEA study, 57.6% (N=34) of patients achieved clinico-histological remission at week 6, with a cumulative rate of clinico-histological remission of 84.7% (N=50) at week 12.[19, 22] This submission focuses on part of the budesonide ODT marketing authorisation – adult patients with EoE who have previously received treatment with PPI, which in the UK is almost always prior to diagnosis of EoE (see Section B.1.3.6)[10]
Comparator 1	Fluticasone (Flixotide 500 mcg Evohaler)	The latest treatment guideline suggests that topical steroids are one of the 1st-line treatments for EoE.[1] Clinical opinion from the UK expert clinicians suggested that the majority of patients are treated 1st-line with swallowed (off-label) fluticasone (see Appendix M). The assumption in the model is that during the active disease health state, patients on fluticasone receive treatment for 12 weeks. This was based on input from the UK clinical experts
Comparator 2	SFED	SFED is a comparator in this appraisal. The latest treatment guideline suggests that food elimination diet is one of the 1st-line treatments for EoE.[1] Clinical opinion from UK expert clinicians suggested that a minority of patients are treated with SFED (see Appendix M). The assumption in the model is that during the active disease health state, patients on SFED continue the diet for 12 weeks. This was based on input from the UK clinical experts and reflects that the economic analysis is for treatment of EoE, not maintenance therapy (as per the budesonide ODT marketing authorisation)

Abbreviations: BID = twice daily; EoE = eosinophilic oesophagitis; N = number of patients evaluable; ODT = orodispersible tablet; PPI = proton-pump inhibitor; SFED = six-food elimination diet; UK = United Kingdom

PPIs and budesonide OVS are not included as comparators in this appraisal. Clinical opinion from UK experts indicates that patients are already treated unsuccessfully with PPIs prior to being diagnosed with EoE (see Section B.1.3.6 and Appendix M). Therefore, PPIs are not included as a comparator in this appraisal. Clinical opinion from the UK clinical experts also suggested that budesonide viscous slurry is only used in exceptional cases. Hence, it is also not included as a comparator in this appraisal.

The cost-utility model allows patients to have to up three lines of treatment (1st, 2nd and 3rd treatment). Given the lack of available treatments, no treatment was used as both 2nd and 3rd line treatment for all comparators in the base-case analysis, as shown in Table B.3.3. A scenario analysis was conducted for an alternative option with active 2nd line treatment for all the comparators.

Table B.3.3. 2nd and 3rd line treatment for the comparators in the base-case analysis

	Budesonide ODT	Fluticasone	SFED
1st treatment	Budesonide ODT	Fluticasone	SFED
2nd treatment	No treatment	No treatment	No treatment
3rd treatment	No treatment	No treatment	No treatment

Abbreviations: ODT = orodispersible tablet; SFED = six-food elimination diet

The response and relapse rates for no treatment are based on the response and relapse rate of placebo. There are no drug costs or AE costs associated with no treatment. Medical resource use for no treatment is based on fluticasone resource use. Fluticasone was chosen as a proxy because no treatment may still cause patients to have contact with HCPs and fluticasone was chosen as representing a conservative estimate of this.

B.3.3 Clinical parameters and variables

Clinical data (histological response/remission, non-response, relapse, mortality and AEs) were derived from clinical trials, the NMA and the published literature. These are summarised below. Further details about the identification and selection of values included in the cost-utility model are provided in Appendix D and Appendix M.

B.3.3.1 Base-case efficacy parameters

B.3.3.1.1 Transition from active disease to remission: response rate

The transition from the active EoE health states to the remission EoE health states is considered the response rate. This was defined as achieving histological remission and was determined by the efficacy of the treatments included in the model. These transition probabilities have been derived from the odds ratios for achieving histological remission for the different treatment pairs calculated through a NMA (see Section B.2.9 and Appendix D).

The absolute response rate for each treatment was calculated based on the response rate to budesonide ODT and each comparator treatment's corresponding OR. These absolute values and the corresponding standard error values for each treatment were used for the beta distributions which fed into the PSA. The same results would have been generated if the ORs were used as inputs for the PSA but this method would have added significant unnecessary complexity to the model.

The response rate for budesonide ODT per 12-week cycle used in the cost-utility model was 94.9%. Given odds ratios of 0.116 for fluticasone and 0.012 for SFED from the NMA, these translate into response rates per 12-week cycle of 68% and 18% for fluticasone and SFED, respectively. The response rate of 4% per 12-week cycle for no treatment was based on data for placebo (OR=0.002).

B.3.3.1.2 Transition from remission to active disease: relapse rate

For the cost-utility model it was necessary to estimate the proportion of patients in remission who develop active disease and transition from the remission health states back to the active disease health states - the 'relapse rate'. Limited data are available from the literature on the relapse rate of EoE in remission (or similar) for patients on the different treatments. Hence, data from the placebo arm of BUL-2/EEA[10] – 88% relapse after 1 year – was applied to all treatments at 22% relapse rate per 12-week cycle. The same rate was also applied to no treatment which is used as 2nd treatment and 3rd treatment for all technologies in the base-

case analysis. The UK clinical experts suggested that this was an appropriate assumption given the lack of data and their lack of experience with budesonide ODT. However, one suggested that budesonide ODT would have a lower relapse rate than fluticasone. Thus, using the same relapse rate for all treatments may be a conservative assumption.

B.3.3.2 Percentage of patients staying on treatment in the event of non-response

There are no available data on the number of patients staying on treatment in the event of non-response (drug failure). A conservative assumption was used that all patients who do not respond are transferred to subsequent treatment. In the base-case analysis, subsequent treatment – i.e. 2nd and 3rd line treatments - are no treatment.

B.3.3.3 Transition matrix

The transition matrix for response, non-response (and move to subsequent treatment) and relapse is shown in Table B.3.4.

Table B.3.4 Transition matrix used in the cost-utility model (base-case analysis)

Treatment	OR for response	Response per cycle (%)	Relapse per cycle (%)	Patients who move to subsequent treatment (%)
Budesonide ODT	-	94.9	22.0	5.1
Fluticasone	0.116	68.0	22.0	32.0
SFED	0.012	18.0	22.0	82.0
No treatment	0.002	4.0	22.0	96.0

Abbreviations: ODT = orodispersible tablet; OR = odds ratio; SFED = six-food elimination diet

B.3.3.4 Mortality

Although EoE does not have an impact on mortality, all-cause mortality was included in the cost-utility model, i.e. general population mortality. The risk of all-cause mortality was estimated based on national life-tables for the UK for the years 2015–2017.[59]

B.3.3.5 Safety – rates of adverse events

The safety data included in the cost-utility model were based on the five studies identified in the SLR and included in the NMA to derive efficacy estimates for budesonide ODT versus fluticasone and SFED (see Appendix D and Appendix E). For the base-case analysis, the highest reported frequencies of AEs are included for all technologies. Based on expert statistical advice, no statistical comparison was performed. The values and sources used to populate the model for each of the AEs considered in the model are shown in Appendix M and summarised in Table B.3.5. The assumption in the model is that AEs were only experienced by patients receiving drug treatment. Thus, patients did not experience any AEs whilst receiving SFED and no treatment.

Table B.3.5 Rates of AEs experienced by patients receiving drug treatment

AE	Patients experiencing each AE (%)	
	Budesonide ODT	Fluticasone
Oral candidiasis	3.4	3.5
Oesophageal candidiasis	16.9	26.3
Sleep problems (decreased cortisol information)	0.0	0.0
Headache	6.8	4.7
Skin disorders	0.0	0.0
GI disorders	16.9	0.0
Cough	0.0	0.0
Pharyngitis	1.7	0.0
Irritation in nose and/or throat	0.0	10.5
Respiratory disorders	0.0	0.0

Abbreviations: AE = adverse event; GI = gastrointestinal; ODT = orodispersible tablet
Source: Alexander et al., 2012;[42] Butz et al., 2014;[60] Dr Falk Pharma, data on file[22] Moawad et al., 2013[43]

B.3.4 Measurement and valuation of health effects

No HRQoL data were available in either of the budesonide ODT clinical studies (BUL-1/AA and BUU-2/EEA)[19, 20] which could be used directly or indirectly to infer utility values for the different health states. Consequently, two structured searches were undertaken to identify suitable utility values to populate the cost-utility model.

B.3.4.1 Health-related quality of life studies

The first structured search focused on HRQoL studies. It was conducted to identify studies with utility values associated with the active disease health state for EoE patients. In particular, it sought to identify studies which used validated and widely used instruments (either the EuroQoL- 5 dimensions [EQ-5D], the Short Form-36 dimensions or the Health Utilities Index instrument) to measure health-related quality of life in EoE patients.

The eligibility criteria implemented and search strategy details are provided in Appendix G. Of particular note, the search strategy included adult patients with EoE or related diseases such as dysphagia, food impaction, GORD, Barrett's oesophagus, oesophageal cancer. The search was initially undertaken in Medline database on 1st March 2018 and updated on 21st January 2019.

Fifty-four full text papers focusing on oesophageal disease were reviewed as part of the initial search. Six additional full-text papers were reviewed as part of the updated search. None of the full-text papers reviewed were for EoE. The studies in oesophageal cancer, oesophageal varices, Barrett's oesophagus and achalasia (n=29) were assessed using the inclusion and exclusion criteria for relevance and determined not relevant/suitable. Similarly, nine of the 19 studies in GORD were assessed and determined not relevant/suitable. Of the other studies/conditions (n=6), none were found to be relevant/suitable. Hence these studies were all excluded (see Appendix G for details).

B.3.4.2 Mapping studies

The second structured search focused on mapping studies i.e. studies in which QoL instruments were mapped to utility values. A structured search was conducted to identify studies mapping disease-specific QoL instruments to utility values. The mapping search was initially undertaken in Medline database on 26th April 2018 and updated on 22nd January 2019.

The eligibility criteria implemented and search strategy details are provided in Appendix G. One paper was identified for full-text review in the initial search but didn't meet the inclusion criteria and was therefore excluded. The updated search did not identify any papers for full-text review. Consequently, the mapping search did not identify any relevant studies in which the results of disease-specific questionnaires could be mapped to the EQ-5D.

B.3.4.3 Selection of utility values for the cost-utility model

The structured search focused on HRQoL studies identified nine relevant studies, all for GORD. For the purposes of the model, it was assumed that GORD was the most similar condition to EoE and data from these studies were extracted for potential inclusion in the model. The utility values were then restricted to those measured by the EQ-5D according to the scope set out by NICE. On that basis, four studies were excluded. A further four studies were excluded on the basis that they represented QoL associated with GORD post-treatment and not during active disease. The remaining study assessed health state utilities in patients with GORD with heartburn in Germany (n=507) and Sweden (n=504).[52] The utility value for the pooled group of patients and all severities was 0.70. By country, this was: Germany=0.70 and Sweden=0.69. By severity, this was: mild=0.78, moderate=0.67 and severe=0.49.

B.3.4.4 Health-related quality of life data used in the cost-effectiveness analysis

Separate utility values were required for the active EoE and EoE in remission health states in the cost-utility model.

Patients in the active EoE health states (i.e. health states 'a', 'c' and 'e') are assumed to have poorer QoL (lower utility) than the general population. These patients are actively seeking treatment for EoE so they may be experiencing "solid food dysphagia, food impaction, and non-swallowing associated chest pain".[1] In practice, this QoL is likely to depend on a number of factors, such as duration of EoE. However, the conservative assumption in the model is that all patients in the active EoE health states have the same utility irrespective of treatment type, duration of treatment, etc.

Based on an extensive review of the literature (described in Appendix G), the final utility value used in the base-case analysis for the active EoE health states (health states 'a', 'c' and 'e') for all treatments is 0.70 (standard deviation 0.24) corresponding to the mean overall utility measured by EQ-5D in a pooled group of German and Swedish patients with GORD and heartburn.[52] This pooled estimate for 1,011 German and Swedish patients is the average of mild, moderate and severe GORD with heartburn.

The UK clinical experts suggested that the use of this study was appropriate in the absence of a specific study in EoE. They believe that QoL would be similar for German, Swedish and UK patients. However, they also suggested that EoE would likely have a lower QoL than GORD. Thus, the use of this study can be considered a conservative approach.

A UK study evaluated QoL in GORD patients with relapse using the EQ-5D.[61] This resulted in a utility value of 0.56; although this may overestimate the QoL impact of GORD relapse, it may better reflect the QoL of patients with EoE, as some UK clinical experts indicated that QoL associated with EoE may be poorer than that associated with GORD. This utility value (0.56) was explored in a scenario analysis.

For the estimation of utilities for the EoE in remission health states (health states ‘b’, ‘d’ and ‘f’), EoE patients in remission are assumed to have the same utility as that of a ‘well’ person. These patients are not actively seeking treatment for EoE. The highest quality estimate of utility for the EoE in remission health states in the cost-utility model would be measured by the EQ-5D in a study of adults with EoE in remission. In the absence of available data, the utility of patients in EoE remission was considered to be comparable to the UK general population. In practice, their QoL may be poorer than that of the general population. However, if they have been affected by active EoE for some time, have responded to treatment and are now ‘well’, they may perceive their QoL to be higher than that of the general population (who may take their ‘wellness’ for granted). Thus, the utility value for the UK general population has been used as a proxy for the utility of patients with EoE in remission.

The utility value for the EoE in remission health states in the model is derived from Kind’s 1999 work on the health state utilities of the UK general population.[55] In a sample of 488 adults, the mean utility value for the UK general population was 0.85 with standard deviation 0.25.

Age-adjusted utilities were not used in the model. The UK general population utility value was used as a proxy for EoE in remission health states. Age-adjusted utilities are available for the UK general population. However, there are limited data on the QoL of EoE. So, a value for GORD had to be used as a proxy. The study from which this utility value was derived only provided utility values for all ages.[52] Consequently, the use of age-adjusted utilities was not possible.

Utility values applied to health states apply for the duration of the cycle (i.e., are the same as long as the patient remains in that cycle). The utility values are applied to the health state and are thus independent of treatment. In addition, they are constant over time. Any difference in accrued (costs and utility) values for the different treatments is thus a result of difference in the proportion of patients passing through each of the model health states, and the costs and utilities arising from these patients. A summary of the utility values used in the base-case analysis are shown in Table B.3.6.

Table B.3.6. Summary of utility values used in the cost-utility model

Health state	Mean utility value	Standard deviation	Reference in submission (Section)	Justification
Base-case analysis				
Active EoE (health states 'a', 'c','e')	0.70	0.24	Kartman 2004[52] (Section B.3.4, Appendix G)	Literature review – pooled Swedish/German data for GORD with heartburn
EoE in Remission (health states 'b', 'd', 'f')	0.85	0.24	Kind 1999[55] (Section B.3.4, Appendix G)	Represents a 'well' patient which has been assumed to be comparable to general UK population
Scenario analysis				
Active EoE (health states 'a', 'c', 'e')	0.56	Not reported	Grant 2008[61] (Section B.3.4, Appendix G, Section B.3.8 scenario analysis)	UK estimate of GORD with relapse

Abbreviations: EoE = eosinophilic oesophagitis; GORD = gastro-oesophageal reflux disease; UK = United Kingdom

B.3.4.5 Utility values for adverse events

Based on a comprehensive review of adverse reactions, the AEs were not judged as sufficiently severe to warrant being included as a disutility in the model. Hence, no disutility for AEs was included.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

B.3.5.1 Resource identification, measurement and valuation studies

A systematic review was undertaken to identify HRU and costs associated with EoE. This formed part of the same review set out to identify published cost-effectiveness studies (Section B.3.1). The search is described in detail in Appendix G. Out of 82 unique records, five studies were deemed eligible for inclusion. However, none of the studies reported resource use or unit cost data which might be used to populate the cost-utility model required for budesonide ODT in line with the NICE scope.

Hence, seven UK EoE expert clinicians were interviewed to obtain information about current treatment patterns of EoE and the associated resource use in the UK. Unit costs were obtained from national tariffs.

B.3.5.2 Intervention and comparators' costs and resource use

B.3.5.2.1 Drug acquisition costs

Intervention and active comparator drug costs are shown in Table B.3.7. Only one of the comparators in this appraisal is a drug. The other comparator – SFED – is not a drug treatment and thus has no associated drug cost. 'No treatment' which is used as 2nd and 3rd treatment in the base-case analysis also has no associated drug cost. The drug costs for budesonide

ODT and fluticasone were based on the list price reported in the British National Formulary.[62, 63]

Table B.3.7. Drug acquisition costs

Drug	Strength	Cost per unit (excluding VAT)	Source
Budesonide ODT	1 mg	90 x 1 mg tablets = £323.00	British National Formulary[62]
Fluticasone (Flixotide Evohaler)	50 mcg	120 x 50 mcg doses = £6.53	British National Formulary[63]

Abbreviations: mcg = microgram; mg = milligram; ODT = orodispersible tablet; VAT = value-added tax

The recommended dose for budesonide ODT is 1 mg BID for 6 weeks or 12 weeks.[18] The assumption in the model is that 57.6% of patients receive budesonide ODT for 6 weeks and the remaining patients (42.4%) receive budesonide ODT for 12 weeks. This was based on the pivotal phase III BUL-1/EEA study.[22, 48] The drug costs for budesonide ODT were £323.00 and £646.00 for 6 weeks and 12 weeks treatment, respectively. This includes wastage, as a pack of 90 tablets will last for 6 weeks and 3 days (two tablets per day). Thus, the average drug cost for budesonide ODT for the 12-week period in the active disease health state is £459.95 ([57.6% * £323.00] + [42.4% * £646.00]).

UK clinical experts suggested that Flixotide 50 mcg Evohaler would be the form of fluticasone used. Fluticasone is used off-label for EoE, hence there is no dose for EoE in the summary of product characteristics (SmPC).[64] The recommended dose for asthma, its licensed indication, is 100 mcg to 1,000 mcg BID for adults and children over 16 years.[64] Whilst the UK clinical experts suggested that the dose of fluticasone would likely be higher for EoE than for asthma, the dose used in the model was the midpoint between the range in the SmPC for asthma – 550 mcg BID.[64] This was considered a conservative approach. The assumption in the model is that patients receive fluticasone for 12 weeks, during the active disease health state, which was based on input from UK clinical experts.

Based on a fluticasone dose of 50 mcg twice daily, 92.4 mg of fluticasone are required over the 12-week period. This equates to 15.4 packs excluding wastage and 16 packs excluding wastage. Thus, the drug cost for fluticasone for the 12-week period in the active disease health state is £104.48.

B.3.5.2.2 Administration cost

As all the drugs used in the model were oral drugs, the costs of administering the drugs were assumed to be zero.

B.3.5.3 Health state unit costs and resource use

B.3.5.3.1 Healthcare professional visit costs

Patients with EoE visit HCPs. The UK clinical experts stated that EoE is seen as a specialist disease and treatment is left to specialists, primarily the gastroenterologist. An assumption in the model is that all patients with EoE will be managed by a gastroenterologist hence visits with other specialists (e.g. ENT specialist) are not included in the economic model. Similarly, another assumption in the model is that patients will not require any GP visits for treatment of

EoE beyond the diagnosis stage. The diagnosis stage was assumed to be the same for all patients (regardless of treatment) and thus not included in the model.

For the gastroenterologist visits, the UK expert clinicians stated that the first visit would be around 20 minutes to 30 minutes duration, with subsequent visits much shorter, around 10 minutes to 15 minutes (see Appendix M). The UK expert clinicians suggested that regardless of treatment, patients in the active EoE health states would have one to two gastroenterologist visits per 12-week cycle. In order to take a conservative approach, the value used in the model is one gastroenterologist visit per 12-week cycle. This applies equally to budesonide ODT, fluticasone and SFED. The assumption was that resource use for no treatment would be the same as fluticasone, hence also the same. Similarly, the UK expert clinicians suggested that patients, regardless of treatment, would not have any gastroenterologist visits during remission (EoE in remission health states).

With respect to a dietician visit, the UK clinical experts stated that patients would only visit a dietician if they were receiving dietary treatment, i.e. SFED. Thus, the assumption in the model is that patients receiving budesonide ODT, fluticasone or no treatment would not visit a dietician during either the active EoE or EoE in remission health states. Patients receiving treatment with SFED would visit a dietician during the active EoE health state – 1.8 visits per 12-week cycle. However, they would not visit a dietician during the EoE in remission health states. A summary of the HCP visits included in the model is provided in Table B.3.8.

Table B.3.8. Summary of HCP visits included in the cost-utility model

HCP visit	Value
Active EoE health states	
Gastroenterologist, first visit (all treatments)	0.0 per cycle
Gastroenterologist, following visits (all treatments)	1.0 per cycle
Dietician (SFED only)	1.8 per cycle
Dietician (budesonide ODT, fluticasone, no treatment)	0.0 per cycle
EoE in remission health states	
Gastroenterologist, first visit (all treatments)	0.0 per cycle
Gastroenterologist, following visits (all treatments)	0.0 per cycle
Dietitian (all treatments)	0.0 per cycle

Abbreviations: EoE = eosinophilic oesophagitis; HCP = healthcare professional; ODT = orodispersible tablet; SFED = six-food elimination diet

Unit costs for HCP visits were obtained from published sources, and are shown in Table B.3.9.[65, 66]

Table B.3.9. Unit costs for HCP visits included in the cost-utility model

HCP visit	Unit cost	Source
Gastroenterologist - first visit	£188.00	Gastroenterology, first visit (code WF01B)[66]
Gastroenterologist - following visits	£72.00	Gastroenterology, following visits (code WF02B)[66]
Dietician	£30.94	Dietitian costs (Band 4)[65]

Abbreviations: HCP = healthcare professional

B.3.5.3.2 Costs for add-on treatment with dilation/emergency food bolus removal

The proportion of patients receiving add-on treatment with dilation and/or emergency food bolus removal in the active disease and remission health states in the base-case analysis were based on the published literature, and are shown in Table B.3.10.

Table B.3.10. Probability of add-on dilation treatment (or emergency food bolus removal) in the cost-utility model

Treatment	Health state	Probability of strictures/bolus impaction per 12-week cycle	Source
Budesonide ODT	Active disease	0.00	BUL-1/EEA[22]
	Remission (without maintenance)	0.15 (60% at 48 weeks)	BUU-2/EEA[21]
Fluticasone	Active disease	0.14 (9.5% at 8 weeks)	Moawad et al., 2013[43]
	Remission (without maintenance)	0.41 (27.0% at 8 weeks)	Dellon et al., 2012[13]
SFED	Active disease	0.01 (8.0% in 24.9 months)	Reed et al., 2017[67]
	Remission (without maintenance)	0.15 (60% at 48 weeks)	BUU-2/EEA[21]
No treatment	Active disease	0.14	Assumption: same as fluticasone
	Remission (without maintenance)	0.41	Assumption: same as fluticasone

Abbreviations: ODT = orodispersible tablet; SFED = six-food elimination diet

The unit cost for dilation/emergency food bolus removal was £448.50. This was the average of food bolus (£343.00) and dilation (£554.00), based on the 2019/20 National Tariff Payment System.[68]

B.3.5.3.3 Monitoring costs

The majority of UK clinical experts consulted did not perform any specific blood tests purely for EoE, nor was there any suggestion that this differed between treatments. Thus, blood tests are excluded from the economic analysis.

For endoscopies, the UK expert clinicians estimated that patients on fluticasone would receive one to three endoscopies per year whilst in the active disease health state. This translates to an average value of 0.47 endoscopies per 12-week cycle. The UK expert clinicians also suggested that patients receiving SFED would receive more endoscopies, around five to six per year. This translates to an average of 1.3 endoscopies per 12-week cycle. And finally, the UK expert clinicians stated that, regardless of treatment, patients would not receive endoscopies during the EoE in remission health states. Table B.3.11 summarises the frequency of endoscopies included in the model.

Table B.3.11. Frequency of endoscopies included in the cost-utility model

Treatment	Frequency of upper endoscopy with biopsy sampling	Source
Active EoE		
Budesonide ODT	0.47	Assumption (same as other drug treatments)
Fluticasone	0.47	UK expert clinician opinion (unweighted average of range provided; range: 1–3 per year = 2 per year = 0.47 per 12-week cycle)
SFED	1.3	UK expert clinician opinion (5–6 per year = 5.5 per year = 1.3 per 12-week cycle)
No treatment	0.47	Assumption that same as fluticasone
EoE in remission		
Budesonide ODT	0.0	UK expert clinician opinion
Fluticasone	0.0	UK expert clinician opinion
SFED	0.0	UK expert clinician opinion
No treatment	0.0	Assumption (same as fluticasone)

Abbreviations: EoE = eosinophilic oesophagitis; ODT = orodispersible tablet; SFED = six-food elimination diet; UK = United Kingdom

The unit cost associated with an upper endoscopy with biopsy sampling was based on the 2018/19 National Tariff, Healthcare Resource Group (UK) code FZ61Z performed as an outpatient procedure costing £391.00.[66]

B.3.5.3.4 Hospitalisation costs

Based on UK expert clinician opinion, the need for inpatient care in the active EoE or EoE in remission health states was minimal. Consequently, hospitalisation costs were not included in the model.

B.3.5.3.5 Costs associated with AEs

The assumption in the model is that AEs were only experienced by patients receiving drug treatments i.e. budesonide ODT or fluticasone. The rate of AEs for budesonide ODT and fluticasone were identified from published sources (see Appendix M).[22, 42, 43, 60] The rate of AEs experienced by patients receiving drug treatment is shown in Section B.3.3.3 (Table B.3.5).

The cost of managing each AE was derived from the interviews with the UK clinical experts as shown in Table B.3.12 (see Appendix M for more detail). The UK clinical experts suggested that most AEs would not be treated. Only oral candidiasis, oesophageal candidiasis and headache would be treated. And the cost of treating these is small.

Table B.3.12. Cost of managing AEs

Adverse Event	Cost per event	Source
Oral candidiasis	£1.68	Resource use based on UK clinical expert opinion; treatment = Nystatin
Oesophageal candidiasis	£1.68	Resource use based on UK clinical expert opinion; treatment = Nystatin
Sleep problems (decreased cortisol information)	£0.00	Resource use based on UK clinical expert opinion; no treatment
Headache	£0.12	Resource use based on UK clinical expert opinion; treatment = paracetamol
Skin disorders	£0.00	Resource use based on UK clinical expert opinion; no treatment
GI disorders	£0.00	Resource use based on UK clinical expert opinion; no treatment
Cough	£0.00	Resource use based on UK clinical expert opinion; no treatment
Pharyngitis	£0.00	Resource use based on UK clinical expert opinion; no treatment
Irritation in nose and/or throat	£0.00	Resource use based on UK clinical expert opinion; no treatment
Respiratory disorders	£0.00	Resource use based on UK clinical expert opinion; no treatment

Abbreviations: AE = adverse event; GI = gastrointestinal; UK = United Kingdom

B.3.5.3.6 Miscellaneous unit costs and resource use

Not applicable.

B.3.6 Summary of base-case analysis inputs and assumptions

B.3.6.1 Summary of base-case *de novo* analysis inputs

Table B.3.13 provides a summary of the variables included in the model.

Table B.3.13. Summary of variables used in the cost-utility model

Variable	Value	Reference to appropriate table or figure in submission	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Utility				
Active EoE (all active EoE health states)	0.70	Table B.3.6	SD 0.24	Section B.3.4; Appendix G
EoE in remission (all remission health states)	0.85	Table B.3.6	SD 0.25	Section B.3.4; Appendix G
Drug cost				
Budesonide ODT – 90 x 1 mg tablets	£323.00	Table B.3.7	Not available	Section B.3.5.2
Fluticasone (Flixotide 500 mcg Evohaler) – 120 x 50 mcg doses	£6.53	Table B.3.7	Not available	Section B.3.5.2
Frequency of resource use - Active EoE				
Dietitian (SFED only)	1.8 per cycle	Table B.3.8	Not available	Section B.3.5.3
Dietician (budesonide ODT, fluticasone, no treatment)	0.0 per cycle	Table B.3.8		Section B.3.5.3
Gastroenterologist, first visit (all treatments)	0.0 per cycle	Table B.3.8	Not available	Section B.3.5.3
Gastroenterologist, following visit (all treatments)	1.0 per cycle	Table B.3.8	Not available	Section B.3.5.3
Add-on treatment with dilation/emergency food bolus removal (budesonide ODT)	Probability 0.00 per cycle	Table B.3.10	Not available	Section B.3.5.3
Add-on treatment with dilation/emergency food bolus removal (fluticasone, no treatment)	Probability 0.14 per cycle	Table B.3.10	Not available	Section B.3.5.3
Add-on treatment with dilation/emergency food bolus removal (SFED)	Probability 0.15 per cycle	Table B.3.10	Not available	Section B.3.5.3
Upper endoscopy with biopsy sampling (SFED)	1.3 per cycle	Table B.3.11	Not available	Section B.3.5.3
Upper endoscopy with biopsy sampling (budesonide ODT, fluticasone, no treatment)	0.47 per cycle	Table B.3.11	Not available	Section B.3.5.3
Frequency of resource use - EoE in remission				
Dietitian (all treatments)	0.0 per cycle	Table B.3.8	Not available	Section B.3.5.3

Variable	Value	Reference to appropriate table or figure in submission	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Gastroenterologist, first visit (all treatments)	0.0 per cycle	Table B.3.8	Not available	Section B.3.5.3
Gastroenterologist, following visit (all treatments)	0.0 per cycle	Table B.3.8	Not available	Section B.3.5.3
Add-on treatment with dilation/emergency food bolus removal (budesonide ODT, SFED)	Probability 0.15 per cycle	Table B.3.10	Not available	Section B.3.5.3
Add-on treatment with dilation/emergency food bolus removal (fluticasone, no treatment)	Probability 0.41 per cycle	Table B.3.10	Not available	Section B.3.5.3
Upper endoscopy with biopsy sampling (all other treatments)	Probability 0.0 per cycle	Table B.3.11	Not available	Section B.3.5.3
Resource use costs				
Dietitian	£30.94	Table B.3.9	Not available	Section B.3.5.3
Gastroenterologist, first visit	£188.00	Table B.3.9	Not available	Section B.3.5.3
Gastroenterologist, following visits	£72.00	Table B.3.9	Not available	Section B.3.5.3
Upper endoscopy with biopsy sampling	£391.00	-	Not available	Section B.3.5.3
Add-on treatment with dilation/ emergency food bolus removal	£448.50	-	Not available	Section B.3.5.3
Frequency of AEs – oral candidiasis, %				
Budesonide ODT	3.4	Table B.3.5	Not available	Section B.3.3; Appendix M
Fluticasone	0.0	Table B.3.5	Not available	Section B.3.3; Appendix M
SFED	0.0	-	Not available	Section B.3.3; Appendix M
No treatment	0.0	-	Not available	Section B.3.3; Appendix M
Frequency of AEs – oesophageal candidiasis, %				
Budesonide ODT	16.9	Table B.3.5	Not available	Section B.3.3; Appendix M
Fluticasone	26.3	Table B.3.5	Not available	Section B.3.3; Appendix M
SFED	0.0	-	Not available	Section B.3.3; Appendix M
No treatment	0.0	-	Not available	Section B.3.3; Appendix M
Frequency of AEs – headache, %				
Budesonide ODT	6.8	Table B.3.5	Not available	Section B.3.3; Appendix M
Fluticasone	4.8	Table B.3.5	Not available	Section B.3.3; Appendix M
SFED	0.0	-	Not available	Section B.3.3; Appendix M
No treatment	0.0	-	Not available	Section B.3.3; Appendix M
AE costs (per event)				
Oral candidiasis	£1.68	Table B.3.12	Not available	Section B.3.5.3; Appendix M

Variable	Value	Reference to appropriate table or figure in submission	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Oesophageal candidiasis	£1.68	Table B.3.12	Not available	Section B.3.5.3; Appendix M
Headache	£0.12	Table B.3.12	Not available	Section B.3.5.3; Appendix M
Response per cycle, %				
Budesonide ODT	94.9	Table B.3.4	Not available	Section B.3.3; Appendix M
Fluticasone	68.0	Table B.3.4	Not available	Section B.3.3; Appendix M
SFED	18.0	Table B.3.4	Not available	Section B.3.3; Appendix M
No treatment	4.0	Table B.3.4	Not available	Section B.3.3; Appendix M
Relapse per cycle for 1st year (after response), %				
Budesonide ODT	22.0	-	Not available	Section B.3.3; Appendix M
Fluticasone	22.0	-	Not available	Section B.3.3; Appendix M
SFED	22.0	-	Not available	Section B.3.3; Appendix M
No treatment	22.0	-	Not available	Section B.3.3; Appendix M

Abbreviations: AE = adverse event; EoE = eosinophilic oesophagitis; mcg = microgram; mg = milligram; ODT = orodispersible tablet; SFED = six-food elimination diet

B.3.6.2 Assumptions

The key assumptions and their justification are detailed in Appendix M.

B.3.7 Base-case results

B.3.7.1 Base-case incremental cost-effectiveness analysis results

The base-case results for budesonide ODT versus fluticasone and budesonide ODT versus SFED are presented in Table B.3.14. This shows that budesonide ODT dominates both fluticasone and SFED, i.e. is associated with improved outcomes and lower costs. Budesonide ODT offers 0.82 additional quality-adjusted life years (QALYs) over fluticasone and 0.98 additional QALYs over SFED. It costs £3,101 less than fluticasone and £3,637 less than SFED. Whilst budesonide ODT is associated with higher drug costs than fluticasone and SFED, these are more than offset by the lower overall costs associated with co-medications (dilation), gastroenterologist visits and endoscopies.

Table B.3.14 Base-case results

	Budesonide ODT	**Fluticasone**	**SFED**
Drug costs	£5,097	£253	£0
Co-medications (dilation)	£5,934	£7,833	£7,163
Medical costs			
Gastroenterologist visits	£3,656	£5,359	£5,693
Dietician visits	£0	£0	£40
Endoscopies	£9,333	£13,677	£14,762
AE costs	£0	£0	£0
TOTAL COSTS	**£24,020**	**£27,122**	**£27,657**
Incremental costs (budesonide ODT versus comparator)	-	–£3,101	–£3,637
TOTAL QALYS	**16.12**	**15.30**	**15.14**
Incremental QALYs (budesonide ODT versus comparator)	-	0.82	0.98
ICER - cost per QALY gained budesonide ODT versus comparator)	**-**	**Budesonide ODT dominates fluticasone**	**Budesonide ODT dominates SFED**

Abbreviations: AE = adverse event; ICER = incremental cost-effectiveness ratio; ODT = orodispersible tablet; QALY = quality-adjusted life year; SFED = six-food elimination diet

B.3.7.2 Expected QALYs by health state for intervention and comparators

Expected QALYs by health state are provided in Table B.3.15. The cost-utility model presents health outcomes as cost per QALY. Cost per life year gained has not been evaluated because budesonide ODT has no impact on mortality. General population mortality is therefore included in the base-case analysis, and a scenario analysis was conducted which did not include general population mortality.

Table B.3.15 Expected QALYs by health state

Health state	QALYs		
	Budesonide ODT	**Fluticasone**	**SFED**
Active EoE – 1st treatment	1.79	0.39	0.11
EoE in remission (without maintenance) – 1st treatment (cycle 1)	2.13	0.39	0.04
EoE in remission (without maintenance) – 1st treatment (cycle 2)	1.65	0.30	0.03
EoE in remission (without maintenance) – 1st treatment (cycle 3)	1.27	0.23	0.03
EoE in remission (without maintenance) – 1st treatment (cycle 4)	0.98	0.18	0.02
EoE in remission (without maintenance) – 1st treatment	0.76	0.14	0.02
Active EoE – 2nd treatment	0.10	0.15	0.16
EoE in remission (without maintenance) – 2nd treatment (cycle 1)	0.01	0.01	0.01
EoE in remission (without maintenance) – 2nd treatment (cycle 2)	0.00	0.01	0.01
EoE in remission (without maintenance) – 2nd treatment (cycle 3)	0.00	0.00	0.01
EoE in remission (without maintenance) – 2nd treatment (cycle 4)	0.00	0.00	0.00
EoE in remission (without maintenance) – 2nd treatment	0.00	0.00	0.00
Active EoE – 3rd treatment	6.30	11.45	12.46
EoE in remission (without maintenance) – 3rd treatment (cycle 1)	0.32	0.58	0.64
EoE in remission (without maintenance) – 3rd treatment (cycle 2)	0.25	0.45	0.49
EoE in remission (without maintenance) – 3rd treatment (cycle 3)	0.19	0.35	0.38
EoE in remission (without maintenance) – 3rd treatment (cycle 4)	0.15	0.27	0.29
EoE in remission (without maintenance) – 3rd treatment	0.22	0.41	0.44
TOTAL	**16.12**	**15.30**	**15.14**

Abbreviations: EoE = eosinophilic oesophagitis; ODT = orodispersible tablet; QALY = quality-adjusted life year; SFED = six-food elimination diet

B.3.7.3 Disaggregated costs by health state for intervention and comparators

Disaggregated costs by health state are provided in Table B.3.16.

Table B.3.16 Disaggregated costs by health state

Health state	Cost (£)		
	Budesonide ODT	Fluticasone	SFED
Active EoE – 1st treatment	7,931	1,033	456
EoE in remission (without maintenance) – 1st treatment (cycle 1)	733	358	15
EoE in remission (without maintenance) – 1st treatment (cycle 2)	566	277	12
EoE in remission (without maintenance) – 1st treatment (cycle 3)	438	214	9
EoE in remission (without maintenance) – 1st treatment (cycle 4)	339	166	7
EoE in remission (without maintenance) – 1st treatment	262	128	5
Active EoE – 2nd treatment	196	307	327
EoE in remission (without maintenance) – 2nd treatment (cycle 1)	5	7	8
EoE in remission (without maintenance) – 2nd treatment (cycle 2)	4	6	6
EoE in remission (without maintenance) – 2nd treatment (cycle 3)	3	4	5
EoE in remission (without maintenance) – 2nd treatment (cycle 4)	2	3	4
EoE in remission (without maintenance) – 2nd treatment	2	3	3
Active EoE – 3rd treatment	12,496	22,713	24,722
EoE in remission (without maintenance) – 3rd treatment (cycle 1)	297	542	590
EoE in remission (without maintenance) – 3rd treatment (cycle 2)	229	418	455
EoE in remission (without maintenance) – 3rd treatment (cycle 3)	176	322	351
EoE in remission (without maintenance) – 3rd treatment (cycle 4)	136	248	271
EoE in remission (without maintenance) – 3rd treatment	206	379	413
TOTAL	24,020	27,130	27,657

Abbreviations: EoE = eosinophilic oesophagitis; ODT = orodispersible tablet; SFED = six-food elimination diet

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

To assess the uncertainty surrounding the variables included in the cost-utility model, a PSA was undertaken using 1,000 iterations. The parameters and distributions around the means are detailed below.

A PSA assesses the joint uncertainty surrounding each and all parameters in the model by assigning predetermined probabilistic distributions and randomly simulating parameter values from these. The distributions used in the model are presented in Table B.3.17

Table B.3.17. Probabilistic distribution according to parameter

Parameter examples	Mean value	Probabilistic value	Distribution (alternative)	Alpha	Beta	SE	Source
Utility parameter							
Active EoE (1st treatment)	0.70	0.69	Beta	2,579.45	1,105.48	0.24	Kartman, Gatz and Johannesson, 2004[52]
EoE in remission (1st treatment)	0.85	0.85	Beta	5,886.08	1,038.72	0.25	Kind, Hardman and Macran, 1999[55]
Active EoE (2nd treatment)	0.70	0.71	Beta	2,579.45	1,105.48	0.24	Kartman, Gatz and Johannesson, 2004[52]
EoE in remission (2nd treatment)	0.85	0.85	Beta	5,886.08	1,038.72	0.25	Kind, Hardman and Macran, 1999 [55]
Active EoE (3rd treatment)	0.70	0.68	Beta	2,579.45	1,105.48	0.24	Kartman, Gatz and Johannesson, 2004[52]
EoE in remission (3rd treatment)	0.85	0.85	Beta	5,886.08	1,038.72	0.25	Kind, Hardman and Macran, 1999[55]
Clinical efficacy parameters							
Budesonide ODT	0.95	0.98	Beta	73.05	3.95	0.02	ITC/NMA
Fluticasone	0.68	0.68	Beta	48.24	22.55	0.05	ITC/NMA
SFED	0.18	0.16	Beta	7.03	31.09	0.06	ITC/NMA

Abbreviations: EoE = eosinophilic oesophagitis; ITC = indirect treatment comparison; NMA = network meta-analysis; ODT = orodispersible tablet; SE = standard error; SFED = six-food elimination diet

The incremental cost-effectiveness results obtained from the PSA are presented in Table B.3.18 and the corresponding scatterplot and cost-effectiveness acceptability curve (CEAC) are presented in Figure B.3.2 and Figure B.3.3, respectively. The results of the PSA derived incremental cost-effectiveness ratios (ICERs) are not dissimilar from the deterministic ICERs reported in the results of the base-case analysis.

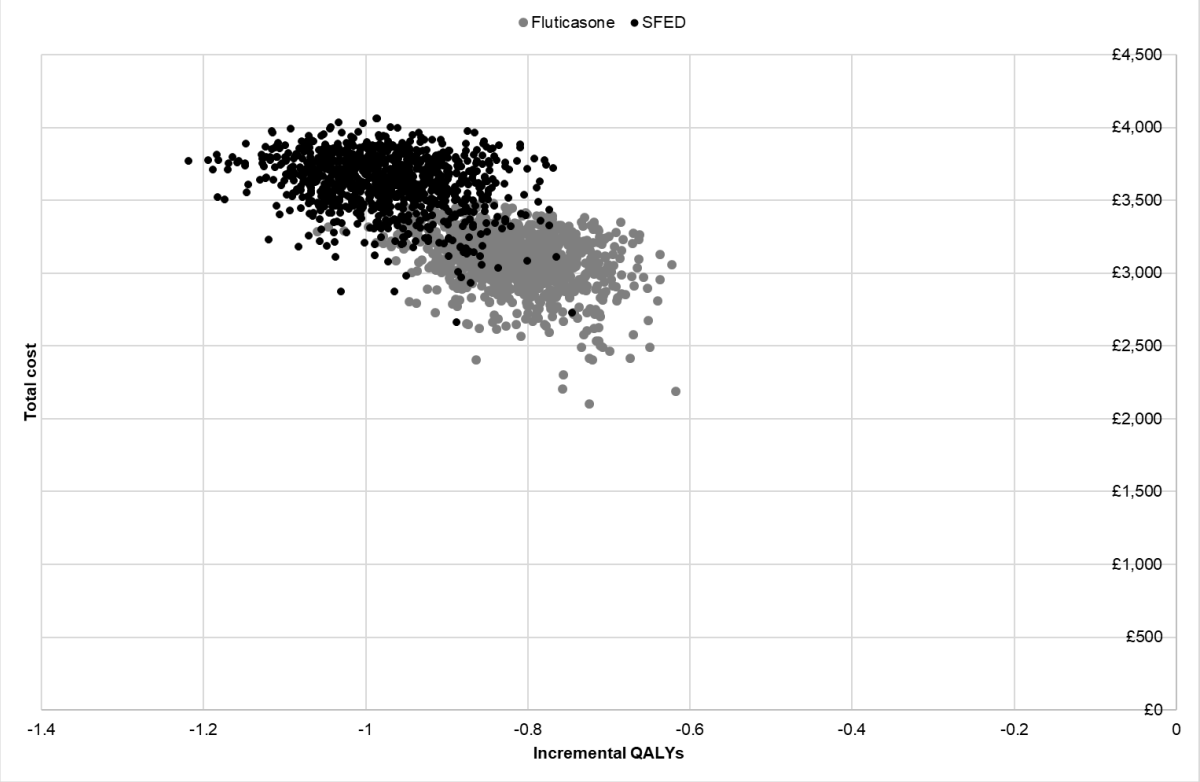
Table B.3.18. Incremental cost-effectiveness results based on PSA

	Total costs (£)	Total QALYs (£)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Budesonide ODT	24,031	16.12	-	-	-
Fluticasone	27,124	15.30	–3,091	0.82	Budesonide ODT dominant
SFED	27,659	15.14	–3,628	0.98	Budesonide ODT dominant

Abbreviations: ICER = incremental cost-effectiveness ratio; ODT = orodispersible tablet; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year; SFED = six-food elimination diet

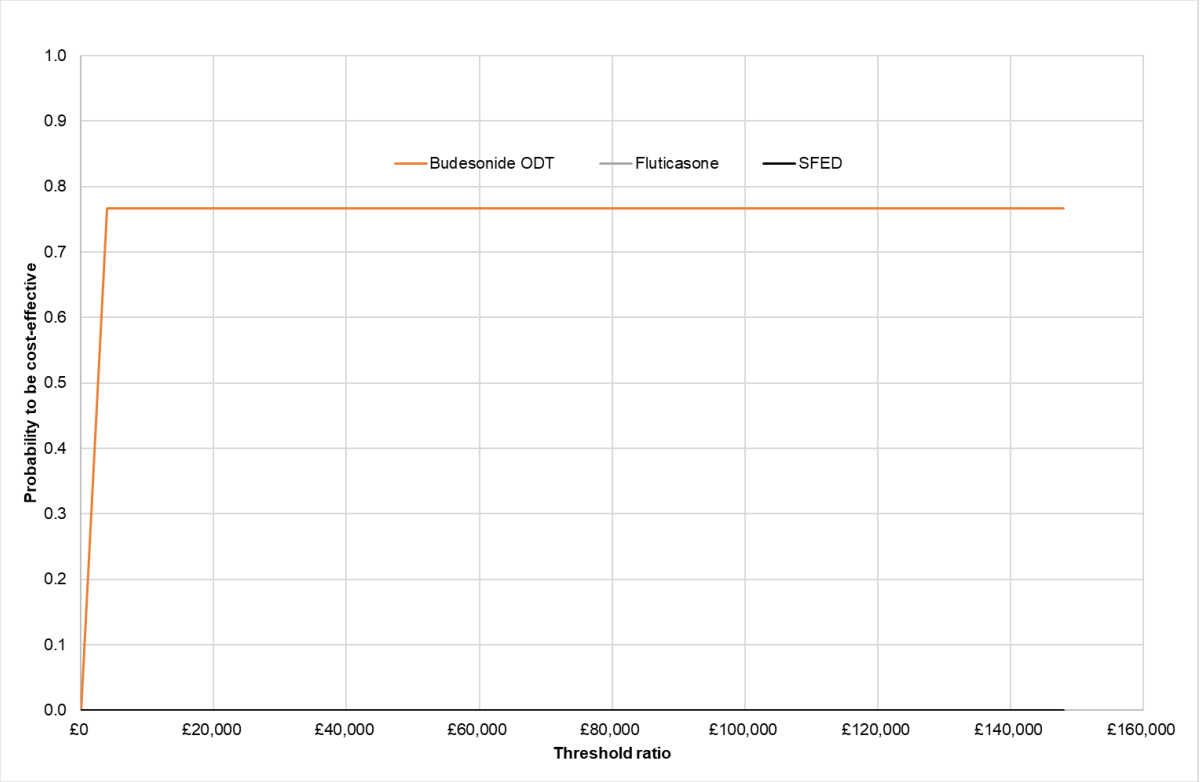
The CEAC shows that for the base-case analysis, there is an approximately 77% probability of budesonide ODT being cost effective at a WTP threshold of £30,000/QALY. In comparison, the CEAC also shows a 0% probability of being cost effective for fluticasone and SFED.

Figure B.3.2. Cost-effectiveness plane



Abbreviations: QALY = quality-adjusted life year; SFED = six-food elimination diet

Figure B.3.3. Cost-effectiveness acceptability curve



Abbreviations: SFED = six-food elimination diet

B.3.8.2 Deterministic sensitivity analysis

DSA were conducted for the following variables using the 5% CI and 95% CIs:

- Response per cycle: budesonide ODT
- Response per cycle: fluticasone
- Response per cycle: SFED
- Response per cycle: no treatment
- Mean utility value: EoE remission (1st treatment)
- Mean utility value: EoE remission (2nd treatment)
- Mean utility value: EoE remission (3rd treatment)
- Mean utility value: EoE active (1st treatment)
- Mean utility value: EoE active (2nd treatment)
- Mean utility value: EoE active (3rd treatment)

Other parameters were included in the DSA for which 95% confidence intervals were not available. The following variables were therefore varied by +/- 20%:

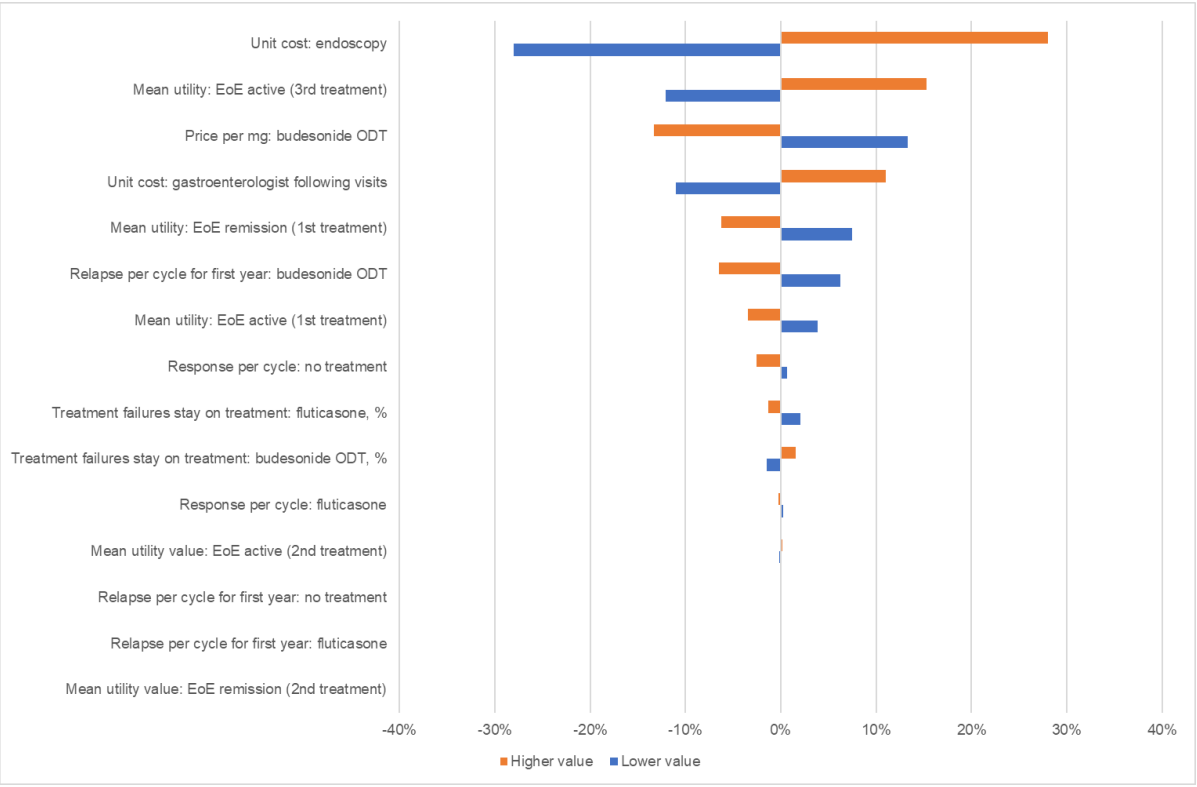
- Price per mg: budesonide ODT
- Price per mg: fluticasone
- Price per pack: budesonide ODT
- Price per pack: fluticasone
- Unit cost: dietician
- Unit cost: gastroenterologist (following visits)
- Unit cost: upper endoscopy with biopsy sampling
- Relapse rate for first year: budesonide ODT

- Relapse rate for first year: fluticasone
- Relapse rate for first year: SFED
- Relapse rate for first year: no treatment
- Percentage of treatment failures who stay on treatment: budesonide ODT
- Percentage of treatment failures who stay on treatment: fluticasone
- Percentage of treatment failures who stay on treatment: SFED
- Percentage of treatment failures who stay on treatment: no treatment

Rates and costs of managing AEs were not included in the DSA as the costs of AEs were negligible in the base-case analysis and thus not considered an important part of the assessment of uncertainty.

A tornado diagram illustrating the results of the DSA for budesonide ODT versus fluticasone is shown in Figure B.3.4. Results versus fluticasone are most sensitive to the mean utility for active EoE (3rd treatment), which is to be expected given the lower response rate for fluticasone versus budesonide ODT, meaning that fluticasone-treated patients will quickly transition to 2nd and 3rd treatment, due to the low response rate for no treatment. These patients will then stay in the EoE active 3rd health state until the end of the model, accruing utilities in this health state. The sensitivity to other utility values is also to be expected; although utility values do not differ by treatment, patients cycle through the different health states at different rates and hence accrue different amounts of utilities. In addition to utilities, results versus fluticasone were sensitive to price per mg of budesonide ODT. Given that the price of budesonide ODT is higher than that of fluticasone, it is expected that varying the price by 20% will impact the cost-effectiveness. Results were also relatively sensitive to response per cycle for Jorveza, mean utility EoE in remission 1st treatment, relapse per cycle for first year, and mean utility EoE active 1st treatment.

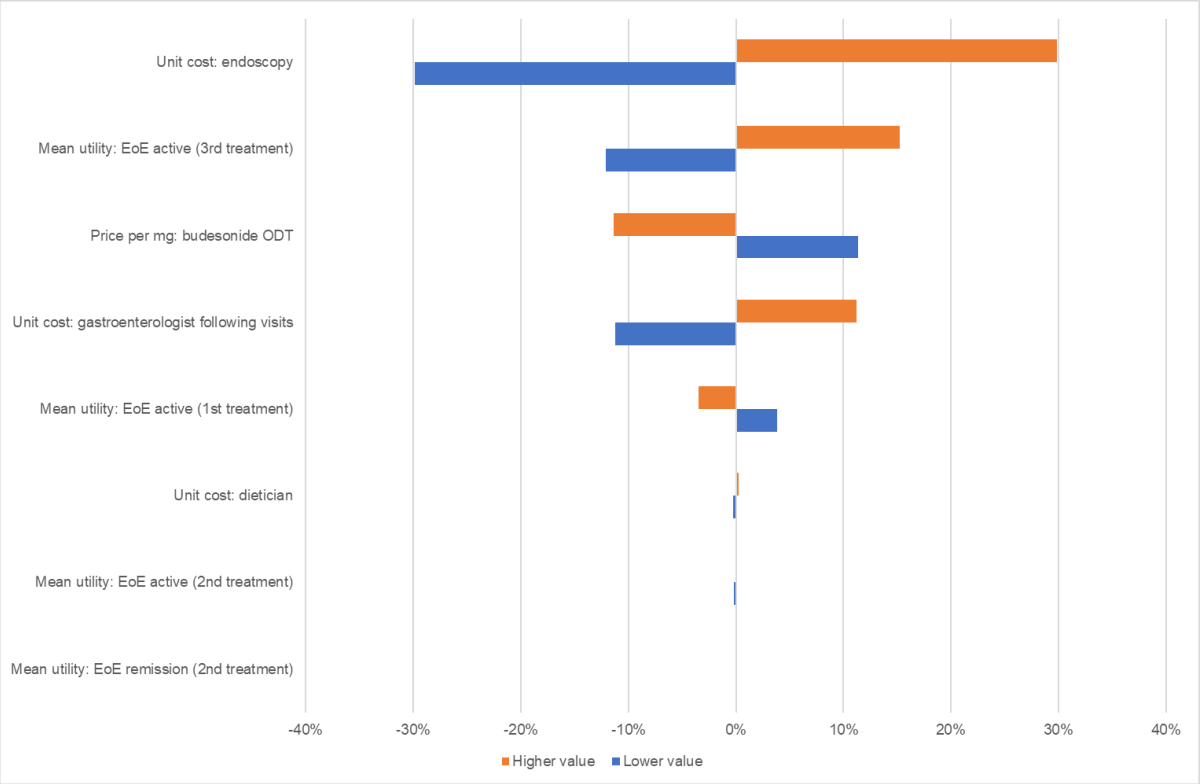
Figure B.3.4. Tornado diagram: Budesonide ODT versus fluticasone



Abbreviations: EoE = eosinophilic oesophagitis; mg = milligram; ODT = orodispersible tablet

A tornado diagram illustrating the results of the DSA for budesonide ODT versus SFED is presented in Figure B.3.5. As with the comparison with fluticasone, the results of the comparison with SFED are most sensitive to the unit cost of endoscopy, mean utility EoE active disease 3rd treatment, price per mg of budesonide and the unit cost of following visits to gastroenterologist. The rationale for this is similar to that for fluticasone. Results were also relatively sensitive to the mean utilities for EoE in remission (1st treatment) and active EoE (1st treatment).

Figure B.3.5. Tornado diagram: Budesonide ODT versus SFED



Abbreviations: EoE = eosinophilic oesophagitis; mg = milligram; ODT = orodispersible tablet

B.3.8.3 Scenario analyses

A number of relevant scenario analyses were conducted to explore the sensitivity of the results to key structural and data assumptions used in the model. All scenario analyses are summarised in the Table B.3.19 below and the results are shown below that.

Table B.3.19. Summary of scenario analyses

Parameter	Base-case analysis	Alternative scenarios
Time horizon	40 years	10 years
Discount rate	3.5%	0.0%
Active EoE health state utility values	Mean utility = 0.70	Mean utility = 0.56
General population mortality	Applied	Not applied
2nd treatments	No treatment	Fluticasone after 1st treatment with SFED; SFED after 1st treatment with budesonide ODT and fluticasone
Budesonide ODT and fluticasone drug wastage	Included	Not included
Duration of budesonide ODT treatment	6 weeks or 12 weeks	12 weeks only

Abbreviations: EoE = eosinophilic oesophagitis; ODT = orodispersible tablet; SFED = six-food elimination diet

B.3.8.3.1 Time horizon of 10 years

The NICE reference case requires a time horizon that is long enough to reflect all important differences in costs or outcomes between the technologies being compared. Thus, the time horizon in the base-case analysis is 40 years. However, due to EoE being a rare disease and limited treatment options for it, the UK clinical experts suggested that a shorter time horizon might be appropriate as there is a lot of uncertainty beyond the immediate 5-year to 10-year period.

The results of the scenario analysis using a time horizon of 10 years are shown in Table B.3.20. As in the base-case analysis, budesonide ODT dominates both fluticasone and SFED. However, the difference in costs and QALYs between budesonide ODT and the comparators is smaller than in the base-case analysis as there is less time for them to accrue.

Table B.3.20. Scenario analysis – 10-year time horizon

	Budesonide ODT	Fluticasone	SFED
Drug costs	£3,150	£249	£0
Co-medications (dilation)	£2,111	£3,491	£2,830
Medical costs	£3,709	£6,967	£8,407
AE costs	£0	£0	£0
TOTAL COSTS	**£8,970**	**£10,707**	**£11,236**
Incremental costs (budesonide ODT versus comparator)	-	–£1,737	–£2,656
TOTAL QALYS	**6.71**	**6.27**	**6.12**
Incremental QALYs (budesonide ODT versus comparator)	-	0.44	0.60
ICER - cost per QALY gained (budesonide ODT versus comparator)	**-**	**Budesonide ODT dominates fluticasone**	**Budesonide ODT dominates SFED**

Abbreviations: AE = adverse event; ICER = incremental cost-effectiveness ratio; ODT = orodispersible tablet; QALY = quality-adjusted life year; SFED = six-food elimination diet

B.3.8.3.2 Discount rate of 0% for costs and effects

The NICE reference case requires a discount rate of 3.5% for both costs and effects. This scenario analysis assesses the impact on the results when discounting is not employed.

The results of the scenario analysis using a discount rate of 0% for both costs and effects are shown in Table B.3.21 below. As in the base-case analysis, budesonide ODT dominates both fluticasone and SFED but with a larger difference in costs and QALYs between budesonide ODT and the two comparators.

Table B.3.21. Scenario analysis – 0% discount rate for costs and effects

	Budesonide ODT	**Fluticasone**	**SFED**
Drug costs	£7,558	£275	£0
Co-medications (dilation)	£11,263	£13,861	£13,134
Medical costs	£26,101	£35,580	£37,161
AE costs	£0	£0	£0
TOTAL COSTS	**£44,922**	**£49,717**	**£50,294**
Incremental costs (budesonide ODT versus comparator)	-	–£4,794	–£5,372
TOTAL QALYS	**29.04**	**27.76**	**27.59**
Incremental QALYs (budesonide ODT versus comparator)	-	1.28	1.46
ICER - cost per QALY gained (budesonide ODT versus comparator)	**-**	**Budesonide ODT dominates fluticasone**	**Budesonide ODT dominates SFED**

Abbreviations: AE = adverse event; ICER = incremental cost-effectiveness ratio; ODT = orodispersible tablet; QALY = quality-adjusted life year; SFED = six-food elimination diet

B.3.8.3.3 Active EoE health state utility value of 0.56

In this scenario analysis, the utility value for active EoE used in the base-case analysis (mean=0.70)[52] was changed to 0.56,[61] based on a UK study which measured the QoL in GORD patients with relapse. The UK expert clinicians suggested that the utility value of active EoE used in the base-case analysis might be an overestimate as patients with EoE generally have poorer QoL than patients with GORD with heartburn. As this scenario analysis focuses only on utilities, the costs are the same as in the base-case analysis.

The results of the scenario analysis are shown in Table B.3.22. As in the base-case analysis, budesonide ODT dominates both fluticasone and SFED, though the incremental utilities are larger in this scenario hence this scenario is more favourable to budesonide ODT.

Table B.3.22. Scenario analysis – active EoE health state utility value of 0.56

	Budesonide ODT	Fluticasone	SFED
Drug costs	£5,097	£253	£0
Co-medications (dilation)	£5,934	£7,833	£7,163
Medical costs	£12,989	£19,036	£20,494
AE costs	£0	£0	£0
TOTAL COSTS	**£24,020**	**£27,122**	**£27,657**
Incremental costs (budesonide ODT versus comparator)	-	–£3,101	–£3,637
TOTAL QALYS	**14.48**	**12.90**	**12.59**
Incremental QALYs (budesonide ODT versus comparator)	-	1.58	1.89
ICER - cost per QALY gained (budesonide ODT versus comparator)	**-**	**Budesonide ODT dominates fluticasone**	**Budesonide ODT dominates SFED**

Abbreviations: AE = adverse event; EoE = eosinophilic oesophagitis; ICER = incremental cost-effectiveness ratio; ODT = orodispersible tablet; QALY = quality-adjusted life year; SFED = six-food elimination diet

B.3.8.3.4 General population mortality not applied

The general population mortality is applied in the base-case analysis. Not applying this in a scenario analysis results in higher costs and utilities for all technologies when compared to the base-case analysis. This is because on average, patients spend more time alive and accrue additional costs and utilities during this time.

The results of the scenario analysis are shown in Table B.3.23. As in the base-case analysis, budesonide ODT dominates both fluticasone and SFED. The results are broadly similar to the results of the base-case analysis.

Table B.3.23. Scenario analysis – general population mortality not applied

	Budesonide ODT	Fluticasone	SFED
Drug costs	£5,170	£253	£0
Co-medications (dilation)	£6,131	£8,050	£7,379
Medical costs	£13,484	£19,637	£21,098
AE costs	£0	£0	£0
TOTAL COSTS	**£24,788**	**£27,941**	**£28,477**
Incremental costs (budesonide ODT versus comparator)	-	–£3,153	–£3,689
TOTAL QALYS	**16.58**	**15.75**	**15.59**
Incremental QALYs (budesonide ODT versus comparator)	-	0.83	0.99
ICER - cost per QALY gained (budesonide ODT versus comparator)	**-**	**Budesonide ODT dominates fluticasone**	**Budesonide ODT dominates SFED**

Abbreviations: AE = adverse event; ICER = incremental cost-effectiveness ratio; ODT = orodispersible tablet; QALY = quality-adjusted life year; SFED = six-food elimination diet

B.3.8.3.5 Active treatment as 2nd treatment

In the base-case analysis, no treatment is used as both 2nd and 3rd treatments for all technologies. In this scenario analysis, an active treatment is used as 2nd treatment with no

treatment as 3rd treatment. The active treatment differs by comparator. For budesonide ODT, the active treatment is SFED. The assumption here is that a clinician would not prescribe fluticasone after budesonide ODT as budesonide ODT is specifically designed to deliver therapeutic levels of budesonide to the oesophagus. If budesonide ODT was not effective, it is unlikely that a clinician would then prescribe a delivery system appropriate for asthma but not for EoE for an essentially similar active ingredient. For fluticasone, the only option for active treatment is SFED. And for SFED, the only option for active treatment is fluticasone.

The results of the scenario analysis are shown in Table B.3.24. As in the base-case analysis, budesonide ODT dominates both fluticasone and SFED. The results are very similar to those of the base-case analysis.

Table B.3.24. Scenario analysis – active treatment as 2nd treatment

	Budesonide ODT	**Fluticasone**	**SFED**
Drug costs	£5,097	£253	£300
Co-medications (dilation)	£5,877	£7,743	£7,756
Medical costs	£13,190	£19,351	£19,207
AE costs	£0	£0	£0
TOTAL COSTS	**£24,164**	**£27,346**	**£27,262**
Incremental costs (budesonide ODT versus comparator)	-	–£3,183	–£3,099
TOTAL QALYS	**16.13**	**15.32**	**15.32**
Incremental QALYs (budesonide ODT versus comparator)	-	0.81	0.81
ICER - cost per QALY gained (budesonide ODT versus comparator)	**-**	**Budesonide ODT dominates fluticasone**	**Budesonide ODT dominates SFED**

Abbreviations: AE = adverse event; ICER = incremental cost-effectiveness ratio; ODT = orodispersible tablet; QALY = quality-adjusted life year; SFED = six-food elimination diet

B.3.8.3.6 Drug wastage with budesonide ODT and fluticasone excluded

In the base-case analysis, drug wastage with budesonide ODT and fluticasone is included. This is because both drugs are supplied in packs, and patients will not use the full pack in order to meet the required dosing over the 12-week treatment cycle. Therefore, in this scenario analysis, drug wastage is excluded. This scenario is more realistic for patients who receive treatment on an ongoing basis as they will have the opportunity to use the excess over a longer time period.

The results of the scenario analysis are shown in Table B.3.25. As in the base-case analysis, budesonide ODT dominates both fluticasone and SFED. The results are very similar to those of the base-case analysis.

Table B.3.25. Scenario analysis – drug wastage with budesonide ODT excluded

	Budesonide ODT	Fluticasone	SFED
Drug costs	£4,757	£243	£0
Co-medications (dilation)	£5,934	£7,833	£7,163
Medical costs	£12,989	£19,036	£20,494
AE costs	£0	£0	£0
TOTAL COSTS	**£23,681**	**£27,112**	**£27,657**
Incremental costs (budesonide ODT versus comparator)	-	–£3,432	–£3,977
TOTAL QALYS	**16.12**	**15.30**	**15.14**
Incremental QALYs (budesonide ODT versus comparator)	-	0.82	0.98
ICER - cost per QALY gained (budesonide ODT versus comparator)	**-**	**Budesonide ODT dominates fluticasone**	**Budesonide ODT dominates SFED**

Abbreviations: AE = adverse event; ICER = incremental cost-effectiveness ratio; ODT = orodispersible tablet; QALY = quality-adjusted life year; SFED = six-food elimination diet

B.3.8.3.7 Budesonide ODT treatment duration of 12 weeks

In the base-case analysis, patients receive treatment with budesonide ODT for either 6 weeks (57.6%) or 12 weeks (42.4%). In this scenario analysis, all patients receive treatment with budesonide ODT for 12 weeks.

The results of the scenario analysis are shown in Table B.3.26. Despite a higher cost associated with budesonide ODT in this scenario, budesonide ODT still dominates both fluticasone and SFED.

Table B.3.26. Scenario analysis – 12-week duration of budesonide ODT treatment

	Budesonide ODT	Fluticasone	SFED
Drug costs	£7,158	£253	£0
Co-medications (dilation)	£5,934	£7,833	£7,163
Medical costs	£12,989	£19,036	£20,494
AE costs	£0	£0	£0
TOTAL COSTS	**£26,082**	**£27,122**	**£27,657**
Incremental costs (budesonide ODT versus comparator)	-	–£1,040	–£1,575
TOTAL QALYS	**16.12**	**15.30**	**15.14**
Incremental QALYs (budesonide ODT versus comparator)	-	0.82	0.98
ICER - cost per QALY gained (budesonide ODT versus comparator)	**-**	**Budesonide ODT dominates fluticasone**	**Budesonide ODT dominates SFED**

Abbreviations: AE = adverse event; ICER = incremental cost-effectiveness ratio; ODT = orodispersible tablet; QALY = quality-adjusted life year; SFED = six-food elimination diet

B.3.8.4 Summary of sensitivity analyses results

PSA was undertaken using 1,000 iterations. The resultant ICERs show budesonide ODT dominates both fluticasone and SFED. The results of the PSA derived ICERs are not dissimilar from the deterministic ICERs reported in the results of the base-case analysis. The CEAC

shows that, for the base-case analysis, there is 77% probability of budesonide ODT being cost effective at a WTP threshold of £30,000/QALY. In comparison, the CEAC also shows that there is a 0% probability of both fluticasone and SFED being cost effective at a WTP threshold of £30,000 per QALY.

The DSA showed that the results are most sensitive to the unit cost of endoscopy, mean utility for active EoE (3rd treatment), price per mg of budesonide ODT and the unit cost of following visits to gastroenterologist.

Budesonide ODT continues to dominate both fluticasone and SFED in all the scenario analyses, even when the duration of budesonide ODT treatment was 12 weeks for all patients. However, in some cases, the deltas were significantly reduced.

B.3.9 Subgroup analysis

No relevant subgroups were identified relevant to the treatment of EoE during the literature reviews.

B.3.10 Validation

B.3.10.1 Validation of *de novo* cost-effectiveness analysis

B.3.10.1.1 External expert validation

External clinical and health economic experts were consulted throughout the development of the cost-utility model. In addition, a series of one-on-one interviews were conducted with seven clinical EoE experts in the UK. The primary purpose of these interviews was to support development of the model structure, determine the base-case scenario and determine key model inputs. Consequently, this included advice for deviating from the NICE reference case with regards selection of the appropriate comparators. The input of these experts is documented in the appropriate sections of this submission.

B.3.10.1.2 Internal validation

The model validation process aims to be consistent with good practice recommendations as reported by the International Society for Pharmacoeconomics and Outcomes Research. The model output was compared against clinical evidence to ensure model validity as well as with previously published models (cross-validation) where applicable to determine the extent to which they calculate similar results.

B.3.10.1.3 Electronic model validation

The Excel® electronic version underwent several rounds of internal quality assessment using both functional and glass box testing by different health economic modellers (from the UK) at Advantage Technoeconomics. No major issues were identified from a structural and conceptual point of view or in the Excel® implementation. It was noted that the model has good quality documentation, clear graphics, as well as many other useful features.

B.3.10.1.4 Generalisability of the analysis to the clinical practice in England and Wales

The analysis is directly applicable to clinical practice in England and Wales since the patient population in the budesonide ODT trials and the *de novo* economic evaluation are reflective of patients with EoE in the UK, as validated by UK expert clinicians. It is the first model of its kind for the disease for NICE. The resource utilisation is reflective of UK clinical practice and was primarily derived from clinician opinion from the seven UK expert clinicians.

B.3.11 Interpretation and conclusions of economic evidence

This submission demonstrates the cost-effectiveness of budesonide ODT versus fluticasone and SFED using a simple and conservative modelling approach, with transparent and explicit reporting of assumptions. During the development of this submission, careful consideration was given to the previous request from the NICE Evidence Review Group (ERG), and the following changes have been incorporated (including within the results for the base-case analysis):

- A longer time horizon (up to 40 years)
- Include general population mortality
- Include age-adjusted utilities
- Include 1st line treatments only with no treatment thereafter
- Include an option to include subsequent treatment line with a mix of treatments according to UK clinical practice.

Age-adjusted utilities were not included, due to a lack of available data for the active EoE health state. A scenario analysis including a subsequent treatment line (2nd treatment) is included. However, due to the limited number of treatment options, this does not include a treatment mix.

The SLR of the economic literature did not identify any relevant published studies assessing the cost-effectiveness of budesonide ODT relevant to this appraisal, so it is not possible to make comparisons with published literature for the intervention of interest.

Extensive literature reviews were conducted to support this appraisal. However, given that EoE is a rare disease, there was a lack of relevant published studies in this area. Consequently, one-on-one interviews with UK experts in EoE were conducted in January and February 2019. These interviews were conducted to support the model development, identify treatment patterns and determine key parameters to populate the model. The same UK experts were also consulted in September 2019 in order to gain additional insights (see Appendix L).

B.3.11.1 Interpretation of the results of the economic evaluation

The base-case analysis demonstrates that budesonide ODT dominates both fluticasone and SFED. The main driver of the cost-effectiveness results is the response rates which are based on the NMA. The response rates for budesonide ODT, fluticasone, SFED and no treatment used in the cost-utility model are 95%, 68%, 18% and 4%, respectively. These response rates determine how patients transition through the model. Hence patients on budesonide ODT will spend more time in the EoE in remission health states which are associated with lower resource utilisation and higher utility values.

The deterministic univariate sensitivity analyses (Section B.3.8) showed that the results are most sensitive to the unit cost of endoscopy, mean utility for active EoE (3rd treatment), price per mg of budesonide ODT and the unit cost of following visits to a gastroenterologist for the comparisons with both fluticasone and SFED.

A number of scenario analyses were conducted (Section B.3.8). In all these scenario analyses, budesonide ODT continued to dominate fluticasone and SFED. The change of utility value for the active EoE health state (from 0.7 to 0.56) had an impact on the results despite it only impacting the QALYs, with the costs remained unchanged. Similarly, the shorter time horizon (from 40 years to 10 years) also impacted the results. The costs and QALYs were significantly lower due to the much shorter time horizon for these to accrue. However, the overall result of dominance over fluticasone and SFED was unchanged.

The utility values used in the model had an impact on the results. The budesonide ODT clinical trials did not include the EQ-5D so utility values could not be obtained from the budesonide ODT clinical trials. Similarly, no published studies were identified in which utility values for EoE could be obtained. Consequently, the resultant utility value used for the active EoE health states in the model was for GORD with heartburn. The UK expert clinicians suggested that QoL for EoE would be lower than QoL for GORD with relapse. And also, that one would expect milder GORD patients than mild EoE patients. Thus, it's likely that the utility value for active EoE is overestimated in the model and hence unfavourable to budesonide ODT. This is thus considered a conservative approach.

The results of the cost-effectiveness analysis only apply to patients who have previously been treated with PPIs. Feedback from the UK expert clinicians was that almost all patients have been treated with PPIs prior to diagnosis of EoE. Hence, PPIs are not a comparator for budesonide ODT in the UK.

This is the first NICE appraisal for EoE and the first cost-effectiveness analysis developed for EoE in the UK. Consequently, there is limited information available on which to compare the results of this analysis.

B.3.11.2 Strengths and weaknesses of the evaluation

The key strengths and weaknesses of the evaluation are shown in Table B.3.27.

Table B.3.27. Key strengths and weaknesses of the evaluation

Strengths of the evaluation
• The structure of the Markov model, with health states for active EoE and EoE in remission aligns well with the natural disease process. It has been used extensively in previous oesophagitis indications and is a transparent method for evaluating costs and health effects over time based on clinical trial data • The cost-utility model is populated with the best currently available evidence for the UK • The model is the first of its kind to estimate the cost-effectiveness of budesonide ODT over other treatment options, including fluticasone and SFED in the UK. This paves the way for future research and recommendations in the management of EoE • The estimation of utility values in the model was based on a SLR. GORD utilities were used to value EoE patient's QoL in the active EoE health state. Although non-EoE-specific utilities had to be used in the model, EoE is often misdiagnosed as GORD, so this could be an adequate representation of the valuation of QoL in the active EoE health state • Resource utilisation and unit costs used in the model are reflective of UK clinical practice, with resource use derived from interviews with UK expert clinicians

• An extensive set of sensitivity and scenario analyses were conducted to explore uncertainty around the model input parameters and structural uncertainty underlying the model. All analyses indicated model outcomes to be relatively stable, irrespective of (structural) uncertainty
Weaknesses of the evaluation
• One of the comparators in the model – fluticasone – is not indicated for the treatment of adults with EoE • The model does not include an option for maintenance treatment as budesonide ODT is not indicated for maintenance treatment. However, treatment of EoE appears to include both maintenance and treatment options • No direct head-to-head clinical trial data were available on efficacy and safety of budesonide ODT in the UK population. This analysis considers the relative treatment effect to be transferable across populations as the body of evidence available is based on trials incorporating patients from many different countries • The response rates used in the model were derived from the NMA and hence the limitations of the NMA are also limitations in the model • The response rates used in the model were based on histological remission whereas in reality physicians are more likely to treat based on symptoms and hence avoid excessive use of endoscopies

Abbreviations: EoE = eosinophilic oesophagitis; GORD = gastro-oesophageal reflux disease; NMA = network meta-analysis; ODT = orodispersible tablet; QoL = quality of life; SFED = six-food elimination diet; UK = United Kingdom

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B.5. Appendices

Appendix C. Summary of product characteristics (SmPC) and European public assessment report (EPAR)

Appendix D. Identification, selection and synthesis of clinical evidence

Appendix E. Subgroup analysis

Appendix F. Adverse reactions

Appendix G. Published cost-effectiveness studies

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Appendix M. Additional information relating to the economic analysis

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Budesonide for treating active eosinophilic oesophagitis [ID1202]

Clarification questions

October 2019

File name	Version	Contains confidential information	Date
ID1202 Budesonide ERG clarification answers v1.0 041119 [noACIC]	1.0	No	04-11-2019

Notes for company

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Section A: Clarification on effectiveness data

Indirect treatment comparison

A1. Please can you clarify the status of the pairwise meta-analysis of budesonide ODT 1mg versus placebo in Figure B.2.4? Is this just for illustration, or is the pooled odds ratio effect estimate used in the network meta-analysis?

The pooled odds ratio presented in Figure B.2.4 was not used in the network meta-analysis and is therefore illustrative.

A2. In Table B.5.7 ‘Inclusion and exclusion criteria’, the study design criterion is stated as ‘Meta-analysis or systematic review’. However, the systematic review of clinical effectiveness studies includes primary studies as well as meta-analyses and systematic reviews. Of note it is stated in D.1.2 that ‘Single-arm studies’ were excluded from the indirect treatment comparison. For the avoidance of doubt please clarify the exact inclusion criteria as regards study design in the systematic review of clinical effectiveness studies, and in relation to the indirect treatment comparison.

The systematic review of clinical effectiveness studies included primary analyses, meta-analyses and systematic reviews. However, there was an error in Table B.5.7, with ‘randomised controlled trial’, ‘non-randomised clinical study’ and ‘retrospective analysis’ omitted from Criterion I6 (publication). Further details of Criteria I7 (region) and I8 (publication year) were also omitted in error. The full inclusion and exclusion criteria are shown in Table 1.

Table 1. Inclusion and exclusion criteria for systematic search for data on clinical efficacy and safety

Criterion		Description
I1	Indication	Adult patients with EoE or PPI-REE. Mixed populations were included, if ≥50% of the patients were adults and/or the mean age of the population was >18 years
I2	Intervention	Treatments for EoE which are recommended in the majority of available guidelines published by relevant institutions in Western developed countries, i.e. topical steroids, PPIs, oesophageal dilation or dietary intervention
I3	Outcomes	Contains data on efficacy and/or safety and/or health-related quality of life
I4	Publication type	Full text publication available
I5	Language	No limit
I6	Publication type	Meta-analysis or systematic review Or randomised controlled trial Or non-randomised clinical study Or retrospective analysis
I7	Region	Priority 1: Western developed countries (Europe or North America or Australia) Priority 2: Rest of world (only eligible if no data from priority regions are available)
I8	Publication year	Original: No limit Update: published between the original search date and the date of the update search
E1–E8		Exclusion criteria were assigned based on the violation of the respective inclusion criterion
E9	Publication type	Secondary or duplicate publication without additional data

Abbreviations: EoE = eosinophilic oesophagitis; PPI = proton-pump inhibitor; PPI-REE = proton-pump inhibitor-responsive oesophageal eosinophilia

A3. Priority question: The inclusion criteria for the indirect treatment comparison are not completely clear. Section D.1.2 reports the exclusion reasons for 35 of 45 primary clinical studies which had met the inclusion criteria for the systematic review of clinical studies specified in Table B.5.7.

a) We note that one study was excluded because it did not completely fulfil the age criterion of the inclusion and exclusion criteria. Age was a criterion for inclusion in the systematic review of clinical studies (Table B.5.7), so any studies failing this criterion should not have been included in the set of 45 clinical studies. Were additional age criteria used for the indirect treatment comparison?

While Butz et al., 2014[1] did not fulfil the pre-specified inclusion/exclusion criteria, the two reviewers initially decided to include the study in the analysis at the time of study selection because, at that time, data appeared scarce, there was no clear evidence to exclude studies and the age range of included patients clearly showed that the study population included adults. Following ERG clarification questions in March 2019, the network meta-analysis (NMA) was updated with Butz et al., 2014 excluded. No additional age criteria were used for the NMA.

b) It is stated that of the remaining 10 studies used to populate the indirect treatment comparison, 5 were excluded. However, the criteria used to exclude these studies are not stated. Please can you confirm the criteria used to exclude studies from the indirect treatment comparison, and provide a bibliographic list of the studies with the reason(s) for the exclusion of each study.

Elements of the company submission were based on work performed prior to NICE's decision to include budesonide orodispersible table (ODT) in the technology appraisal process. As this work was performed to satisfy the reimbursement and pricing requirements of several European countries (including the development of a global health economic model), the search was kept intentionally broad regarding potential comparator treatments. However, as described in Section B.1.3.6, expert clinical opinion suggested that patients with eosinophilic oesophagitis (EoE) in the UK are typically already treated unsuccessfully with protein pump inhibitors (PPIs) prior

to diagnosis, and with a limited set of off-label treatments after diagnosis, including fluticasone, six-food elimination diet (SFED) and budesonide oral viscous solution (OVS). As such, the final subset of five studies was selected based on the comparators of interest (fluticasone and SFED, with placebo and budesonide OVS included to connect the intervention and comparators).[2-6] Other than the criteria described in Table 1, no further formal inclusion/exclusion criteria were used to select studies for the NMA. Rather, five studies were excluded as they included treatment arms not relevant to UK clinical practice and/or did not contribute to the comparison of budesonide ODT with fluticasone, SFED budesonide OVS or placebo.[7-11] A list of excluded studies is shown in Table 2.

Table 2. Studies included in the systematic review but excluded from the NMA

Authors	Title	Publication
Dellon ES, Sheikh A, Speck O et al.	Viscous topical is more effective than nebulized steroid therapy for patients with eosinophilic esophagitis	Gastroenterology 2012; 143(2): 321–324
Moawad FJ, Veerappan GR, Dias JA et al.	Randomized controlled trial comparing aerosolized swallowed fluticasone to esomeprazole for esophageal eosinophilia	Am J Gastroenterol 2013; 108(3): 366–372
Peterson KA, Thomas KL Hilden K et al.	Comparison of esomeprazole to aerosolized, swallowed fluticasone for eosinophilic esophagitis	Dig Dis Sci 2010; 55(5): 1313–1319
Rodriguez-Sanchez J, Gomez Torrijos E, Lopez Viedma B et al.	Efficacy of IgE-targeted vs empiric six-food elimination diets for adult eosinophilic oesophagitis	Allergy 2014; 69(7): 936–942
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

Abbreviations: NMA = network meta-analysis

c) It is mentioned that UK expert clinical opinion suggests that EoE patients are typically treated unsuccessfully with PPIs prior to diagnosis. We infer from this statement that treatment with a PPI post-diagnosis was an exclusion criterion from the indirect treatment comparison. If this is correct please could you provide a scenario analysis in which studies of PPI treatment post-diagnosis are included with the existing studies, thus allowing an indirect comparison of budesonide ODT versus PPI treatment. This would be informative in case the NICE appraisal committee takes the view that PPI treatment is relevant to current UK practice.

Studies of PPIs were not included in the NMA presented in the company submission, reflecting clinical expert opinion on the UK treatment pathway (see Section B.1.3.6) and the decision problem addressed in the company submission (see Section B1.1). Currently, patients typically receive PPIs prior to diagnosis of EoE, and this is not expected to change following the introduction of budesonide ODT. Therefore, budesonide ODT is effectively a second-line therapy for those patients who are unresponsive to PPIs. As such, PPIs would not be used in place of budesonide ODT and are therefore not a relevant comparator.

Although PPIs are therefore not a relevant comparator, in response to March 2019 ERG questions, an NMA was performed based on a wider network of ten studies,[2,3,7,4,5,8,9,6,10,12] which included those evaluating PPIs. Based on the deviance information criteria (DIC), the fixed-effects model was chosen (84,474 and 85,186 for the fixed-effects and random-effects models, respectively). Results of this NMA are shown in Table 3.

Table 3. Fixed-effects NMA based on analysis of rates of remission (defined as <16 eos/mm^2 hpf)

Budesonide ODT 1 mg BID versus:	OR	95% CrI
Budesonide OVS	1.99	0.242, 13.700
Fluticasone	2.44	0.095, 32.940
PPI	0.97	0.036, 16.770
SFED	18.22	1.937, 166.000

Abbreviations: BID = twice daily; CrI = credible interval; eos = eosinophil; hpf = high-power field; mg = milligram; mm = millimetre; NMA = network meta-analysis; ODT = orodispersible tablet; OR = odds ratio; OVS = oral viscous solution; PPI = proton pump inhibitor; SFED = six-food elimination diet

d) The ERG's assumption is that placebo and budesonide OVS are included in the network only to connect the treatments that met the inclusion criteria. Therefore, they are not relevant comparators to budesonide ODT. Please can you confirm if this is this assumption is correct.

This assumption is correct.

A4. It is stated in B.2.9 that an examination of clinical heterogeneity did not show substantial variations between comparisons with respect to "known effect modifiers". It is not stated what these known effect modifiers are and there isn't a tabulated comparison of baseline characteristics. Please can you provide this (you may want

to cite any relevant information that you provided in answer to clarification question A12 in the previous set of clarification questions in March 2019).

Data were extracted for studies included in the NMA on key aspects of study participants' characteristics, study interventions and outcomes measurement. These are presented in Table 4, Table 5 and Table 6, respectively. For a discussion of clinical heterogeneity, see company submission (CS) Section B.2.9.1.2.

Table 4. Summary of baseline characteristics

Study	Treatment arm	N	Mean age, years (SD/range)	Male, %	Race	Mean BMI (SD)	Mean symptom duration, (SD)	New EoE diagnosis, %	Mean time since diagnosis (SD)	Concomitant/ history of atopic/ allergic disease	History of PPI, %	History of endoscopic dilatation, %	Total mean peak eos (SD/range)
Alexander et al., 2012[2]	Fluticasone	21	37 (19–59)	85.7	NR	NR	1–5 years	100	0 months	66.7% seasonal allergies 9.5% asthma	52.3*	0	40 (20–100)
	Placebo	21	38 (20–57)	76.2	NR	NR	>5 years	100	0 months	47.6% seasonal allergies 19.0% asthma	57.1*	0	38 (20–80)
BUL-1/EEA (Lucendo et al., 2019)[13,14]	Budesonide ODT	59	37.0 (11.47)	81.4	100% White	24.4 (2.86)	134.2 (104.6) months	1.7	48.8 (44.3) months	97.7%	100	15.3	242 (140.7)
	Placebo	29	36.9 (9.20)	86.2	100% White	25.6 (4.08)	139.0 (98.8) months	6.9	57.6 (49.3) months	79.3%	100	17.2	239 (125.0)
BUU-2/EEA (Miehlke et al., 2016)[15,5]	Budesonide ODT	19	38.9 (12.6)	89.5	100% White	25.5 (4.41)	8.3 (7.8) years	36.8	1.9 (3.4) years	73.7	47.4	10.5	242 (144) eos/mm^2 hpf
	Budesonide OVS	19	46.5 (14.1)	73.7	100% White	25.9 (2.35)	10.8 (9.0) years	31.6	2.6 (3.3) years	57.9	31.6	21.1	201 (185) eos/mm^2 hpf
	Placebo	19	36.3 (9.9)	84.2	100% White	23.7 (3.16)	7.9 (7.5) years	42.1	2.6 (5.1) years	52.6	36.8	5.3	320 (309) eos/mm^2 hpf
Dellon et al., 2017[3]	Budesonide OVS	51	22.3 (7.9)	69	48% White	23.9	NR	NR	38.5 (34.3) months	NR	69	NR	157.8 (96.1)
	Placebo	42	20.8 (7.5)	69	40% White	23.3	NR	NR	36.5 (42.6) months	NR	69	NR	133.0 (81.6)

Philpott et al., 2016[6]	Budesonide OVS SFED	82	34 (11)	84	98% White 1% Asian 1% Middle Eastern	NR	NR	NR	NR	44% seasonal rhinitis 19% asthma, 7% food allergy 2% coeliac disease	100	NR	Upper: 24 (9) Middle: 32 (9) Lower: 29 (7)

Abbreviations: BMI = body mass index; EoE = eosinophilic oesophagitis; eos = eosinophil; hpf = high-power field; mm = millimetre; NR = not reported; ODT = orodispersible tablet; OVS = oral viscous suspension; PPI = proton-pump inhibitor; SD = standard deviation; SFED = six-food elimination diet
* For part of patient population enrolled after consensus definition of EoE changed in 2007 (100% PPI non-responders)

Table 5. Interventions

Study	Design	Treatment arm	N	Dose	Method of administration	Treatment duration, weeks	Concomitant PPI, %
Alexander et al., 2012[2]	RCT	Fluticasone	21	880 µg BID	Aerosolised (swallowed)	6	26.3
		Placebo	21	NR			0.0
BUL-1/EEA (Lucendo et al., 2019)[13,14]	RCT	Budesonide ODT	59	1 mg BID	Oral	6–12	11.9
		Placebo	29	BID			10.3
BUU-2/EEA (Miehlke et al., 2016)[15,5]	RCT	Budesonide ODT	19	1 mg BID	Oral	2	15.8
			19	2 mg BID			5.3
		Budesonide OVS	19	2 mg BID			15.8
		Placebo	19	NR			15.8
Dellon et al., 2017[3]	RCT	Budesonide OVS	49	2 mg BID	Oral	12	71
		Placebo	38	NR			67
Philpott et al., 2016[6]	CT	Budesonide OVS	25	1 mg BID	Oral	6	0
		SFED	56	N/A	N/A		100

Abbreviations: BID = twice daily; CT = controlled trial; N = number of patients evaluable; N/A = not applicable; NR = not reported; ODT = orodispersible tablet; OVS = oral viscous suspension; PPI = proton-pump inhibitor; RCT = randomised controlled trial; SFED = six-food elimination diet

Table 6. Outcomes

Study	Definition of remission	Data for <5eos remission fraction	Measuring method	Analysis set
Alexander et al., 2012{Alexander, 2012 #33	<2 eos/hpf	No (<2 eos)	Mean eos count	ITT
BUL-1/EEA (Lucendo et al., 2019) [13,14]	Peak of <16 eos/mm^2 hpf	Yes	Peak eos count	ITT
BUU-2/EEA (Miehlke et al., 2016) [15,5]	Mean of <16 eos/mm^2 hpf	Yes	Mean/peak eos counts	ITT
Dellon et al., 2017[3]	Peak of <6 eos/hpf	No (< 6 eos)	Peak eos count	mITT
Philpott et al., 2016[6]	<5 eos/hpf	Yes	Peak eos count	ITT

Abbreviations: eos = eosinophil; hpf = high-power field; ITT = intention-to-treat; mITT = modified intention-to-treat; mm = millimetre

A5. **Priority question:** It is stated that the decision whether to use the random or fixed effects model's results was based on the deviation information criterion (DIC). As the DIC was lower for the random effects model, the results of this model are reported in the submission. Please can you provide the DIC values and total residual deviance as these are not reported in the submission. Please can you also report the NMA results according to the fixed-effect models, for comparison.

The DIC were 45,551 for the random-effects model and 49,771 for the fixed-effects model. The results of the fixed-effects NMA are shown in Table 7.

Table 7. Fixed-effects NMA based on analysis of rates of remission (defined as <16 eos/mm^2 hpf)

Budesonide ODT 1 mg BID versus:	OR	95% CrI
Budesonide OVS	14.71	1.212, 428.800
Fluticasone	9.62	0.116, 494.800
SFED	52.86	3.683, 1,760.000

Abbreviations: BID = twice daily; CrI = credible interval; eos = eosinophil; hpf = high-power field; mg = milligram; mm = millimetre; NMA = network meta-analysis; ODT = orodispersible tablet; OR = odds ratio; OVS = oral viscous solution; SFED = six-food elimination diet

A6. Priority question: Please can you clarify the meaning of the statement in D.1.3.4 "as there was very sparse evidence, data from homogenous intervention/control arms were pooled". What specifically does this mean for how the data were used in the NMA?

Data used in the NMA were not pooled. This was an error in the CS.

A7. D1.2.1.1 Table B5.9 footnote states that for the Philpott et al 2016 study, the PPI and the budesonide inhaler arms (respectively) were not included in the NMA due to "uncertainty in reported results". Please could you explain what this means.

While considering NICE's March 2019 questions (A15 and A19), the decision was made to include only two estimates of remission from Philpott et al., 2016 (budesonide OVS and SFED) in the updated NMA, in order to minimise bias, given uncertainty regarding the study's overall design and transparency of reporting. For these treatment arms, reporting in the publication was clear and unambiguous, and it was possible to calculate efficacy estimates based on the intention-to-treat (ITT) population.

Further review of Philpott et al., 2016, at the time of the current (September 2019) clarification questions, indicates that the study did not include a budesonide inhaler arm, but rather states that 'many patients had received budesonide (albeit in dry powder form') previously. Therefore budesonide inhaler should not have been listed as a study treatment in Table B.5.9. In addition, the PPI treatment arm does not provide data of relevance to UK clinical practice, as clinical opinion indicates that patients are typically already treated with PPIs (and would therefore not be treated with PPIs in place of budesonide ODT).

A8. In section 'B2.9.3 Uncertainties in the indirect and mixed treatment comparisons' it states that studies "had different … observation periods". B2.9.1.2.2 mentions treatment duration (2-12 weeks) but we could not find data on follow-up tabulated anywhere. Please can you provide this for all the studies included in the indirect treatment comparison.

Treatment and follow-up durations for the five studies included in the NMA are shown in Table 8.

Table 8. Treatment and follow-up durations of studies included in the NMA

Study	Treatment duration	Post-treatment follow-up duration
Alexander et al., 2012[2]	6 weeks	N/A
BUL-1/EEA[4]	6–12 weeks	4 weeks
BUU-2/EEA[5]	2 weeks	2 weeks
Dellon et al., 2017[3]	12 weeks	4 weeks
Philpott et al., 2016[6]	3–9 months	N/A

Abbreviations: N/A = not applicable; NMA = network meta-analysis

A9. Priority question: There does not appear to be an assessment of inconsistency between the direct and indirect evidence included in the NMA. Please can you

provide this assessment for example, using methods specified by the NICE Decision Support Unit Technical Support Document 4 such as node splitting or inconsistency model. (http://nicedsu.org.uk/wp-content/uploads/2016/03/TSD4-Inconsistency.final_.15April2014.pdf)

The network incorporates one closed loop (budesonide ODT – budesonide OVS – placebo), which was investigated using the Bucher approach. Evidence from each pair-wise contrast was separately synthesised and used to form an indirect estimate, which was compared to the complementary direct effect (log odds ratio). An estimate of inconsistency (ω) was formed by subtracting the indirect estimate from its direct complement. The variance of the inconsistency measure was calculated as the sum of variances of all three direct estimators. The null hypothesis (the absence of inconsistency) was tested by referring $z=\omega/\sqrt{(Var(\omega))}$ to the standard normal distribution. The inconsistency test did not result in a rejection of the null hypothesis. Results are shown in Table 9.

Table 9. Assessment of inconsistency

Loop	trt1	trt2	ln (OR)	SE (ln(OR))	ln(OR)ind	var(OR)ind	omega	var(omega)	z	p
Budesonide ODT–placebo–budesonide ODT	Budesonide ODT	Placebo	6.708	1.203	2.808	3.57	3.900	5.01	1.742	0.959
	Budesonide ODT	Budesonide OVS	1.151	1.665	-2.749	2.24	3.900	5.01	1.742	0.959
	Budesonide OVS	Placebo	3.959	0.892	5.557	4.22	-1.598	5.01	-0.714	0.238
Direct estimates										
Comparison	**Studies**	**n_Arm1**	**N_Arm1**	**n_Arm2**	**N_Arm2**	**OR**	**SE**	**CI_l**	**CI_u**	
Budesonide ODT vs placebo	BUL-1/EEA BUU-2/EEA	73	78	0	48	819.000	1.203	77.55	8649.68	*inverse variance weighted pairwise meta-analysis
Budesonide OVS vs placebo	Dellon et al., 2017 BUU-2/EEA	36	68	1	57	52.400	0.892	9.13	300.83	*inverse variance weighted pairwise meta-analysis
Budesonide ODT vs budesonide OVS	BUU-2/EEA	19	19	18	19	3.162	1.665	0.12	1369.47	

Abbreviations: CI = confidence interval; N = number of patients evaluable; n = number of patients in the category; ODT = orodispersible tablet; OR = odds ratio; OVS = oral viscous suspension; SE = standard error

A10. Priority question: There is large uncertainty in the NMA results (as demonstrated by very wide credible intervals). These appear to be driven by the zero remission rates in the placebo arms. It may be more conservative to use a continuity correction for studies which have zero events for placebo and the BUU-2 study where all Budesonide ODT patients have the event (adding 0.5 to the R cells and 1 to the N cells in applicable studies for the NMA). Please could you re-run the NMA in this way as a scenario analysis.

The NMA has be re-run with the above continuity correction and results of the fixed- and random-effects models are shown in Table 10 and Table 11, respectively. The DIC were similar: 53,489 for the fixed-effects model and 53,531 for the random-effects model.

Table 10. Fixed-effects NMA based on analysis of rates of remission (defined as <16 eos/mm^2 hpf) with continuity correction

Budesonide ODT 1 mg BID versus:	OR	95% CrI
Budesonide OVS	8.861	1.141, 107.5
Fluticasone	11.83	0.413, 214.7
SFED	31.91	3.263, 439.1

Abbreviations: BID = twice daily; CrI = credible interval; eos = eosinophil; hpf = high-power field; mg = milligram; mm = millimetre; NMA = network meta-analysis; ODT = orodispersible tablet; OR = odds ratio; OVS = oral viscous solution; SFED = six-food elimination diet

Table 11. Random-effects NMA based on analysis of rates of remission (defined as <16 eos/mm^2 hpf) with continuity correction

Budesonide ODT 1 mg BID versus:	OR	95% CrI
Budesonide OVS	7.049	0.059, 590.4
Fluticasone	8.015	0.024, 2,181
SFED	36.62	0.102, 1,0350

Abbreviations: BID = twice daily; CrI = credible interval; eos = eosinophil; hpf = high-power field; mg = milligram; mm = millimetre; NMA = network meta-analysis; ODT = orodispersible tablet; OR = odds ratio; OVS = oral viscous solution; SFED = six-food elimination diet

A11. There is limited presentation of NMA results (i.e. Budesonide ODT vs fluticasone/SFED, respectively) in Tables B.2.20 to B2.22. Since placebo/no treatment is included in the economic model, please also present all treatment comparisons versus placebo from the NMA.

Results of the random- and fixed-effects NMAs versus placebo are shown in Table 12 and Table 13, respectively.

Table 12. Random-effects NMA based on analysis of rates of remission (defined as <16 eos/mm^2 hpf)

Placebo versus:	OR	95% CrI
Budesonide ODT	0.007	0.000, 0.780
Budesonide OVS	0.101	0.003, 5.868
Fluticasone	0.057	0.000, 12.170
SFED	0.552	0.004, 102.200

Abbreviations: BID = twice daily; CrI = credible interval; eos = eosinophil; hpf = high-power field; mg = milligram; mm = millimetre; NMA = network meta-analysis; ODT = orodispersible tablet; OR = odds ratio; OVS = oral viscous solution; SFED = six-food elimination diet

Table 13. Fixed-effects NMA based on analysis of rates of remission (defined as <16 eos/mm^2 hpf)

Placebo versus:	OR	95% CrI
Budesonide ODT	0.001	0.000, 0.007
Budesonide OVS	0.013	0.002, 0.057
Fluticasone	0.008	0.000, 0.094
SFED	0.046	0.006, 0.274

Abbreviations: BID = twice daily; CrI = credible interval; eos = eosinophil; hpf = high-power field; mg = milligram; mm = millimetre; NMA = network meta-analysis; ODT = orodispersible tablet; OR = odds ratio; OVS = oral viscous solution; SFED = six-food elimination diet

Outcome measures

A12. Please provide details about the subjective happiness scale e.g. published reference for this scale, method of scoring, score range etc. Please also indicate how the score was modified to provide the modified SHS score.

The name of the scales in the CS was an error – SHS should have referred to the Short Health Scale and not the Subjective Happiness Scale. The Short Health Scale (SHS) is a valid, reliable and responsive measure of subjective health and has recently been described in patients with ulcerative colitis, collagenous colitis and Crohn's disease.[16-18] In BUL-1/EEA, the SHS was modified (modSHS) for use in EoE by replacing terms related to the underlying disease (e.g. replacing 'bowel' with 'oesophageal').[13]

The modSHS was a simplified four-item questionnaire, representing each of four health dimensions: 1) symptom burden, 2) social function, 3) disease-related worry, and 4) general wellbeing. Patients answered a total of 4 questions (health dimensions) which concerned the effects of illness on quality of life, at baseline and at all subsequent visits. Responses were scored by the patient by making a vertical dash through each of the four 100 mm horizontal visual analogue scales (VAS), resulting in individual scores for each of the following four questions:[13]

1) How severe are the symptoms you suffer from your oesophageal disease?

No symptoms	(0)----------(100)	Very severe symptoms

2) Do your oesophageal problems interfere with your activities in daily life?

Not at all	(0)----------(100)	Interfere to a very high degree

3) How much worry does your oesophageal disease cause?

No worry	(0)----------(100)	Constant worry

4) How is your general feeling of well-being?

Very good	(0)----------(100)	Dreadful

Section B: Clarification on cost-effectiveness data

Model assumptions and estimates

B1. We note the company's justification for using histological remission as the measure of treatment effect in the economic model (Company submission, footnote to Table B.3.1). However, we think that the intrinsic model assumption that patients above the threshold for histological remission are asymptomatic and patients below the threshold for histological remission are symptomatic is not realistic. This is because clinical remission rates for budesonide-treated patients in the BUL-1 trial were lower than histological remission rates (59% vs 93% respectively). Please could you conduct a scenario analysis in which clinical remission is a treatment effect measure used to inform the model, either solely, or combined with histological-remission. Please fully describe the methods and data used to inform this scenario analysis.

The clinical remission rate of 59.3% (versus a histological remission rate of 93.2%) for budesonide ODT in the BUL-1/EEA trial was at 6 weeks (ITT analysis). Clinical remission was defined as symptoms severity of ≤ 2 points on each 0–10 numeric rating scale for dysphagia and odynophagia, respectively on each day in the week before EoT.[4] However, clinical remission is not always included as an endpoint in clinical trials, hence it was not included as an outcome in the NMA. In addition, assessment of clinical response in EoE is challenging because the major symptom of solid food dysphagia depends not only on the activity of the disease, but also on the eating behaviour of the patient.

While one study of SFED was included in the NMA for SFED (Philpott et al., 2016), it did not include clinical remission as an endpoint.[6] Similarly, the one study of fluticasone included in the NMA (Alexander et al., 2012) did not include clinical remission as an endpoint.[2] However, the primary endpoint was dysphagia response at 6 weeks, which can be considered a proxy for clinical remission. Dysphagia response was a complete symptom response, defined as an answer of 'no' to the question, 'In the past 2 weeks, have you had trouble swallowing, not associated with other cold symptoms (such as strep throat or mononucleosis)?' on the Mayo dysphagia questionnaire 2-week version. At the end of the 6-week study, dysphagia response and histological response were 42.9% and 61.9%, respectively (ITT analysis) for fluticasone.[2]

A scenario analysis was conducted for budesonide ODT and fluticasone in which the treatment effect (i.e. response per cycle) was based on the mean rates of clinical remission and histological remission. SFED was not included due to lack of data for clinical remission. For budesonide ODT, the treatment effect was reduced from 94.9% to 76.3% (average of clinical remission and histological remission rates at 6 weeks) For fluticasone, the treatment effect was reduced from 68.1% to 52.4% (average of dysphagia response and histological response at 6 weeks). The results of the scenario analysis are shown in

Table 14. Total costs increase for both budesonide ODT and fluticasone, although the increase is greater for budesonide ODT. Drug costs decrease due to fewer patients continuing treatment with budesonide ODT or fluticasone. Medical costs and the cost of co-medications increase for both groups, due to patients spending more time in the active disease health states compared with the base-case analysis.

Table 14. Scenario with alternative treatment effect (response rate) for budesonide ODT

	Budesonide ODT	Fluticasone
Drug costs	£1,514	£159
Co-medications (dilation)	£6,855	£7,545
Medical costs	£18,426	£19,662
AE costs	£0	£0
TOTAL COSTS	**£26,796**	**£27,366**
Incremental costs (budesonide ODT versus comparator)	-	-£570
TOTAL QALYS	**15.38**	**15.22**
Incremental QALYs (budesonide ODT versus comparator)	-	0.17
ICER - cost per QALY gained (budesonide ODT versus comparator)	**-**	**Budesonide ODT dominates fluticasone**

Abbreviations: AE = adverse event; ICER = incremental cost-effectiveness ratio; ODT = orodispersible tablet; QALY = quality-adjusted life year;

B2. Priority question: At present, individuals in the model receive multiple add-on dilation treatment (or emergency food bolus removal), i.e. more than 20 times each. Please confirm whether this is realistic in clinical practice. If not, please include alternative assumptions in the model, clearly stating the sources.

The number of add-on dilation treatments (or emergency food bolus removal) in the model is over the 40-year time horizon. In a systematic review of endoscopic dilation in children and adults with EoE, the median number of dilations was 3 (range 1 – 35).[19] Although not all studies included the duration of follow-up, as an example, one study reported 157 dilations in 95 patients (mean age of 30 years) over a 24-month period,[20] which is higher than that estimated in the model.

It appears that the number of add-on dilation treatments (or emergency food bolus removal) is highly variable and there is minimal comparative data available, particularly during remission. Thus, a scenario analysis is provided in which the costs of co-medications (add-on dilation treatment or emergency food bolus removal) are excluded from the analysis (Table 15). Under this scenario, total costs decrease for all interventions, although the decrease is more pronounced for budesonide ODT. However, budesonide ODT still dominates fluticasone and SFED in this scenario.

Table 15. Scenario analysis with co-medication costs excluded

	Budesonide ODT	Fluticasone	SFED
Drug costs	£5,097	£260	£0
Co-medications (dilation)	£0	£0	£0
Medical costs	£12,989	£19,036	£20,494
AE costs	£0	£0	£0
TOTAL COSTS	**£18,086**	**£19,289**	**£20,494**
Incremental costs (budesonide ODT versus comparator)	-	-£1,203	-£2,409
TOTAL QALYS	**16.12**	**15.30**	**15.14**
Incremental QALYs (budesonide ODT versus comparator)	-	0.82	0.98
ICER - cost per QALY gained (budesonide ODT versus comparator)	**-**	**Budesonide ODT dominates fluticasone**	**Budesonide ODT dominates SFED**

Abbreviations: AE = adverse event; ICER = incremental cost-effectiveness ratio; ODT = orodispersible tablet; QALY = quality-adjusted life year; SFED = six-food elimination diet

B3. Priority question: The relapse rate for those on remission with maintenance is the same as those on remission without maintenance. Please provide a justification for this.

The CS did not include remission with maintenance, hence no value for the relapse rate for those on remission with maintenance was identified. The model was developed with the option to include remission with and without maintenance. Whilst the model states that the same relapse rate was used for remission with and without maintenance, the model had not been updated and it is not our expectation that relapse rates would be the same. In the response to Question B4 below, a lower rate for relapse with maintenance (than relapse without maintenance) is used.

B4. Priority question: Please provide a scenario analysis where patients receive maintenance therapy whilst on remission instead of no maintenance therapy.

A scenario analysis in which all patients receive maintenance therapy during remission is provided. The same rates of add-on dilation treatment (or food bolus removal), healthcare professional visits and endoscopies apply to the remission with maintenance health states as were used for the remission without maintenance health states in the base case analysis. Hence, the differences between the scenario analysis and the base case analysis relates to relapse rate and drug costs only.

In the base case analysis, the relapse rate was 88% relapse after 1 year, applied to all treatments at a rate of 22% per 12-week cycle. It is expected that the relapse rate for remission with maintenance would be lower. In the BUL-2/EEA study, 73.5% of patients in the budesonide ODT 0.5 mg twice daily (BID) arm (double-blind full analysis set) were free from treatment failure after 48 weeks of treatment.[21] Assuming the same response rate of 94.9% per 12-week cycle as in the base-case analysis, this equates to a relapse rate of 21.4% at 48 weeks (5.4% per 12-week cycle). In the absence of comparable data for the comparators, this value was used for budesonide ODT and the comparators in the scenario analysis. This is considered a very conservative assumption as it is expected that budesonide ODT would have a lower relapse rate than the comparators.

During remission with maintenance, the assumption was that the dose of budesonide ODT would be 0.5 mg BID, as patients would require a lower dose during maintenance. This is also justified by the results of BUL-2/EEA, where there was little difference between the number of patients free from treatment failure after 48 weeks for the two budesonide ODT doses (0.5 mg bid and 1.0 mg BID). A further assumption is that patients would receive the full 12-weeks of treatment with budesonide ODT during the active disease health states. Given that maintenance is ongoing, wastage was not included in the estimation of drug costs. Thus, the drug costs for budesonide ODT were £602.93 during the active disease health states and £301.47 during the remission with maintenance health states.

Similarly, for fluticasone, the assumption was that the dose of fluticasone would be lower during the remission with maintenance health states than during the active disease health states. In the model, the dose of fluticasone used during the remission with maintenance health states was 550 µg/day (half of that used during the active disease health states). As with budesonide ODT, wastage was not included in the estimation of drug costs. Thus, the drug costs for fluticasone were £100.56 and £50.28 during the active and remission with maintenance health states, respectively.

The results of the scenario analysis are shown in Table 16. As fewer patients relapse back into the active disease health states, the number of QALYs increases and the costs (medical and co-medications) decrease for all technologies. Drug costs increase due to the utilisation of maintenance therapy during remission. As budesonide ODT is associated with higher drug costs than fluticasone, the increase in drug costs is higher for budesonide ODT. However, whilst budesonide ODT no longer dominates fluticasone and SFED, it is still cost-effective compared with fluticasone and SFED, with ICERs of £12,123 and £6,813 per QALY gained, respectively.

Table 16. Scenario analysis where all patients receive maintenance therapy during remission

	Budesonide ODT	Fluticasone	SFED
Drug costs	£18,641	£668	£0
Co-medications (dilation)	£6,248	£5,935	£7,446
Medical costs	£10,594	£17,530	£19,810
AE costs	£0	£0	£0
TOTAL COSTS	**£35,483**	**£24,133**	**£27,257**
Incremental costs (budesonide ODT versus comparator)	-	£11,350	£8,226
TOTAL QALYS	**16.44**	**15.51**	**15.23**
Incremental QALYs (budesonide ODT versus comparator)	-	0.94	1.21
ICER - cost per QALY gained (budesonide ODT versus comparator)	**-**	**£12,123**	**£6,813**

Abbreviations: AE = adverse event; ICER = incremental cost-effectiveness ratio; ODT = orodispersible tablet; QALY = quality-adjusted life year; SFED = six-food elimination diet

B5. In CS table B3.10, the study by Dellon et al investigates active EoE for treatment with budesonide, However, it has been used for remission (without maintenance) for fluticasone. Please explain the rationale for this.

In the absence of data on the rate of add-on dilation treatment (or emergency food bolus removal) for fluticasone during remission (without maintenance), it was assumed that the rate would be similar to the higher reported rate for active treatment. This is because the rates for dilation for budesonide ODT and SFED were higher for the remission health states than the active disease health states. A scenario analysis was conducted in which the dilation rate for fluticasone for remission (without maintenance) was the same as that for active disease (0.14 per 12-week treatment period). The result of the scenario analysis is shown in

Table 17. Under this scenario, the costs for fluticasone are reduced slightly, but budesonide ODT continues to dominate both fluticasone and SFED.

Table 17. Scenario analysis with dilation rate of 0.14 per 12-week period for fluticasone for both remission and active disease health states

	Budesonide ODT	Fluticasone	SFED
Drug costs	£5,097	£253	£0
Co-medications (dilation)	£5,934	£7,084	£7,163
Medical costs	£12,989	£19,036	£20,494
AE costs	£0	£0	£0
TOTAL COSTS	**£24,020**	**£26,373**	**£27,657**
Incremental costs (budesonide ODT versus comparator)	-	-£2,353	-£3,637
TOTAL QALYS	**16.12**	**15.30**	**15.14**
Incremental QALYs (budesonide ODT versus comparator)	-	0.82	0.98
ICER - cost per QALY gained (budesonide ODT versus comparator)	**-**	**Budesonide ODT dominates fluticasone**	**Budesonide ODT dominates SFED**

Abbreviations: AE = adverse event; ICER = incremental cost-effectiveness ratio; ODT = orodispersible tablet; QALY = quality-adjusted life year; SFED = six-food elimination diet

B6. The Moawad et al study reports that no dilations were performed during the treatment period (or on follow-up endoscopy). Please explain how the values for the probability of add-on dilation treatment in table B3.10 for fluticasone with active disease have been calculated.

In Moawad et al. 2013, 19% of patients had food impaction.[8] The assumption in the model is that these patients would require food bolus removal and that this would be equally distributed between the two treatment arms, hence 9.5% for fluticasone over the 8-week treatment period.

Costs

B7. Priority question: There are no medical costs associated with the remission health states, however there are medical costs associated with the no treatment health states (active EoE) (second and third treatment). Please provide a justification for this.

The assumption in the model is that during active disease, patients are symptomatic and thus will incur medical costs regardless of whether or not they are receiving treatment. A scenario analysis was conducted in which no medical costs were applied to no treatment during active disease health states (see Table 18). This scenario is more favourable to

fluticasone and SFED than budesonide ODT, as patients receiving initial treatment with fluticasone or SFED spend more time on 'no treatment' in the active disease health states.

Table 18. Scenario analysis with no medical costs applied to no treatment during active disease health states

	Budesonide ODT	Fluticasone	SFED
Drug costs	£5,097	£253	£0
Co-medications (dilation)	£5,934	£7,833	£7,163
Medical costs	£2,834	£618	£453
AE costs	£0	£0	£0
TOTAL COSTS	**£13,866**	**£8,704**	**£7,616**
Incremental costs (budesonide ODT versus comparator)	-	£5,162	£6,250
TOTAL QALYS	**16.12**	**15.30**	**15.14**
Incremental QALYs (budesonide ODT versus comparator)	-	0.82	0.98
ICER - cost per QALY gained (budesonide ODT versus comparator)	**-**	**£6,324**	**£6,401**

Abbreviations: AE = adverse event; ICER = incremental cost-effectiveness ratio; ODT = orodispersible tablet; QALY = quality-adjusted life year; SFED = six-food elimination diet

B8. Please provide the Healthcare Resource Group (HRG) codes for food bolus and dilation (CS p77).

The cost for dilation of £554.00 is the mean of two endoscopy HRGs: (i) HRG code FE02C (Major therapeutic Endoscopic, Upper or Lower Gastrointestinal Tract Procedures , 19 years and over, with CC score 0) – Level 2 tariff of £608; and (ii) HRG code FE20Z (Therapeutic Endoscopic Upper Gastrointestinal Tract Procedures, 19 years and over) – Level 2 tariff of £499. These costs were obtained from the 2019/20 National Tariff Payment System.[22]

The cost of emergency food bolus removal is incorrectly referenced in the submission, and should be referenced as 'Dr. Falk, data on file' as it was obtained from a study conducted for Dr. Falk on healthcare resource use in EoE. Unfortunately, the methodology, HRG codes and year used to derive this value are not available. However, the value of £343.00 is similar to HRG codes VB01Z (Emergency Medicine, Any Investigation with Category 5 Treatment) and VB02Z (Emergency Medicine, Category 3 Investigation with Category 4 Treatment) from the 2019/20 National Tariff Payment System (£338.00).[22] Using this value (£338.00) for emergency food bolus removal instead of the value used in the CS (£343.00) results in a mean cost for dilation/food bolus removal of £446.00. This has minimal impact on the results, as shown in Table 19.

Table 19. Scenario using different value for dilation / food bolus removal

	Budesonide ODT	Fluticasone	SFED
Drug costs	£5,097	£260	£0
Co-medications (dilation)	£5,901	£7,789	£7,123
Medical costs			
Gastroenterologist visits	£3,656	£5,359	£5,693
Dietician visits	£0	£0	£40
Endoscopies	£9,333	£13,677	£14,762
AE costs	£0	£0	£0
TOTAL COSTS	**£23,987**	**£27,078**	**£27,617**
Incremental costs (budesonide ODT versus comparator)	-	-£3,091	-£3,630
TOTAL QALYS	**16.12**	**15.30**	**15.14**
Incremental QALYs (budesonide ODT versus comparator)	-	0.82	0.98
ICER - cost per QALY gained (budesonide ODT versus comparator)	**-**	**Budesonide ODT dominates fluticasone**	**Budesonide ODT dominates SFED**

Abbreviations: AE = adverse event; ICER = incremental cost-effectiveness ratio; ODT = orodispersible tablet; QALY = quality-adjusted life year; SFED = six-food elimination diet

Other issues

B9. There is an error in the macro that runs the DSA (relating to the charts). Please fix the DSA macro so that it runs without an error.

We have not able to reproduce this error when running the DSA macro, and the charts (tornado diagrams) are produced.

B10. CS section B 3.2,1 reports that no suitable cost-effectiveness studies were identified. However in the company's previous submission to NICE for EoE in March 2019, it was reported that three cost-effectiveness studies were identified in the disease area of EoE (p108). Please explain why those studies identified in the previous NICE submission are not considered relevant to the current submission.

A systematic review was undertaken to identify resource use, cost and cost-effectiveness studies associated with EoE to identify values to populate the economic model. The review was undertaken to (i) identify published cost-effectiveness studies to inform the economic model; and (ii) identify potential data inputs for the economic model. The eligibility criteria implemented, search strategy details, selection process and quality assessment are provided in CS Appendix G. The searches were undertaken in the Centre for Reviews and Dissemination database on 21st January 2019 and in PubMed on 25th January 2019.

Out of 82 unique records, 5 studies were deemed eligible for inclusion. The PRISMA flow chart is provided in CS Appendix G. Of the five studies identified, four studies were cost analyses or estimations of resource utilisation. Only one study was a cost-effectiveness analysis.[23] However, this estimated the cost-effectiveness of endoscopic biopsy for the diagnosis of EoE in patients with refractory gastro-oesophageal reflux disease without dysphagia, and is therefore not directly relevant to the decision problem. Thus, none of the five studies were relevant cost-effectiveness studies and it was stated in the CS that no studies relevant to the decision problem were identified by the systematic literature review.

In the company's previous submission to NICE, two additional studies were identified. One study (Cotton et al., 2017), which had been excluded during the eligibility stage of the review (due to irrelevant outcomes) was a cost-effectiveness study.[24] A further study (Schneider et al., 2016), which was identified independently, was also a cost-effectiveness study.[25] However, it was published only as an abstract and hence limited information on the study were available. Both studies assessed the cost-effectiveness of treatments for EoE and are thus relevant to the decision problem. These two studies are summarised in Table 20.

Table 20. Summary of published cost-effectiveness studies

Study	Schneider et al., 2016[25]	Cotton et al., 2017[24]
Summary of model	Cost-effectiveness analysis of treatment options for adult EoE using a Markov model	Cost-utility analysis of topical steroids compared with dietary elimination for treatment of EoE
Patient population	A model comparing the cost-effectiveness of 3 initial therapy options for a 30-year old man with a new diagnosis of EoE	Median female age: 35.5 years Median male age: 32.8 years
QALYs (intervention, comparator)	SFED=4.89 Budesonide=4.88 Fluticasone=4.87	SFED rescue fluticasone=4.29 SFED rescue budesonide=4.26 Fluticasone rescue SFED=4.24 Budesonide rescue SFED=4.17
Costs (currency) (intervention comparator)	SFED=US$10,629; Budesonide=US$13,456; Fluticasone=US$27,100	SFED rescue fluticasone=US$5720 SFED rescue budesonide=US$7276 Fluticasone rescue SFED=US$9262 Budesonide rescue SFED=$21,609
ICER (per QALY gained)	Budesonide=US$579.30 Fluticasone=$3,382.14	SFED rescue budesonide=$49,861 Fluticasone rescue SFED=$71,522 Budesonide rescue SFED=US$137,826

Abbreviations: EoE = eosinophilic oesophagitis; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; SFED = six-food elimination diet; US = United States

Section C: Textual clarification and additional points

C1. The probability of add-on dilation treatment for patients in remission (without maintenance) is taken from the BUU-2EEA trial in CS Table 3.10. Please provide the page number or table number in the clinical study report where these data can be found.

This appears to have been obtained from the placebo arm of the BUL-2/EER trial (not the BUU-2/EEA trial) – rate of patients with a clinical relapse, have experienced a food impaction which needed endoscopic intervention, or needed an endoscopic dilation during the DB treatment phase. The rate was assumed for SFED and then also applied to budesonide ODT. However, the BUL-2/EER trial states that this is mostly attributable to a clinical deterioration in EoE rather than food bolus impaction or need for dilation.

Note that a scenario analysis is provided in response to Question B2 above in which patients do not receive add-on dilation treatment (or emergency food bolus removal) during remission. Under this scenario, budesonide ODT still dominates fluticasone and SFED.

References

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Budesonide for treating eosinophilic oesophagitis [ID1202]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**British Society of Allergy and Clinical Immunology**
3. Job title or position	**Specialist Allergy Dietitian**

4. Are you (please tick all that apply):	x an employee or representative of a healthcare professional organisation that represents clinicians? **x** a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**The BSACI is the national, professional and academic society which represents the specialty of allergy at all levels. Its aim is to improve the management of allergies and related diseases of the immune system in the United Kingdom, through education, training and research.**
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**no**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To induce histological remission and stop progression to fibrosis and stricturing. To reduce symptoms of dysphagia and food bolus impactions.

7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Change in oesophageal eosinophil count to below 15 or reduction of at least 50% from baseline.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Despite evidence that swallowed topical corticosteroids such as budesonide and fluticasone are effective for the treatment of EoE, until very recently there were no licensed formulations and considerable variation in prescribing practices. There is therefore an unmet need for criteria and guidelines for use of budesonide.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	With proton pump inhibitors (up to 50% effective), elimination diets (up to 70% effective), and swallowed topical corticosteroids (typically asthma inhalers – swallowed not inhaled i.e. off licensed use)
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	European guidelines: Lucendo A.J., MolinaInfante J., Arias A., et al (2017) Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. *United European Gastroenterol J.* 5 (3), 335-358 International guidelines:

	Liacouras, C. A., Furuta, G. T., Hirano, I., et al (2011) Eosinophilic esophagitis: Updated consensus recommendations for children and adults. *J Allergy Clin Immunol.* 128 (1), 3-20. Dellon E, Liacouras C, Molina-Infante J, et al. Updated international consensus diagnostic criteria for eosinophilic esophagitis: proceedings of the AGREE conference. *Gastroenterology.* 2018;155(4):1022-1033
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Care will vary from centre to centre depending on local expertise and resources. In my experience many NHS centres treat adults with proton pump inhibitors or various steroids (or both). Despite dietary management also being effective, there is a perception that it is too challenging in adults, results in weight loss and is associated with poor adherence. However in centres with dietetic support, patients can be managed effectively with diet as first line treatment. In addition patients are often not routinely monitored on treatment.
• What impact would the technology have on the current pathway of care?	A licensed formulation of budesonide fits into the current pathway of care as a suitable treatment option for swallowed topical corticosteroids.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Until recently the only treatment options for swallowed corticosteroids have been products designed for asthma prescribed off-license. These include inhalers (eg Flixotide Evohaler, swallowed rather than inhaled) and nebulising solutions (eg Pulmicort respules mixed with powder or honey). However in practice often less suitable products are prescribed. The technology would therefore provide a standardised appropriate formulation.
• How does healthcare resource use differ	

between the technology and current care?	
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care and specialist clinics.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Probably small.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes- current care is variable and not standardised so I would expect this to be more effective.
• Do you expect the technology to increase length of life more than current care?	No
• Do you expect the technology to increase health-related quality of	Yes as it is likely to be more effective.

life more than current care?	
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The risk of adrenal suppression is likely to be higher in people who are significantly undernourished.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability	It will be easier than current treatments, for which the route of administration is being modified and requires education.

or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Treatment response should be monitored with repeat oesophageal biopsies.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	no
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related	Yes

benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes
• Does the use of the technology address any particular unmet need of the patient population?	Yes- there are no other licensed products for EoE available.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Swallowed corticosteroids have been reported to have a 10% chance of developing oral/ oesophageal candidiasis. This can affect quality of life but is easily treated with antifungals. Other potential long-term adverse events are bone mineral density loss and adrenal suppression and the risks of these are unknown.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	There has been one clinical trial on the efficacy of the technology, published very recently and showing very positive results. This showed outcomes at 6 and 12 weeks, assessed endoscopically and clinically. In

	UK practice, routine endoscopies are not always performed and symptoms are not measured using validated tools. Treatment may not be initiated for these defined periods.
• If not, how could the results be extrapolated to the UK setting?	Treatment could be initiated for 12 weeks and biopsies/ symptoms measured at this point to define response.
• What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcomes are oesophageal eosinophil count and symptoms, which were both measured in the trial.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	n/a
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None known
19. Are you aware of any relevant evidence that might	No

not be found by a systematic review of the trial evidence?	
20. How do data on real-world experience compare with the trial data?	n/a
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	None known
22b. Consider whether these issues are different from issues with current care and why.	

23. In up to 5 bullet points, please summarise the key messages of your submission.

- There is an unmet need for a standardised formulation of budesonide specific for EoE
- In current practice topical corticosteroids are used off-label with varying doses and inappropriate products often used
- Dietary intervention in adults is also highly effective as an alternative treatment
- Evidence for this technology is positive but limited to one phase 3 randomised controlled trial
- The long-term effects on bone mineral density and adrenal suppression are unknown

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Budesonide for treating eosinophilic oesophagitis [ID1202]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	EOS Network
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Our charity is funded by public donations. Due to our recent restructure we have 3 member/trustees and a new registration system to ensure that we are gdpr compliant. We currently have over 2000 followers on Facebook who are primarily, patients or carers.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	**I been personally involved with Eosinophilic patient advocacy for the past 16 years initially running a yahoo support group for 7 years and then as a founder of FABED (families affected by eosinophilic disorders) which was set up as a charity in 2011 and recently converted to EOS Network charity in 2019.** **I also have 2 children with Eosinophilic diseases one aged 12 and one aged 17.** **Over the years our organisation has used various tools such as blogs, facebook groups, yahoo groups, surveys, educational days, family events and telephone support to discuss and learn about the experiences of living with Eosinophilic Oesophagitis.** **I have also attended multiple international conferences for patients and professionals during this period.**

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	This disease has an impact emotionally, socially, physically and financially. To be able to eat without pain is a human function we take for granted. Eating and sharing food is the centre of all social events it brings us together in family and relationships, work meetings etc. It becomes isolating when you cannot eat the same food as your family friends, colleagues without difficulty i.e. problems swallowing food, choking, chest pain, regurgitation etc. These reactions can be to a known or previously unknown substance making it very difficult to manage. This affects everyone as the sufferer feels embarrassed upset and anti-social and the people around them feel embarrassed for them and awkward if they cannot share the same meal. The process of eating can be difficult and take longer than your eating companions because the sufferer is taking extra time to chew, it may be difficult for the person to talk whilst eating. Often a sufferer's diet can become extremely restricted whilst trying to discover safe foods this becomes impossible for some to manage whilst others will withdraw from social activities in order to maintain their restrictions. Majority of sufferers will avoid eating out for fear of having a reaction and will choose to carry their own prepared food everywhere. For young children this impacts their daily social lives and friendship development i.e. absence from school, not being invited to sleep overs and Birthday parties etc. In addition to this for adolescents it makes what is already a challenging time feel impossible for anyone to understand what it is like to live with EOE. Throughout this time care givers are required to support them with special diets, emotional support and medical care. Into adulthood this condition impacts your work and social life as it can be very difficult to maintain a special diet or eating habits and when you are unable to manage your symptoms you then can become unable to attend your normal daily commitments.

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	• Restricted diets can leave you nutritionally incomplete unfortunately many patients struggle to access knowledgeable dieticians support. • Elemental formula is not always prescribed and due to palatability often people will not tolerate the necessary quantity required or manage to maintain compliance of the restricted diet alongside the formula. • NG tubes and Feeding Pumps MICI buttons etc. are only used in extreme nutritionally required circumstances but in the event, they are, this can have huge impact on daily life for patients and carers and can need 24 hour support. • Using an asthma pump to deliver steroid treatment by swallowing instead of inhaling can be very tricky as is requires someone to not do what is on the instructions and there are no guarantees that the drug is delivered as needed to treat EOE. • Using a slurry to deliver steroid treatment is open to many wrong administrations from mixing incorrectly to ingesting incorrectly. • Many patients struggle to receive the treatments currently used off label as due to the above difficulties and lack of awareness they are not prescribed. • Due to lack of awareness sufferers are often having to travel long distances to find appropriate care, this can sometimes take years. • Lack of management and accessible treatments for EOE symptoms can result in multiple hospital visits, tests and loss of work and school attendance.

8. Is there an unmet need for patients with this condition?	• Patients need a treatment that is specifically designed and prescribed for eosinophilic oesophagitis. • Patients need clear instructions for a treatment that is easy to administer to maintain compliance. • Patients consider that unfortunately there may not yet be a magic treatment that cures their chronic condition, but they would hope for something that may improve their day to day quality of life i.e. eating, working and socialising. • Patients accept that a treatment may only be part of managing their symptoms. • Patients accept that steroids maybe needed but would prefer to know that they are getting the optimal treatment to the area that needs it i.e. the oesophagus. • Patients would like to eat without fear of choking or pain.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	As this drug is awaiting HTA approval for funding by NHS we have a limited amount of feedback but as follows is a statement provided by an EoE adult patient who has been taking the drug Jorveza – Budesonide dispersible tablet since December 2018 “I have felt a big improvement in my symptoms since taking the drug

	Jorveza (budesonide), whilst it has not cured my disease it has made living with it easier. I feel this is due to the convenience and simplicity of taking the right dose of medication in a dispersible tablet, especially when away from home. I am still cautious about eating out in public due to my past experiences, but I feel I have had less episodes of choking on food since taking Jorveza.(budesonide) I Know I have been fortunate to be put on this drug as its not widely available in the UK yet. I have had a long history of EOE for which my GP has experienced the difficulties in treating and therefore was able to prescribe it for me. I understand this is not the case for many other patients in the UK.”
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	None reported. Only concerns raised when they have been unable to access it through the NHS.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	The benefit would be equal to all who receive it.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**Only currently when this is not available to all patients through the NHS.**

Other issues	
13. Are there any other issues that you would like the committee to consider?	We would ask that in the future you consider this treatment to become available to adolescents and eventually children. As described previously this condition has a huge impact especially on adolescents when they are trying to develop friendships and independence but sadly, they cannot partake in normal social eating without feeling different or suffering the consequences of trying to eat the same foods as their companions. Many patients will already be using this medication budesonide or other steroid treatment through asthma pumps and will not be compliant with the swallowing or slurry technic. A dispersible tablet would be a simple alternative treatment that dramatically increases the chance of efficacy.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- This condition affects every part of a patient and carers/family life: at home, work, pleasure and social interaction.
- Eating is not just a necessity but a crucial social activity and should be done without the fear of chocking and pain.

- Many patients will already be using this medication -budesonide or other steroid treatment through asthma pumps and will not be compliant with the swallowing or slurry technic. A dispersible tablet would be a simple alternative treatment that dramatically increases the chance of efficacy.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Oesophagitis (eosinophilic, active) - budesonide [ID1202]

We thank you for taking the time to review this important additional submission which includes updated patient experience from a public survey completed in July 2020. Covid -19 has resulted in a year's delay to this appraisal and we would urge you to also consider the treatment for maintenance use within this appraisal to avoid further impact to patients ongoing care.

Summary

Eosinophilic Oesophagitis (EoE) is an chronic inflammatory delayed response often to an unknown food substance, it causes symptoms such as: problems swallowing food, choking, mild to severe chest pain, regurgitation and food bolus obstruction (food stuck) meaning you are unable to swallow even water

A recent patient experience survey identified the following::

Areas where Eosinophilic Oesophagitis has negatively affected quality of life include diet and eating, work, social life and travel.

Symptoms experienced include food sticking in the throat with or without mild to moderate or severe pain, stricturing (narrowing), weight loss and food avoidance.

One person describes the challenges of living with this condition:

"I choke drinking water now. I've had this for the past 30 years and I think my oesophagus is really scarred and damaged. My consultant has discharged me because he doesn't know what to do. I've asked for a PEG so I can have a break from the pain, inflammation, pain cycle but it was a no. I choke every time I eat and drink. I'm an ITU nurse and my best mates are nurses and doctors. When I choke and can't swallow/ breath/ speak it even scares them. To the point that at work the other day someone was going to get the crash trolley. I drink at least a litre of water with every meal to push each mouthful of food down."

Current off label medications are part of a potluck standard of care. The benefits of approving Budesonide ODT (Jorveza) as an NHS treatment would include:

- patients avoiding taking ineffectual medications
- reduced need for restricted diets and elemental tube feeding
- reduced GP, dietitian and hospital appointments
- reduced A and E visits due to Food Bolus Obstructions
- reduced medical procedures to remove food or (dilatation) stretching the oesophagus due to long term stricture damage
- reduced stress and anxiety caused by inconsistent care

Jorveza orodispersible (Budesonide) tablet a simple effective treatment that dramatically increases the chance of efficacy and compliance, improving symptoms and quality of life for 8 out of the 10 Jorveza (Budesonide) users in our survey.

Registered Charity 1143267

Oesophagitis (eosinophilic, active) - budesonide [ID1202]

How we gathered information about the experiences of patients and carers to help inform this additional submission.

EOS Network is the only Eosinophilic Diseases, UK Charity.

We exist to:

- Support the community of patients with Eosinophilic Diseases, their families and professional carer's.
- Increase awareness, diagnosis and treatment of Eosinophilic Diseases.

The roots of EOS Network go back to 2005 initially set up as a yahoo support group, FABED' Families Affected by Eosinophilic Diseases' became a registered Charity in 2011.

The eosinophilic community voiced the need to bring global research and growing medical knowledge to British sufferers, to improve their medical care.

In 2019 the Charity was restructured as EOS Network, strengthened by new trustee experience, a knowledgeable medical advisory board including an adult Eosinophilic patient with nurse experience and new working associations with professional British and Global medical institutions.

February 2020 we launched our community's information hub www.eosnetwork.org.

On a personal level, I Amanda Cordell have two children born with Eosinophilic diseases now aged 13 and 17 this has inspired me to be an active Eosinophilic patient advocate for the past 16 years. During which I have attended and or participated in multiple Eosinophilic international conferences for patients and professionals and qualified as EURORDIS patient expert for research and drug development within rare diseases.

Over the years our organisation has used various tools to communicate with our community such as: blogs, Facebook groups, yahoo groups, surveys, educational days, family events and telephone support to discuss and learn about the experiences of living with Eosinophilic Oesophagitis.

In this report, we included:

- Statistics and quotes from our July 2020 UK Adult EoE patient experience survey, jointly undertaken with GUTS UK Charity. This survey was open to our 2000+ followers on social media we received 39 completed forms.
- Our experiences as an Eosinophilic patient advocacy organisation.
- Quotes from patient/carer registration forms
- Past comments from social media
- Personal comments from patient review

How does this condition affect the day to day lives of people living with it?

Oesophagitis (eosinophilic, active) - budesonide [ID1202]

Eosinophilic Oesophagitis (EoE) is an inflammatory delayed response often to an unknown food substance, it causes symptoms such as: problems swallowing food, choking, mild to severe chest pain, regurgitation and food bolus obstruction (food stuck) meaning you are unable to swallow even water.

Without appropriate affective treatment long term damage can result in strictures (narrowing) reported in 69% of our survey participants which can then require regular dilatation (stretching of the Oesophagus) reported in 31% of our survey participants.
Survey participants also reported impact of the condition on social life (54%), eating (95%), travel (41%), diet (90%), work (46%), mood (74%), financial costs (39%).

Symptoms experienced include food sticking with or without mild to moderate pain (87%), with severe pain (49%), food bolus obstruction/impaction (74%), stricturing (narrowing) (69%), food avoidance (77%), weight loss (28%) and stretching of the oesophagus (31%). This condition has an impact emotionally, socially, physically and financially to the patient and their family/carers. To be able to eat without pain is a human function we take for granted. Eating and sharing food is the centre of all social events it brings us together in family and relationships, work meetings etc. It becomes isolating when you cannot eat the same food as your family, friends and colleagues.

Quote *"Affects relationship"*

The process of eating can be challenging, slower than others due to additional chewing and it may be difficult for the person to talk whilst eating.

Quote "Feeling scared to eat in front of others in case I 'choke'"

This affects everyone as the sufferer feels embarrassed upset and anti-social and the people around them feel embarrassed for them and awkward if they cannot share the same meal.
As this is non (IGE) delayed reaction there are no effective tests to indicate the foods to avoid only trial and error 78% reported food avoidance in our survey this becomes even more challenging when 29% of our survey found it difficult to access a dietician for treatment.

Often a sufferer's diet can become extremely restricted whilst trying to discover safe foods 57 % eliminating 6 or more food groups from their diet i.e. (egg, dairy, wheat, soya, fish, nut and more). This becomes impossible for some to manage whilst others will withdraw from social activities in order to maintain their restrictions. Majority of sufferers will avoid eating out for fear of having a reaction and will choose to carry their own prepared food everywhere.

Currently there are no standardised treatments resulting in random pathways of care, lengthy time to acknowledgment and diagnosis, leading onto a trial and error process of off label dugs and diet.
This causes psychological distress for patient and carer.
Quote *"I have developed anxiety, physically shake at times, for 3 yrs the dr prescribed Acid reducing medication without establishing the cause, it was when I complained of food sticking and physical choking episodes did they ref me to an ENT specialist who diagnosed silent reflux, it's a long slow process waiting for appointments which causes more anxiety. Stress makes the symptoms worse, I also stopped eating when at work for fear of choking. Ideally I'd prefer to attend a centre of excellence for this conditions and see drs specially*

Oesophagitis (eosinophilic, active) - budesonide [ID1202]

trained in this area, to me it's bonkers that different primary care trust use different methods to treat this disease"

How well do medicines which are currently available in NHS England help patients manage this condition?

Currently there are no approved NHS treatments for Eosinophilic Oesophagitis (EoE).

PPI's Omeprazole, Lansoprazole or Esomeprazole

92% (36) of our survey participants had been prescribed PPI's for their symptoms.
72% felt that the treatment did not improve their quality of life.
18% were satisfied with this as a treatment for EoE.

Patients struggle to receive treatments beyond treating acid suppression symptoms due to lack of awareness and a reluctance to prescribe off label.

Fluticasone (Flixotide) Asthma Pump or Budesonide (Pulmicort) Slurry

72% (28) of our participants had tried these as a treatment for their symptoms.
57% (16) felt these medications did improve their quality of life.

These medications need to coat the Oesophagus like a topical cream on the inside, so you must not wash it away (food or drink) till it is absorbed ie a minimum of 30 minutes.

- Using an asthma pump to deliver steroid treatment such as fluticasone by swallowing instead of inhaling the substance is difficult and inaccurate.

Quote*" I had two prescriptions after diagnosis, the first was a normal asthma inhaler which was difficult to use, and I never knew when it had run out. The second came as a nasal spray so it was much easier to use. All in I only used Fluticasone for about two months. Then I went on an elimination diet."*

- Mixing budesonide Respules with Splenda or honey to make a slurry for swallowing is open to many wrong administrations from mixing incorrectly to ingesting incorrectly.

Quote*" This medication helped me as it improved my symptoms, but it was difficult to take and I was very unhappy taking 5 teaspoons of Splenda daily. I try to avoid artificial sweeteners and I was worried about the long term effects of taking Splenda. I also felt I put on weight whilst using Splenda."*

- Both options require patient/carer to disregard the patient leaflet instructions and verbal or limited instructions from the prescriber are open to miss interpretation.
- 25% (7) of surveyed Patients or carers struggled to be compliant with these off-label technics of administration as an organisation we regularly find patients are unclear as to how to correctly administer their medication.
- There are no guarantees that the drug is delivered as needed to treat EOE but still carries the risk of the listed (steroid) side effects.

Quote *"I found it difficult to know whether I was swallowing enough to make any difference. It gave me oral thrush."*

Oesophagitis (eosinophilic, active) - budesonide [ID1202]

Dietary Treatments

There are various forms of dietary restrictions the most common being the 6-food elimination diet (egg, dairy, wheat, soya, fish, nut) as per 32% of responders this was closely followed by 25% avoiding more than 6 foods.
This is a challenge financially, physically and emotionally for patients and their families/carers.
59% of respondents reported it as difficult to follow a diet when away from home i.e. work and travel, pleasure or social.

Quote *"It's very restricted and so most of the time you eat alone because you cannot eat what others are eating. It can be quite depressive as foods have an ability to lift your mood. Eating the same restricted meals all the time is not great."*

Long term success of dietary treatment requires strict compliance to removal of foods that you are sensitised to. Global recommendations are to remove of 4 or 6 food groups, wait for symptoms to stabilise and then biopsy by endoscope to confirm remission. Once this is confirmed you can reintroduce one food at a time (approximately 6 weeks if no reaction) and then biopsy after each introduction to look for inflammation which can present even when symptom free. This treatment process requires multiple endoscopes.
Patients comments confirm this is not a standardised process in the UK.

Quote *"Hard following diet treatment as some consultants unwilling to scope or do not fully understand the condition."*
29% of our patients find it difficult to access the essential knowledgeable dietetic support needed to use it as a treatment and are often left trying to work out how to self-manage food trials and dietary restrictions. Which can often cause further complications both physically and emotionally.

Quote *"I finally saw a dietitian when I was diagnosed with oral allergy syndrome, so I had a whole other food group to eliminate. The dietitian had never heard of eoe and oral allergy syndrome and didn't really give any advice or follow up. Just to continue to try and avoid foods that trigger reaction."*
Quote *"The dietitian didn't know about EoE or how to treat it /me, totally disregarded the information leaflet she gave me, and took 2 years to admit she didn't know what she was doing with me."*
We report that 7% of our responders were on prescription elemental feed diets, usually used in the need for nutrition or in cases refractory to treatment. These medical feeds are broken down to be fully digested but avoid the hypersensitivity reactions causing the inflammation. Whilst they can provide full nutrition, they have poor palatability and may require an NG tube or more permanent MICI button or Peg to be surgically inserted for the patient to receive the necessary volume. The feed is then given by gravity or mechanical pump this has a huge impact on daily life for patients and carers and can need 24-hour support. Many suffer further complications of site infections.

How would Jorveza Budesonide improve a patient's quality of life and experience of care?

Oesophagitis (eosinophilic, active) - budesonide [ID1202]

As outlined in the Summary of key points, Jorveza orodispersible (Budesonide) tablet is a simple and effective treatment and 8 out of 10 (80%) patients felt it improved their quality of life.
Access to this treatment and its higher rates of efficacy and ease of compliance would improve earlier management of symptoms:

- Reducing GP and hospital appointments
- Reducing food bolus obstructions requiring A and E visits and emergency endoscopy procedures to remove food impactions (unable to swallow even water). Currently experienced by 74% of the survey participants.
- Reducing long term damage to the oesophagus (strictures) experienced by 69% in our respondents and 31% of respondents needing a dilatation to stretch their oesophagus.

The oral - dispersible tablet is easy and discrete to administer even when away from home.

Quote *"I have felt a big improvement in my symptoms since taking the drug Jorveza (budesonide), whilst it has not cured my disease it has made living with it easier. I feel this is due to the convenience and simplicity of taking the right dose of medication in a dispersible tablet, especially when away from home. I am still cautious about eating out in public due to my past experiences, but I feel I have had less episodes of choking on food since taking Jorveza.(budesonide) I know I have been fortunate to be put on this drug as its not widely available in the UK yet. I have had a long history of EOE for which my GP has experienced the difficulties in treating and therefore was able to prescribe it for me. I understand this is not the case for many other patients in the UK."*

Patients appreciate that there maybe be side effects when taking a steroid treatment but feel that the benefits of Jorveza out way the risk far more than the ineffectual off label use of steroids via slurries and asthma pumps.

"Taking Jorveza has much improved my quality of life in a positive way, in comparison to taking budesonide slurry with Splenda. Jorveza also fits in better with my lifestyle. It has transformed my life, I feel "normal" again."

Having an effective standardised treatment and NHS guidelines would give structure to education and awareness of EoE, improving the patient's pathway of care and ultimately their quality of life.

Quote *"I have yet to access this drug, my gastro consultant said ask your gp my gp says go ask your consultant it's insane I can't access the medication I need my gp is useless and has absolutely no idea what the drug is or what eoe even is. It's so not on gp's radar. Some have never even heard of it".*

What kind of impact would treating a patient with this medicine have on a patient's family or carers?

As per our previous comments poorly managed or undiagnosed this condition affects every part of a patient and carers/family life: at home, work, sleep(coughing), pleasure and social interaction.
Receiving this treatment would mean:

Less hospital and GP visits, less time off work and traveling to appointments.

Quote *"The fluticasone inhaler was a little tricky to initially use - e.g. swallowing and not breathing in, however I found that this medication really helped my symptoms, at the time I*

was choking often, my throat felt sore, hoarse voice, coughing at night and it stopped everything, I was also taking Mucogel at the time (my gp switched me from Gaviscon) and I also felt that helped. However, after the four weeks of prescribed medication the symptoms all returned, my gp prescribed another 4-week course and the same thing happened again so I was referred back to hospital to see the consultant"

Being able to eat out socially without fear and eating together as a family.

Quote*" It's been a long process and my husband gets annoyed with the limitations if he's cooking"*
Quote *"It's hard as there is no change in your meals day in day out. Been on it now 6 months straight."*

Less stress in the family, better sleep for all, as no coughing in the night.

Quote *"Unexplained coughing at night, wake coughing and choking, runny nose, migraines, thick head / brain fog, itchy mouth numerous times. However, whilst taking Jorveza zero choking or coughing episodes, still experience itchy mouths, runny nose at times"*

Being able to travel as a family without worrying about food or choking.

Reduce financial family burden for specialist foods.

Are there any disadvantages of the new medicine compared to current standard treatments?

We received reported side effects for all the treatments mentioned in the report.
Omeprazole: multiple reports of increased gastrointestinal problems forcing them to stop.

Quote *"Omeprazole for me in bigger doses give me stomach problems and seems to cause intolerance like symptoms. My sleep is massively effected."*
Fluticasone Asthma pump / Budesonide Slurry: Multiple reports of oral thrush without benefit of the medication.
Quote *"Oral thrush and no benefit"*
We also received comments on Jorveza (Budesonide):
Brittle hair and nails, pancreatitis both patients also commented on their complexities and restricted diets.
One patient also made the following comment
"It gives me an instant head rush when taking the tablet and I have been suffering with constant headaches. I have only been taking it for two weeks though"
This patient has since updated us and confirmed that the headaches/head rush have stopped and the swallowing difficulties due to EoE have resolved, she is currently at week 4 of her Jorveza treatment

We have directed all patients to the Yellow Card to report their concerns.

This information has been completed by Amanda Cordell for and on behalf of EOS Network

Oesophagitis (eosinophilic, active) - budesonide [ID1202]

10/11/20

NICE National Institute for Health and Care Excellence

Clinical expert statement

Budesonide for treating eosinophilic oesophagitis [ID1202]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Hannah Hunter**
2. Name of organisation	**British Society of Allergy and Clinical Immunology**

3. Job title or position	**Specialist Allergy Dietitian**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☒ yes

Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	It is reflected in the sense that the first goal of treatment is to induce clinico-histological remission. However other current treatments would be continued indefinitely in order to maintain this remission. It is unknown how long remission would be maintained following a cessation of the 12 week as this data is not yet available. Publication is also awaited on maintenance of remission with lower doses of this orodispersible budesonide. Given that relapse is apparent histologically within 3 weeks of ceasing dietary restriction, I would be surprised if remission would be maintained for more than 2 months following cessation of budesonide.

NICE National Institute for Health and Care Excellence

Clinical expert statement

Budesonide for treating eosinophilic oesophagitis [ID1202]

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Jack Winter**
2. Name of organisation	**Glasgow Royal Infirmary**

3. Job title or position	**Consultant Gastroenterologist**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To improve symptoms and quality of life in patients with chronic dysphagia due to Eosinophilic Oesophagitis (EoE) and to therefore reduce likelihood of progression to chronic oesophageal fibrosis and therefore recalcitrant dysphagia.
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	.Significant reduction in the patient's symptoms and associated histological improvement on endoscopic biopsies
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. There is no licensed treatment for this condition, which is becoming increasingly common and which can significantly affect the quality of life of sufferers. Proton pump inhibitors are often used off licence but help in the minority of patients. Topical corticosteroids are effective but, other than the technology being assessed, there is no dedicated delivery mechanism to the oesophagus for this condition. This means that dosing is often suboptimal, administration is time-consuming and difficult, and adherence is poor. This product appears to satisfactorily address a clear unmet need for the management of sufferers.

What is the expected place of the technology in current practice? I would anticipate it being the primary therapy in most patients who have an unequivocal diagnosis of eosinophilic oesophagitis and who have frequent symptoms of oesophageal dysfunction which negatively impact upon their quality of life.	
10. How is the condition currently treated in the NHS?	A minority of patients respond to proton pump inhibitors. Otherwise, topical corticosteroids are administered using a metered dose steroid inhaler licensed for asthma, but adapting the technique, or by swallowing the liquid content of corticosteroid respules and mixing with a viscous foodstuff. Delivery is difficult and mis-prescribing is frequent, resulting in inadequate control.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes (1) European Guidelines. Lucendo *et al* United European Gastroenterol J. 2017 Apr; 5(3): 335–358. (2) American College of Gastroenterology guidelines . Dellon *et al*. American Journal of Gastroenterology: May 2013 - Volume 108 - Issue 5 - p 679-692
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Pathway of care in adults is to treat with either PPI or topical corticosteroid, and to offer dietary treatment if patients do not respond to these treatments, or would prefer this mode. In reality, dietetic pathways in adult hospitals for EoE are at a rudimentary stage, and most adult patients prefer medication. This is based on my experience in Scotland, but is shared by most colleagues from NHS England who I have spoken with.
• What impact would the technology have on the current pathway of care?	It would allow a clear method of administering topical steroid in an effective manner. Topical steroid is the most effective treatment for this condition, but its success is currently hampered by absence of an adequate delivery mechanism, which this technology addresses.

11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes. I am using this technology currently as it is licensed, although not yet SMC or NICE approved.
• How does healthcare resource use differ between the technology and current care?	I don't think this technology will impact much on healthcare resource use. Current treatments are failing as patients find it difficult to continue topical corticosteroids due to ineffective delivery mechanisms.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Currently I would recommend the technology be initiated in specialist secondary care clinics. Primary care physicians see inadequate numbers of patients with this condition to adequately discuss the diagnosis and its implications, and to be confident about the correct choice of treatment
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	I do not envisage any change of facilities being needed to introduce this treatment
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes

• Do you expect the technology to increase length of life more than current care?	No. EoE causes morbidity, but is not known to affect mortality
• Do you expect the technology to increase health-related quality of life more than current care?	Yes
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	I do not think so. In my experience only highly motivated patients manage to adhere to other “off-licence” delivery mechanisms for topical steroids.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for	Much easier for both Single dose, single administration route, easier administration method. I cannot see clinical management of these patients changing otherwise due to adopting this technology. It will not change follow up plans etc.

example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Generally endoscopy is repeated to ensure the treatment is effective, regardless of symptom response. However this approach is already taken with current treatments so no change. Dietary therapy is very demanding of endoscopy, as multiple repeat scopes are often needed to assess the impact of different food exclusions. Currently the technology is only licensed for treatment, and not for maintenance. Duration of treatment is limited by the produce licence
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the	I think there is a realistic chance that there will be a future benefit in terms of reducing the development of fibrostenotic stricturing disease and therefore need for recurrent dilatations in the future by better controlling the disease due to use of this technology when it is at an earlier, inflammatory stage.

quality-adjusted life year (QALY) calculation?	
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes. Topical corticosteroids are undoubtedly effective, but their use is limited by the lack of a licensed dose of product with an adequate delivery mechanism. This technology is innovative in standardising dose and improving delivery mechanism
• Is the technology a 'step-change' in the management of the condition?	Yes - through being the first licensed produce and having the first effective licensed delivery mechanism
• Does the use of the technology address any particular unmet need of the patient population?	Yes – as above
18. How do any side effects or adverse effects of the technology affect the	

management of the condition and the patient's quality of life?	It is very well tolerated. Only recognised risk is of oral candida, which can be readily diagnosed and treated and is generally mild
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	The trials have very impressive results for benefit over placebo in both symptom control and in histological response. The gain compared with placebo is very impressive for any medical technology
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Don't know
• Are there any adverse effects that were not apparent in clinical trials	

but have come to light subsequently?	Not to the best of my knowledge
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance?	No
22. How do data on real-world experience compare with the trial data?	Real world experience is in its infancy, but the small cohort of patients I have treated with this medication have greatly benefited from it, and are now limited by lack of a licence for maintenance treatment
Equality	
23a. Are there any potential equality issues that should be	I don't think so

taken into account when considering this treatment?	
23b. Consider whether these issues are different from issues with current care and why.	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your statement.

- Topical corticosteroids are recognised as most effective treatment for Eosinophilic oesophagitis
- Lack of a licensed product means patients are often underdosed, and receive inadequate drug delivery, and struggle to have adequate response and maintain compliance
- This technology has very impressive gains versus placebo for both symptom control and histological improvement
- Technology is safe and well tolerated
- Technology does not otherwise increase healthcare utilisation of the patient cohort, and is likely to decrease it by achieving better control of the disease

Thank you for your time.

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Clinical expert statement

Budesonide for treating eosinophilic oesophagitis [ID1202]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Dr Jason Dunn**
2. Name of organisation	Guy's & St Thomas' NHS Foundation Trust British Society of Gastroenterology

3. Job title or position	**Consultant Gastroenterologist**
4. Are you (please tick all that apply):	x an employee or representative of a healthcare professional organisation that represents clinicians? **x** a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	x yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	1) To improve patient QoL – dysphagia and nutritional impact as a result, food avoidance and psychological impact, reduce emergency admissions with food bolus obstruction 2) To modify disease progression – reduce stenosing disease, leading to problems swallowing as illustrated above
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	1) Reduction in eosinophils count - <5/hpf (deep remission), < 15/hpf, 50% reduction 2) Improvement in stenosis 3) Improvement in symptoms
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, the current unlicensed treatments lead to wide variation in practice leading to sub-optimal care for the majority of patients. As this is a progressive disease, with organ damage as a result of untreated inflammation (oesophageal stenosis) then there is a need for patients to receive higher standard of care. A licenced treatment would contribute to this.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	Highly variable depending on local accessibility. Few centres have a dedicated dietietics service, or access to dietitians. Most are treated with swallowed steroid inhalers, with variation in dosimetry, delivery method and length of follow up.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	UEG guidance (Lucendo et al) often cited as best practice but they are > 3 years old. BSG is writing clinical guidelines, likely publication date April 2021.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Varies significantly, largely dependent on local expertise and interest. Although in general this is managed by gastroenterologists, often patients are discharged to primary care with little in the way of follow up plan.
• What impact would the technology have on the current pathway of care?	Improve significantly, provided its use is limited to secondary care.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, although one would hope there would be some improvement in clinic follow up as repeat treatments would need to be authorised from specialist clinic.

• How does healthcare resource use differ between the technology and current care?	Very little
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care minimum, specialist clinics desirable for complex cases.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No new investment required.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, as there is wide variation.
• Do you expect the technology to increase length of life more than current care?	No

• Do you expect the technology to increase health-related quality of life more than current care?	Yes
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No, as for other patients with confirmed diagnosis of EoE.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	Easier

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	I would suggest that a baseline eosinophil count from endoscopy should be documented prior to starting treatment. At 12 weeks this would need to be repeated to assess response. This should be current standard of care anyway (for flixotide for example), but is not always done.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes, including reduction in hospital admissions with food bolus obstruction
17. Do you consider the technology to be innovative in its potential to make a significant and substantial	Yes

impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes I think it is, because the vast majority who are treated at present are with swallowed inhaled steroid preparations– and as there is such variation in drug delivery we are porbably undertreating a large population, the effect of which may not be seen until many years later when the have end organ damage.
• Does the use of the technology address any particular unmet need of the patient population?	Yes, as currently there is no licensed treatment
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Very little, low risk drug.
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Patient QoL and symptom scoring, reduction in eosinophils count. Both measured in trial.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not that I am aware of
20. Are you aware of any relevant evidence that might	No

not be found by a systematic review of the trial evidence?	
21. How do data on real-world experience compare with the trial data?	I have treated 5 patients in the private sector, while we await local pharmacy approval. They all have had excellent response, and given they were resistant to diet then this is even more impressive.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	
Key messages	

23. In up to 5 bullet points, please summarise the key messages of your statement.

- EoE is poorly managed in the UK with wide variation in practice
- EoE, if left untreated, can lead to reduction in QoL and increased healthcare costs
- Jorveza has proven to be safe and effective for EoE treatment
- Other unlicensed inhaled steroids have unreliable delivery systems and a similar cost burden
- Jorveza prescribing should be limited to gastroenterologists, ideally with a specialist interest

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Patient expert statement

Budesonide for treating active eosinophilic oesophagitis [ID1202]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**Amanda Cordell**
2. Are you (please tick all that apply):	☐ a patient with the condition? **X**☐ a carer of a patient with the condition? **X**☐ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	EOS Network – Eosinophilic Diseases Charity
4. Did your nominating organisation submit a submission?	**X**☐ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	**X**☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	**X**☐ yes

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Evidence Review Group Report commissioned by the NIHR Systematic Reviews Programme on behalf of NICE

Budesonide for treating eosinophilic oesophagitis

Produced by Southampton Health Technology Assessments Centre (SHTAC)

Authors Dr Joanna Picot, Senior Research Fellow, SHTAC
Dr Keith Cooper, Senior Research Fellow, SHTAC
Mrs Neelam Kalita, Research Fellow, SHTAC
Mr David A. Scott, Director, Diligent Agile Synthesis Limited
Dr Jonathan Shepherd, Principal Research Fellow, SHTAC

Correspondence to Dr Jonathan Shepherd
Southampton Health Technology Assessments Centre (SHTAC)
Wessex Institute
Alpha House
Enterprise Road, University of Southampton Science Park
Southampton SO16 7NS
www.southampton.ac.uk/shtac

Date completed 27th November 2019

Source of funding: This report was commissioned by the NIHR Systematic Reviews Programme as project number 127897

Acknowledgements

We are grateful to the following who provided expert clinical advice to the ERG:
Dr Chris Haigh, Consultant gastroenterologist and head of service for gastroenterology, Northumbria Healthcare NHS Foundation Trust;
Dr Efren Eren, Consultant and Honorary Senior Lecturer in Immunology and Allergy, University Hospital Southampton NHS Foundation Trust.

We are also grateful to Dr Irina Tikhonova, Senior Research Fellow, SHTAC, for acting as internal editor on a draft of this report, and Lois Woods, Senior Research Assistant, SHTAC for critically appraising the company's literature search strategies.

Declared competing interests

The authors declare no competing interests. Dr Chris Haigh declares no competing interests. Dr Efren Eren has attended two meetings on eosinophilic oesophagitis sponsored/organised by Dr Falk Pharma (non-financial interest).

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Systematic Reviews Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Picot J., Cooper K., Kalita, N., Scott, D.A., and Shepherd, J. Budesonide for treating eosinophilic oesophagitis: A Single Technology Appraisal. Southampton Health Technology Assessments Centre (SHTAC), 2019.

Contributions of authors

Joanna Picot critically appraised the clinical effectiveness systematic review, critically appraised the network meta-analysis, and drafted the report. Keith Cooper critically appraised the health economic systematic review, critically appraised the economic

evaluation and drafted the report. Neelam Kalita critically appraised the health economic systematic review, critically appraised the economic evaluation and drafted the report. David Scott critically appraised the network meta-analysis and drafted the report. Jonathan Shepherd critically appraised the clinical effectiveness systematic review, critically appraised the network meta-analysis, drafted the report, project managed the review and is the project guarantor.

Word count: 31,983

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LIST OF ABBREVIATIONS

AE	Adverse event
AMS	Avoidance, modification, and slow eating
BID	Twice daily
BMI	Body mass index
BNF	British National Formulary
CI	Confidence interval
CRD	Centre for Reviews and Dissemination
CS	Company submission
CSR	Clinical study report
DIC	Deviance Information Criterion
DSU	Decision Support Unit
EEsAI	Eosinophilic Oesophagitis Activity Index
EEsAI-PRO	Eosinophilic Oesophagitis Activity Index – Patient-Reported Outcome
EMA	European Medicines Agency
EoE	Eosinophilic oesophagitis
EoE-QoL-A	Adult Eosinophilic Oesophagitis Quality of Life questionnaire
eos	Eosinophils
EPAR	European Public Assessment Report
EQ-5D	EuroQol 5-Dimension
ERG	Evidence Review Group
FAS	Full analysis set
FAS-DB	Full analysis set-double blind (phase)
FDA	Food and Drug Administration
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
GORD	Gastro-oesophageal reflux disease
hpf	High-power field
HRQoL	Health related quality of life
ICER	Incremental cost effectiveness ratio
IgE	Immunoglobulin E
ITC	Indirect treatment comparison
ITT	Intention-to-treat
modSHS	Modified Short Health Scale
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
NRS	Numerical rating scale
OD	Once daily
OLI	Open-label induction (phase)
ORR	Objective response rate
PatGA	Patient's Global Assessment
PP	Per-protocol
PPI	Proton pump inhibitor
PPI-REE	Proton pump inhibitor-responsive oesophageal eosinophilia
PRO	Patient reported outcome
PSSRU	Personal Social Services Research Unit

QALY	Quality adjusted life year
QoL	Quality of life
RCI	Repeated confidence interval
RCT	Randomised controlled trial
SAE	Serious adverse event
SAF	Safety set
SD	Standard deviation
SmPC	Summary of Product Characteristics
SOC	System Organ Class
STA	Single Technology Appraisal
TEAE	Treatment-emergent adverse event
VAS	Visual analogue scale
VDQ	Visual Dysphagia Question

SUMMARY

Scope of the company submission

The company submission (CS) presents evidence for the clinical effectiveness and cost-effectiveness of budesonide formulated as an orodispersiblte tablet (ODT) (Jorveza, Dr Falk Pharma) for the treatment of eosinophilic oesophagitis (EoE). Budesonide is a non-halogenated glucocorticosteroid which has high topical anti-inflammatory activity. The orodispersible formulation of budesonide has been developed with the aim of delivering budesonide to the oesophagus to combat inflammation. The recommended dose is a 1 mg ODT taken twice daily (BID) for six weeks. Treatment duration may be extended to 12 weeks for patients who do not respond completely.

The patient population described in the company's decision problem and included in the CS is adults with EoE who have received prior treatment with a proton-pump inhibitor (PPI). This is a narrower population than specified in the NICE scope and covered by the marketing authorisation both of which indicate adults with EoE (without a requirement for prior PPI treatment).

The CS reports a comparison of the effects of budesonide ODT in comparison to placebo and, using network meta-analysis methods, in comparison to fluticasone and the six food elimination diet (SFED).

Summary of submitted clinical effectiveness evidence

Relevant clinical effectiveness evidence was identified by a systematic literature review. Two randomised controlled trials (RCTs) of orodisperdible budesonide versus placebo were identified, BUU-2/EEA and BUL-1/EEA. No direct trial evidence comparing orodispersible budesonide versus the comparators fluticasone or SFED were identified.

BUU-2/EEA was a four-arm phase IIa double-blind, double-dummy, placebo-controlled RCT to evaluate two different formulations of budesonide (ODT and viscous suspension) with different daily dosages. The four arms were:

- 1 mg BID budesonide ODT (n=19)
- 2 mg BID budesonide ODT (n=19)
- 5 mL (0.4 mg/mL) BID budesonide viscous suspension (n=19)
- Placebo BID (n=19)

For the purposes of this single technology appraisal the 1mg BID budesonide ODT and the placebo BID arms are relevant. Data from the budesonide viscous suspension arm contributed data to an indirect treatment comparison via network meta analysis (NMA). The trial was conducted across 21 European centres. Each treatment was given for 14 days followed by a two-week follow-up phase.

The primary end-point was histological remission at week two [defined as a mean of <16 eosinophils (eos)/mm^2 high-powered field (hpf)]. The co-primary endpoint was change in the mean numbers of eosinophils/mm^2 high-powered field (eosinophil load) from baseline to week two. The secondary objectives were to identify the optimum dose for the induction of remission in EoE, and to assess safety and tolerability and patient health-related quality of life (HRQoL).

BUL-1/EEA is the company's pivotal phase III double-blind, placebo-controlled RCT. The trial was conducted in 19 European centres and patients either received 1mg budesonide ODT BID (n=59) or a matching placebo BID (n=29) for six weeks. The trial also included an optional open-label extension for a further six weeks for participants who did not achieve remission at the end of the double-blind treatment phase.

The primary outcome measure was clinico-histological remission at week six. This was a composite outcome measure defined as achieving:

(i) histological remission at end of treatment (peak eosinophil count <16 eos/mm^2 hpf)

AND

(ii) Clinical remission i.e. no or only minimal problems (defined as a symptom severity of ≤2 points on each 0 to 10-point numerical rating scale (NRS) for dysphagia and for odynophagia (pain during swallowing) on each day in the week prior to end of treatment

Secondary outcomes included symptoms, HRQoL, laboratory parameters and adverse events.

Results of the BUL-1/EEA and BUU-2/EEA RCTs

Histological remission

The results for histological remission (defined as peak eos count <16 eos/mm^2 hpf) inform the economic model via their inclusion in the NMA. This definition of histological remission is a secondary outcome of both trials. No participants in the placebo group of either trial achieved remission whereas for the budesonide 1mg ODT BID participants 93.2% achieved

remission after 6 weeks in the BUL-1/EEA RCT and 84.2% achieved remission after 2 weeks in the BUU-2/EEA RCT. In BUU-2/EEA using an alternative definition of remission (mean of <16 eos/mm^2 hpf, primary outcome) 100% of participants in the budesonide 1mg ODT BID arm achieved remission.

Clinico-histological remission

This composite outcome was the primary outcome for the BUL-1/EEA RCT. In the budesonide ODT arm 57.6% of participants achieved clinico-histological remission in comparison to 0% of the placebo arm ($p<0.0001$).

Change in numbers of eosinophils

Statistically significant differences between the budesonide ODT and placebo arms of both trials were observed. In the BUL-1/EEA budesonide ODT arm a mean fall in peak eos/mm^2 from baseline to week 6 of -226, SD 150.4 compared to a fall of -4.3, SD 135.6 in the placebo arm. In BUU-2/EEA a mean fall in peak eos/mm^2 from baseline to week two in the budesonide ODT arm of -227, SD not reported in comparison to -30, SD not reported in the placebo arm.

Other secondary outcomes

For other secondary outcomes reported by one or both of the trials, results were numerically in favour of the budesonide ODT arm but were not always statistically significantly different from the placebo arm.

HRQoL

HRQoL was measured using the modified Short Health Scale (modSHS) and the EoE-QoL-A in the BUL-1/EEA trial and the modSHS in the BUU-2/EEA trial. In the BUL-1/EEA trial the mean change from baseline values in the modified SHS indicated statistically significant improvements from baseline to week six in all four domains for participants in the budesonide ODT arm and in two of the four domains (symptom burden and social function) in the placebo arm. The intragroup differences (budesonide versus placebo) were all in favour of budesonide ODT with the CS stating a statistically significant superiority of budesonide versus placebo for social function and disease-related worry (no p-value reported). No numerical results were presented for the BUU-2/EEA trial and the CS states that no differences in changes from baseline between the treatment groups could be concluded.

For the BUL-1/EEA trial statistically significant differences between the budesonide ODT and placebo trial arms in the changes from baseline in EoE-QoL-A were reported in the CS for two of the sub-scores (eating/diet impact 10 items and eating/diet impact 4 items).

Subgroups

The BUL-1/EEA and BUU-2/EEA trial primary outcomes and key secondary outcomes (BUL-1/EEA) or co-primary outcomes (BUU-2/EEA) were analysed with respect to a number of pre-planned subgroups and one post-hoc subgroup. The results appear to be consistent with the full trial analysis for the subgroups analysed but because no participants in receipt of placebo achieved the primary outcome, the utility of the subgroup analyses is limited.

Adverse events

In both trials a higher proportion of participants experienced a treatment-emergent adverse event (TEAE) in the 1mg BID budesonide ODT arm than in the placebo arm (BUL-1/EAA 62.7% versus 41.1% respectively; BUU/2 EEA 36.8% versus 10.5% respectively). Across the two trials only one participant experienced a severe TEAE (food impaction requiring endoscopic surgery), this participant received placebo in the BUL-1/EEA RCT and this was the only event that caused a participant to withdraw prematurely from either trial. The most common TEAEs were local fungal infections that only occurred among participants receiving budesonide ODT. Similar types and proportions of TEAEs occurred during the six week open label extension phase of the BUL-1/EEA RCT as had been observed during the 6-week double blind treatment phase.

Network meta-analysis

As no head-to-head trials are available comparing budesonide ODT to relevant comparator treatments the company conducted a Bayesian NMA to indirectly compare treatments.

The NMA comprises a relatively small network of five trials, two of which are the company's RCTs of budesonide ODT. Only treatments considered by the company's expert clinicians to be routinely used in UK practice were included: fluticasone and SFED. PPI treatment is not included as a comparator as clinical advice to the company is that most patients will have received (and failed) PPI treatment prior to their diagnosis. Budesonide ODT is compared indirectly to fluticasone, via placebo and indirectly to the SFED via budesonide oral viscous solution (OVS).

Histological remission was the chosen outcome measure for the NMA (and the economic evaluation). The results of the company's random effects and fixed-effect NMAs indicate

that budesonide ODT has greater efficacy in terms of histological remission than either of the comparators (i.e. fluticasone or SFED), and also greater efficacy than budesonide OVS. However, credible intervals are very wide indicating a high degree of uncertainty. The company use the results of their random effects NMA in their base case economic analysis. When the ERG re-ran the NMA analyses using a frequentist approach (which automatically adds a continuity correction for zero values caused by no histological remissions in placebo groups) the results also indicated that budesonide ODT had greater efficacy than the comparators but confidence intervals were narrower. The results from this ERG analysis were used in our base-case economic analysis. The superior efficacy of budesonide ODT was maintained in the NMA sensitivity analyses conducted.

Summary of submitted cost effectiveness evidence

The CS includes:

- A systematic review of published economic evaluations in studies associated with EoE;
- A description of the company's de novo economic model developed to assess the cost-effectiveness of budesonide ODT compared with fluticasone and SFED for the treatment of adults with EoE.

The company conducted a systematic review to identify published studies for resource use, costs and economic evaluations for EoE. The search identified five studies, although four of these were cost analyses or estimation of resource utilization. The other study was on the cost-effectiveness of endoscopic biopsy for EoE in patients with refractory gastro-oesophageal reflux disease (GORD). However, the company argued that this study did not meet the inclusion criteria as the patient population was not directly comparable to the cohort within the scope of the current appraisal. The CS therefore states that no suitable cost-effectiveness studies were identified for EoE.

The company's economic model is a Markov model with health states: EoE active (on treatment); EoE remission without maintenance therapy, and death. There are three lines of treatment where the first line treatment is either budesonide ODT, fluticasone or SFED and the two subsequent lines of treatment are 'no treatment'. The model uses a 40-year time horizon and costs and quality adjusted life years (QALYs) are discounted at an annual rate of 3.5%.

The patient cohort enters the model in the EoE active (on treatment) health state. Patients progress to the remission without maintenance health state if they respond to the treatment or progress to second-line treatment (EoE active health state, second treatment) if they do not respond. Patients in the remission without maintenance health state remain in that health state until they relapse, when they return to the EoE active (first treatment) health state. Rates of movement between health states are taken from the company's NMA for remission and from the placebo arm of BUL-2/EER. Notably the model does not include health states for remission with maintenance therapy.

The model accumulates costs associated with drug acquisition, endoscopic dilation to resolve oesophageal strictures, and health state resource use and treatment of adverse events. QALYs are estimated by applying utility values to the time spent in the remission or active EoE health states. Base case utility estimates were taken from studies identified in a review of the literature. Due to limited available utility data for patients with EoE the company uses data relating to a proxy condition. Thus, the utility values used for active EoE in the base case analysis was from a study of patients with GORD with heartburn.

Base case results are presented as an incremental cost effectiveness ratios (ICERs). Budesonide ODT is estimated to be a dominant treatment, i.e. it is cheaper and more effective than fluticasone and SFED.

Table 1 Base-case cost-effectiveness results

	Budesonide ODT	**Fluticasone**	**SFED**
Drug costs	£5,097	£253	£0
Co-medications (dilation)	£5,934	£7,833	£7,163
Medical costs			
Gastroenterologist visits	£3,656	£5,359	£5,693
Dietician visits	£0	£0	£40
Endoscopies	£9,333	£13,677	£14,762
Adverse event costs	£0	£0	£0
TOTAL COSTS	**£24,020**	**£27,122**	**£27,657**
Incremental costs (budesonide ODT versus comparator)	-	–£3,101	–£3,637
TOTAL QALYS	**16.12**	**15.30**	**15.14**
Incremental QALYs (budesonide ODT versus comparator)	-	0.82	0.98
ICER - cost per QALY gained budesonide ODT versus comparator)	**-**	**Budesonide ODT dominates fluticasone**	**Budesonide ODT dominates SFED**

The company conducted deterministic sensitivity analyses, probabilistic sensitivity analyses and scenario analyses. The model results are most sensitive to changes to the utility values, unit costs for endoscopy and gastroenterologist visits and relapse rates for budesonide ODT.

Commentary on the robustness of submitted evidence

Strengths

- The CS is based on a systematic review of clinical effectiveness and the ERG believes that all the relevant evidence for budesonide ODT has been identified.
- The company's two RCTs of budesonide ODT were well conducted and it is unlikely that these trials are at a significant risk of bias.
- The economic model is in line with the NICE scope and follows the NICE reference case.

Weaknesses and areas of uncertainty

- No head-to-head evidence comparing budesonide ODT with either of the relevant comparators (fluticasone and SFED) is available.

- The level of clinical heterogeneity between the populations in the studies that have been included in the NMA is unclear and the company have not discussed evidence for effect modifiers for EoE.
- The single outcome of histological remission was chosen for inclusion in the NMA because this was an endpoint reported by all the studies that met the inclusion criteria for the company's systematic review of clinical effectiveness. Expert clinical advisors to the ERG agreed that this is an appropriate key outcome measure. However, the ERG considers it would have been informative if an NMA for the outcome of clinical remission (based on symptom scores) could have also been undertaken. This was requested by the ERG but the company stated that clinical remission rates are not consistently reported in treatment studies (nevertheless a scenario analysis for budesonide ODT versus fluticasone was provided).
- The outcomes from the NMA should be treated cautiously because of the uncertainty about clinical heterogeneity between studies, the inclusion of a non-randomised trial, issues caused by multiple zero values in placebo arms and the inappropriate use of a non-vague prior probability distribution to estimate treatment effect.
- The economic evaluation does not include maintenance therapy following response to induction treatment. The ERG considers this inconsistent with current clinical practice.
- The model overestimates the health care resources used during a patients' lifetime, including endoscopic dilation treatment.
- HRQoL estimates have not been obtained from a study of patients with EoE. The ERG considers that more representative utility values are available. In addition, the model does not include age-adjusted utility values.

Summary of additional work undertaken by the ERG

We corrected discrepancies in the model and re-ran the company's analyses. Changes to the results were minimal.

In addition, we ran an ERG base case analysis, including our preferred assumptions and model parameters (Table 2). These included the inclusion of maintenance treatment, changes to the time horizon, the remission rate, the endoscopic dilation rate, health care resources, utility values and the relapse rate. We also present selected scenario analyses to reflect key uncertainties.

Table 2 ERG's preferred model assumptions

Parameter	Company base case	ERG base case
Time horizon	40 years	20 years
Remission	Remission rates from company's random effects NMA	Remission rates from ERG's random effects NMA
Maintenance	No maintenance treatment after induction therapy for either budesonide ODT, fluticasone, or SFED.	Maintenance therapy with budesonide ODT after induction therapy with budesonide ODT. Maintenance therapy with fluticasone, and SFED after induction with fluticasone and SFED respectively.
Endoscopic dilation rate	Varies by treatment	Assumed same for all treatments
	Estimated from short-term studies	Uses long term study by Runge et al. (Dilation rate of 2% per cycle)
Health care resources	Applied for whole time horizon for active EoE health states.	No health state resources in active EoE if treatment is 'no treatment'. Initial health care costs applied for a short time period (6 months), including remission health states. Thereafter monitored by GP only. (Resources: in remission states no health care costs; in active EoE 1 GP visit / cycle, 0.5 gastroenterologist appointments / cycle, 0.25 endoscopies / cycle).
Utility	Uses values for proxy condition of GORD with heartburn (0.85 for remission, 0.7 for relapse)	Uses values for EoE patients. Incorrect values used in Kind et al. (0.93 for remission, 0.86 for relapse).
	Age-adjusted utilities not included	Age-adjusted utilities included
Relapse rate	No relapse rate for those in remission on maintenance as maintenance not included in CS	Assumes different relapse rate for those in remission on maintenance treatment or not on maintenance treatment.
	Relapse rate of 22% for those in remission on maintenance	Relapse rate of 11% for those in remission on maintenance.

Results of the ERG base case are shown below in (Table 3). The ICERs for budesonide ODT are £45,735 per QALY and £33,630 per QALY versus fluticasone and SFED, respectively. Incorporating the ERG preferred assumptions has a significant impact on the company's base case results. In the company's base case, budesonide dominates fluticasone as well as SFED; while in the ERG preferred base case, the pairwise ICERs of budesonide versus the two comparators are above £30,000 per QALY.

ERG scenario analyses (section 4.4.2 of this report) indicate that the model is most sensitive to the inclusion of maintenance therapy and changes to the utility values.

Table 3 ERG base case results

	Total costs (£)	**Total QALYs (£)**	**Incremental costs (£)**	**Incremental QALYs**	**ICER (£/QALY) Incremental**	**ICER (£/QALY) Pairwise BUD vs each treatment**
SFED	£1,528	12.48				
Fluticasone	£2,539	12.64	£1,012	0.16	£6,466	£33,630
Budesonide ODT	£18,595	12.99	£16,056	0.35	£45,735	£45,735

1 Introduction to the ERG Report

This report is a critique of the company's submission (CS) to NICE from Dr. Falk Pharma on the clinical effectiveness and cost effectiveness of orodispersible budesonide (brand name Jorveza) for eosinophilic oesophagitis (EoE). It identifies the strengths and weakness of the CS. Clinical experts were consulted to advise the ERG and inform this report.

Clarification on some aspects of the CS was requested from the company by the ERG via NICE on 18th October 2019. A response from the company via NICE was received by the ERG on 5th November 2019 and this can be seen in the NICE committee papers for this appraisal.

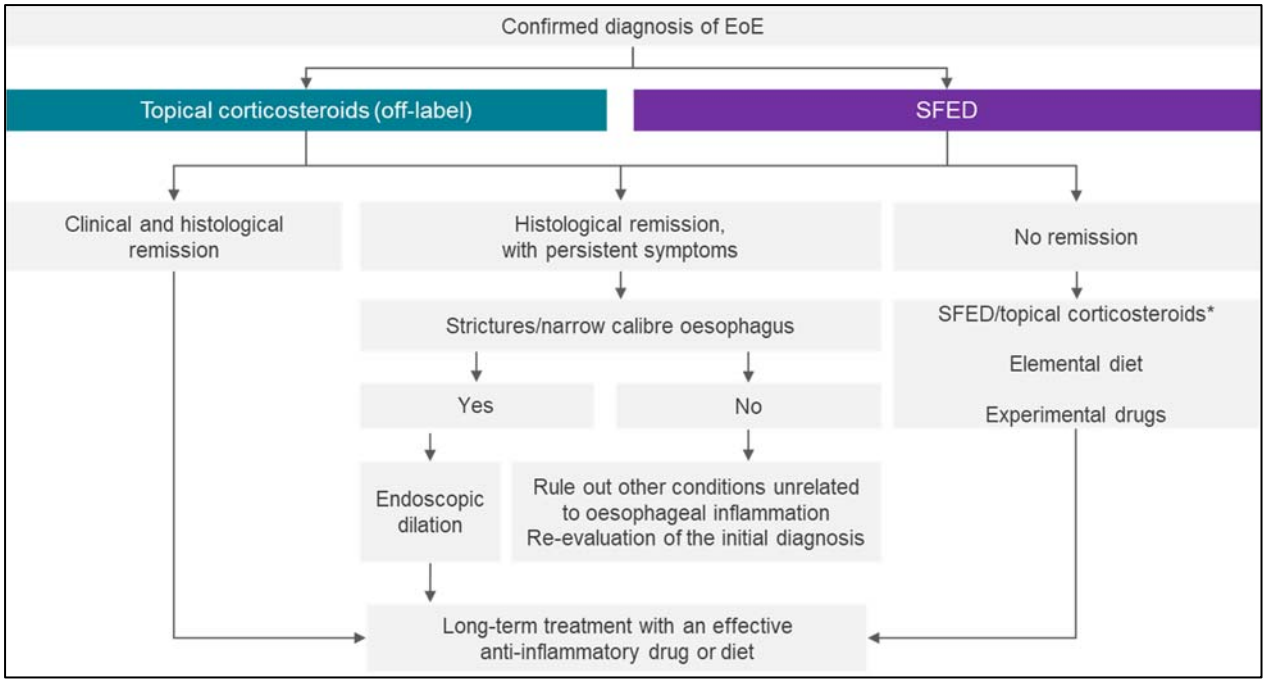
2 BACKGROUND

2.1 Critique of company's description of underlying health problem

The CS provides a brief overview of the epidemiology and key clinical features of EoE. The CS indicates that EoE is a chronic disorder and states that without treatment persistent symptoms and inflammation eventually lead to oesophageal remodelling. The time-frame over which oesophageal remodelling occurs is not stated. The CS states oesophageal remodelling results in fibrosis, possible stricture formation and functional abnormalities.

2.2 Critique of company's overview of current service provision

The only current management guidelines are the 2017 Lucendo et al. guidelines[1] on the diagnosis and management of EoE in children and adults. The CS highlights that awareness of EoE is generally low, UK-specific clinical practice guidelines are in development and there is no routine clinical practice for EoE in the UK. Despite asserting that clinical practice is not uniform, the CS does nevertheless present what it says is the current therapeutic algorithm following a confirmed EoE diagnosis in UK clinical practice (CS Figure B.1.1, reproduced below as Figure 1).



Source: Reproduction of CS Figure B.1.1 which is adapted from Lucendo et al., 2017[1]
Abbreviations: EoE = eosinophilic oesophagitis; SFED = six-food elimination diet
*Choice dependent on previous therapy

Figure 1 EoE treatment pathway

The treatment pathway shown in Figure 1 differs from the therapeutic algorithm shown in the Lucendo et al. guidelines[1] in that it does not include PPI therapy as a treatment option. This is because the CS states that in typical UK clinical practice patients will have already been treated unsuccessfully with PPIs before being diagnosed with EoE. Expert clinical advice to the ERG concurs with this assertion.

Treatment for EoE focusses on targeting the inflammation associated with EoE either with topical corticosteroids or with dietary modifications. The complications of EoE such as stricture formation can be treated by endoscopic dilation. Swallowed topical steroids are an off-label treatment option and the six-food elimination diet (SFED) or an elemental diet can be hard to persevere with. Orodispersible budesonide is the first, and therefore only, licensed treatment for EoE. There is no existing NICE appraisal guidance for EoE and also no related NICE clinical guidelines. The CS states that orodispersible budesonide is expected to become the preferred first-line treatment once a diagnosis of EoE has been confirmed. For some patients PPI therapy may be continued alongside orodispersible budesonide if clinically indicated.

2.3 Critique of company's definition of decision problem

Population

The population described in the decision problem differs slightly to that specified in the NICE scope. The NICE scope specifies adults with active EoE whereas the company decision problem population is adults with EoE (although the company does not specify that this should be active EoE the ERG believes that this is the intended population because this is the population enrolled in the key clinical trials for this appraisal) who have received prior treatment with a PPI. Although the company does not specify that the decision problem population should have failed prior treatment with a PPI, CS Table B.1.1 "Rationale if different from the final NICE scope" suggests that the PPI treatment should have been unsuccessful. The company's decision problem population is appropriate for the NHS. The clinicians the ERG consulted agreed that the decision problem population was reasonable but one expert raised concerns that initial PPI treatment might not always be optimal (in terms of dose and duration of treatment) and ideally PPI non-response should be based on endoscopy and biopsy.

Intervention

The intervention described in the decision problem is budesonide orodispersible tablets (ODT) 1mg. The decision problem does not specify the frequency of dosing but this is provided in CS Table B.1.2 as 1mg taken twice daily. This is in line with the scope and matches the dose stated in the summary of product characteristics (SPC).

Comparators

The comparators described in the decision problem, fluticasone (off-label) and SFED, are appropriate and align with those stated in the NICE scope. PPIs, which are listed as a potential comparator in the NICE scope, are not included because the decision problem patient group are expected to have already received and failed on treatment with PPIs (as stated above). In some circumstances (e.g. concerns about the rigor of an initial PPI trial) a clinician might trial PPIs ensuring optimum treatment and assessing response by endoscopy after at least six weeks treatment. Elemental diet is not included and the ERG views this as appropriate because the EoE treatment pathway indicates elemental diet would be a potential subsequent therapy after failure of both topical corticosteroids and SFED. The omission of budesonide slurry is also appropriate because the NICE scope specifies established clinical management without budesonide.

Outcomes

The outcomes listed in the decision problem predominately match those in the NICE scope with the exceptions that the company have not included relapse or mortality. The company state that relapse rates are not included because data on relapse were not collected in their two pivotal randomised controlled trials (RCTs) and mortality is not included because life expectancy does not appear to be directly affected by EoE. Expert clinical advice to the ERG concurs with this.

ERG conclusion

The company's decision problem does not fully adhere to the NICE scope, in terms of the included population and comparators. This is because the company have limited their decision problem population to adults with EoE who have been unsuccessfully treated previously with a PPI. Consequently, the company does not include PPIs as a comparator in their decision problem. However, expert clinical opinion concurs that many patients will have failed PPI therapy prior to their EoE diagnosis and would be unlikely to receive PPI treatment again.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the company's approach to systematic review

3.1.1 Description of company's search strategy

The CS reports literature searches for clinical effectiveness (in Appendix D), for cost-effectiveness (in Appendix G), and for health-related quality of life (HRQoL) utilities in (Appendix H). All searches were initially carried out in January 2018 and then updated in January 2019. The main concerns of the ERG are that all the searches are now eight months out of date; that there is no grey literature search; and that only the Cochrane Central Register of Controlled Trials (CENTRAL) was searched for trials, which might not be sufficient to capture ongoing trials information. The ERG, therefore, carried out supplementary update searches as detailed below.

The clinical effectiveness searches included the databases Medline, Embase, Cochrane Library, and the Centre for Reviews and Dissemination for the NHS Economic Evaluation Database (NHS EED), the Database of Abstracts of Reviews of Effectiveness (DARE) and the Health Technology Assessment (HTA) database. Appropriate search terms were used and combined accurately. All relevant MeSH (Medical Subject Headings) index terms were

used in Medline, however, not all relevant Emtree index terms (for Embase) were used (e.g. for drug names, for 'elimination diet/', for 'esophageal dilatation/'). The free text terms, however, are believed to have been sufficiently comprehensive to retrieve relevant studies.

The ERG updated the clinical effectiveness searches by repeating the company search strategy, in Medline only, from 22nd January 2019 to 22nd October 2019. We also searched the trials databases ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) to provide better coverage of ongoing trials information.

The ERG's update searches identified one new relevant reference published since the company's literature search in January 2019. This was the trial journal publication of the Phase III BUL1/EEA RCT.[2] The ERG identified references to 17 clinical trials from ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP). Publications for these trials had already been identified via the company's database literature search.

The cost-effectiveness searches are not reported in such a way that they could be reproduced due to lack of clarity in the CS. The CS reports searching PubMed, and then reports searching Medline, for which four separate tables of search terms are provided (including MeSH terms). From the search syntax and the table headings, it looks like a PubMed search was carried out, but it is not recorded how the search terms between the four tables were combined. The table headings state that the searches are for systematic reviews although they include no systematic review terms or limits.

Two utilities searches were carried out in Medline database, one for utilities generally and another as a search to *"determine whether disease-specific instruments had been used to assess disease progression and response through patients' symptoms or the disease-specific QoL scores had been mapped to any instruments which can be readily converted to utilities."* (CS Appendix H.1.2.). The searches include comprehensive use of both free text terms and MeSH terms. The flow diagram (CS B5.9) shows that four references were found by hand-searching; however, what material was hand-searched is not reported.

The ERG considers that the cost-effectiveness and utilities searches, although not easily reproducible, are likely to have retrieved the relevant studies based on the databases and search terms that were used, and so we have not updated them.

ERG conclusion

Overall, the search strategies are not presented consistently, and several elements of the reporting are unclear. However, we consider that the searches retrieved all relevant studies.

3.1.2 Statement of the inclusion/exclusion criteria used in the study selection

The inclusion and exclusion criteria for the systematic review of clinical effectiveness are reported in CS Appendix D Table 5.7. The ERG asked the company to clarify the exact inclusion criteria (clarification question A2) particularly with regard to the study designs eligible for inclusion. In response, the company stated there had been an error in CS Appendix D Table 5.7 and full inclusion and exclusion criteria are presented in Table 1 as part of the company's response to clarification question A2.

The interventions permitted for inclusion were treatments for EoE *"which are recommended in the majority of available guidelines published by relevant institutions in Western developed countries, i.e. topical steroids, PPIs, oesophageal dilation or dietary intervention".*

The inclusion criteria accord with the NICE scope but describe a wider patient population group than specified in the company's decision problem. This is because studies of patients with PPI-responsive EoE were permitted for inclusion in the company's systematic review, whereas the company's decision problem only includes patients treated unsuccessfully with PPIs (as discussed earlier – section 2.3).

Of note, there was no restriction on study design, thus randomised and non-randomised studies were eligible for inclusion.

The results of the literature search and inclusion / exclusion screening process are illustrated in flow-charts (CS Appendix D Figure B.5.1 and Figure B.5.2).

The next section describes the studies included in the company's systematic review. As will be seen, a further set of inclusion / exclusion criteria were used to identify studies.

3.1.3 Identified studies

A total of 68 studies were included (23 reviews and 45 primary studies). A second round of inclusion/exclusion criteria was then applied in which studies were excluded if:

- They did not report results for histological remission (n=9);

- Included interventions not recommended by clinical guidelines (n=1);
- Did not address the underlying inflammation associated with EoE (e.g. dilation) (n=9);
- Were single-armed studies (n=14)
- Did not completely fulfil the age criterion of the inclusion and exclusion criteria.

A total of 35 of 45 primary studies were excluded according to these criteria leaving 10 remaining studies included in the systematic review of clinical effectiveness.

A subset of five of these ten studies was selected to perform an indirect treatment comparison. The criteria used to select this subset were not explicitly stated therefore the ERG asked the company to confirm (clarification question A3b). In response, the company stated that the literature search had been broad to cover the reimbursement and pricing requirements of several European countries, but that expert clinical opinion had suggested UK patients eligible for budesonide ODT would typically have already been treated unsuccessfully with PPIs prior to diagnosis. This would leave a limited set of off-label treatments available for use after diagnosis and therefore the final subset of five studies was selected based on the two comparators of interest: fluticasone and SFED. Although the clinicians we consulted agreed with the company's rationale for the choice of UK relevant treatments it was noted that

i) a number of tertiary referral centres use Pulmicort Respules (budesonide nebulised suspension 0.5mg) prior to trying fluticasone (but note that the NICE scope did not include budesonide as a comparator) and
ii) due to the difficulty of compliance with the SFED there is a trend moving towards simpler two- and four- food elimination diets.

Studies including budesonide oral viscous solution (OVS) and placebo were included for the sole purpose of enabling relevant treatments to be connected together in a network meta-analysis (NMA) (see section 3.1.7 of this report for a critique of the NMA). The company provided a table listing the five studies that had been excluded (clarification response to question A3b Table 2).

The five included studies included the following EoE treatments:

- Budesonide ODT[2,3]
- Budesonide OVS[3,4]
- Fluticasone[5]

- Placebo[2-5]
- SFED[6]

All the studies were RCTs except for one which was described in the CS as a prospective observational study.[6]

Of the five studies, two evaluated budesonide ODT. Both of these were sponsored by the company and form a major part of their clinical trial programme for this drug. These are described below.

3.1.3.1 Phase II BUU-2/EEA RCT[3]

This was a double-blind, double-dummy, randomised, placebo controlled, parallel multicentre Phase IIa dose-finding study to evaluate the efficacy and safety of two different formulations of budesonide: oral dispersible tablet and vicious suspension, with different daily dosages. There were four arms:

- 1 mg twice daily (BID) orodispersible budesonide tablet (n=19)
- 2 mg BID orodispersible budesonide tablet (n=19)
- 5 mL (0.4 mg/mL) BID budesonide viscous suspension (n=19)
- Placebo BID (n=19)

Each treatment was given for 14 days and there was a two-week follow-up phase. The primary end-point was histological remission. The secondary objectives were to identify the optimum dose for the induction of remission in EoE, and to assess safety and tolerability and patients QoL. The study took place across 21 European Centres (16 in Germany, three in Switzerland and two in Belgium), no patients from the UK were included.

For the purposes of this report the 1mg BID budesonide ODT and placebo arms of this RCT provide relevant clinical effectiveness data and are reported in section 3.3. Evidence from the budesonide viscous suspension arm contributes data to the NMA as described in section 3.1.7, with the NMA results presented in section 3.3.11.

3.1.3.2 Phase III BUL1/EEA RCT[2]

This was a pivotal double-blind, randomized, placebo-controlled, multicentre phase III trial.

The lowest dose of oral dispersible budesonide from the phase II trial (i.e. 1 mg BID) was chosen for confirmatory evaluation in the phase III trial (though the phase II trial failed to demonstrate the superiority of one dose over the other).

There were two trial arms:

- 1 mg BID budesonide orodispersible tablet (n=59)
- Matching placebo (n=29)

The primary outcome measure was clinico-histological remission in adult patients with active EoE. Secondary outcomes included symptoms, health-related quality of life, laboratory parameters and adverse events. The trial was conducted in 19 European centres (10 in Germany, 6 in Spain, 2 in Switzerland and 1 in the Netherlands), no patients from the UK were included.

CS Figure B.2.1 shows how participants moved through the different phases of the trial. Treatment was given for six weeks, with an optional open-label extension of a further six weeks for patients without remission at the end of the double-blind phase. Participants who did not enter the optional open-label extension received four weeks of follow-up.

Participants who did achieve clinico-histological remission by the end of either the double-blind phase or the open-label extension were eligible to enter the optional 48-week, double-blind, randomised, placebo-controlled, maintenance of clinico-histological remission study (BUL-2/EER). Participants who chose not to enter the maintenance study were followed up for four weeks.

Both the Phase II BUU-2/EEA and Phase III BUL1/EEA RCTs used adaptive two-stage group sequential designs, which we discuss later in this report (section 3.1.6.1).

Participant demographics and baseline characteristics

The ITT populations of the Phase II BUU-2/EEA (arms relevant to this appraisal only) and Phase III BUL1/EEA RCT are summarised in Table 4. There were some minor differences in each trial between the budesonide and placebo groups. One of our clinical advisors indicated that in their experience the degree of inflammation before starting treatment was an important factor in predicting response to treatment. In the phase III BUL-1/EEA trial a slightly higher proportion of participants in the placebo group had three inflamed segments (79.3% versus 72.9% in the budesonide group) whereas in the phase II BUU-2/EEA trial only

47.4% of the placebo group had three inflamed segments in comparison to 73.7% in the budesonide group.

Table 4 Participant demographics and baseline characteristics

	Phase III BUL1/EEA RCT		Phase II BUU-2/EEA	
	Budesonide ODT 1 mg BID (N=59)	**Placebo (N=29)**	**Budesonide ODT 1 mg BID (N=19)**	**Placebo (N=19)**
Sex, n (%)				
Male	48 (81.4)	25 (86.2)	17 (89.5)	16 (84.2)
Female	11 (18.6)	4 (13.8)	2 (10.5)	3 (15.8)
Race, n (%)				
White	59 (100.0)	29 (100.0)	19 (100.0)	19 (100.0)
Mean (SD) age, years	37.0 (11.47)	36.9 (9.20)	38.9 (12.6)	36.3 (9.9)
Mean (SD) BMI, kg/m^2	24.4 (2.86)	25.6 (4.08)	25.5 (4.41)	23.7 (3.16)
Smoking status, n (%)				
Current	3 (5.1)	0 (0)	3 (15.8)	0 (0.0)
Former	5 (8.5)	3 (10.3)	3 (15.8)	1 (5.3)
Never	51 (86.4)	26 (89.7)	13 (68.4)	18 (94.7)
Concomitant allergic disease, n (%)	47 (80)	23 (79)	14 (73.7)	10 (52.6)
Concomitant PPI use, n (%)	7 (11.9)	3 (10.3)	3 (15.8)	3 (15.8)
Mean (SD) duration since first symptoms	months 134.2 (104.6)	months 139.0 (98.8)	years 8.3 (7.8)	years 7.9 (7.5)
Mean (SD) duration since diagnosis	months 48.8 (44.3)	months 57.6 (49.3)	years 1.9 (3.4)	years 2.6 (5.1)
Diagnosis of EoE, n (%)				
Established	58 (98.3)	27 (93.1)	12 (63.2)	11 (57.9)
New	1 (1.7)	2 (6.9)	7 (36.8)	8 (42.1)
Number of inflamed segments, n (%)				
1	6 (10.2)	2 (6.9)	1 (5.3)	4 (21.1)
2	10 (16.9)	4 (13.8)	3 (15.8)	6 (31.6)
3	43 (72.9)	23 (79.3)	14 (73.7)	9 (47.4)
Localisation of inflammation, n (%)				
Proximal	47 (79.7)	25 (86.2)	14 (73.7)	13 (68.4)
Mid	52 (88.1)	26 (86.7)	18 (94.7)	14 (73.7)
Distal	56 (94.9)	28 (96.6)	18 (94.7)	16 (84.2)
Peak eos/mm^2 hpf				
Mean (SD)	242 (140.7)	239 (125.0)	242 (144.2)	320 (309.0)
Median (range)	205 (56–611)	197 (99–620)	206 (78–635)	183 (58–977)
Mean (SD) blood eos/mm^3	427 (255.4)	455 (255.5)	470 (453.3)	372 (224.7)

Source: CS Tables B.2.5 and B.2.7

BID - twice daily; BMI - body mass index; EoE - eosinophilic oesophagitis; eos - eosinophils; hpf - high-power field; mg - milligram; mm - millimetre; n/N – number of patients/total number of patients; ODT - orodispersible tablet; PPI - proton-pump inhibitor; SD - standard deviation.

The advisor also believed that more distal disease might have an effect on response to treatment (potentially because the drug may not reach this region as effectively), this was similar between the trial arms in the BUL-1/EEA trial (94.9% budesonide arm versus 96.6% placebo arm) but in the BUU-2/EEA trial 94.7% of the budesonide arm had distal disease in contrast to 84.2% of the placebo arm.

Other more notable differences that were observed when comparing between the two trials (only taking into account the two relevant arms of the phase II trial) were:

- a higher proportion of the BUL-1/EEA RCT participants had concomitant allergic disease (79.5% versus 63.2% in the relevant arms of the BUU-2/EEA RCT)
- there were very few participants with newly diagnosed EoE in the BUL-1/EEA RCT (3.4% versus 39.5% in the relevant arms of the BUU-2/EEA RCT).
- participants in the BUL1/EEA RCT had a longer duration since first symptoms (approximately 11 years) and a longer duration since diagnosis (approximately 4 years) than participants in the BUU-2/EEA trial (approximately 8 years and 2 years respectively).

Expert clinical advice to the ERG was that, although not impossible, it is very unlikely that any of the differences between the participants in the relevant arms of the two RCTs would have influenced the results.

The remaining three studies included by the company, which provide evidence for the two comparators of interest (fluticasone[5] and six-food elimination diet[6]) and contribute data to the NMA,[4] are discussed in section 3.1.7 of this report.

The ERG is not aware of any additional studies of budesonide ODT that have been completed or are in progress.

3.1.4 Description and critique of the approach to validity assessment

The company used the GRADE approach (Grading of Recommendations, Assessment, Development and Evaluations) to assess the quality of the evidence included in the indirect treatment comparison, but they did not provide quality assessments for the individual studies. The ERG has used the NICE criteria to assess the two key budesonide ODT studies (Table 5).

Table 5 ERG assessment of trial quality

NICE quality assessment criteria for RCTs	BUL-1/EEA	BUU-2/EEA
1. Was the method used to generate random allocations adequate?	Yes	Yes
2. Was the allocation adequately concealed?	Yes	Yes
3. Were the groups similar at the outset of the study in terms of prognostic factors, e.g. severity of disease?	Yes	Yes
4. Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Yes	Yes
5. Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	A higher proportion of participants in the placebo arm than in the budesonide arm prematurely withdrew (15.4% versus 5.1% respectively). All of these withdrawals were due to a lack of efficacy. Results are presented for the ITT population with missing data estimated using the last observation carried forward method (see section 3.1.6.6).	There were no premature withdrawals in either study arm. Two patients in the placebo arm were judged to violate the protocol due to insufficient baseline disease activity but these patients were both included in the ITT analyses.
6. Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
7. Did the analysis include an intention to treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes

ERG conclusion

Both trials appear to have been well conducted and are unlikely to be at a significant risk of bias.

3.1.5 Description and critique of company's outcome selection

The outcomes included in the CS match those specified in the NICE scope, with the exceptions that i) as already noted, relapse and mortality were not included in the decision problem and ii) complications such as stricture formation, which are included in the decision problem outcomes, are not reported. The absence of reporting on complications such as stricture formation may be because the two key trials, Phase II BUU-2/EEA RCT[3] and Phase III BUL1/EEA RCT,[2] had a relatively short duration (Phase II RCT two weeks of treatment, Phase III RCT six weeks double blind treatment with optional further six week open-label induction and four week follow-up for those not in remission at the end of the double blind phase, giving a maximum period of 16 weeks).

3.1.5.1 Primary outcomes

The primary outcome of the Phase III BUL1/EEA RCT was the rate of clinico-histological remission at week six (end of treatment). This was a composite outcome measure defined as achieving:

(i) histological remission at end of treatment (peak eosinophil count <16 eos/mm^2 hpf) AND

(ii) clinical remission i.e. no or only minimal problems (defined as a symptom severity of ≤2 points on each 0 to 10-point numerical rating scale (NRS) for dysphagia and for odynophagia (pain during swallowing) on each day in the week prior to end of treatment.

Any patient who experienced food impaction, who needed endoscopic intervention or dilation or who withdrew prematurely was assessed as a treatment failure and so did not fulfil the definition for clinico-histological remission.

There are no internationally accepted definitions of complete remission and complete response in EoE and the 2018 systematic review by Eke et al.[7] found a lack of consistent remission criteria in published studies which makes comparing the effectiveness of different treatments difficult. The CS states that the European Medicines Agency (EMA) agreed that a cut-off of <16 eos/mm^2 hpf for defining histological remission was acceptable, as this criterion was used in most of the previous studies in the field.

Clinical remission was defined as having only minimal or no problems on the numerical rating scales for dysphagia and odynophagia (which are the main EoE symptoms). The EMA's recommendation was to record these symptoms daily to avoid recall bias.

The clinically meaningful difference in clinico-histological remission rates between treatments was agreed with the EMA to be approximately 40% (providing the safety profile of 1mg orodispersible budesonide was not relevantly different from previously licensed formulations of budesonide administered within the gastro-intestinal tract).

The primary outcome of the Phase II BUU-2/EEA RCT was histological remission at week two (defined as a mean of <16 eos /mm^2 hpf). The co-primary endpoint was change in the mean numbers of eos/mm^2 hpf (eosinophil load) from baseline to week two (end of treatment).

Histological remission was the outcome measure included in the company's NMA. We discuss this in section 3.1.7 of this report.

3.1.5.2 Secondary outcomes

In the Phase III BUL1/EEA RCT the key secondary endpoints were ordered:

1. Rate of patients with histological remission, defined as a peak of <16 eos/mm^2 hpf at week six
2. Change in the peak eos/mm^2 hpf from baseline to week six
3. Rate of patients with clinical remission, defined as a severity of ≤2 points on 0-10 numerical rating scale for dysphagia AND a severity of ≤2 points on 0-10 numerical rating scale for pain during swallowing on each day in the week prior to week six
4. Rate of patients with total weekly EoE Activity Index – Patient Reported Outcome (EEsAI-PRO) score of ≤20 at week six. The EEsAI-PRO[8] is a validated measure for adults, composed of seven PRO items that assess oesophageal symptoms over a seven day recall period. The instrument accounts for behavioural adaptations such as avoidance of specific food textures and meal-time length in adults with EoE.
5. Rate of patients with an improvement from baseline to week six in the weekly Visual Dysphagia Question (VDQ) score. The CS does not define the VDQ but it is described in the clinical study report (CSR) for this trial as a subscore of the EEsAI-PRO. The published paper on the development and validation of the EEsAI-PRO[8] states that the VDQ includes eight items from various food groups and assesses dysphagia caused by eating foods of different consistencies. The VDQ ranges from 0 to 10.
6. Rate of patients with an improvement from baseline to week six in the weekly 'Avoidance, Modification, and Slow-eating' (AMS) score. The AMS is also not defined in the CS but is another subscore of the EEsAI-PRO. It assesses

behavioural adaptations in respect of different food consistencies. The AMS score ranges from 0 to 10.

The phase II BUU-2/EEA RCT key secondary endpoints are listed in the CS as:

- Rate of histological remission defined as (mean of <16 eos/mm^2 hpf at week two)
- Change in the peak eos/mm^2 hpf from baseline to week two
- Change in the total endoscopic intensity score and its subscores
- Change in blood eosinophil counts from screening visit two to week two
- Course and change of the dysphagia score within the study
- Physician's global assessment
- Change of modified Short Health Scale (SHS) in the course of the study

Some of the key secondary endpoints of the phase II RCT listed in the CS were not defined, nor were any references provided aside from the modified SHS for which the BUU-2/EEA CSR was cited. However, when the ERG checked the BUU-2/EEA CSR we found that the SHS was not the Subjective Happiness Scale, as stated in the CS abbreviations list, but the Short Health Scale.

Definitions or references were available in the published journal article for the phase II RCT[3] as follows:

- Total endoscopic intensity score: seven endoscopic abnormalities (white exudates, furrows, oedema, fixed rings, crepe paper sign, short-segment stenosis and long-distance stenosis) were recorded and classified as either absent (score 0); mild (score 1), moderate (score 2) or severe (score 3). Thus, the total endoscopic intensity score could range from 0 to 21.
- Dysphagia score. A non-validated score used in a previous RCT. The frequency and intensity of dysphagia were scored as 0 to 4 (none to several times a day) and 0 to 5 (unhindered swallowing to long-lasting complete obstruction requiring endoscopic intervention) respectively. Total scores therefore ranged from 0 to 9. A clinical response was defined as a decrease in the dysphagia score of at least 3 points compared with baseline.
- Physician's global assessment of EoE activity (0-10 NRS)
- Modified Short Health Scale. The Short Health Scale is described in the CSR as a valid, reliable and responsive measure of subjective health described for ulcerative colitis[9] and Crohn's disease patients.[10] It was modified by replacing the underlying disease terms i.e. replacing 'bowel' by the term 'oesophageal'.

3.1.5.3 Other outcomes

In addition to the six key secondary endpoints listed above for the BUL-1/EEA RCT, a further 11 outcomes described as "exploratory secondary efficacy outcomes" from the double-blind phase of the RCT were listed in the CS.

Five clinical exploratory outcomes:

- Mean change from baseline to week six in the Patient's Global Assessment (PatGA) concerning the severity of EoE symptoms (NRS 0-10)
- Number (%) of patients with overall symptoms resolution, defined as PatGA ≤2, at week 6
- Mean change from baseline to week six in Physician's Global Assessment of EoE activity (NRS 0-10. Note that the CS lists the PatGA but from cross-checking with the CSR the ERG believes that this should be the Physician's rather than the Patients' Global Assessment.
- Median time (days) to first symptom resolution (dysphagia and pain during swallowing)
- Mean change from baseline to week six in blood eos/cm^3

Four endoscopy exploratory outcomes:

- Number (%) of patients with 'no endoscopic findings' at week six
- Mean change from baseline to week six in total modified EEsAI endoscopic sub-score (0-9)
- Mean change from baseline to week six in 'inflammatory signs' sub-score of modified EEsAI endoscopic score (0-4)
- Mean change from baseline to week six in 'fibrotic signs' sub-score (consisting of 'fixed rings' and 'stricture') of modified EEsAI endoscopic score (0-4)

Two HRQoL exploratory outcomes:

- Mean changes from baseline in the modified Short Health Scale score
- Mean changes from baseline at week six in the disease-specific Adult EoE Quality of Life (EoE-QoL-A) Questionnaire and its sub-scores.

No other outcomes are listed for the BUU-2/EEA RCT.

3.1.5.4 Safety outcomes

For both the Phase III BUL1/EEA and Phase II BUU-2/EEA RCTs the CS states that *"Safety was assessed on the basis of AEs, vital signs and body weight, physical examination, laboratory parameters including morning serum cortisol, and assessment of tolerability by the investigator and the patient".* Treatment-emergent adverse events (TEAEs) are summarised for both of the included RCTs. For the Phase III RCT TEAEs are also described by the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms for any TEAE that occurred in two or more patients in either trial arm. TEAEs are reported for the double-blind and open-label phases of the trial.

ERG conclusion

The CS reports a range of efficacy measures based on those included in the phase III BUL1/EEA[2] and the phase II BUU-2/EEA[3] RCTs. Histological remission was the primary outcome of the Phase II RCT and was the first of six ordered key secondary endpoints in the phase III RCT. This outcome was defined slightly differently between the two trials (Phase II definition: a mean of <16 eos/mm^2 hpf at week two; Phase III definition: a peak of <16 eos/mm^2 hpf at week six) and was the outcome that informed the clinical effectiveness estimates in the economic model (via an NMA that is described in section 3.1.7 of this report).

3.1.6 Description and critique of the company's approach to trial statistics

This section focuses on the phase III BUL-1/EAA trial as this is the pivotal trial that informs estimates of clinical effectiveness and cost effectiveness of oral dispersible budesonide. Some information is also provided for the phase II BUU-2/EEA trial because this contributes data to the NMA.

3.1.6.1 Trial design

The BUL-1/EAA trial is described as having an "adaptive 2-stage group sequential design" (CS B.2.4.2.3). The clinical study report states that this allowed for the possibility of sample size adaptation and early stopping for efficacy at the interim analysis.

The trial had four possible phases (CS Figure B.2.1):

- a one to six-week screening period
- a six-week randomised double-blind (DB) treatment period – this is the main phase during which efficacy and safety outcomes were measured.
- an optional six-week open-label induction (OLI) treatment with 2 x 1 mg/d budesonide orodispersible tablets in patients eligible for OLI-treatment (e.g. clinico-

histological non-remitters and patients who dropped out after at least four weeks of DB treatment due to lack of efficacy).

- a four-week follow-up period (if the patient was not eligible for or chose not to switch into the 48-week maintenance study).

Adaptive clinical trials are a relatively new approach to clinical trial design whereby modifications can be made to key aspects of the trial design whilst data are being collected.[11] For example, changes can be made to the allocation ratio, the sample size, eligibility criteria, the number of trial arms and other design features. In the case of the BUL-1EAA trial the main possible adaptation was to the sample size, as described below. The EMA Assessment Report for Jorveza[13] describes the initial discussions with the company regarding the pre-requisites for the product's clinical trial programme. The trial design was accepted by the regulator though with some required changes made to the primary outcome measure, the superiority threshold for clinical relevance and the trial duration.

3.1.6.2 Sample size calculation

The primary outcome measure was the induction of clinico-histological remission at week six (see section 3.1.5 of this report for outcome measure definitions). For randomisation in a 2:1 ratio a sample size of 54 patients was required in the intervention group and 27 in the placebo group (i.e. total sample size of 81 patients) to achieve an overall power of >90% (Fisher's exact test for rates based on a one-sided alpha level of 0.025). This was based on the assumption of a remission rate of 10% for the placebo group and 50% for the intervention group. The sample size was increased to 90 patients under the assumption of a 10% drop-out rate. A total of 88 patients were subsequently randomised.

The CS does not report the rationale for these assumed remission rates in the sample size calculation. However, the CSR mentions the histological remission rates observed in two previous budesonide trials, one of which is the BUU-2/EEA phase IIa trial. The CSR states that the assumptions made about remission rates for the BUL-1EAA trial (which give a smaller difference in histological remission between placebo and budesonide than the other trials) are conservative.

A planned interim data analysis was performed by an Independent Data Monitoring Committee once 54 patients had been recruited (corresponding to an information rate of 0.667 / 67%). The rationale for the interim data analysis was stated in the CSR to be because a reliable estimate of the magnitude of the expected treatment effect using the newly proposed clinico-histological remission endpoint used was not possible. The CSR states (CSR sections 3.2, 3.7.1.2 and 3.7.1.8) that the results of the interim analysis were to

be used to verify the sample size calculations or to recalculate the sample size if necessary. The results could also be used to stop the trial for confirmed efficacy according to pre-defined inverse normal test statistic critical values. The study was stopped early after the interim analysis due to confirmed efficacy of the primary outcome and because the final anticipated sample size of about 90 patients was reached. At this time-point, 18 patients in the placebo and 36 patients in the active treatment group (54 patients in total) had been randomised. The “overrun” cohort included 34 additional patients recruited while the interim analysis was conducted (11 in the placebo, and 23 in the active treatment group).

The confirmatory hypothesis analysis as defined for the interim analysis was repeated with the overrun patients supplemented. The primary confirmatory analysis is based on the results obtained in the total patient population, with 54 patients in the interim analysis and 34 patients overrun (total n=88).

3.1.6.3 Analysis populations

The analysis populations are listed in CS Table B.2.8 without being defined, however information was available in the CSR.

There were six analysis sets used in the BUL-1EAA trial.

- The full analysis set (FAS) of the double-blind phase **(FAS-DB)** using the intention-to-treat (ITT) principle (n=88 patients; n=29 placebo, n=59 BUL 1mg BID). This set includes all randomised patients who received at least one dose of the Investigational Medicinal Product (BUL 1mg BID). The primary analysis for confirmatory testing of the primary endpoint was based on the FAS-DB. The FAS-DB was also used for the analysis of the secondary efficacy variables.
- The per-protocol analysis set (**PP**) defined as all patients of the FAS-DB, except for patients with major protocol violations) (n=77 patients; n=26 placebo, n=51 BUL 1mg BID). The PP set was used for the analysis of the primary efficacy outcome and the secondary efficacy variables. The CS does not report results according to the PP analysis.
- The safety analysis set for the DB phase (**SAF-DB**) was used for the evaluation of safety during the DB phase. This included all randomised patients (as treated) who received at least one dose of BUL 1mg BID during the DB phase (n=88 patients).
- The open-label induction (OLI) phase efficacy evaluation was based on the **FAS-OLI** (all FAS-DB patients who received at least one dose of BUL 1mg BID during the OLI phase) (n=51).

- The safety analysis set for the open label induction (OLI) phase (**SAF-OLI**) was used for the evaluation of safety during the OLI phase. This was defined as all FAS-DB patients who received at least one dose of BUL 1mg BID during the OLI phase (n=51).
- The full analysis set for analysis of the follow-up visit (**FAS-FU**) during the follow-up phase (n=22 patients).

Of the above analysis sets, only the FAS-DB is used to inform the clinical effectiveness estimates in the economic model (for the outcome of histological remission) and the SAF-DB for adverse events in the model.

3.1.6.4 Statistical tests

The study was conducted according to a two-stage group-sequential test design with O'Brien and Fleming shaped boundaries. O'Brien and Fleming[14] describe a multiple testing procedure for determining when one treatment performs markedly better than the other, thus providing the opportunity for a trial to be stopped early.

The primary hypothesis was tested at a one-sided type I error rate level of 0.025 using Fisher's exact test. The inverse normal method of combining the p-values of Fisher's exact test for comparing two rates was planned to be used.

Efficacy significance testing for six *a priori* ordered key secondary outcomes proceeded in a hierarchical fashion until the first p-value for the difference between BUL 1mg BID versus placebo was >0.025 (in the FAS-DB population). Once a non-significant p-value was observed, all subsequent statistical significance tests were considered exploratory. The ordering of secondary outcomes starts with histological measures of eosinophils, followed by a selection of patient-reported measures of symptoms (see section 3.1.5 of this report for a list of these outcomes). The rationale for the ordering of these outcomes is not stated. Given the relatively large number of secondary outcome measures included (six key ordered outcomes, and eleven exploratory secondary outcomes listed in the CS), a hierarchical testing procedure is appropriate to avoid multiplicity of inferences leading to an inflated rate of false positive conclusions.[15]

3.1.6.5 Subgroup analyses

The primary efficacy outcome was not adjusted for covariates. The CS states which covariates were used for pre-planned subgroup analyses of the BUL-1/EEA and BUU-2/EEA

RCTs (Table 6). There was also one post-hoc subgroup analysis for the primary outcome on the use of any dietary approach to treat EoE.

Table 6 Pre-planned subgroups in the BUL-1/EEA and BUU-2/EEA RCTs

BUL-1/EEA subgroup analyses	BUU-2/EEA subgroup analyses
Stage 1 and overrun patients, respectively	
Localisation of the inflammation at baseline (unique categories): o Proximal, median, and distal oesophagus, respectively o One, two, or three oesophageal segments affected (defined as peak eos/mm² hpf ≥16)	Localisation of the inflammation at baseline (unique categories) (proximal/mid/distal oesophagus)
	Number of inflamed segments at baseline (one segment/two segments/three segments),
Concomitant use of PPIs (yes/no) during the DB phase	Concomitant use of PPIs (yes/no)
History of allergic diseases (yes/no)	Concomitant allergic diseases (yes/no)
Baseline PatGA	
Duration of disease (i.e. time from first symptoms to baseline [years]): < median (years) and ≥ median (years)	Duration of disease (time from first symptoms to baseline (years)) (< median [years] and ≥ median [years])
	30 hpfs each at baseline and at EoT available (yes/no)
	At least one biopsy for all three segments at baseline and EOT available (yes/no)

The results of these analyses for the primary efficacy outcome of clinical-histological remission at week six are reported in CS Appendix E. The NICE scope does not specify any subgroups to be included, and the CS states that no relevant subgroups were identified during reviews of the literature that were relevant to the treatment of EoE.

The CSR does not state whether any statistical interaction tests were used in the subgroup analyses but mentions that subgroups were analysed "descriptively" (CSR 3.7.1.4)

3.1.6.6 Missing data

Missing data for efficacy and safety outcomes at the end of treatment/withdrawal visit in the double-blind phase of both trials were estimated using the last observation obtained during the double blind treatment phase (last observation carried forward - LOCF). No justification

is given for the use of the LOCF approach in the CS but the CSRs for the two RCTs both justify this approach by stating that patients would have discontinued any EoE specific treatment four weeks prior to baseline assessment, thus no worsening of outcomes would be expected after baseline. Also, no spontaneous remissions were expected to occur. The ERG's clinical experts agreed that spontaneous remissions were unlikely. The ERG is aware that the last observation carried forward approach can be associated with bias in some circumstances. We also note that no sensitivity analyses appears to have been conducted using different assumptions about missing data. However, given the justifications provided by the company above, the relatively short length of the treatment period (six weeks in BUL1/EEA) and the fact that 92% of patients completed the double blind treatment phase, the use of LOCF appears to be reasonable in this trial. For the two outcomes based on diary entries (numerical rating scale for dysphagia and pain during swallowing) if one or two days of diary values were missing within the week prior to the visit, the available values for that week would be summed, divided by the number of days with valid data and then multiplied by seven to generate a value for that week. If more than two days of data were missing the outcome was deemed not evaluable for that week.

ERG conclusion

The statistical procedures in the BUL-1/EAA trial are appropriate for the assessment of clinical effectiveness of oral dispersible budesonide. The sample size calculation was appropriate and the planned number of participants were recruited. The trial was stopped at the planned interim analysis for confirmed efficacy, and the final efficacy results were based on the total sample recruited (including patients recruited after the interim analysis). An ITT analysis was used for the primary and secondary efficacy outcomes. Although pre-planned subgroup analyses were conducted these are not formally reported in the CS and are not used to inform cost-effectiveness.

3.1.7 Description and critique of the company's approach to the evidence synthesis

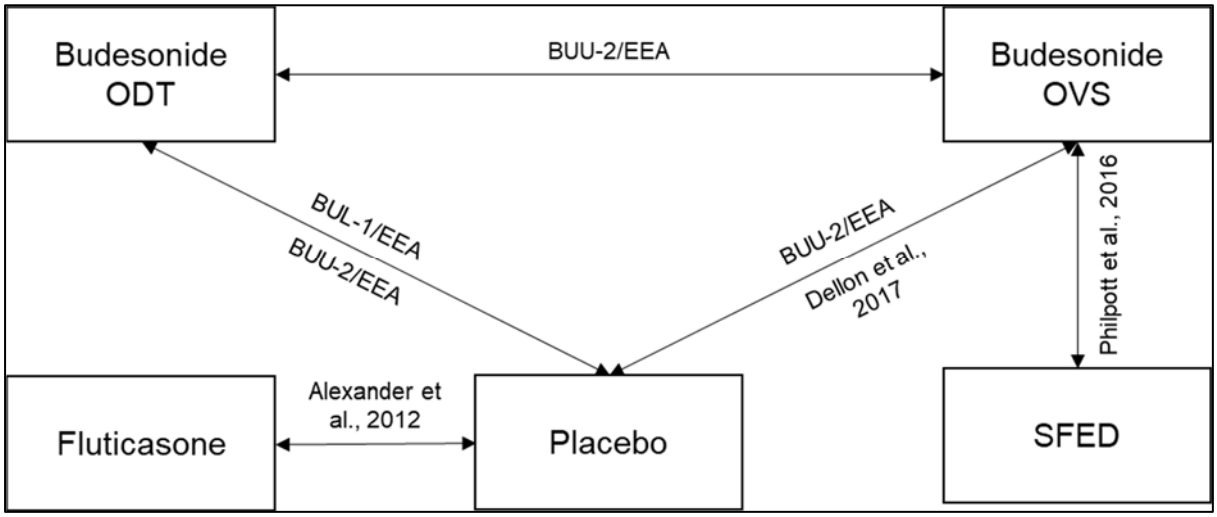
The company conducted a fixed-effect inverse weighted pairwise meta-analysis of budesonide ODT 1mg versus placebo based on the two trials of budesonide ODT (BUL-1/EAA and BUU-2/EEA). (CS Figure B.2.4). The outcome was the rate of histological remission (16 eos/mm^2 hpf, corresponding to <5 eos/hpf) estimated as a pooled odds ratio with 95% CI. The ERG asked the company to clarify the status of the meta-analysis (e.g. whether the pooled effect estimate was used in the company's NMA) (clarification question A1). The company responded that the meta-analysis is illustrative only and is not used in the NMA.

Given that the budesonide ODT trials compare the drug against placebo, other doses of budesonide ODT, or other budesonide formulations (e.g. OVS), it was necessary for the company to conduct an indirect treatment comparison of budesonide versus relevant comparators. A network meta-analysis (NMA) was conducted for this purpose. We describe and critique the methods used to conduct the NMA in the following sub-sections, and we report the results of the NMA in section 3.3.11.

3.1.7.1 Overview of network meta-analysis (NMA)

The company's inclusion criteria for the NMA (as discussed earlier in section 3.1.3) permitted inclusion of comparator treatments considered by expert clinicians to be routinely used in UK practice. These were: fluticasone and SFED. As discussed earlier in this report, treatment with PPI was not considered a relevant comparator by the company as their clinical advice suggests that the majority of patients are treated unsuccessfully with PPIs before EoE diagnosis and therefore once diagnosed would be unlikely to receive it again.

Figure 2 illustrates the composition of the network and the five included studies. Budesonide ODT is compared indirectly to fluticasone, via placebo and budesonide OVS and indirectly to the SFED via budesonide OVS and placebo. Placebo and budesonide OVS are therefore included in the network only to connect relevant treatments (though the ERG notes that placebo is included in the company's economic model as standard of care and comparisons to placebo in the NMA are therefore of interest). Relevant comparators fluticasone and SFED are connected to the network via one trial each.



Source: CS Figure B.2.5

Figure 2 Network diagram

Outcome measures

The outcome measure chosen for the NMA was histological remission, defined as <16 eos/mm^2 hpf (eosinophils per millimetre squared high power field). This outcome is used to estimate treatment effectiveness in the company's economic model. The individual studies in the NMA defined histological remission as <5 eos/hpf (eosinophils per high power field), but the size of the high-power field can vary according to the area of the hpf of the microscope used in different studies (CS Appendix D.1.3 and CS Appendix Table B.5.10). To account for this the company standardised the measures of eos/hpf from the included studies to eos/mm^2 hpf. The ERG agrees that this is an appropriate method to ensure studies are measuring the same threshold of remission.

The ERG has checked the company's calculations to standardise histological remission to eos/mm^2 hpf. We identified what appear to be minor errors but none of these make a material difference to the standardised remission rates the company have calculated:

- using unrounded values for the size of the hpf the ERG calculates the BUL-1/EEA and BUU-2/EEA studies both have an eos/mm^2 equivalent to <5 eos/hpf of 16.28 and the value for the Alexander study is 16.29, whereas CS Appendix Table B.5.10 reports 16.29 eos/mm^2 for BUU-2/EEA and the Alexander study and 16.28 for the BUL-1/EEA trial.
- We calculate the eos/mm^2 for the Philpott study to be 23.81 whereas CS Appendix Table B.5.10 reports 23.58.

We also note that the size of the hpfs reported in the published journal articles for the company's two trials differ to the sizes reported in the CSRs. The calculations reported in the CS and checked by the ERG are based on the values reported in the CSRs (hpf size 0.3072 mm^2) and not those reported in the published papers (BUL-1/EEA 0.345 mm^2 and BUU-2/EEA two types of microscope 0.260 mm^2 and 0.345mm^2). The ERG is uncertain why the size of the hpf for the company's two trials is recorded differently in the published papers to the CSRs.

Histological remission was chosen as the sole outcome measure for inclusion in the NMA because, according to the CS, treatment guidelines consider histological assessments to be integral to assessing disease progression and response.[1] This outcome was also the single endpoint reported by all studies meeting the inclusion criteria for the company's systematic review of clinical effectiveness. Expert clinical advice to the ERG agrees that this is an appropriate key measure of treatment effectiveness, in preference to clinical symptoms which may be less reliable and not always correlated with disease activity.

The CS does not comment on whether any other outcome measures were considered for inclusion in the NMA (and the economic model). The ERG notes that the primary outcome in the phase III BUL-1EAA trial was clinico-histological remission, and that clinical remission rates (based on symptom scores) were also reported. We asked the company to consider doing a cost effectiveness scenario analysis based on clinical remission rates either solely or combined with histological remission (clarification question B1). The company responded that clinical remission rates are not consistently reported in treatment studies, and hence why it was not included in the NMA. The ERG agrees that this is a reasonable justification. In response to this clarification question the company were able to conduct a scenario analysis comparing budesonide ODT versus fluticasone based on dysphagia response at six weeks (the primary outcome measure in the fluticasone trial[5]), which they consider as proxy for clinical remission, and also based on histological remission (NB. they don't state which method was used for indirectly comparing these treatments on this outcome measure). This reduced the treatment effect (response per model cycle) for budesonide ODT and fluticasone, but this did not change the cost-effectiveness conclusions (i.e. that budesonide ODT dominates fluticasone – see section 4.3.9 of this report for the cost effectiveness results).

Sensitivity analyses

The results of the NMA were subjected to sensitivity analyses according to the following factors:

1. eos/hpf (analysis not standardised by mm^2 hpf but based on the rates of remission reported in the respective study publications)
2. An alternative histological remission outcome definition used in the BUU-2/EEA trial (peak eos/hpf instead of mean eos/hpf)
3. Removing the non-randomised study[6] from the NMA (thus leaving only randomised trials in the NMA). This means that the SFED is absent from this analysis as the non-randomised study[6] was the only study to evaluate this treatment. The ERG notes that combining randomised and non-randomised evidence within the same meta-analysis/NMA is not recommended in the methodological literature. Thus, the exclusion of this study is appropriate (though note our comment below about the lack of influence of this study on the overall NMA estimates, section 3.1.7.4)

The ERG considers that these sensitivity analyses are appropriate for exploring uncertainty in the results of this NMA.

3.1.7.2 Clinical heterogeneity assessment

The CS states that potential clinical heterogeneity was considered at various stages of the systematic review and planning and conduct of the NMA. It is reported that although the studies differed in terms of participants, interventions and outcomes, the studies did not show substantial variations between comparisons with respect to known effect modifiers. The ERG asked the company to provide tabulated study characteristics to facilitate an independent assessment of potential clinical heterogeneity (only limited detail is provided in the CS), and also to state what the known effect modifiers are (clarification question A4). The company provided the tabulated characteristics, but did not confirm which of these can be considered effect modifying or whether any potential treatment-effect modifiers were missing. Therefore, the ERG is not able to judge whether the NMA is affected by heterogeneity in known effect modifying variables.

One clinical expert consulted by the ERG stated that EoE patients are heterogeneous with a spectrum of mild to severe inflammation, and clarification is required on which characteristics are effect modifying or prognostic. In his experience a high degree of inflammation at diagnosis (e.g. measured histologically in terms of eos/hpf) is a worse prognostic indicator, associated with greater resistance to treatment. Another clinical expert to the ERG stated that potential effect modifiers might include age, sex, smoking, associated atopic disease, duration of symptoms before diagnosis, severity of inflammation and presence of established fibrostenotic disease (a progression from chronic eosinophilic inflammation, characterised by oesophageal rings, strictures, or narrowing). However, in his clinical experience the only factor that he would typically expect to be associated with a poor response to treatment would be established fibrostenotic disease.

The ERG observes from the tabulated characteristics provided by the company (clarification response document Table 4) that the studies were generally similar in terms of race (mostly Caucasian patients); age (mean age 30-40 years); sex (mostly male); and weight (body mass index in the mid-20s). There was variation between studies in terms of mean symptom duration and mean time since diagnosis (1-8 years, and 0-4 years, respectively). All studies included patients pre-treated with PPIs, but the proportion of such patients varied between around 30% to 100%.

The ERG notes that there was variation between studies in terms of treatment duration and length of follow-up outcome assessment (company response to ERG clarification question A8). Treatment lasted between 2-12 weeks in four of the studies, and in the fifth study

treatment lasted between three and nine months.[6] Post-treatment follow-up duration was between two and four weeks (NB. This was not reported in Phillpot et al.[6]).

The ERG's interpretation of the data available is that there is potential clinical heterogeneity for certain patient and study characteristics between the studies included in the NMA. It is unknown whether there is heterogeneity in any known effect modifiers. The impact of potential heterogeneity on the results of the NMA are unknown. Consequently, caution should be exercised in the interpretation of the results.

3.1.7.3 Critical appraisal of trials included in the NMA

The CS provides a quality assessment of the studies in the NMA using the GRADE criteria. The criteria allow a quality rating to be given for a given outcome measure based on all of the studies together as a body of evidence. The criteria include ratings for study design; risk of bias; inconsistency in study results; indirectness of study populations (i.e. whether they match the decision problem); imprecision (of effect estimates); publication bias; and other factors as applicable to the outcome/intervention in question. A separate GRADE assessment is made for the RCTs and for the prospective cohort study (CS Appendix D.1.2.3). The ERG notes that GRADE is not commonly used as a quality assessment tool in company evidence submissions to the NICE Single Technology Appraisal programme. Rather, it is more common to provide a risk of bias assessment/quality assessment for each individual study (see section 3.1.4 for the ERG's risk of bias assessment of the two budesonide ODT trials).

The ERG has assessed the company's two trials using the criteria suggested by NICE (see section 3.1.4 and Table 5). We have not formally assessed the other three studies but have briefly checked their methods. As stated, Dellon 2017[4] and Alexander 2012[5] were both RCTs. The method used to generate random allocation and to conceal allocation seems to have been appropriate in both studies (albeit Alexander 2012 provides limited information on the generation of the randomisation schedule). The patient groups in each arm of the two RCTs have similar baseline characteristics (with 38% of the Dellon 2017 participants being under 18 years of age) and both RCTs are described as double-blind (some details are provided as to how blinding was achieved). In both studies a greater proportion of patients in the placebo arm dropped out than in the experimental arm. The outcome included in the NMA (histological remission) was a secondary outcome in the Alexander et al. RCT and an ITT analysis was reported for this outcome. In Dellon et al. histological remission was one of two co-primary outcomes and this was analysed as a modified ITT analysis (i.e. there were some missing data). The company could have conducted an ITT analysis for Dellon et al.

using an assumption that those who dropped out of the study did not achieve remission but this was not done. The company's GRADE assessment notes *"Sample size was too small (high dropout rate, underpowered) in the Alexander et al., 2012 and Dellon et al., 2017 studies".* Overall in our opinion the Dellon 2017 and Alexander 2012 RCTs are likely to be at a low risk of bias.

The Philpott 2015 prospective observational study is judged by the company to be at a very serious risk of bias and the ERG agrees with this assessment. There was no blinding in this study and patients chose between different treatment options which, whilst reflecting what might occur in a real-world setting, makes it difficult to have confidence that the results of the comparison between SFED and budesonide OVS would be reproducible in a different group of patients.

3.1.7.4 Statistical approaches used

The NMA was conducted according to a Bayesian approach using WinBUGS software and using vague prior probability distributions (priors). The model used a burn-in of 10,000 simulations followed by a further 20,000 for parameter estimation. No details are provided on the assessment of model convergence. The WinBUGS code for random effects models, including study outcome data formatted for the analysis, was provided in CS appendix section D.1.3.4. The model code and data were verified by the ERG. Whilst the prior for the treatment effect $d_k \sim N(0,10)$ was labelled as vague, in fact it is likely to be informative. A more traditional vague prior is to use $d_k \sim N(0,10000)$. Vague priors were used for the between-trial standard deviation and study-level baselines.

There is limited presentation of the NMA results in CS Tables B.2.20 to B2.22. Whilst budesonide ODT was compared to fluticasone and to SFED, no other treatment comparisons were presented. The ERG requested the company to provide results for comparisons against placebo (clarification question A11), as placebo is included in the economic model to represent standard care. The company provided results for placebo versus the other treatments, rather than other treatments versus placebo as would be expected. However, the reciprocal effect estimates can easily be calculated.

There is one closed loop in the evidence network which has both direct and indirect evidence (budesonide ODT->budesonide OVS->Placebo). Nevertheless, the CS did not report an analysis of inconsistency between the direct and indirect evidence. In their response to clarification question A9, the company found no evidence of inconsistency using the Bucher method.[16] The ERG agrees with this conclusion.

There is a large uncertainty in the credible intervals around the median odds ratios, driven by the presence of zero values in the placebo arms of three of the included studies[2,3,5] (i.e. where no patients experienced histological remission) (CS Tables B.2.20 to B2.22). The ERG is of the opinion that it would be more conservative to use a continuity correction by adding 0.5 to each of the cells or use a frequentist approach such as that offered by MetaInsight software.[17] The company used a continuity correction in their (WinBUGS Bayesian) analysis in response to clarification question A10. The 95% credible intervals were markedly tighter and the Deviance Information Criterion (DIC) value was similar between fixed-effect and random effects models.

However, the ERG assumes this analysis was conducted using the same non-vague prior on treatment effects as the base case. Hence, the ERG reran the company's base case analysis and confirmed that the uncertainty around treatment effects was influenced by the informative prior. The ERG found that the Bayesian NMA model would not converge with a vague prior, therefore we reran the analysis using MetaInsight software (see section 3.3.11).

Finally, the ERG considers that the inclusion in the NMA of the non-randomised study by Philpott et al,[6] which compared SFED versus budesonide OVS, in the NMA does not significantly bias the overall results because it does not influence any of the other treatment effects and it does not create a loop in the network. However, we would caution that the interpretation of the budesonide ODT versus SFED results are more uncertain due to the limitations of the non-randomised study design.

3.1.7.5 Choice between random effects and fixed-effect models

The DIC was used to choose between fixed-effect and random-effects models. Random effects had a lower DIC and was preferred by the company for the base case and sensitivity analyses. However, only random effects NMA results are presented. No fixed-effect, DIC nor total residual deviance for model fit comparison are presented in the CS. The ERG requested these from the company (clarification question A5). The company provided DIC values and NMA results based on a fixed-effect model (though total residual deviance was not reported).

The ERG agrees with the company's choice of the random effects model given the presence of clinical heterogeneity between studies. The ERG's preference, therefore, is to use random effects results in the ERG economic analysis (section 4.4 of this report).

3.1.7.6 Summary of ERG critique of the NMA

The NMA comprises a relatively small network of five trials, two of which are the company's RCTs of budesonide ODT. Only treatments considered by expert clinicians to be routinely used in UK practice were included: fluticasone and SFED. PPI treatment is not included as a comparator as clinical advice to the company is that most patients will have received PPI prior to their diagnosis. Budesonide ODT is compared indirectly to fluticasone via placebo and budesonide OVS, and indirectly to the SFED via budesonide OVS and placebo.

Histological remission was the chosen outcome measure for the NMA (and the economic evaluation) on the basis that it is the most robust measure of disease progression available, and has been consistently included in treatment studies. The ERG concurs with this assertion, though considers that clinical remission (e.g. based on patient reported symptoms) would also be informative for inclusion in the NMA and the economic model. Data limitations restricted these analyses, though the company did supply a scenario analysis comparing budesonide ODT versus fluticasone (with no resulting material changes to cost effectiveness conclusions).

The ERG considers there to be potential clinical heterogeneity across the included studies, for certain patient characteristics such as mean symptom duration and mean time since diagnosis. Known effect modifiers have not been specified in the CS and it is unclear whether there is heterogeneity between studies on these. Random effects are thus preferable.

The ERG believes the use of a non-vague prior in the NMA has influenced the uncertainty around treatment effects. The ERG has thus rerun the NMA using a frequentist approach which incorporates a continuity correction to overcome wide confidence intervals caused by zero response rates in the placebo arms of some of the trials.

Overall, the ERG suggests caution in the interpretation of the results of the NMA due to the above-mentioned limitations.

3.2 Summary statement of company's approach to systematic review

The ERG considers the systematic review processes followed good practice, with all steps of the screening process performed independently by two reviewers. However, it would have been beneficial if the company had assessed the methodological quality and risk of the studies individually. A summary of the ERG's quality assessment of the company's systematic review of clinical effectiveness is presented in Table 7.

Table 7 Quality assessment (CRD criteria) of CS review

CRD Quality Item: score Yes/ No/ Uncertain with comments	
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes. Inclusion and exclusion criteria were reported in CS Appendix D Table B.5.7 but aspects of these criteria were unclear to the ERG. In response to clarification question A2 the company indicated that there were some errors and omissions in their original table and a new table (Table 1 in the response to clarification question A2) was provided. The same criteria were used to identify relevant evidence for the NMA.
2. Is there evidence of a substantial effort to search for all relevant research? I.e. all studies identified	Yes. Although the searches were eight months out of date at the time of submission and there was no grey literature search the ERG believes that the searches were sufficiently comprehensive to retrieve all relevant studies. The ERG's own targeted update search did not yield any new studies.
3. Is the validity of included studies adequately assessed?	No. The company did not assess the validity of the individual studies (their own RCTs and the studies included in the NMA) using NICE's criteria or other similar criteria. Instead the company used the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach. GRADE criteria enable a quality rating to be assigned for a given outcome measure based on a group of studies together that contribute data on that outcome measure. Although the criteria cover aspects including study design, risk of bias and inconsistency in study results and other factors it would have been more informative to have also included a risk of bias assessment/quality assessment for each of the individual studies included in the CS.
4. Is sufficient detail of the individual studies presented?	Yes. Sufficient details were reported for the individual studies.
5. Are the primary studies summarised appropriately?	Yes. The included studies have been appropriately summarised.

3.3 Summary of submitted evidence

3.3.1 Summary of results for histological remission

Histological remission (defined as peak eos count <16 eos/mm^2 hpf) is the outcome measure that is used in the NMA, the results of which inform estimates of clinical effectiveness in the economic model. Histological remission defined in this way was the first of six a priori ordered key secondary outcomes of the BUL-1/EEA RCT and is a secondary outcome of the BUU-2/EEA RCT. In the BUL-1/EEA RCT 55 of the 59 participants (93.2%) receiving budesonide ODT achieved histological remission after six weeks of treatment, in contrast to zero patients in receipt of placebo (Table 8).

In the BUU-2/EEA RCT, 16 (84.2%) participants in the budesonide ODT arm achieved histological remission after two weeks of treatment whereas none of the participants in the placebo arm did. In the BUU-2/EEA RCT an alternative definition of histological remission was used (mean of <16 eos/mm^2 hpf) which was the primary outcome of this trial. After two weeks of treatment the difference between the arms was statistically significant with all the patients in receipt of budesonide ODT having achieved a mean of <16 eos/mm^2 hpf but none of the participants in the placebo arm.

Table 8 Rate of histological remission

	Histological remission definition and timepoint	**Bud 1mg ODT BID**	**Placebo**	**p-value**
BUL-1/EEA phase III 2ry outcome (1st of 6[a])	Peak eos count <16 eos/mm^2 hpf, week 6, n/N (%)	55/59 (93.2%)	0/29 (0.0%)	p<0.0001
BUU-2/EEA phase II 2ry outcome	Peak of <16 eos/mm^2 hpf, week 2, n/N (%)	16/19 (84.2)	0/19 (0)	NR
1ry outcome	Mean of <16 eos/mm^2 hpf from baseline to week 2, n/N (%)	19/19 (100)	0/19 (0%)	p<0.0001[b]

Source: CS Tables B.2.11 and B.2.17
1ry – primary; 2ry – secondary; BID – twice daily; Bud ODT – budesonide orodispersible tablet; eos – eosinophil; hpf – high-powered field; n/N – number of patients/total number of patients; NR – not reported;
[a] Note that this outcome, the first of six ordered secondary endpoints, forms part of the composite primary outcome for this study presented in section 3.3.2 below.
[b] p<0.0001 for comparison against placebo

3.3.2 Summary of results for clinico-histological remission

Clinico-histological remission is a composite outcome and it was the primary outcome of the BUL-1/EEA trial. To achieve this outcome patients had to have histological remission (presented in section 3.3.1 above) and resolution of symptoms (defined as a severity of ≤2 points on the 0-10 numerical rating scale for dysphagia and a severity of ≤2 points on the 0-10 numerical rating scale for pain during swallowing on each day in the week prior to week six). In the budesonide ODT arm of the trial 34 patients (57.6%) achieved clinico-histological remission after six weeks of treatment in comparison to zero patients in the placebo arm (p<0.0001, Table 9)

Table 9 Rate of clinico-histological remission (composite outcome)

	Outcome and timepoint	Bud 1mg ODT BID	Placebo	p-value
BUL-1/EEA phase III (FAS-DB)	Clinico-pathological remission at week 6, n/N (%)	34/59 (57.6)	0/29 (0.0)	<0.0001

Source: CS Table B.2.10. BID – twice daily; Bud ODT – budesonide orodispersible tablet; n/N – number of patients/total number of patients;

3.3.3 Summary of results for change in the peak and mean eos/mm^2 hpf

The CS also reports on the changes in the number of eosinophils from baseline to the end of treatment in the two trials (Table 10).

Table 10 Changes in numbers of eosinophils

	Outcome and time point	Bud 1mg ODT BID	Placebo	p-value
BUL-1/EEA phase III 2ry outcome (2nd of 6)	Change in peak eos/mm^2 hpf from baseline to week 6, mean (SD)	-226 (150.4) (N=59)	-4.3 (135.6) (N=29)	p<0.0001
BUU-2/EEA phase II 2ry outcome	Change in mean peak eos/mm^2 hpf from baseline to week 2	-227 (NR)	-30 (NR)	p=0.0006
Co-primary outcome	Mean change in eos/mm^2 hpf from baseline to week 2	-120 (N=19)	-8 (N=19)	p<0.0003

Source: CS Tables B.2.11 and B.2.1.7 and text in CS section B.2.6.2.1
2ry – secondary; BID – twice daily; Bud ODT – budesonide orodispersible tablet; eos – eosinophil; hpf – high-powered field; NR – not reported; SD – standard deviation

In the BUL-1/EEA trial the peak eos/mm^2 hpf in the budesonide ODT arm fell after six weeks of treatment by a mean of -226 eos (SD 150.4) whereas the mean fall was just -4.3 eos/mm^2 hpf (SD 135.6) in the placebo arm. A similar outcome was observed in the BUU-2/EEA trial where after two weeks of treatment the mean fall in peak eos/mm^2 hpf was -227 in comparison to -30 in the placebo arm (standard deviations not reported). The results for the co-primary outcome of BUU-2/EEA (mean change in eos/mm^2 hpf from baseline to week two) were consistent with the mean change in peak eos/mm^2 hpf results.

3.3.4 Summary of results for resolution of symptoms

The third of the six ordered secondary outcomes for the BUL-1/EEA trial was resolution of symptoms, defined as clinical remission on each day in the week prior to week six. There was a statistically significant difference in the proportions of patients achieving this outcome between the budesonide ODT arm (59.3%) and the placebo arm (13.8%) (Table 11).

Table 11 Resolution of symptoms

	Outcome	Bud 1mg ODT BID	Placebo	p-value
BUL-1/EEA phase III 2ry outcome (3 of 6)	Clinical remission[a] on each day in the week prior to week 6, n/N (%)	35/59 (59.3)	4/29 (13.8)	p<0.0001

Source: CS Table B.2.11
2ry – secondary; BID – twice daily; Bud ODT – budesonide orodispersible tablet
[a] Note that this outcome, the third of six ordered secondary endpoints, forms part of the composite primary outcome for this study presented in section 3.3.2 above. Clinical remission defined as a symptom severity of ≤2 points on each 0-10 NRS for dysphagia and odynophagia on each day in the week prior to end of treatment (week 6).

3.3.5 Summary of results for total weekly EEsAI-PRO score

A statistically significant difference was observed in the proportion of patients whose weekly EEsAI-PRO score was 20 or less at week six in the BUL-1/EEA trial (budesonide ODT arm 50.8% versus placebo arm 6.9%, p<0.0001) (Table 12).

Table 12 EEsAI-Pro score of ≤20 at week 6

	Outcome and time point	Bud 1mg ODT BID	Placebo	p-value
BUL-1/EEA phase III 2ry outcome (4 of 6)	Total weekly EEsAI-PRO score of ≤20 at week 6, n/N (%)	30/59 (50.8)	2/29 (6.9)	p<0.0001

Source: CS Table B.2.11
2ry – secondary; BID – twice daily; Bud ODT – budesonide orodispersible tablet; n/N – number of patients/total number of patients; EEsAI-PRO - Eosinophilic Esophagitis Activity Index – Patient-Reported Outcome

3.3.6 Summary of results for dysphagia symptoms

Dysphagia was assessed differently in the BUL1/EEA and BUU-2/EEA RCTs (Section 3.1.5) but neither trial found a statistically significant difference between the budesonide ODT and placebo arms (Table 13). In the BUL-1/EEA trial, a greater proportion of participants had an improvement in dysphagia as measured by the weekly visual dysphagia question score at week 6 (budesonide ODT 50.8% versus placebo 37.9%). In the BUU-2/EEA trial, the decrease in the mean dysphagia score from baseline to week two was -2.7 in the budesonide ODT arm in comparison to -2.0 in the placebo arm.

Table 13 Dysphagia symptoms

	Outcome and time point	Bud 1mg ODT BID	Placebo	p-value
BUL-1/EEA phase III	Improvement from baseline to week 6 in the weekly VDQ score, n/N (%)	30/59 (50.8)	11/29 (37.9)	p=0.1804

2ry outcome (5 of 6)				
BUU-2/EEA phase II 2ry outcome	Decrease in mean dysphagia score from baseline to end of treatment (week 2)	-2.7 p=0.0001	-2.0 p=0.0001	Nsd between groups[a]

Source: CS Table B.2.11
2ry – secondary; BID – twice daily; Bud ODT – budesonide orodispersible tablet; n/N – number of patients/total number of patients; VDQ – visual dysphagia question
[a] Two weeks after the end of treatment (i.e. at week 4) improvement sustained in the OD Bud 1mg BID group was statistically significantly superior versus placebo (p=0.0196).

3.3.7 Summary of results for improvement in the Avoidance, Modification, and Slow-eating (AMS) score

The proportions of participants who had an improvement from baseline to week six in the weekly avoidance, modification and slow-eating score were similar in the budesonide ODT and placebo groups in the BUL-1/EEA RCT (budesonide ODT 11.9% versus placebo 10.3%, p= 0.5703) (Table 14).

Table 14 Improvement in the Avoidance, Modification, and Slow-eating (AMS) score

	Outcome and time point	**Bud 1mg ODT BID**	**Placebo**	**p-value**
BUL-1/EEA phase III 2ry outcome (6 of 6)	Improvement from baseline to week 6 in weekly AMS score, n/N (%)	7/59 (11.9)	3/29 (10.3)	p=0.5703

Source: CS Table B.2.11
2ry – secondary; AMS – Avoidance, modification, and slow-eating; BID – twice daily; Bud ODT – budesonide orodispersible tablet; ; n/N – number of patients/total number of patients.

3.3.8 Summary of results from the BUL-1/EEA phase III RCT open label induction phase

The main exploratory secondary endpoint in the open-label induction (OLI) phase was the rate of patients with clinico-pathological remission at week six OLI. Twenty-three of the 59 participants in the budesonide ODT arm of the double-blind phase of the trial entered the open label extension and all but only one of the 29 participants in the placebo arm. With an additional six weeks of budesonide treatment 69.6% of participants from the budesonide arm achieved clinico-histological remission. A higher proportion (78.6%) of participants who had previously received placebo achieved clinico-histological remission when they received six weeks treatment in the open-label phase of the study (Table 15).

Table 15 Open-label induction phase exploratory secondary outcomes

	Time point & outcome	**Bud 1mg ODT BID**	
BUL-1/EEA phase III OLI	Entered the OLI at the end of the double-blind treatment phase	23/59 from Bud 1mg **ODT** arm	28/29 from placebo arm

	Clinico-histological remission at week 6 OLI, n/N (%)	16/23 (69.6)	22/28 (78.6)
	Histological remission at OLI week 6, n (%)	19 (82.6)	25 (89.3)
	Clinical remission at OLI week 6*, n (%)	17 (73.9)	23 (82.1)
	Change in peak eos/mm^2 hpf from week 6 DB to week 6 OLI, mean (95% CI)	-12 (-39, 15)	-206 (-247, -165)[a]

Source: CS Table B.2.16
BID - twice daily; Bud ODT – budesonide orodispersible tablet; CI - confidence interval; eos - eosinophils; hpf - high-power field; mm - millimetre; n/N - number of patients/total number of patients; OLI = open-label induction
[a] CS states that significant changes from the end of treatment (EoT) double-blind phase to EoT OLI were demonstrated because 0 was excluded from the 95% CI

3.3.9 Summary of health-related quality of life (HRQoL)

HRQoL was measured using the modified SHS and the EoE-QoL-A in the BUL-1/EEA trial and the modified SHS in the BUU-2/EEA trial. In the BUL-1/EEA trial the mean change from baseline values in the modified SHS indicated statistically significant improvements from baseline to week six in all four domains for participants in the budesonide arm (CS Table B.2.14). In the placebo arm the mean change from baseline was statistically significant for two of the four domains (symptom burden and social function) and improved but not statistically significant for the other two domains (disease-related worry and general well-being burden). The intragroup differences (budesonide versus placebo) were all in favour of budesonide and, although no intragroup p-values are reported, the CS states that the results indicated a statistically significant superiority of budesonide versus placebo for two of the four domains (social function and disease-related worry). For the BUU-2/EEA trial no numerical results for the modified SHS are reported in the CS. The CS states that although scores decreased (improved) from baseline to week two in the budesonide arm no differences in changes from baseline between the treatment groups could be concluded.

For the disease-specific EoE-QoL-A, measured for the BUL-1/EEA trial only, the changes from baseline to week six in the budesonide arm were all statistically significant (CS Table B.2.15). In the placebo arm improvements from baseline to week six were observed but these were not statistically significant for all sub-scores. The CS states that statistically significant differences between the budesonide and placebo trial arms were observed for two of the sub-scores (eating/diet impact 10 items and eating/diet impact 4 items).

3.3.10 Sub-group analyses results

As described earlier in section 3.1.6.5, both the BUL-1/EEA and BUU-2/EEA trial results (for primary and key secondary outcomes of BUL-1/EEA and for primary and co-primary

outcomes for BUU-2/EEA) were analysed with respect to a number of pre-planned subgroups and one post-hoc subgroup. The results of the subgroup analyses for the primary outcomes of both trials are summarised narratively in CS document B. The tabulated data are presented in CS Appendix E (note there is an error in Appendix E which for study BUU-2/EEA subgroup by number of inflamed segments at baseline reports data for the 2mg BID arm of the trial instead of the placebo arm). Because none of the participants in the placebo groups of either trial achieved the primary outcome the utility of the subgroup analyses is limited. Nevertheless, the results appear to be consistent for the subgroups analysed.

3.3.11 Indirect treatment comparison results

In this section we summarise:
1) The Bayesian NMA results presented in the CS and additional results presented by the company in response to ERG clarification questions; and
2) NMA results from the ERG obtained using a frequentist approach incorporating a continuity correction

Please refer to section 3.1.7 for our discussion of the evidence network and the statistical procedures used to conduct the NMAs.

The CS reports the random effects NMA results and in response to clarification question A5 the company also provided fixed-effect NMA results. We have combined these in Table 16. The results indicate that budesonide ODT has greater efficacy than either of the comparators (i.e. fluticasone and SFED) and greater efficacy than budesonide OVS.

Table 16 Company NMA results for histological remission (<16 eos/mm^2 hpf)

Budesonide ODT 1 mg BID versus:	Random effects NMA		Fixed-effect NMA	
	OR	95% CrI	OR	95% CrI
Budesonide OVS	NR	NR	14.71	1.212, 428.800
Fluticasone	8.657	0.009, 7,508.000	9.62	0.116, 494.800
SFED	81.840	0.109, 63,620.000	52.86	3.683, 1,760.000

Source: CS Table B.2.20; company clarification response document Table 7
CrI – credible interval, NR – not reported

The company uses the random effects NMA odds ratios for fluticasone and SFED in their base-case economic model (see section 4.3.5.1 of this report for a discussion of how treatment effectiveness was modelled). However, the credible intervals for the company's random effects and fixed-effect NMA results in Table 16 are very wide, particularly for the

comparison of budesonide ODT versus SFED, indicating a high degree of uncertainty. In part this is caused by the zero values for the placebo arms of some of the trials in the NMA (i.e. where no patients experienced histological remission). In response to clarification question A10, the company reported both random effects and fixed-effect NMA results after applying a continuity correction for zero values in the trials' placebo arms. This narrowed the 95% credible intervals but the ERG found that this credible interval was constrained by the informative prior the company used in their analysis (Table 17).

Table 17 Company NMA results for histological remission with continuity correction

With continuity correction				
Budesonide ODT 1 mg BID versus	**Random effects NMA**		**Fixed-effect NMA**	
	OR	**95% CrI**	**OR**	**95% CrI**
Budesonide OVS	7.049	0.059, 590.4	8.861	1.141, 107.5
Fluticasone	8.015	0.024, 2,181	11.83	0.413, 214.7
SFED	36.62	0.102, 1,0350	31.91	3.263, 439.1

Source: clarification response document Tables 10 and 11
CrI – credible interval, NR – not reported

When the ERG tried to re-run the Bayesian NMA model using a vague instead of an informative prior the model would not converge. Therefore, the ERG reran the analysis using MetaInsight software[17] which takes a frequentist statistical approach and which automatically adds a continuity correction. These results also indicate that budesonide ODT has greater efficacy than the comparators (Table 18). Confidence intervals are generally narrower under a frequentist approach using a continuity correction than credible intervals under a Bayesian vague prior approach. We use the random effects NMA odds ratios from this frequentist NMA in our base-case economic analysis (see section 0 of this report). Placebo is included as it represents standard care in the economic model.

Table 18 ERG frequentist NMA results for histological remission (includes continuity correction)

With continuity correction				
Budesonide ODT 1 mg BID versus:	**Random effects NMA**		**Fixed-effect NMA**	
	OR	**95% CI**	**OR**	**95% CI**
Placebo	475.19	39.58, 5705.32	437.02	47.42, 4207.86
Fluticasone	6.96	0.11, 441.71	6.40	0.16, 253.31
SFED	23.24	0.85, 635.07	24.72	1.83, 333.94

NMA sensitivity analyses results

Three sensitivity analyses were conducted by the company to examine whether NMA results would change if:

1. The analysis used rates of remission as reported in the included studies according to eos/hpf thresholds (i.e. not standardising the analysis by mm^2/hpf)
2. The alternative remission definition used in the BUU-2/EEA trial (peak eos/hpf instead of mean eos/hpf).
3. Only RCTs were included in the network (i.e. omitting the Philpott 2016 study[6], thereby omitting the only study to include SFED from the analysis).

In these analyses the superior efficacy of budesonide ODT versus the comparators was maintained (Table 19).

Table 19 NMA sensitivity analyses

	Budesonide ODT 1 mg BID versus:	**Company sensitivity analyses Random effects**		**ERG sensitivity analyses[1] Random effects**	
		OR	**95% CrI**	**OR**	**95% CI**
Base-case	Fluticasone	8.657	0.009, 7,508.000	6.96	0.11, 441.71
	SFED	81.840	0.109, 63,620.000	23.24	0.85, 635.07
Sensitivity analyses					
1. Analysis based on eos/hpf (instead of eos/mm^2 hpf)	Fluticasone	9.734	0.009, 8,372.000	7.91	0.13, 473.03
	SFED	156.700	0.177, 113,200.000	83.09	2.69, 2562.66
2. BUU-2/EEA peak eos/hpf definition (instead of mean eos/hpf)	Fluticasone	2.302	0.004, 999.800	2.17	0.07, 65.26
	SFED	23.590	0.066, 9,405.000	8.75	1.56, 48.99
3. Only RCTs included	Fluticasone	9.277	0.009, 7,625.000	NR	NR

Source: CS tables B.2.20 to B.2.22
[1] Based on a frequentist approach with a non-informative prior

The ERG also ran the first two sensitivity analyses using the frequentist approach described above, with the continuity correction (Table 19). Similar results were obtained, though with narrower confidence intervals. The ERG did not run the third sensitivity analysis for the reason discussed earlier in section 3.1.7.4 (i.e. the non-randomised study is not likely to bias the results because it does not influence any of the other treatment effects and it does not create a loop in the network).

3.3.12 Summary of adverse events

In the BUL-1/EEA RCT a higher proportion of participants in the budesonide arm experienced a Treatment-emergent adverse event (TEAE) than in the placebo arm (62.7% versus 41.1% respectively). The majority (23/37) of the TEAEs in the budesonide arm were

considered to be related to the study drug but in the placebo arm only one of the 12 TEAEs was considered related to the study drug. The only severe TEAE in the trial, which was food impaction requiring endoscopic surgery, occurred in the placebo arm and this was also the only TEAE that caused a participant to withdraw from the trial. The number of participants who experienced TEAEs in the BUU-2/EEA RCT was unclear because information presented in was not consistent: CS section B.2.10.2.1 states TEAEs occurred in seven patients in the budesonide arm and two patients in the placebo arm but CS Table B.2.26 shows eight patients in the budesonide arm and one patient in the placebo arm. The ERG considered that Table B.2.26 could be reporting events rather than patients (in which case a patient could experience more than one event). The ERG therefore cross-checked with the CSR for the BUU-2/EEA study which seems to report nine TEAEs that have occurred in seven patients in the budesonide 1mg BID arm and two TEAEs among two patients in the placebo arm. Regardless of the uncertainty about the number of TEAEs and patients it is clear that, in common with the BUL-1/EEA trial more TEAEs were reported in the budesonide arm compared to the placebo arm. The majority of the TEAEs in the budesonide arm were considered related to the study drug but neither of the two events in the placebo arm were. No participants in the BUU-2/EEA RCT experienced a severe TEAE or withdrew due to a TEAE (Table 20).

The company provided details on the TEAEs that occurred in two or more participants in either treatment group in the BUL-1/EEA trial and on the TEAEs that occurred in the BUU-2/EEA trial but, as noted above, the reporting for the BUU-2/EEA trial was unclear hence we have taken the information from the CSR.

Table 20 Summary of treatment-emergent adverse events in the BUL-1/EEA and BUU-2/EEA RCTs

	BUL-1/EEA SAF-DB		**BUU-2/EEA**	
	Budesonide ODT 1 mg BID (N=59)	**Placebo (N=29)**	**Budesonide ODT 1 mg BID (N=19)**	**Placebo (N=19)**
Total TEAEs, n (%)	37 (62.7)	12 (41.1)	7[a] (36.8)	2 (10.5)
TEAEs related to study drug, n (%)	23 (39.0)	1 (3.4)	4[a] (21.1)	0 (0.0)
Severe TEAE, n (%)	0 (0.0)	1 (3.4)[b]	0 (0.0)	0 (0.0)
TEAEs leading to withdrawal, n (%)	0 (0.0)	1 (3.4)	0 (0.0)	0 (0.0)

Source: CS Table B.2.24 and text in CS B.2.10.2.1

[a] the CSR for this RCT suggests seven patients experienced nine TEAEs. Four patients experienced five TEAEs that were considered at least possibly related to budesonide ODT

[b] CS Table B.2.24 shows zero events but the CS text and the table in the published paper indicate there was one serious AE in the placebo group.

Table 21 Types of TEAE occurring in the BUL-1/EEA and BUU-2/EEA RCTs

BUL-1/EEA SAF-DB			BUU-2/EEA		
TEAEs occurring in ≥2 patients in any treatment group, n (%)	**Budesonide ODT 1 mg BID (N=59)**	**Placebo (N=29)**	**TEAEs, n (%) of patients**	**Budesonide ODT 1 mg BID (N=19)**	**Placebo (N=19)**
GORD	3 (5.1)	0 (0.0)			
Nausea	2 (3.4)	0 (0.0)	Nausea	0 (0.0)	1 (5.3)
Infections and infestations	21 (35.6)	6 (20.7)			
Suspected local fungal infection[a]	14 (23.7)	0 (0.0)	Oesophageal candidiasis	2 (10.5)	0 (0.0)
			Fungal oesophagitis	1 (5.3)	0 (0.0)
Histologically confirmed	10 (16.9)	0 (0.0)			
Histologically confirmed with suspected endoscopic signs	8 (13.6)	0 (0.0)			
Histologically confirmed with suspected endoscopic signs and clinical systems	3 (5.1)	0 (0.0)			
Nasopharyngitis	2 (3.4)	1 (3.4)	Nasopharyngitis	2 (10.5)	0 (0.0)
Pharyngitis	1 (1.7)	2 (6.9)			
Blood cortisol decreased	3 (5.1)	0 (0.0)			
Nervous system disorders	5 (8.5)	1 (3.4)			
Headache	4 (6.8)	1 (3.4)	Headache	1 (5.3)	0 (0.0)
Asthma	0 (0.0)	2 (6.9)			
Hypertension	2 (3.4)	0 (0.0)	Hypertension	1 (5.3)	0 (0.0)
			Pruritus	1 (5.3)	0 (0.0)
			White blood cell count increased	1 (5.3)	0 (0.0)
			Deterioration of EoE	0 (0.0)	1 (5.3)

Source: CS Tables B.2.24 and the CSR for BUU-2/EEA
[a] Included suspected cases of candida infection, oesophageal candidiasis, oral candidiasis and oropharyngeal candidiasis

The TEAEs reported for the six-week open-label extension phase of the BUL-1/EEA RCT were similar in both quantity and type to those that occurred during the double-blind phase of this trial (Table 22).

Table 22 TEAEs in the open-label extension phase of the BUL-1/EEA RCT

	Budesonide-budesonide 1 mg BID (N=23)	Placebo-budesonide (N=28)
Total TEAEs, n (%)	13 (56.5)	16 (57.1)
TEAEs related to study drug, n (%)	6 (26.1)	13 (46.4)
Serious adverse event, n (%)	0 (0)	0 (0)
TEAEs leading to withdrawal, n (%)	0 (0)	1 (3.6)
TEAEs occurring in ≥2 patients in any treatment group, n (%)		
GORD	3 (13.0)	2 (7.1)
Infections and infestations	4 (17.4)	12 (42.9)
Suspected local fungal infection	4 (17.4)	10 (35.7)
Histologically confirmed	2 (8.7)	7 (25.0)
Histologically confirmed with suspected endoscopic signs	1 (4.3)	6 (21.4)
Histologically confirmed with suspected endoscopic signs and clinical systems	0 (0)	0 (0)
Nervous system disorders	4 (17.4)	1 (3.6)
Headache	4 (17.4)	1 (3.6)

Source: CS Table B.2.25
GORD - gastro-oesophageal reflux disease

3.4 Summary of clinical effectiveness

- The company's decision problem population is narrower than that specified in the NICE scope and in the marketing authorisation. This is because the company limit their decision problem population to adults with EoE who have previously been unsuccessfully treated a PPI.
- The company has conducted two RCTs, both judged by the ERG to be at a low risk of bias, that show that budesonide ODT is more effective than placebo across a range of outcome measures including (but not limited to) histological remission and clinico-histological remission. For other measures, for example dysphagia symptoms and the AMS score, there was no evidence for a statistically significant difference between budesonide ODT and placebo.
- No head-to-head evidence for budesonide versus either of the comparators (fluticasone or SFED) is available. The company therefore conducted an NMA for the outcome of histological remission.
- The company asserts that the studies included in the NMA did not show substantial variation with respect to known effect modifiers. Although asked, the company did not confirm which patient characteristics can be considered effect modifying nor whether any potential treatment-effect modifiers were missing. The ERG is therefore not able to judge whether the NMA is affected by heterogeneity in effect-modifying variables. The ERG believes there is potential clinical heterogeneity for certain patient and study characteristics among the studies included in the NMA. Caution

should be exercised in the interpretation of NMA results because the impact of potential heterogeneity on the results is unknown.

- The company did not assess the risk of bias for the individual studies included in the NMA. Instead, a GRADE assessment was undertaken for the body of evidence as a whole. The ERG believes that the four RCTs included in the NMA are likely to be at a low risk of bias but the prospective observational study included in the NMA (which provides evidence for SFED versus budesonide OVS) is at a very serious risk of bias.
- In three of the RCTs included in the NMA there were zero histological remissions in the placebo arm. The inclusion of zero values in the NMA leads to very wide credible intervals indicating substantial uncertainty. The option to use a continuity correction to help overcome this was not explored by the company.
- The prior probability distribution that the company used for treatment effect was described as a vague but the ERG believes it was likely to be an informative prior. When the ERG tried to use a more traditional vague prior for treatment effect the random effects model would not converge. The ERG believes the random effects model is the appropriate choice given the suspected clinical heterogeneity between the studies in the NMA. We therefore reran the random effects NMA using a frequentist software package to overcome the problem of very wide confidence intervals caused by zero remissions in some placebo arms. We use these results in the ERG economic base case.

4 COST EFFECTIVENESS

4.1 Overview of company's economic evaluation

The CS includes:

- A systematic review of published economic evaluations in studies associated with EoE (CS B.3.1 and Appendix G);
- A description of the company's de novo model developed to assess the cost-effectiveness of budesonide ODT compared with fluticasone and SFED for the treatment of adults with EoE.

We summarise and critique these elements of the CS in sections 4.2 and 4.3 below. Additional ERG analyses, including model validation and alternative scenarios are presented in section 4.4.

4.2 Company's review of published economic evaluations

The company conducted a systematic review to identify published studies for resource use, costs and economic evaluations for EoE (see section 3.1.3 of this report for our critique of the company's literature search strategies).

The company identified five studies: four of which related to cost analyses or estimation of resource utilization.[18-21] The remaining study by Miller et al. 2011[22] estimated the cost-effectiveness of endoscopic biopsy for EoE in patients with refractory GORD. However, the company argued that this study did not meet the inclusion criteria as the patient population was not directly comparable to the cohort within the scope of the current appraisal.

The ERG notes that the company identified two economic evaluations in their previous submission to NICE in March 2019.[23] [24] In the current submission to NICE in October 2019, the CS states that no studies relevant to the decision problem were identified by the systematic literature review. In response to ERG Clarification Question B10, a summary of these two studies was provided. However, the company did not consider these studies to be relevant. On the contrary, the ERG view these studies would provide useful information for model validation and hence should have been included.

The study by Schneider et al.[24] developed a Markov model to compare the cost-effectiveness of three initial therapy options (fluticasone, budesonide viscous, SFED) for 30 year old men with a new diagnosis of EoE. Health states included were active EoE, remission and death. Patients progressed to a second-line therapy if they failed one therapy

(SFED if steroid first or budesonide if SFED first), and then a third-line option (elemental diet). The model had a payer perspective, three-month cycles and a five-year time horizon. The conference abstract only reported limited information on model parameter inputs. SFED was the most cost-effective treatment as it dominated budesonide viscous and fluticasone (i.e. it was cheaper and more effective).

Cotton et al.[23] performed a cost-utility analysis of topical corticosteroids compared with the SFED for the treatment of EoE. This US based study conducted their analysis from a payer's perspective. A modified Markov model (microsimulation approach within a Markov model) was developed where patients transitioned between health states, depending on their histological response (defined as an eosinophil count less than 15 eos/hpf). The model time horizon was five years, with a cycle length of three months. The study concluded that whilst topical corticosteroids and SFED were similar in effectiveness for first-line treatment of EoE, SFED was, on average, cheaper and more cost effective in most simulations compared with topical budesonide and topical fluticasone, without accounting for patient-level costs or quality of life. We use the study by Cotton et al. for our external validation of the company's modelled outcomes, details of which are presented in section 4.4.2.

In addition to the above studies, the ERG identified a narrative study by Dellon et al.[25] which examined costs and their sources related to EoE, alongside investigating a possible approach for cost-effective care in EoE. The author of this US-based study concluded that EoE is associated with high costs, predominantly driven by diagnostic delays; requirement for upper endoscopy with biopsy for diagnosis and monitoring of disease activity; expensive medications currently used off-label; increased food costs related to dietary elimination treatment; frequent visits to the doctors with subspecialists; and disease related complications or exacerbations. Few studies on costs or approach to cost-effective care in EoE were identified. The author advocated a patient-centric approach and shared decision-making model as an optimal option for the provision of cost-effective care, alongside consideration of a rational strategy for diagnosis and initial treatment; effective maintenance therapy for disease control and prevention; and appropriate long-term monitoring of the condition.

4.3 Critical appraisal of the company's submitted economic evaluation

4.3.1 NICE reference case checklist

The ERG's assessment of whether the CS meets the NICE reference case requirements for economic evaluations is summarised in Table 23. We consider that the company's economic analysis meets all the NICE reference case requirements.

Table 23 NICE reference case checklist

Criterion	Included?	Comment
Decision problem as in scope	Yes	
Comparators as listed in scope	Yes	CS explains that PPI treatment has not been included as a comparator as patients are expected to have been treated unsuccessfully with PPIs prior to diagnosis of EoE.
Perspective on costs: NHS and PSS	Yes	
Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes	
Perspective on outcomes: All direct health effects, whether for patients or, when relevant, carers	Yes	
Cost utility analysis with fully incremental analysis	Yes	
Synthesis of evidence on outcomes based on a systematic review	Yes	Systematic review of clinical effectiveness studies, with random effects NMA for rates of remission (CS B 2.9)
Time horizon: Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes	Time horizon of 40 years. The ERG considers a shorter time horizon of 20 years to be sufficient.
Health effect expressed in QALYs. EQ-5D is preferred measure of health-related quality of life	Yes	EQ-5D values used, however not for EoE, but for a proxy condition: gasto-oesophageal reflux disease (GORD)
Health related quality of life reported directly by patients and/or carers.	Yes	
Preference data from representative sample the UK population	Yes	
An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.	Yes	
Discount rate: 3.5% per annum for costs & health effects	Yes	

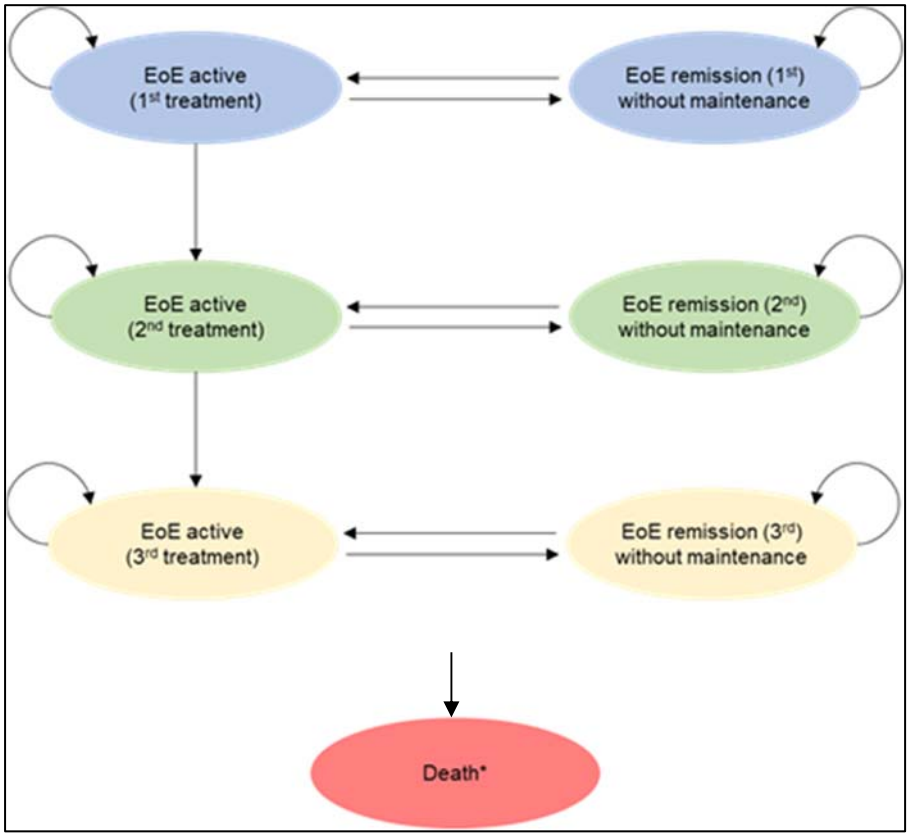
4.3.2 Model structure

4.3.2.1 Overview of model structure

The company describes the model structure in CS section B.3.2.4. They have developed a Markov model in Microsoft Excel, consisting of seven health states including death. The

modelled cycle length is 12 weeks with a 40-year time horizon. The company conducted their cost-effectiveness analysis from a UK NHS and PSS perspective. A half-cycle correction is incorporated. Costs and QALYs are discounted at an annual rate of 3.5%. The company's illustration of the model is reproduced in Figure 3.

The company justify the time horizon by stating that it is "*long enough to reflect important differences in costs or outcomes between technologies being compared*" (CS Table B 3.1). The ERG considers that a shorter time horizon of 20 years is sufficient to include the difference in costs and/or outcomes between the treatments, especially with the changes made to health care resource use in the EoE active 'no treatment' health state in the ERG base case. We use a 20-year time horizon in the ERG analyses (section 4.4).



Source: reproduction of CS Figure B.3.1

Figure 3 A schematic of the cost-effectiveness model

Six of the model health states are defined by stage of treatment (first line-; second line-; and third line treatments) and level of disease control (active EoE; or remission without maintenance treatment). The economic evaluation does not include health states for remission with maintenance therapy (though the economic model does incorporate this function if required). We describe the model health states in Table 24 below.

Table 24 Summary of the model health states

	Health states	Description
1st treatment	EoE active	Patients enter the model in this state where they receive 1st treatment for EoE. They commence treatment with budesonide ODT or a comparator. Patients may remain in this state; respond to treatment and transition to EoE with remission health state; or transition to receive 2nd line of treatment.
	EoE remission without maintenance therapy	A proportion of active EoE patients who respond to the 1st treatment and are "better/well" transition to this state. In this state they are not treated with maintenance therapy. Patients in this state may remain in this state or may experience a relapse in which case they transition to the EoE Active state where they receive the 1st line of treatment again.
2nd treatment	EoE active	Patients in this state receive 2nd line of treatment as they have failed to respond to 1st line of treatment and are still unwell with EoE.
	EoE remission without maintenance therapy	Patients who respond to second treatment and are considered 'better/well' transition to the remission state where they are not treated with maintenance therapy.
3rd treatment	EoE active	Patients who remain unwell and did not respond to the 2nd line of treatment transition to this health state where they receive the 3rd line of treatment. Patients remain in this health state if they do not respond to the 3rd line of treatment.
	EoE remission without maintenance therapy	This health state comprises of patients who have responded to the 3rd line of treatment and are 'better/well'. Similar to the previous two lines of treatment, these patients are not treated with maintenance therapy.
	Dead	This is an absorbing state, which patients can transition to from any of the above health states. The CS argues that EoE has no impact on mortality; therefore this health state reflects general population mortality.

The model has tunnel states to capture time-dependency. Tunnel states are temporary states used to add memory to a Markov model. In the company's model, tunnel states are used to count the number of cycles a patient is in an EoE remission health state.

Movement of patients between the health states is determined by a set of transitional probabilities, obtained from the NMA and the published literature. We present a critique of the clinical parameters for response and relapse in the following section. The model estimates QALYs by multiplying utility values for the health states by the proportion of the cohort in those states and adding these over time. The model includes costs for: drug acquisition; co-medication; costs associated with medical resource use; adverse events costs (described in more detail in section 4.3.7).

ERG conclusion

We agree with the company's use of a simple state-transition Markov model to estimate patient transition between the health states. However, we have reservations against the company's approach to exclude 'remission with maintenance therapy' health state from the model structure. Following expert clinical advice, we view this as an unrealistic assumption and anticipate that exclusion of the maintenance health state would lead to higher health care resource use due to a higher relapse rate.

4.3.3 Population

The company's economic model evaluates outcomes for an adult population (aged ≥18 years) who are diagnosed with EoE (CS section B.3.2). This matches the NICE scope for this appraisal and the marketing authorisation. All patients are assumed to be pre-treated with PPI prior to receiving a diagnosis of EoE.

The average starting age of the cohort used in the economic model is 30 years and 53.8% of individuals are male. The age of the cohort and the proportion of male individuals was consistent with the characteristics of those with EoE seen by our clinical experts. Compared to the company's two budesonide ODT trials, the cohort used in the model was of a younger age with a lower proportion of males. The patient demographic characteristics of the company's trials are shown in Table 4. The ERG notes that differences in the starting age and proportion of males between the trials and the model cohort have minimal effect on the model results.

4.3.4 Interventions and comparators

The company includes topical corticosteroids (fluticasone) and diet (SFED) as comparators. The ERG was advised by clinical experts that budesonide OVS is sometimes used in clinical practice. However, the NICE scope does not permit inclusion of other formulations of budesonide as comparators.

Budesonide ODT is administered orally at 1mg dose twice daily according to the marketing authorisation. The usual duration of treatment is 6 or 12 weeks, however budesonide ODT is not currently licensed for maintenance use (i.e. beyond 12 weeks). It is unclear what the recommended dose is for fluticasone as it is used off-label for EoE. The company assumes a dose of 550 mcg twice daily in the economic model.

4.3.5 Treatment effectiveness

The model includes input parameters for clinical effectiveness for the remission rate, relapse rate, adverse events and mortality rates.

4.3.5.1 Transition from active EoE to remission health states: response rate

The remission rates for the treatments were defined as the histological remission rate (presented earlier in this report, section 3.3.1). The odds ratios (ORs) for achieving histological remission for the different treatments were calculated through an NMA (described earlier in section 3.1.7 of this report). The absolute remission rate, referred to in the CS as the response rate, for each treatment was calculated based on the response rate for budesonide ODT and each comparator's corresponding ORs. The ORs from the random effects NMA and the calculated remission values used in the economic model are shown in Table 25 (CS Table 3.4).

The response rate for budesonide ODT, fluticasone and SFED was 94.9%, 68% and 18% respectively.

Table 25 Transition matrix used in the cost-utility model (base-case analysis)

Treatment	OR for response	Response per cycle (%)	Relapse per cycle (%)	Patients who move to subsequent treatment (%)
Budesonide ODT	-	94.9	22.0	5.1
Fluticasone	0.116	68.0	22.0	32.0
SFED	0.012	18.0	22.0	82.0
No treatment	0.002	4.0	22.0	96.0

Source: Reproduction of CS Table B.3.4
Abbreviations: ODT = orodispersible tablet; OR = odds ratio; SFED = six-food elimination diet

In response to an ERG clarification question (A10), the company re-ran the NMA with a continuity correction for zero remissions in the placebo groups, for the fixed-effect and random effects models. The results of these analyses are described in section 3.3.11 of this report and we use the ERG's random effects NMA results in our base case (section 4.4).

4.3.5.2 Transition from remission to active heath state: relapse rates

Patients in remission may relapse and return to active EoE. The CS comments that there are limited data on the relapse rate of EoE in remission. The relapse rates used in the model for those not on maintenance therapy are assumed to be same as observed in the placebo arm of the company's BUL-2/EER maintenance study, i.e. 88% relapse in one year. The relapse rate per cycle is calculated from the study by assuming that events occur at a constant rate over time, i.e. 22% per 12-week cycle. The company did not include remission with maintenance in the analysis. In response to clarification question B3, the company includes

a scenario analysis with maintenance therapy where they assume the relapse rate would be lower for those on maintenance treatment.

Expert clinical advice to the ERG is that EoE patients in remission would typically relapse if they stopped treatment but those who continue on maintenance therapy would mostly remain in remission. Furthermore, in the study by Straumann et al,[26] all patients in the placebo arm (i.e. not receiving maintenance therapy) relapsed. 'Lucendo et al[1] commented "*When pharmacological treatment for EoE is stopped, symptoms and/or esophageal eosinophilia typically recur over a 3–6 month period*".

The company assumes that patients who respond to induction treatment do not then receive maintenance treatment. They justify this by stating that budesonide (all formulations including ODT) and fluticasone are not licensed for maintenance therapy (CS p63). However, the ERG notes that fluticasone and SFED are not licensed for induction therapy. (NB. As stated earlier in this report, a 48-week, double-blind, randomised, placebo-controlled, maintenance of clinico-histological remission study is in progress: BUL-2/EER NCT02493335; EudraCT 2014-001485-99) with an estimated study completion date of December 2020. This suggests that a marketing authorisation for maintenance treatment may be sought in the near future). Furthermore, expert clinical advice to the ERG is that patients responding to fluticasone or SFED induction therapy would be likely to continue receiving these as maintenance therapy. We have therefore included maintenance therapy for patients who receive fluticasone and SFED in the ERG base case analyses in section 4.4.

The ERG conducted a review of the relapse rate for those patients who received maintenance therapy of fluticasone, budesonide or SFED. We found six studies (Reed et al,[27] Eluri,[28] Straumann et al,[26] Andraea et al,[29] Butz et al,[30] Oliva et al[31]). Across these studies the relapse rate per three-month cycle varied between 5-27%. The studies identified are shown in Table 26. We pooled the results from the studies which produced a relapse rate of 11% per 12-week cycle. However, we note that in many of the studies the maintenance dose was half that of the induction dose. As discussed above, the relapse rate is likely to be lower if a higher dose is used. The relapse rate for remission with maintenance for budesonide ODT in theBUL-2/EER maintenance study was 5.4% per cycle (clarification question response B4). We used this relapse rate in a scenario analysis in section 4.4.

Table 26 Relapse rates for maintenance therapy in selected studies

Study	Treatment	N	n remain remission	Months of study	Relapse rate, study	Cycles	Relapse / cycle
Reed et al[27]	SPED	21	10	24	0.524	8.000	0.0886
Eluri et al[28]	CS / Bud	33	13	27	0.606	9.000	0.0983
Straumann et al[26]	Budesonide	14	5	12	0.643	4.000	0.2269
Oliva et al[31]	Budesonide	20	17	5.5	0.150	1.846	0.0843
Andraea et al[29]	Fluticasone	43	30	20.0	0.302	6.667	0.0526
Butz et al[30]	Fluticasone	15	11	3.0	0.270	1.000	0.2700
Total		**146**	**86**				**0.111**

4.3.5.3 Subsequent treatments

The company's assumption is that all patients who do not respond to an initial treatment transition to a subsequent treatment. In the company base case, the second line and third line treatments are assumed to be "No treatment" but they have the same health care costs as treatment with budesonide ODT and fluticasone. As described in section 4.4.3, patients in the model spend a long time period in the third line Active EoE 'no treatment' health state and thus incur unrealistically high health resources. The ERG suggests a better approach is to have no health resources associated with the 'no treatment' Active EoE health state. We have used this approach in the ERG base case in section 4.4.

4.3.5.4 Adverse events

The economic model includes the adverse events of the treatments for EoE. The safety data were based on the same studies that were used for the histological remission estimates.[2,5,30,32,33] The highest reported frequencies of adverse events were included in the model for all comparators. The adverse events used in the economic model are shown in CS Tables B 3.5. There were no adverse events for SFED and no treatment. The most common adverse events are shown in Table 27. The CS reports that there were zero adverse events for sleep problems, skin disorders, cough and respiratory disorders.

Table 27 Most common adverse events for treatments for EoE

Adverse event	Patients experiencing each AE (%)	
	Budesonide ODT	Fluticasone
Oral candidiasis	3.4	3.5
Oesophageal candidiasis	16.9	26.3
Headache	6.8	4.7
GI disorders	16.9	0.0
Pharyngitis	1.7	0.0
Irritation in nose and/or throat	0.0	10.5

Source: Reproduction of CS Table B.3.5
Abbreviations: AE = adverse event; GI = gastrointestinal; ODT = orodispersible tablet

Adverse events in the budesonide ODT trials have been presented earlier in section 3.3.12. The CS states that the vast majority of adverse events were mild or moderate in severity although the Serious Adverse Event (SAE) grade has not been given. The ERG notes that in most economic evaluations, only SAEs grade 3+ are usually included.

The costs of treating these adverse events are described in section 4.3.7.

4.3.5.5 Mortality rates

The model uses general population all-cause mortality rates for the UK for the years 2015-2017.[34] The all-cause mortality rates were adjusted according to the proportion of male and females in the model population. The CS notes that EoE does not have an impact on mortality, and clinical expert advice to the ERG concurs.

ERG conclusion

The intervention and comparators included in the model are consistent with the NICE scope and current clinical practice. The economic evaluation does not include health states for remission with maintenance therapy (though the economic model does incorporate this function if required). The ERG considers this does not reflect current clinical practice. The model does not include relapse rates for patients in remission with maintenance therapy. We have conducted a review of the literature tor the relapse rate for those in remission with maintenance therapy. To test the impact of these assumptions, we conducted a range of scenario analyses, details are presented in section 0.

4.3.6 Health-related quality of life

4.3.6.1 Company's review of health-related quality of life studies

The company conducted a structured search to identify studies with utility values for patients with EoE (see section 3.1.3 of this report for our critique of the company's literature search strategies).

After screening titles and abstracts, the company identified 54 full text papers focussing on oesophageal disease. The papers were for the following conditions: GORD, achalasia, Barrett's Oesophagus, oesophageal cancer and oesophageal varices.

As there were no studies identified for EoE, the company compared EoE to the conditions above to determine which provided the best proxy (CS Appendix H). The company concluded that GORD provided the most similar condition to EoE. After full paper screening there were ten GORD studies that were relevant and included. Of the studies identified, the company considered that the study by Kartman et al[35] was most representative of EoE patients with symptoms. Kartman et al[35] assessed health state utilities in 1011 German and Swedish patients with GORD with heartburn using EQ-5D and other HRQoL instruments. The study used the UK tariff for the EQ-5D valuation.

For patients with Active EoE, the utility of GORD patients with average symptoms was selected (u=0.70). For patients in remission, the utility value was taken from UK general population norms (u=0.85).[36] In a scenario analysis, the company used the utility values of 0.56 for GORD relapse for those with Active EoE (u=0.56). The EQ-5D utility values used in the economic model are shown in Table 28.

Table 28 Utility values used in the cost-utility model

Health state	Mean utility value	Standard deviation	Reference in submission (Section)	Company justification
Base-case analysis				
Active EoE	0.70	0.24	Kartman 2004[35]	Literature review – pooled Swedish/German data for GORD with heartburn
EoE in Remission	0.85	0.24	Kind 1999[36]	Represents a 'well' patient which has been assumed to be comparable to general UK population
Scenario analysis				
Active EoE	0.56	Not reported	Grant 2008[37]	UK estimate of GORD with relapse

Source: CS Table B.3.6
Abbreviations: EoE = eosinophilic oesophagitis; GORD = gastro-oesophageal reflux disease; UK = United Kingdom

The CS states that age-adjusted utilities were not used in the model. The CS justifies this by stating that the study from which the utility value was derived only provided utility values for all ages and so therefore the use of age-adjusted utilities was not possible. The ERG disagrees with the rationale given by the company for not including age adjusted utilities and has therefore included them in the ERG analyses in section 4.4.

The ERG has the following concerns about the company's approach to estimating HRQoL. Firstly, the health state utility values have not been taken from a study of patients with EoE. Instead they have been taken from patients with a proxy condition (GORD) and it is unclear how similar the HRQoL is for these patients to those with EoE. The ERG has therefore investigated using mapping from SF-36 to EQ-5D for patients with EoE using the mapping algorithm described by Ara and Brazier.[38]

Lucendo et al 2017[39] identified eight studies that measured SF-36 or SF-12 in patients with EoE. Two of these are abstracts. Of the remaining studies, Hewett et al[40] is considered the most relevant by the ERG as it compares SF-36 scores for UK patients with EoE to a control group. The ERG mapped SF-36 scores to EQ-5D for this study using the mapping algorithm described by Ara and Brazier.[38] The EQ-5D scores were 0.88 and 0.95 for EoE patients with active disease and controls respectively, i.e. a disutility of 0.07 for those with EoE. We use this disutility in the ERG base case analyses in section 4.4.

In addition, the population used in the model has an average starting age of 30 years. The UK population norm EQ-5D values for individuals of age 30 are 0.93 in Kind et al,[36] not 0.85 as used in the company model. We use u=0.93 for the utility value for patients in remission in the ERG base case analyses in section 4.4.

ERG conclusion

The utility values in the economic model for Active EoE are taken from a study of patients with a disease considered to be a proxy for EoE (GORD). The ERG considers an alternative study of EoE patients provides a better source of utility values. The utility value for patients in remission is taken from UK population norms, however the incorrect value has been used for this population. Age-adjusted utilities have not been included in the economic model.

4.3.7 Resources and costs

The economic model includes the following costs:

- Drug acquisition
- Follow-up monitoring and care
- Adverse event costs

The company conducted a search of published resource use data and costs associated with EoE treatment. None of the studies identified reported resource use or unit cost data which might be able to populate the economic model.

4.3.7.1 Drug acquisition costs

The company based the dosages for the treatments on the relevant Summary of Product Characteristics or from the electronic Medicines Compendium (eMC) (www.medicines.org.uk\emc). The assumption used to estimate the dosages are described in CS Appendix I. The acquisition costs were taken from the British National Formulary (BNF).[41] The dosages and acquisition costs of the treatments are shown in Table 29 (CS Table B 3.7).

Table 29 Unit costs and doses associated with the treatments in the economic model

Drug	Strength	Dose per day	Cost per unit (excluding VAT)	Source
Budesonide ODT	1 mg	2 x 1mg	90 x 1 mg tablets = £323.00	British National Formulary[41]
Fluticasone (Flixotide Evohaler)	50 mcg	1.1 mg	120 x 50 mcg doses = £6.53	British National Formulary[41]
Source: Reproduction of CS Table B.3.7 Abbreviations: mcg = microgram; mg = milligram; ODT = orodispersible tablet; VAT = value-added tax				

The recommended dose for budesonide ODT is 1 mg BID for six or 12 weeks. Based on the company's BUL1/EEA trial, 57.6% of patients receive budesonide ODT for six weeks and the remainder receive budesonide ODT for 12 weeks. The drug costs are £323 for six weeks treatment, including wastage. Fluticasone is used off-label and there is no fixed dose for use on patients with EoE. The company notes that the recommended daily dose for asthma is 100 – 1000 mcg BID for adults and children over 16 years old. The company assumes the dose used was the midpoint of this range for asthma, i.e. 550 mcg BID. There were no drug administration costs as the drugs were either oral medicines or self-administered.

The ERG suggests that the cost of fluticasone should be using the larger inhaler with 250mcg doses (120 doses = £36.14), rather than 50 mcg doses, as this is more consistent with the recommended dosage. Further the dose of fluticasone should be 1 mg per day (rather than 1.1 mg per day), i.e. 2 x 250mcg / dose, twice a day. Making these changes to the dose for fluticasone has minimal effect on the model results and so we have not included these changes in our base case analyses.

In the scenario analysis (including maintenance therapy) provided in response to clarification question B4, patients who are in remission and are treated with maintenance therapy are assumed to have a dosage of 50% of that used for the initial treatment. Expert clinical advice to the ERG is that patients would be maintained on a reduced dosage compared to their initial treatment, although there is some uncertainty over which dosage. Lucendo et al[1] comment '"*the long-term therapeutic strategy and best maintenance doses for*

pharmacologic therapies are yet to be defined. An approach where the dose is progressively decreased to the lowest dose that keeps the disease in remission seems reasonable until more data are available." The study by Eluri et al[28] analysed patients remaining in remission compared to their maintenance dose. They concluded that "*Patients who were maintained on a high (daily>1000 mcg of budesonide or >880 mcg of fluticasone) steroid dose had lower odds of loss of response compared to those who had a decrease in steroid dose (daily ≤1000 budesonide or ≤ 880 mcg of fluticasone) after achieving initial histologic response.*" In the study, patients with an ongoing response had a mean daily dose of 1.4 mg for budesonide and 0.7mg for fluticasone.

4.3.7.2 Follow-up monitoring and care

The economic model includes health care costs for upper endoscopy with biopsy sampling, consultation with gastroenterologists and dietitians. The health care resources used were based upon UK expert opinion. The unit costs of the resources are shown in Table 30, based on the 2018/2019 National Tariff[42] and Unit Costs of Health and Social care.[43]

Table 30 Costs of health care resources

Items	Unit cost	Reference
Upper endoscopy with biopsy sampling:	£391.00	2018/19 National Tariff (code FZ61Z) [42]
Gastroenterologist - first visit	£188.00	2018/19 National Tariff (code WF01B) [42]
Gastroenterologist - following visits	£72.00	2018/19 National Tariff (code WF02B) [42]
Dietitian visit	£30.94	2018/19 PSSRU[43]

Source: CS Table B.3.9 and CS section B.3.5.3.3

The frequency of the use of health care resources for patients with EoE is shown in Table 31 (CS Table 3.8) and the CS states that patients on fluticasone would receive one to three endoscopies per year whilst in the active disease health state. Assuming two endoscopies per year, this converts to an average of 0.47 endoscopies per 12-week cycle. Patients receiving SFED would receive more endoscopies, about 5-6 per year, i.e. an average 1.3 endoscopies per 12-week cycle. UK expert clinicians advised the company that patients would not receive endoscopies during the EoE in remission health states. The frequency of endoscopies in the model is shown in Table 32 (CS Table 3.11) for the active disease and remission health states. UK clinical experts advising the company suggested that patients would not have gastroenterology visits during disease remission.

Table 31 Healthcare professionals resources used in each model cycle for the model health states

Healthcare professional visit	Active EoE health states	EoE in remission health states
Gastroenterologist, first visit (all treatments)	0.0 per cycle	0.0 per cycle
Gastroenterologist, following visits (all treatments)	1.0 per cycle	0.0 per cycle
Dietician (SFED only)	1.8 per cycle	0.0 per cycle
Dietician (budesonide ODT, fluticasone, no treatment)	0.0 per cycle	0.0 per cycle

Source: CS Table 3.8
Abbreviations: EoE = eosinophilic oesophagitis; HCP = healthcare professional; ODT = orodispersible tablet; SFED = six-food elimination diet

The CS assumes that patients have already had a first visit with a gastroenterologist for diagnosis. Hence all gastroenterologist visits included in the model are subsequent visits. The CS states that UK expert opinion is of the view that EoE is followed-up by a clinical specialist, and would not need GP visits after diagnosis. Expert clinical advice to the ERG disagrees with this and suggested that patients would be discharged to GP follow-up from clinical specialists after remission. Based on this we have changed the cost for consultation visits to that for a GP (£37.40 per consultation).

Table 32 Frequency of endoscopies included in the cost-utility model

Treatment	Frequency of upper endoscopy with biopsy sampling	Source
Active EoE		
Budesonide ODT	0.47	Assumption (same as other drug treatments)
Fluticasone	0.47	UK expert clinician opinion (unweighted average of range provided; range: 1–3 per year = 2 per year = 0.47 per 12-week cycle)
SFED	1.3	UK expert clinician opinion (5–6 per year = 5.5 per year = 1.3 per 12-week cycle)
No treatment	0.47	Assumption that same as fluticasone
EoE in remission		
Budesonide ODT	0.0	UK expert clinician opinion
Fluticasone	0.0	UK expert clinician opinion
SFED	0.0	UK expert clinician opinion
No treatment	0.0	Assumption (same as fluticasone)

Source: Reproduction of CS Table B.3.11
Abbreviations: EoE = eosinophilic oesophagitis; ODT = orodispersible tablet; SFED = six-food elimination diet; UK = United Kingdom

The ERG agrees that the frequencies of endoscopies are appropriate. However, this would not apply to the whole time horizon as the frequency of endoscopies would be higher during the initial time period. As discussed in section 4.4.2, using this frequency of endoscopies

over the whole time horizon results in an unfeasibly large number of endoscopies per person.

The ERG considers that a better approach for health care resource use in the model is for those resources in Table 31 and Table 32 to be used for the initial treatment period. If patients respond to treatment and are in remission after six months, they would then be discharged to be monitored by primary care. If they had a disease relapse they would have the following health care resource uses: 1 GP visit / cycle, 0.5 gastroenterologist appointment / cycle, 0.25 endoscopies / cycle. We make these changes in the ERG analyses in section 4.4.

The model includes costs for add-on treatment with endoscopic dilation and / or emergency food bolus removal in the active disease and remission health states. The unit cost for dilation/emergency food bolus removal is £448.50. This was the average of food bolus (£343.00) and dilation (£554.00), based on the 2019/20 National Tariff Payment System.[42] The company provides more detail of the sources used for the dilation and emergency food bolus removal cost in response to clarification question B8. The frequency of add-on dilation treatment in the cost-utility model is based on published sources and is shown in Table 33 (CS Table B 3.10).

The ERG does not consider the approach taken to estimate add-on dilation treatment to be representative of clinical practice. As discussed in section 4.4.2, the estimates used in Table 33 produces more than 25 dilation treatments per person over the time horizon. This appears to be a large overestimation. According to retrospective cohort study by Runge et al,[46] 509 EoE patients were dilated a total of 486 times over 12 years. We therefore consider a more realistic probability of add-on treatment is 2% per 12-week cycle for those in active disease and remission. We do not consider that the evidence is strong enough to differentiate by treatment. We explore the impact of this in our additional analyses in section 4.4.

Table 33 Probability of add-on dilation treatment (or emergency food bolus removal) in the cost-utility model

Treatment	Health state	Probability of strictures/bolus impaction per 12-week cycle	Source
Budesonide ODT	Active disease	0.00	BUL-1/EEA[33]
	Remission (without maintenance)	0.15 (60% at 48 weeks)	BUU-2/EEA[44]
Fluticasone	Active disease	0.14 (9.5% at 8 weeks)	Moawad et al., 2013[32]
	Remission (without maintenance)	0.41 (27.0% at 8 weeks)	Dellon et al., 2012[45]
SFED	Active disease	0.01 (8.0% in 24.9 months)	Reed et al., 2017[27]
	Remission (without maintenance)	0.15 (60% at 48 weeks)	BUU-2/EEA[44]
No treatment	Active disease	0.14	Assumption: same as fluticasone
	Remission (without maintenance)	0.41	Assumption: same as fluticasone

Source: Reproduction of CS Table B.2.10
Abbreviations: ODT = orodispersible tablet; SFED = six-food elimination diet

4.3.7.3 Adverse event costs

The economic model includes the costs of treating adverse events associated with the treatments for EoE. The rate of adverse events for budesonide ODT and fluticasone were identified from published sources (see CS Appendix M). The rate of adverse events experienced by patients receiving drug treatment is shown in CS Section B 3.3.3. The cost of managing each AE was derived from the interviews with the UK clinical experts. The UK clinical experts suggested that most AEs would not be treated. Only oral candidiasis, oesophageal candidiasis and headache would be treated and the cost of treating these is small.

The ERG notes that these costs are included as a one-off cost in the initial cycle of treatment. The costs of treating the adverse events are shown in Table 34. The ERG notes that only a cost has been given and no details on how this cost has been derived. However, these adverse event costs do not have a significant impact on model results.

Table 34 Cost of treating adverse events

	Oral candidiasis	Oesophageal candidiasis	Headache
Cost per event	£ 1.68	£ 1.68	£ 0.12

ERG conclusion

The economic model does not include maintenance therapy (and therefore the drug costs) for patients in remission. This is not consistent with current clinical practice. Health care costs have been overestimated for endoscopy, gastroendoscopy consultation and dilation treatment. The resource use estimated is not representative of clinical practice. These costs have been applied throughout the 40-year time horizon while in active EoE, including when patients are receiving 'no treatment'. In practice the health care costs would be for a short time period and the costs would then be lower as patients are monitored in primary care.

4.3.8 Model assumptions

A summary of the company's model assumptions alongside ERG's comments are discussed in Table 35. The ERG agrees with many of the company's assumptions, however disagrees on the length of the time horizon, the non-inclusion of maintenance therapy, the sources used for utility values and relapse values, and the method of including health care resource costs and dilation costs.

Table 35 Summary of the company's model assumptions with ERG's comments

Model parameter	Company's base-case assumption	Company's justification	ERG comment
Model structure	Markov state transition model with seven health states (three active disease health states, three remission health states and death).	Model structure reflects the chronic relapsing and remitting nature of EoE. Patients move back and forwards between the active disease and remission health states. Despite the 40-year time horizon, the model only allow three lines of treatment as there are limited treatment options available for this rare disease.	The model does not include 'remission with maintenance' health state. We view this as an unrealistic assumption and anticipate that exclusion of the maintenance health state would lead to higher resource use due to a higher relapse rate. In addition, we consider a 20-year time horizon to be sufficient as that length time horizon captures the differences in costs and QALYS between the treatments.
Population	Adults (>18 years) with EoE who have already received treatment with PPIs. They also have confirmed (diagnosed) EoE as per recent guidelines (i.e. >15 eos/hpf).[1]	Budesonide ODT is licensed for adults (> 18 years) with EoE. According to UK clinical experts, in typical current UK clinical practice, patients are pre-treated unsuccessfully with PPIs prior to receiving a diagnosis of EoE, hence prior to receiving budesonide ODT.	The ERG agrees
Time on treatment	The treatment duration is 12 weeks for all comparators. Thus, each cycle in the model is 12 weeks.	Budesonide ODT is indicated for treatment (1 mg twice daily) for 6 or 12 weeks. Budesonide ODT is not indicated for maintenance treatment. Fluticasone is used off-label for the treatment of EoE. Thus, the treatment duration is not specified. However, the UK clinical experts confirmed that treatment with fluticasone would be for 12 weeks.	Expert clinical advice to the ERG disagrees that treatment with fluticasone and SFED would be limited to 12 weeks. Rather, those patients who responded would continue treatment.
Endpoint	The main clinical endpoint used in the economic model was histological remission.	Histologic remission is the more robust, objective endpoint with which to assess disease activity compared to histologic response and assessing patients' symptoms. Consequently, histoligical response is regularly used as endpoint in clinical trials.	The ERG agrees.
Response rates	The response rates for budesonide ODT and the alternative treatments were derived from the NMA: Budesonide ODT – 94.9%;	In the absence of head-to-head comparative data, the NMA was the next best alternative in terms of evidence. However, any limitations of the NMA will feed into the cost-effectiveness analysis.	The NMA has been implemented correctly but there is potential clinical heterogeneity.

	Fluticasone – 68%; SFED – 18%; No treatment – 4%.		
Relapse rates	Relapse rates without maintenance were the same for all treatments – 88% per year.	In the absence of head-to-head comparative data, relapse rates were considered to be the same. The UK clinical experts suggested that this was an appropriate assumption given the lack of data and their lack of experience with budesonide ODT. However, one of them suggested that budesonide ODT would have a lower relapse rate than fluticasone. The relapse rate of 88% per year was based on the placebo arm of the BUL-2/EER maintenance study.	The ERG agrees.
HRQoL – active disease health states	Utility values for GORD with heartburn are representative of those for EoE (0.70 for active EoE health states).	There was a lack of available data on utility values for EoE. The UK clinical experts suggested that the use of a GORD study (GORD with heartburn) was appropriate in the absence of a specific study in EoE. This study was conducted with German and Swedish patients and the UK experts believe that HRQoL would be similar to UK patients. However, they also suggested that EoE would likely have a lower quality of life than GORD with heartburn. Thus, the use of this study can be considered a conservative approach.	The ERG considers a better source of utility data is a mapping study of patients with EoE by Hewett et al.[40]
HRQoL – remission health states	HRQoL in the remission health states is similar to that for the general population (0.85 for remission health states).	There was a lack of available data on utility values for EoE – for both active disease and remission. As patients in remission are not experiencing bothersome symptoms, it was reasonable to assume that their quality of life would be similar to that of the general population, as estimated by Kind in 1999[36]	The ERG agrees.
Drug costs	Drug dosing in the SmPCs reflects clinical practice and thus is appropriate to use in the estimation of drug costs. 57.6% of patients receive budesonide ODT for 6 weeks and the remaining patients (42.4%) receive budesonide ODT for 12 weeks. As fluticasone is used off-label for EoE, the dose used in the model represents the midpoint between the	The recommended dose for budesonide ODT is 1 mg twice daily for 6 or 12 weeks. The pivotal phase III BUL-1/EEA study showed that 57.6% achieved histological remission at 6 weeks. Hence, it is reasonable to assume that not all patients require treatment with budesonide ODT for 12 weeks. The UK clinical experts suggested that the dose of fluticasone would likely be higher for EoE than for asthma. Thus, the assumption used in the model is a conservative one.	The ERG agrees

	range in the SmPC for asthma patients.		
Gastroenterologist visits	EoE patients are managed by gastroenterologists. They visit the gastroenterologist during active disease i.e. whilst experiencing symptoms (once per active disease cycle). They do not visit the gastroenterologist during remission.	The UK clinical experts stated that EoE is seen as a specialist disease and treatment is left to specialists, primarily the gastroenterologist. They only visit the gastroenterologist whilst experiencing symptoms. The UK expert clinicians suggested that, regardless of treatment, patients in the active EoE health states would have one to two gastroenterologist visits per 12-week cycle. In order to take a conservative approach, the value used in the economic model was one gastroenterologist visit per 12-week cycle.	The ERG disagrees. Based on expert clinical advice to the ERG patients would be seen by the gastroenterologist initially and then discharged to care by a GP.
Dietician visits	Only patients receiving dietary therapy (i.e. SFED) visit a dietician. These patients visit the dietician during active disease (i.e. whilst experiencing symptoms (average = 1.8 per active disease cycle). They do not visit the dietician during remission.	The UK clinical experts stated that patients would only visit a dietician if they were receiving dietary treatment i.e. SFED. They also stated that patients receiving treatment with SFED would only visit a dietician during the active EoE health state. The estimate of 1.8 visits per 12-week cycle was based on the responses from all the UK clinical experts.	The ERG agrees although as stated above this only occurs for a limited period.
Add-on dilation (or emergency food bolus removal)	Probability of patients receiving add-on dilation during active disease health states: Budesonide ODT – 0.0; fluticasone 0.14; SFED – 0.01; no treatment – 0.14. Probability of patients receiving add-on dilation during remission health states: Budesonide ODT – 0.15; fluticasone 0.41; SFED – 0.15; no treatment – 0.41.	In the absence of comparative date, the values were obtained from the literature for budesonide ODT, fluticasone and SFED. The assumption was that no treatment would be the same as fluticasone. These assumptions are based on the best available evidence in the absence of comparative data.	The ERG considers that the evidence is not sufficient to have different dilation rates by treatment. Further, the dilations rates used in the model overestimate the expected number of dilations in this population.
Endoscopies	Frequency of endoscopies during active disease health states is 0.47 for all treatments except SFED. For SFED, the frequency of endoscopies	There is a lack of published data on the frequency of endoscopies for patients with EoE. The assumption was based on input from the UK expert clinicians - that patients on fluticasone would receive one to three endoscopies per year whilst in the active disease health state. This translates to an average value of 0.47 endoscopies per 12-week cycle. The UK expert clinicians also suggested that patients receiving SFED	As above, the model overestimates the number of endoscopies. The endoscopies should be restricted to when patients are seeing the gastroenterologist (i.e. during the first year).

	during active disease health states is 1.3. Patient do not receive endoscopies during remission.	would receive more endoscopies, around five to six per year. This translates to an average of 1.3 endoscopies per 12-week cycle. And finally, the UK expert clinicians stated that, regardless of treatment, patients would not receive endoscopies during the remission health states.	
Adverse event costs	AEs in EoE and the costs of managing them are minor (also see Section A.11 above for discussion on rate of AEs).	The UK clinical experts suggested that the AEs encountered with Budesonide ODT or the comparators are not substantial. This is reflected in the results of the economic model.	The ERG agrees
Subsequent therapy costs	No treatment is the subsequent therapy (second-line and third-line) for all comparators.	Due to a lack of available treatments for EoE, it seems reasonable to suggest that patients' subsequent treatment would be no treatment. Very few patients are willing to try dietary treatment as it is very restrictive. The UK clinical experts also confirmed that the limited treatment options mean that many patients go untreated. Even with the introduction of budesonide ODT, it's unlikely that patients would receive subsequent treatment with fluticasone. Budesonide ODT is specifically designed to deliver therapeutic levels of budesonide to the oesophagus. If budesonide ODT was not effective, it is unlikely that a clinician would then prescribe a delivery system appropriate for asthma but not for EoE for an essentially similar active ingredient.	The ERG agrees
End-of-life costs	Not applicable	Not applicable	Not applicable

4.3.9 Cost effectiveness results

Results for the company's base case analysis are presented as pairwise incremental cost effectiveness ratios (ICERs) for budesonide ODT vs fluticasone and vs SFED (Table 36). In this analysis budesonide ODT is a dominant treatment, i.e. it is cheaper and more effective than fluticasone and SFED.

Table 36 Base-case results

	Budesonide ODT	**Fluticasone**	**SFED**
Drug costs	£5,097	£253	£0
Co-medications (dilation)	£5,934	£7,833	£7,163
Medical costs			
Gastroenterologist visits	£3,656	£5,359	£5,693
Dietician visits	£0	£0	£40
Endoscopies	£9,333	£13,677	£14,762
AE costs	£0	£0	£0
TOTAL COSTS	**£24,020**	**£27,122**	**£27,657**
Incremental costs (budesonide ODT versus comparator)	-	–£3,101	–£3,637
TOTAL QALYS	**16.12**	**15.30**	**15.14**
Incremental QALYs (budesonide ODT versus comparator)	-	0.82	0.98
ICER - cost per QALY gained budesonide ODT versus comparator)	**-**	**Budesonide ODT dominates fluticasone**	**Budesonide ODT dominates SFED**

Source: Reproduction of CS Table B.3.14
Abbreviations: AE = adverse event; ICER = incremental cost-effectiveness ratio; ODT = orodispersible tablet; QALY = quality-adjusted life year; SFED = six-food elimination diet

Disaggregated results are shown for QALYs and costs in CS Table B3.15 and B 3.16 respectively. These show that for fluticasone and SFED, most of the costs and QALYs are accrued in the Active EoE third line treatment health states. The ERG notes that most patients treated with fluticasone or SFED enter this health state and then remain there for the duration of the model time horizon.

4.3.10 Assessment of uncertainty

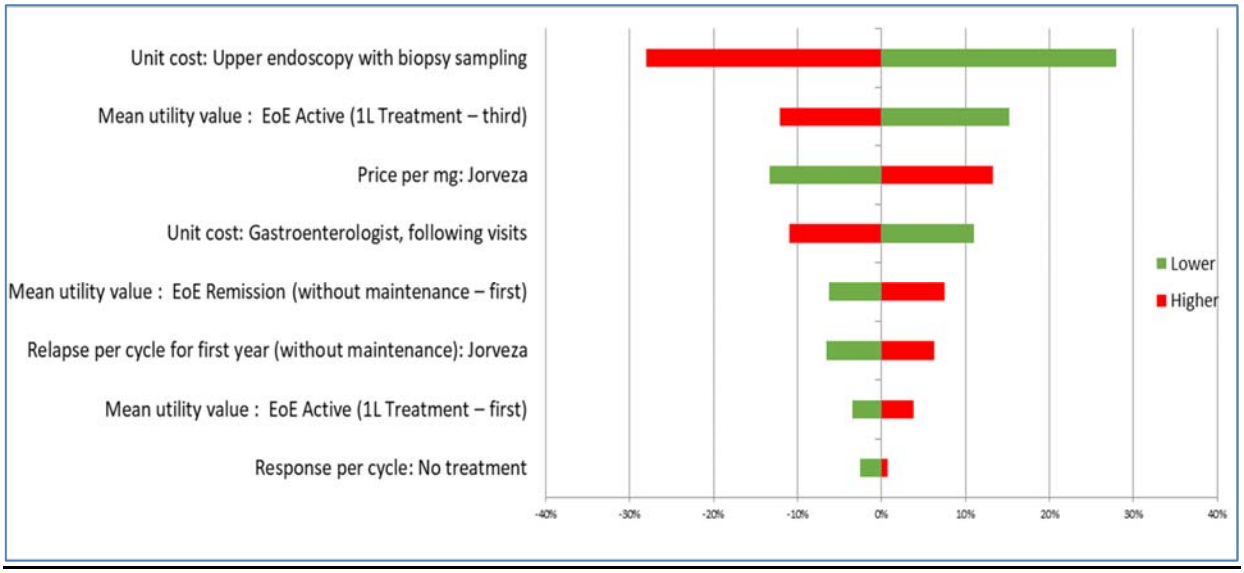
Deterministic sensitivity analysis

The company conducted deterministic sensitivity (DSA) analyses, varying parameters between the 5% and 95% CIs or, where CIs were not available, between +/- 20% of the base case value. The parameters varied are listed in CS section B3.8.2. These include the histological response

rate, utility values, drug costs, health care costs, relapse rate, percentage of treatment failures that stay on treatment. The ERG considers that the company has included all relevant parameters in the deterministic sensitivity analysis.

A tornado diagram comparing budesonide ODT versus fluticasone is shown in Figure 4 (CS Figure B 3.4). The model results are most sensitive to changes to the utility values, unit costs for endoscopy and gastroenterologist visits and relapse rates for budesonide.

The ERG notes that there is large uncertainty around the histological remission ORs reported by the company from their NMA. It is unclear where the uncertainty estimates for the remission ORs have been taken from in the model, but these are not the same uncertainty estimates the CS reports in the results of the NMA. The ERG therefore considers that the deterministic sensitivity analyses does not reflect the full uncertainty around the model parameters.



Source: Reproduction of CS Figure B.3.4

Figure 4 Tornado diagram: Budesonide ODT versus fluticasone

Probabilistic sensitivity analysis

The company conducted a probabilistic sensitivity analysis (PSA) to assess the uncertainty surrounding the model parameters. The utility values and clinical efficacy parameters (response) are varied in the model using the beta distribution (CS Table 3.17). The ERG considers that the PSA is not comprehensive because many of the model parameters have not

been varied. As a minimum, all parameters included in the DSA should have been included in the PSA. The results from the PSA show similar results to the deterministic base case results (Table 37).

Table 37 Incremental cost-effectiveness results based on PSA

	Total costs (£)	Total QALYs (£)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Budesonide ODT	24,031	16.12	-	-	-
Fluticasone	27,124	15.30	–3,091	0.82	Budesonide ODT dominant
SFED	27,659	15.14	–3,628	0.98	Budesonide ODT dominant
Source: Reproduction of CS Table B.3.18					

Scenario analysis

The company conducted the following scenario analyses:

- Time horizon of 10 years
- Discount rate for 0% for costs and effects
- Active EoE health state utility value of 0.56
- General population mortality not applied
- Inclusion of second line treatment (fluticasone after first line treatment with SFED; SFED after first line treatment with budesonide ODT and fluticasone)
- Drug wastage with budesonide ODT and fluticasone excluded
- Budesonide ODT treatment duration of 12 weeks

Details of the scenarios are given in CS section B 3.8.3 and the results are shown in CS Tables B 3.20 – B 3.26. For all the scenarios, budesonide ODT continues to dominate fluticasone and SFED, i.e. budesonide ODT is cheaper and more effective than other treatments.

4.3.11 Model validation conducted by the company

The company describes their approach to model validation in CS section B.3.10. They reported that:

- Internal validation of the economic model was conducted as per the recommendations by the International Society for Pharmacoeconomics and Outcomes Research;

- Model outputs were compared against clinical evidence as well as previously published models;
- External clinical experts and health economists were consulted for external model validation;
- Internal quality assessment of the economic model was conducted using functional as well as glass box testing.

ERG conclusion

We view that the company has followed a systematic approach to validate the economic model. However, the CS does not provide any comparisons of the modelled outcomes with those from clinical evidence or other published literature. We are therefore unable to comment on the validity of these comparisons.

4.4 Evidence Review Group's additional analyses

4.4.1 ERG model validation

We checked the economic model for transparency and validity. The visual basic code used within the model was accessible. We conducted a range of tests to verify model inputs, calculations and outputs:

- Cross-checking of all parameter inputs against values in the CS and cited sources;
- A range of extreme value and logic tests to check the plausibility of changes in results when parameters are changed; and
- Checking all model outputs against results reported in the CS, including the base case, PSA, DSA and all the scenarios.

The company's model was generally well implemented, with no substantive errors in parameter inputs or coding. However, we identified two errors in the model, discussed in section 4.4.4 below.

4.4.2 Face validity check of the model outputs undertaken by the ERG

The ERG examined the number of treatments and resources used in the company's model. The results are shown in Table 38. These show that for each patient in the model they would have at

least 25 dilation treatments, 102 clinical visits and 48 endoscopies over the time horizon. Patients receiving budesonide were treated 16.4 times.

The ERG considers that these estimates of resource use in the model do not show face validity and far exceed the likely resources and treatments that would be used in clinical practice. The majority of the resources are used when patients are in the EoE Active (third treatment) health state as patients remain there for most of the time horizon (31 years out of 40 for those treated with fluticasone). The ERG's base case includes alternative assumptions so that there would be much lower resource use and these assumptions are shown in Table 42.

Table 38 Number of resources and treatments in the company's model

	Dilation treatment	Clinician visits	Endoscopy	Treatment EoE
Budesonide ODT	25.1	102	48	16.4
Fluticasone	30.9	139	65	2.6
SFED	29.3	144	68	0.7

4.4.3 Cross validity check of the model outputs undertaken by the ERG

We compare the modelled QALY estimates from the current appraisal with those from the study by Cotton et al.[23] (Table 39). As discussed earlier, Cotton et al. conducted a cost-utility analysis of topical corticosteroids compared with the SFED for the treatment of EoE. Despite methodological differences between the two models, they provide some means of cross-validation. We note that the QALY estimates from the CS are lower than those from Cotton et al.[23]

Table 39 Comparison of modelled outcomes

Source (time horizon)	QALYs			
Current appraisal (Lifetime)	SFED		Fluticasone	
	27.59		27.76	
Current appraisal (5 years)	3.64		3.79	
Cotton et al. (5 years)*	SFED rescue fluticasone	SFED rescue budesonide	Fluticasone rescue SFED	Budesonide rescue SFED
	4.29	4.26	4.24	4.17

*The results are for the base case with cross over for historic failure of first treatment

4.4.4 ERG corrections to the company's model

The ERG identified two errors in the company's economic model, described in Table 40.

Table 40 Errors identified by the ERG in the company's model

Item	Company's approach	ERG correction
Drug acquisition costs	The drug acquisition costs are calculated in the model after the half cycle correction is implemented. In the first cycle, all patients in the Active EoE (first treatment) health state receive treatment, however the drug acquisition costs is calculated based on half the patients.	In first cycle, the drug acquisition cost is calculated based on all patients receiving treatment. Formula in cell EX10 changed to K9 * INDEX (Calculations!$G$12:$AM$21, $D$3,EX$5)
Transition matrix	There is an error in the calculation of formula of transition matrix formula cell formula for active EoE transition to Active EoE. For example for Jorveza work sheet the formula in cell g25 is =1-SUM(I25:U25)	Corrected the formula in cell G25 to 1-sum(H25:U23). Similar correction made for fluticasone, SFED and no treatment.

We have corrected both these errors and the results for the corrected model are shown in Table 41. Incorporating these corrections increased the total costs of fluticasone by £52 and that of budesonide ODT by £228. Overall, these changes had minimal impact on the cost-effectiveness outcomes.

Table 41 Company base case results with ERG corrections applied

	Total costs (£)	Total QALYs (£)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY) Incremental	ICER (£/QALY) Pairwise vs BUD vs each treatment
SFED	£27,657	15.14	-	-	-	
Fluticasone	£27,174	15.30	-£483	0.16	Fluticasone dominates	Budesonide dominates
Budesonide ODT	£24,248	16.12	-£2,925	0.82	Budesonide dominates	Budesonide dominates

4.4.5 ERG's preferred assumptions

This section details the ERG's further exploration of the issues and uncertainties raised in our review and critique of the company's cost effectiveness analyses. We present our preferred assumptions in Table 42. These consist of the inclusion of maintenance treatment, changes to

the time horizon, remission rate, dilation rate, health care resources, utility values and relapse rate. Other parameters and assumptions in the model, not included in the table, have not been changed from the company's base case analysis.

Table 42 ERG's preferred model assumptions

Parameter	Company base case	ERG base case
Time horizon	40 years	20 years
Remission	Remission rates from company's random effects NMA	Remission rates from ERG's random effects NMA
Maintenance therapy	No maintenance treatment after induction therapy for either budesonide ODT, fluticasone, or SFED.	Maintenance therapy with budesonide ODT after induction therapy with budesonide ODT. Maintenance therapy with fluticasone, and SFED after induction with fluticasone and SFED respectively.
Endoscopic dilation rate	Varies by treatment	Assumed same for all treatments
	Estimated from short-term studies	Uses long term study by Runge et al. (Dilation rate of 2% per cycle)
Health care resources	Applied for whole time horizon for active EoE health states.	No health state resources in active EoE if patients receive 'no treatment'. Initial health care costs applied for a short time period (6 months), including remission health states. Thereafter monitored by GP only. (Resources: in remission states no health care costs; in active EoE 1 GP visit / cycle, 0.5 gastroenterologist appointments / cycle, 0.25 endoscopies / cycle).
Utility	Uses values for proxy condition of GORD with heartburn (0.85 for remission, 0.7 for relapse)	Uses values for EoE patients. Incorrect values used in Kind et al. (0.93 for remission, 0.86 for relapse).
	Age adjusted utilities not included	Include age adjusted utilities
Relapse rate	Assumes same relapse rate for all treatments for remission without maintenance therapy. Remission with maintenance not included in CS. Relapse rate of 22% per cycle for those in remission without maintenance.	Assumes different relapse rate for those in remission on maintenance treatment or not on maintenance treatment.
	Relapse rate of 22% for those in remission on maintenance	Relapse rate of 11% for those in remission on maintenance.

The results of the ERG's base case analysis are shown in Table 43. The ICERs for budesonide ODT are £45,735 per QALY and £33,630 per QALY versus fluticasone and SFED, respectively.

Incorporating the ERG preferred assumptions has a significant impact on the company's base case results. In the company's base case (ERG corrected version), budesonide dominates fluticasone as well as SFED; while in the ERG preferred base case, the pairwise ICERs of budesonide versus the two comparators are above £30,000 per QALY.

Table 43 ERG base case results

	Total costs (£)	Total QALYs (£)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY) Incremental	ICER (£/QALY) Pairwise BUD vs each treatment
SFED	£1,528	12.48				
Fluticasone	£2,539	12.64	£1,012	0.16	£6,466	£33,630
Budesonide ODT	£18,595	12.99	£16,056	0.35	£45,735	£45,735

Table 44 shows the disaggregated results for the number of life years spent in each health state. This shows that patients treated with budesonide ODT spend significantly longer in the remission state than those treated with fluticasone and SFED.

Table 44 ERG base case disaggregated results for life years spent in each health state

		Life years	
Health state	**Budesonide**	**Fluticasone**	**SFED**
Active EoE 1st treatment	1.6	0.7	0.3
Remission with maintenance	13.7	5.0	1.7
Remission without maintenance	0	0	0
Active EoE 2nd treatment	0.1	0.2	0.2
Remission with maintenance	0	0	0
Remission without maintenance	0	0	0
Active EoE 3rd treatment	3.9	12.3	15.6
Remission with maintenance	0	0	0
Remission without maintenance	0.5	1.6	2.0
Total	19.8	19.8	19.8

We conducted a range of scenario analyses around the ERG preferred base case to explore the impact of the ERG's assumptions on the model results (Table 45). The ICER for budesonide versus fluticasone varies between £12,346 per QALY (Scenario: Maintenance treatment with fluticasone) and £80,796 per QALY (Scenario: maintenance dose same as the induction dose). The ICER for budesonide versus SFED varies between £10,533 per QALY (Scenario:

maintenance with fluticasone) and £59,774 per QALY (Scenario: maintenance dose same as the induction dose). The model results are most sensitive to the inclusion of maintenance therapy for budesonide ODT and the changes to the utility values.

4.5 Conclusions on cost effectiveness

4.5.1 Maintenance therapy

The company did not include maintenance therapy for patients in remission. Expert clinical advice to the ERG considered this would be unrealistic of current clinical practice. If patients in remission are not treated with maintenance therapy, they would be likely to relapse more quickly and therefore incur more health care resources. Further, expert clinical advice considers that if budesonide ODT is recommended by NICE, then patients who start induction therapy with budesonide ODT and respond would likely be maintained with budesonide ODT. We have therefore included maintenance therapy in the ERG base case. This has a large impact on model results.

4.5.2 Health care costs

We consider that the model overestimates the health care resources used for patients, including dilation treatment. The resource use estimated is not representative of clinical practice. These costs have been applied throughout the 40-year time horizon while in Active EoE, including when patients are receiving 'no treatment'. This is particularly significant, because patients remain in the EoE Active health state after third line 'no treatment' if they do not respond to 'no treatment'. Expert clinical advice to the ERG suggests that in practice the health care costs would be for a short time period and the costs thereafter would be lower as patients are monitored in primary care. Further, there are unlikely to be health care resource costs when in the Active EoE health state receiving 'no treatment'. We have included these changes in our base case analysis.

4.5.3 Health utility

The company's approach to estimating health state utility is generally reasonable and consistent with the NICE reference case. However, the company did not include studies of patients with EoE using the SF-36 instrument, which can be mapped to the EQ-5D. The ERG considers a study of EoE patients by Hewett et al[40] provides a better source of utility values. The utility value for patients in remission is based on UK population norms, however the incorrect value has been used for this population. Age-adjusted utilities have not been included in the economic

model. We have included these changes in the model and the model results are sensitive to them.

Table 45 Scenario analyses conducted on the ERG preferred base case

Parameter	Scenarios	Total costs			Total QALYs			ICER vs Fluticasone	ICER vs SFED
		Budesonide	Fluticasone	SFED	Budesonide	Fluticasone	SFED		
Base case		£ 18,595	£ 2,539	£ 1,528	12.99	12.64	12.48	£45,735	£33,630
Time horizon	10 years	£ 12,297	£ 2,058	£ 1,289	7.75	7.56	7.44	£54,779	£35,685
	40 years	£ 24,064	£ 2,865	£ 1,791	18.99	18.49	18.33	£42,466	£33,531
Remission	Original values in CS	£ 18,595	£ 2,292	£ 1,116	12.99	12.61	12.43	£42,729	£31,291
	Fixed effect NMA	£ 18,595	£ 2,640	£ 1,500	12.99	12.66	12.48	£48,060	£33,742
Maintenance therapy for budesonide	No maintenance	£ 5,930	£ 2,539	£ 1,528	12.84	12.64	12.48	£16,601	£12,205
	Maintenance with fluticasone	£ 6,874	£ 2,539	£ 1,528	12.99	12.64	12.48	£12,346	£10,533
Endoscopic dilation	Original values in CS	£ 21,987	£ 8,608	£ 5,624	12.99	12.64	12.48	£38,111	£32,243
	Costs for dilation not included	£18,038	£1,982	£971	12.99	12.64	12.48	£45,735	£33,630
	No dilation treatment whilst in remission	£18,187	£2,337	£1,415	12.99	12.64	12.48	£45,151	£33,048
Health care resources	Original values in CS	£ 18,648	£ 2,435	£ 1,310	12.99	12.64	12.48	£46,184	£34,164
	Health state costs for no treatment as for other treatments	£ 20,540	£ 8,885	£ 9,804	12.99	12.64	12.48	£33,199	£21,154
	Monitoring period 1 year	£ 19,032	£ 2,866	£ 2,013	12.99	12.64	12.48	£46,051	£33,536
Maintenance treatment dose	Same as induction dose	£31,863	£3,499	£1,528	12.99	12.64	12.48	£80,796	£59,774
	75% of induction dose	£25,229	£3,019	£1,528	12.99	12.64	12.48	£63,266	£46,702

Parameter	Scenarios	Total costs			Total QALYs			ICER vs Fluticasone	ICER vs SFED
		Budesonide	Fluticasone	SFED	Budesonide	Fluticasone	SFED		
Utility values	Original values in CS	£ 18,595	£ 2,539	£ 1,528	11.54	10.77	10.43	£20,788	£15,329
Relapse rate for maintenance treatment	Original values in CS	£ 18,006	£ 2,217	£ 1,535	12.84	12.53	12.44	£50,974	£40,952
	Relapse rate of 5.4% for BUD only	£18,927	£2,539	£1,528	13.09	12.64	12.48	£35,860	£28,363
	Relapse rate of 5.4% for all treatments	£18,927	£2,879	£1,497	13.09	12.77	12.55	£48,724	£31,916
	Relapse rate of 5.4% for patients who remain in remission longer than 1 year	£18,782	£2,752	£1,506	13.06	12.72	12.52	£46,909	£32,087
Age adjusted utility	Not included	£ 18,595	£ 2,539	£ 1,528	13.02	12.65	12.49	£43,556	£32,193

5 End of life criteria

The CS does not make a justification for budesonide ODT to be considered under end of life cost-effectiveness criteria as EoE is not considered to be a life-threatening treatment. The ERG concurs with this assertion.

6 Innovation

The CS states that budesonide ODT is considered innovative due to its unique mode of delivery - it is specifically designed to directly target the area of inflammation within the oesophageal mucosa. The CS points to the practical limitations of existing (off-label) treatments such as the fact that patients receiving other budesonide formulations must swallow the nebulised medicine or open the respules and use the contents to make a slurry with a carrier, such as sucralose. It is suggested that there might be difficulties adhering to dietary interventions to manage EoE.

Expert clinical advice to the ERG is that the mode of administration of existing treatments such as fluticasone do not negatively impact treatment adherence. Furthermore, experts commented that existing drug treatments also directly target inflammation in the same way as budesonide ODT. One expert commented that if budesonide ODT was recommended for use in the NHS he would prescribe it as first line treatment in place of existing off-label drug treatments.

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Evidence Review Group Report commissioned by the NIHR Systematic Reviews Programme on behalf of NICE

Addendum

Budesonide for treating eosinophilic oesophagitis

Produced by Southampton Health Technology Assessments Centre (SHTAC)

3rd January 2020

Table 1 ERG preferred assumptions applied incrementally to the company's base case analysis

Parameter	Value	Total costs			Total QALYs			ICER vs Fluticasone	ICER vs SFED
		Budesonide	Fluticasone	SFED	Budesonide	Fluticasone	SFED		
Company's base case		£24,020	£27,122	£27,657	16.12	15.30	15.14	Budesonide dominates	Budesonide dominates
+ Apply corrections	See Table 40 of ERG report	£24,248	£27,174	£27,657	16.12	15.30	15.14	Budesonide dominates	Budesonide dominates
+ Time horizon	20 years	£15,922	£18,351	£18,834	11.13	10.45	10.29	Budesonide dominates	Budesonide dominates
+ Remission	From ERG's random effects NMA	£15,963	£18,328	£18,712	11.12	10.47	10.32	Budesonide dominates	Budesonide dominates
+Maintenance therapy	Include maintenance therapy after all induction treatments	£26,411	£18,730	£18,712	11.12	10.47	10.32	£11,780	£9,555
+ Endoscopic dilation rate	2% per cycle	£23,211	£13,725	£14,585	11.12	10.47	10.32	£14,548	£10,706
+ Health care resources	No health state resources in active EoE if patients receive 'no treatment'. Initial health care costs applied for a short time period (6 months), including remission health states.	£17,642	£2,098	£1,540	11.12	10.47	10.32	£23,840	£19,986

Parameter	Value	Total costs			Total QALYs			ICER vs Fluticasone	ICER vs SFED
		Budesonide	Fluticasone	SFED	Budesonide	Fluticasone	SFED		
+ Utility	(0.93 for remission, 0.86 for relapse)	£17,642	£2,098	£1,540	12.81	12.51	12.43	£51,086	£42,826
	Include age adjusted utility	£17,642	£2,098	£1,540	12.76	12.49	12.43	£58,023	£47,907
+ Relapse rate	11% for remission with maintenance	£17,939	£2,181	£1,546	12.82	12.52	12.43	£52,796	£42,897
+ Relapse rate after 1 year	Same relapse rate as other cycles*	£18,595	£2,539	£1,528	12.99	12.64	12.48	£45,735	£33,630

*In the company's base case model, after 1 year all patients in remission relapse.

More details of ERG's preferred assumptions can be found in Table 42 of the ERG report.

Picot J., Cooper K., Kalita, N., Scott, D.A., and Shepherd, J. Budesonide for treating eosinophilic oesophagitis: A Single Technology Appraisal. Southampton Health Technology Assessments Centre (SHTAC), 2019.

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Evidence Review Group Report commissioned by the NIHR Systematic Reviews Programme on behalf of NICE

Budesonide for treating eosinophilic oesophagitis: Additional analyses conducted by the ERG for dilation treatment and remission rate for no treatment

Produced by Southampton Health Technology Assessments Centre (SHTAC)

Authors Dr Keith Cooper, Senior Research Fellow, SHTAC
Mrs Neelam Kalita, Research Fellow, SHTAC
Dr Jonathan Shepherd, Principal Research Fellow, SHTAC

Date completed 22nd January 2020

Additional analyses requested by the technical team 21st January 2020

Dilation treatment.

We have included a scenario where individuals have a lower risk of dilation treatment (either 0% or 1%) whilst in remission than when having active EoE disease when the risk of dilatation treatment is 2% per cycle. Results are shown in Table 1. The effect of this change has a minimal effect on model results.

Spontaneous remission

We have included a scenario where individuals do not have the possibility of spontaneous remission whilst on no treatment. Results are shown in Table 1. The effect of this change is a decrease in the ICER of about £6,000 per QALY to £39,701 per QALY for budesonide vs fluticasone and a decrease of about £4,000 per QALY to £29,139 per QALY for the ICER vs SFED.

Table 1 Scenarios conducted by the ERG using the ERG base case assumptions

Parameter	Scenarios	Total costs			Total QALYs			ICER vs Fluticasone	ICER vs SFED
		Budesonide	Fluticasone	SFED	Budesonide	Fluticasone	SFED		
Base case		£ 18,595	£ 2,539	£ 1,528	12.99	12.64	12.48	£45,735	£33,630
Dilation treatment	0% whilst in remission	£18,187	£2,337	£1,415	12.99	12.64	12.48	£45,151	£33,048
	1% whilst in remission	£18,391	£2,428	£1,471	12.99	12.64	12.48	£45,443	£33,339
Remission	No remission on no treatment	£ 18,595	£ 2,539	£ 1,528	12.97	12.56	12.38	£39,701	£29,189

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

ERG report – factual accuracy check

Budesonide for treating active eosinophilic oesophagitis [ID1202]

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies, you must inform NICE by **5pm on Friday 6 December 2019** using the below comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Relapse rate for remission with and without maintenance

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
"The economic evaluation does not include maintenance therapy following response to induction treatment. The ERG considers this inconsistent with current clinical practice. Consequently, the company has not included a relapse rate for patients in remission on maintenance therapy and assumed it to be the same as for those in remission but not on maintenance therapy." P15	"The economic evaluation does not include maintenance therapy following response to induction treatment. The ERG considers this inconsistent with current clinical practice."	As highlighted in the response to ERG Clarification Question B3: The CS did not include remission with maintenance, hence no value for the relapse rate for those on remission with maintenance was identified. The model was developed as a core global model (and adapted for the UK in the CS) with the option to include remission with and without maintenance. Whilst it is stated in the model (not in the CS) that the same relapse rate was used for remission with and without maintenance, the CS did not include the maintenance therapy option in the analysis, hence this does not apply to the CS. As highlighted in the response to ERG Clarification Question B4, the company expects a lower rate of relapse to be associated with remission with maintenance compared to remission without maintenance.	We have amended the text as suggested.
"Assumes same relapse rate for those in remission on maintenance or not on maintenance. Relapse rate of 22% for those in remission on maintenance." P16	"No relapse rate for those in remission on maintenance as maintenance not included in CS."		We have amended the text as suggested.
"The company assumed that the relapse rate with maintenance treatment per cycle is the same as the relapse rate without maintenance treatment. However, in their response to clarification question B3 the company notes that this is a mistake and the relapse rate would be lower for those on maintenance treatment." P68	"The company did not include remission with maintenance in the analysis. In response to clarification question B3, the company includes a scenario analysis with maintenance therapy where they assume the relapse rate would be lower for those on maintenance treatment".		We have amended the text as suggested.

“The model does not include relapse rates for patients in remission with maintenance therapy and the relapse rate is assumed to be the same for those in remission with maintenance therapy as those in remission without maintenance therapy.” P70	“The model does not include relapse rates for patients in remission with maintenance therapy.”		We have amended the text as suggested.
“Patients who are in remission and are treated with maintenance therapy are assumed in the model to have a dosage of 50% of that used for the initial treatment (although, as noted earlier, the maintenance treatment functionality in the model has not been used by the company).” P74	“In the scenario analysis (including maintenance therapy) provided in response to clarification question B4, patients who are in remission and are treated with maintenance therapy are assumed to have a dosage of 50% of that used for the initial treatment.”		We have amended the text as suggested.
“Relapse rates were the same for all treatments – 88% per year.” P80	“Relapse rates for remission without maintenance were the same for all treatments – 88% per year.”		We have amended the text as suggested.
“The ERG does not agree that the relapse rate would be the same for those in remission on maintenance treatment as those in remission with no maintenance.” P80	Delete		We have amended this text to: ‘The ERG agrees’
“Assumes same relapse rate for those in remission on maintenance treatment or not on maintenance treatment. Relapse rate of 22% for	“Assumes same relapse rate for all treatments for remission without maintenance therapy. Remission with maintenance not included in CS. Relapse		We have amended the text as suggested.

those in remission on maintenance.” P89	rate of 22% per cycle for those in remission without maintenance.”		

Issue 2 Exclusion of health states for maintenance therapy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
“The economic evaluation does not include maintenance therapy following response to induction treatment. The ERG considers this inconsistent with current clinical practice.” p15	“In line with the decision problem, the economic evaluation does not include maintenance therapy following response to induction treatment. Budesonide ODT is not indicated for use as maintenance therapy and NICE confirmed that it could not consider budesonide ODT for maintenance therapy as it was not licensed for this indication.”	Jorveza is not indicated for use as maintenance therapy. In a teleconference between Dr Falk Pharma and NICE on 1st May 2019, NICE stated that it could not consider reviewing maintenance as it was not a licensed indication. This is in line with the NICE remit (https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/technology-appraisal-processes-guide-apr-2018.pdf): “2.4.6 Unless the Department of Health and Social Care specifically indicates otherwise, NICE will not publish guidance on the use of a technology for indications that have not been given regulatory approval in the UK (that is, for unlicensed or ‘off-label’ use outside the terms of the technology’s marketing authorisation)”	Not a factual error. None of the treatments are indicated for use as maintenance therapy, yet their use as maintenance therapy is standard practice.

Issue 3 Time horizon in company base case

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
"40 years" p16	"40 years (as previously requested by the ERG)"	Time horizon of up to 40 years was requested by the ERG in the previous clarification letter– Clarification Question B8 (March 2019).	Not a factual error. The ERG suggested exploring time horizons up to 40 years.

Issue 4 Utility values

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
"Uses values for EoE patients. Incorrect values used in Kind et al. (0.93 for remission, 0.86 for relapse)." P16	"Uses values for EoE patients. (0.93 for remission (age-adjusted), 0.86 for relapse)."	The utility value used for remission in the CS is not age-adjusted, hence it's not incorrect. The CS uses the utility value for the full population (all ages).	We disagree, the utility values should be age adjusted to the mean age of the patients being treated. Hence this is not a factual inaccuracy.
"In addition, the population used in the model has an average starting age of 30 years. The UK population norm EQ-5D values for individuals of age 30 are 0.93 in Kind et al,[36] not 0.85 as used in the company model." P72	"In addition, the population used in the model has an average starting age of 30 years. The UK population norm EQ-5D values for individuals of age 30 are 0.93 in Kind et al,[36]. The utility value used in the company model (u=0.85) if for the full population (all ages)."		See above
"The utility value for patients in remission is taken from UK population norms, however the incorrect value has been used for this population. Age-adjusted utilities have not been included in the economic model." P72	"The utility value for patients in remission is taken from UK population norms, however the value used is for the full population (all ages). Age-adjusted utilities have not been included in the economic model."		See above

Issue 5 Publication of British Society of Gastroenterology guidelines

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
"UK-specific clinical practice guidelines are in development (the British Society of Gastroenterology states that the anticipated publication is 2019)" P18	"UK-specific clinical practice guidelines are in development by the British Society of Gastroenterology"	Personal communication between Dr Falk Pharma and the lead author indicates that publication is unlikely to be before 2021	Amended as requested

Issue 6 Adaptive clinical trial design

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
"The European Medicines Agency (EMA)[12] conducted a pilot project on 'adaptive pathways' to explore the practical implications of the adaptive pathways concept with medicines under development. The report on the pilot listed a number of learning points including that "adaptive pathways should focus on medicines that can plausibly address an unmet medical need in a defined population, where there is scope to explore feasible data collection plans (RCTs and registries) based on reliable, clear-cut and actionable endpoints" (page 3). The EMA Assessment Report for Jorveza[13] describes the initial discussions with the company regarding the	Delete	This section mixes the terms 'adaptive trial design' and 'adaptive pathway'. Dr Falk Pharma did not discuss (or apply for) any adaptive pathway with the EMA. The discussion of adaptive pathways is not relevant to the adaptive trial design used in the budesonide ODT trials	We have deleted references to the EMA adaptive pathway, as requested.

pre-requisites for the product's clinical trial programme, though these discussions appear to pre-date the adaptive pathways pilot mentioned above." P35			

Issue 7 Company's review of published economic evaluations

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
"The ERG notes that the company identified two economic evaluations in their previous submission to NICE in March 2019.[23] [24] In the current submission the CS does not provide any justification for excluding these two studies. We view that these studies would provide useful information for model validation and hence should have been included." P61	"The ERG notes that the company identified two economic evaluations in their previous submission to NICE in March 2019.[23] [24] In the current submission to NICE in September 2019, the CS states that no studies relevant to the decision problem were identified by the systematic literature review. In response to ERG Clarification Question B10, a summary of these two studies was provided. Neither of the studies was considered relevant to the decision problem."	This was addressed in the response to ERG Clarification Questions B10 which is not made clear in the ERG report.	We have amended the text as follows: The ERG notes that the company identified two economic evaluations in their previous submission to NICE in March 2019.[23] [24] In the current submission to NICE in September 2019, the CS states that no studies relevant to the decision problem were identified by the systematic literature review. In response to ERG Clarification Question B10, a summary of these two studies was provided. However, the company did not consider these studies to be relevant. On the contrary, the ERG view these studies would provide useful information for model validation and hence should have been included.

Issue 8 Health states for remission with maintenance therapy

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
"The economic evaluation does not include health states for remission with maintenance therapy (though the economic model does incorporate this function if required)." P65	"The economic evaluation does not include health states for remission with maintenance therapy. The economic model does incorporate this function if required (though the data for these health states are not mandated by the CS)."	The model was developed as a core global model (and adapted for the UK in the CS) with the option to include remission with and without maintenance. The CS did not include remission with maintenance, hence any values in the model for remission with maintenance have not been validated by the company. In order to conduct a scenario analysis for remission with maintenance, a number of assumptions had to be made. These would potentially be different if the company were providing a submission for both maintenance and without maintenance therapy.	Not a factual inaccuracy. No changes necessary.

Issue 9 Response rates

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
"The response rate for budesonide ODT, fluticasone and SFED was 94.9%, 69% and 18% respectively." P67	"The response rate per cycle for budesonide ODT, fluticasone and SFED was 94.9%, 68% and 18% respectively."	The response rate per cycle for fluticasone was 68% (not 69%).	Amended as requested

Issue 10 Correction of study numbers

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
"The relapse rates used in the model for those not on maintenance therapy are assumed to be same as observed in the placebo arm of the company's phase II BUL-2/EEA study, i.e. 88% relapse in one year." P68	The relapse rates used in the model for those not on maintenance therapy are assumed to be same as observed in the placebo arm of the company's BUL-2/EER study, i.e. 88% relapse in one year.	Correction of BUL-2/EER study number. Errors in the ERG report are due to an error in the CS, in which the phase III BUL-2/EER maintenance study was incorrectly referred to as BUL-2/EEA. The relapse rate of 88% per year was based on the placebo arm of BUL-2/EER, not the phase II BUU-2/EEA study.	Amended as requested
"The relapse rate for remission with maintenance for budesonide ODT in the phase II BUL-2/EEA study was 5.4% per cycle (clarification question response B4)." P68	"The relapse rate for remission with maintenance for budesonide ODT in the BUL-2/EER study was 5.4% per cycle (clarification question response B4).		
"The relapse rate of 88% per year was based on the placebo arm of BUL-2/EEA study data." P80	"The relapse rate of 88% per year was based on the placebo arm of BUL-2/EER study data."		

Issue 11 Gastroenterologist visits

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
"The ERG notes that the model uses gastroenterologist (first visit) for both initial and subsequent consultations, instead of using gastroenterologist (following visits) for subsequent consultations." P75	"The CS assumes that patients have already had a first visit with a gastroenterologist for diagnosis. Hence all gastroenterologist visits included in the model are following visits."	This is incorrect. See cells R28:T37 in worksheet 'Medical Cost_MRU'.	We have amended the text as suggested.

Issue 12 Errors identified by the ERG in the company's model

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
"Corrected the formula in cell G25 to 1-sum(H25:U23)." P88	"Corrected the formula in Jorveza worksheet - cell G25 to 1-SUM(H25:U25). Similar correction made for fluticasone, SFED and no treatment."	Should be cell U25 (not cell U23). And assume the correction also made for fluticasone, SFED and no treatment. Note that this applies for active EoE transition to Active EoE for first, second and third treatments (e.g. cells G25, L30 and Q35 for Jorveza). This was picked up by the company when conducting the scenario analysis for maintenance. A similar error was identified for transition from 'Active EoE (first treatment') to 'EoE in remission with maintenance (first treatment) first cycle' for all treatments except Jorveza. For example, for cell H45 in worksheet 'Transition Matrix' for No Treatment), the formula should be =INDEX(Parameters!$H$13206:$H$13215,F44,1)*M226.	We have amended text as suggested.

Clinical expert: Hannah Hunter

Specialist Allergy Dietitian (Adults) at Guy's and St Thomas' NHS Foundation Trust

Teleconference date: 3rd February 2020

Technical team members present: Juliet Kenny, Rufaro Kausi, Janet Robertson

Summary of the comments made by the clinical expert

- Typically, patients present first in primary care with difficulty swallowing. They are then referred to see a gastroenterologist in secondary care where they receive gastroscopy. Diagnosis is based on visible signs of disease and histology of 15 or more eosinophils (eos)/high-powered field (hpf). The gold standard is to conduct 6 biopsies to inform the diagnosis.
- EoE is a progressive disease rather than a relapsing remitting disease – it is very rare that a patient will get better without treatment and untreated disease gets worse over time.
- The term 'active EoE' is probably synonymous with 'untreated EoE'. Likewise, 'inactive EoE' probably means 'EoE that is being controlled with treatment'
- The aim of treatment is clinico-histological remission. People can achieve histological remission without achieving clinical remission. Maintaining clinico-histological remission would be expected to reduce the risk of long-term poor outcomes (oesophageal remodelling, strictures, fibrosis). Histological remission alone may be enough to reduce the risk of these long-term poor outcomes even if patients are still experiencing some symptoms.
- The aims of drug and diet treatments are the same; if the trigger foods can be identified and eliminated permanently then it should be possible to achieve and sustain clinico-histological remission on diet alone.
- Dietary interventions can be hard to maintain, there are practical and financial implications, specialist support it not always available and adherence is often low.
- Currently, the available treatment options for EoE are proton pump inhibitors (PPIs), swallowed off-label cortico-steroids, budesonide slurries and dietary interventions. Historically patents had to have had PPIs prior to receiving an EoE diagnosis – the guidelines have now changed. Often patients will receive PPIs as first line treatment for EoE, then try a diet or steroids. Treatment choice is mainly determined by patient preference rather than disease stage. More established disease is harder to treat.
- Treatment benefit in terms of clinic-histological remission could probably be measured within 6 to12 weeks but it would probably take 5 to 10 years to understand whether a has treatment reduced the rate of fibrosis/scarring due to the time it takes for these outcomes to occur
- Patients who opt for drug treatment are ideally re-scoped at 6 to 12 weeks to check if the drug is working. After this, they will have yearly follow-up appointments unless symptoms reoccur or may be discharged back to primary care.

- Patients who have dietary interventions require more intense initial monitoring with a minimum of 4 (but usually more) endoscopies to check the impact of eliminating different foods or food combinations on histology. If patients achieve remission on diet, long-term monitoring would be like that of patients on drug treatments i.e. yearly visits unless symptoms reoccur.
- Although a threshold of 20 or more eos/hpf was used in the studies (rather the 15 or more eos/hpf threshold that is used in practice) this is probably not important because most patients present with counts over 30 eos/hpf and counts over 100 eos/hpf are common so the difference between 15 and 20 is relatively small given the overall range. Also, it is probably not problematic that patients in the company's trials had 6 biopsies, whereas the number of biopsies in the other studies could have been lower. This is because only one positive biopsy is needed to establish a diagnosis – the reason why multiple biopsies are taken is because inflammation can be patchy. Overall, the study populations seem relatively similar and the patients are probably representative of patients in the NHS.
- Around half of people with EoE require experience food bolus obstruction requiring emergency extraction, more commonly when disease has been present long enough to develop strictures (i.e. 5 to 10 years). For those affected, these severe episodes are not very frequent, and may occur around 2 times a year. Self-limiting food impaction requiring regurgitation or that may pass spontaneously is more common and can range from affecting people on a daily basis to a few times per year.

Clinical expert: Jack Winter

Consultant Gastroenterologist at Glasgow Royal Infirmary

Teleconference date: 3rd February 2020

Technical team members present: Juliet Kenny, Janet Robertson

Summary of the comments made by the clinical expert

- There have been 10 to 15 new diagnosis per year of EoE in the expert's practice since 2017 and he currently provide care for about 60 patients with EoE in total. The average age of patients in his practice with EoE is 33.
- Historically patients often presented first in A&E with a food bolus obstruction requiring emergency treatment. Now more often patients will present to their GP with difficulty swallowing (dysphagia) – since this is a symptom that can be caused by oesophageal cancer, they are usually then referred for endoscopy. The endoscopists that the expert works with now routinely look for evidence of EoE/perform biopsies. The diagnosis of EoE is based history of impaction/dysphagia combined with a histology of 15 or more eosinophils (eos)/high-powered field (hpf).
- Most patients will have received proton pump inhibitors in primary care before being diagnosed with EoE.
- The main treatment options for adults currently are off-label fluticasone delivered by inhaler but swallowed, budesonide slurries or budesonide ODT. Dietary interventions are offered as first line treatment more commonly in pediatric settings. Dietary interventions may be offered second line to adults if topical steroids fail but there is uncertainty about how to implement elimination diets and monitoring response is very resource intensive due to the need for repeat endoscopies. In practice there is also a lack of dietetic expertise to support patients with dietary interventions.
- There are also several practical barriers that mean that adherence to off-label drug treatments is low. Whether delivered by inhaler or mixed into a slurry these drugs are not being administered as originally intended – this means that underdosing is problem and relatively high doses must be used. In the expert's experience the optimum dose for fluticasone delivered by inhaler is 4 puffs of a 250µg inhaler twice per day. Furthermore, there is often confusion at primary care level when patients using inhalers try to renew their prescriptions and they often end up getting reassessed in asthma clinics and issued with other types inhalers in error, often dry powder devices which make oesophageal delivery more difficult – and occasionally bronchodilators inappropriately. Patients who use slurries often make up the mixture using apple sauce – this requires an additional out of pocket expense and inconvenience on behalf of the patient. The main advantage of budesonide ODT compared with other existing treatment options is the improved mode of administration and the more accurate dosing and delivery this facilitates.

- The expert has been prescribing budesonide ODT since it received its marketing authorisation in 2018 in line with the current indication (1 mg ODT taken twice daily, for 6 weeks, which may be extended to 12 weeks for patients who do not respond appropriately). It is appropriate to use it episodically (that is, to offer it again if symptoms reoccur) and there is no limit to how many times it can be prescribed. The expert is aware of the ongoing trial of maintenance budesonide ODT but is unable to comment on the effectiveness of maintenance treatment as the results have not been published in a peer reviewed journal yet. In his practice he has obtained permission from the hospital to prescribe budesonide ODT on an ongoing basis to one patient who has advanced disease because they were very concerned about further progression and fibrosis and their symptoms relapsed quickly when the budesonide ODT was discontinued. Unlike budesonide ODT, other off-label drugs are not used episodically but on a continuous basis.
- Patients who opt for drug treatment are typically re-scoped at 12 weeks and biopsy is performed. The expert will see them 2 to 3 weeks after this for a clinical review – no specific symptom scoring systems are used to determine whether the treatment has worked, it is usually based on the patient's reported outcomes regarding improvement in symptoms and the histology of the oesophageal biopsies demonstrating significant improvement or resolution of the eosinophilia. If treatment is successful, patients are then offered a routine return appointment 6 to 9 months later and the option to call back sooner if symptoms reoccur.
- Evidence on long-term outcomes is limited. It would probably take 5 to 9 years for fibrotic disease to occur. A study conducted in the USA has suggested that for every year that EoE goes undiagnosed, the risk of strictures increases by 9%. Some patients have strictures/fibrosis at presentation. It is reasonable to assume that maintaining clinic-histological remission will result in a reduced risk of strictures and fibrosis.
- Food bolus obstruction requires emergency care and hospital admission (overnight). Typically, patients present to A&E with food stuck in the oesophagus that cannot be regurgitated or swallowed and hyper salivation. They are often given a fizzy drink to see if this helps to dislodge the bolus and are monitored for several hours, often overnight. If there is no improvement the food bolus is then removed under general anesthetic to protect the airway. Sometimes, endoscopic dilatation will be performed at the same time.
- Endoscopic dilatation is performed when narrowing of the oesophagus prevents the passage of the endoscope – the procedure involves inserting a balloon into the narrowed part and inflating it. It's usually an elective and safe procedure but there is a small risk of perforation – this is a serious adverse event which involves patient being admitted to hospital and being unable to ingest any food or drink for several days while the perforation heals. It also entails a small mortality risk.
- EoE is a disease that requires management in secondary care because GPs do not see enough patients with it to have the relevant experience to diagnose

and treat it effectively. The expert believes, certainly at the present time, that budesonide ODT should be initiated by a hospital specialist after a confirmed diagnosis of EoE is made based on symptoms AND histology.

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Draft technical report

Budesonide orodispersible tablet for treating eosinophilic oesophagitis

This document is the draft technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

The technical report includes:

- topic background based on the company's submission
- a commentary on the evidence received and written statements
- technical judgements on the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

Issue date: February 2020

1. Topic background

1.1 Disease background

- Eosinophilic oesophagitis (EoE) is a chronic disorder in which a type of white blood cell (eosinophils) infiltrate the tissue that lines the surface of the oesophagus (oesophageal epithelium)
- It is caused by exposure to allergens, typically food allergens, most commonly those found in milk, egg, wheat, soy, peanuts, beans, rye and beef.
- EoE is characterised by the following clinical and histological factors:
  - Clinical: symptoms of oesophageal dysfunction such as difficulty in swallowing solid food (dysphagia), obstruction of the oesophagus by swallowed food (food-bolus impaction) and swallowing/non-swallowing-associated chest pain
  - Histological: eosinophil-predominant inflammation.
- EoE is a rare disease:
  - prevalence: 5,956 adult patients in England and Wales
  - incidence: 963 cases per year
    (estimates based on a study conducted in the Netherlands in 2017 [no UK-specific data] and applied to 2018 population estimates for England and Wales)
- EoE has been reported throughout the life span, but most cases occur in children, adolescents and adults younger than 50 years.
- Complications:
  - Uncertainties remain about progression and long-term consequences – EoE is a progressive condition if untreated and is usually associated with persistent symptoms and inflammation, eventually leading to oesophageal remodelling, resulting in fibrosis with possible stricture formation and functional abnormalities.
  - There is no evidence that EoE is a pre-malignant condition; mortality due to EoE has not been reported

- Symptoms of EoE can be unpleasant, socially embarrassing and restricting, meaning that people with EoE experience reduced quality of life
- There are no-UK specific clinical guidelines. The only international guidelines for the diagnosis and management of EoE were published in 2017 by Lucendo et al. According to these guidelines EoE should be diagnosed as follows:
  - ◊ at least six biopsies are required from the proximal, mid and distal sections of the oesophagus, focusing on areas with endoscopic mucosal abnormalities, for accurate diagnosis
  - ◊ the accepted threshold of eosinophil density for the diagnosis of EoE is ≥15 eosinophils (eos) per high-power field (hpf; standard size of ~0.3 mm^2, equivalent to 50 eos/mm^2) in the oesophageal mucosa
- The CS notes that EoE is often misdiagnosed as gastro-oesophageal reflux disease (GORD) and consequently patients are prescribed proton-pump inhibitors (PPI) – non-response to PPIs can be used for differential diagnosis, although GORD and EoE can co-exist.
- There is variation in clinical practice regarding treatment for EoE:
  - international guidelines recommend treatment with dietary elimination, off-label PPIs or off-label topical corticosteroids
  - the company argues that:
    - ◊ NHS practice is not uniform and there is no standard guideline on the optimal sequence of therapy
    - ◊ in NHS practice, patients are already treated unsuccessfully with PPIs prior to receiving a diagnosis of EoE
- The CS states that budesonide ODT is expected to become the preferred 1st-line treatment following a confirmed diagnosis of EoE, replacing off-label corticosteroids and a dietary intervention called the six-food elimination diet (SFED)
- There are two main treatments for managing complications of EoE:

- emergency intervention for food bolus impaction (which requires hospital admission and general anaesthetic)
- endoscopic dilation for oesophageal strictures and fibrotic complications (usually an elective procedure, where a balloon is inserted into the narrowed part of the oesophagus and inflated).

1.2 The technology

UK approved name and brand name	Budesonide (Jorveza) 1 mg orodispersible tablet (ODT)
Mechanism of action	Budesonide is a non-halogenated glucocorticoid, that inhibits antigen-stimulated secretion of pro-inflammatory molecules in the oesophageal epithelium Budesonide orodispersible tablet (ODT) is an immediate-release tablet - when placed on the tongue, it begins to effervesce, stimulating the production of saliva. As the saliva is swallowed, the mucins it contains help coat the oesophagus, delivering high concentrations of budesonide to the site of inflammation
Marketing authorisation	Granted 8 January 2018
Indications, method of administration and dosage described in the summary of product characteristics (SmPC)	Treatment of EoE in adults 1 mg twice daily, taken orally for 6 weeks, which may be extended to 12 weeks for patients who do not respond appropriately (Budesonide ODT 1 mg twice daily is **currently not licensed for maintenance use**)
Additional tests or investigations	None
List price and average cost of a course of treatment	List price: £323 (pack of 90 tablets) Cost for 6 weeks treatment: £323 (including wastage) Cost for 12 weeks treatment: £646 (including wastage)
Patient access scheme (if applicable)	N/A

Source: CS table B.1.2 and appendix C

1.3 Decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission (as stated in the CS)
Population	Adults with active eosinophilic oesophagitis (EoE)	Adults (>18 years) with EoE who have received prior treatment with a PPI
Intervention	Budesonide orodispersible tablet (ODT)	Budesonide 1 mg ODT tablets
Comparator(s)	Established clinical management without budesonide, which may include proton pump inhibitors (PPIs), other corticosteroid formulations and dietary intervention	Fluticasone (off-label) SSFED
Outcomes	Disease activity (remission, response, relapse) Symptoms of oesophagitis Complications such as stricture formation Mortality Adverse effects of treatment Health-related quality of life (HRQoL)	Disease activity (remission, response) Symptoms of oesophagitis Complications such as stricture formation Adverse effects of treatment HRQoL

Source: CS table B.1.1.

1.4 Clinical evidence: Budesonide versus placebo

Key trials

Trial name	BLU-1/EEA	BUU-2/EEA
Study Design	Multicentre, randomised study incorporating 6-week double blind phase; N=88 The study also included 6-week open-label extension phase for patients without remission at the end of the double-blind phase (N=51 [n=23 budesonide ODT, n=28 placebo]) Participants in clinico-histological remission at end of double-blind phase or open-label extension were eligible to enter the optional 48-week, double-blind, randomised, placebo-controlled, maintenance of clinico-histological remission study (BUL-2/EER)	Randomised double-blind, placebo-controlled study BUU-2/EEA; N=76
Interventions	2 arms during 6-week double blind phase (both treatments given for 6 weeks): • Budesonide orodispersible tablet [1 mg twice daily for 6 weeks] n=59 • Matching placebo n=29	4 arms (all treatments were given for 2 weeks): • Budesonide orodispersible tablet [1 mg twice daily] n=19 • Budesonide orodispersible tablet [2 mg twice daily] (n=19) • Budesonide viscous suspension 5 mL [0.4 mg/mL twice daily] (n=19) • Placebo twice daily (n=19)
Primary outcome	Clinico-histological remission at week 6	Histological remission at week 2
Secondary outcomes	• Histological remission at week 6 • Change in peak eos/mm^2 hpf from baseline to week 6 • Clinical remission* on each day in the week prior to week 6 • Three other patient reported outcome measures	Secondary objectives included: • Identification of the optimum dose for induction of remission in EoE • Safety and tolerability (AEs, laboratory parameters and patient's QoL)

Source: CS section: B.2.3.1 and B.2.3.2

Trial Results

The results indicate that budesonide ODT improves histological remission compared with placebo.

BLU-1/EEA trial results at week 6

Outcome	Budesonide ODT 1 mg twice daily	Placebo	Odds ratio (95% CI)	P value
Clinico-histological remission*	34/59 (57.6%)	0/29 (0%)	NR	NR
Histological remission**	55/59 (93.2%)	0/29 (0%)	727.67 (37.87 to 13982.64)	< 0.0001

*Clinico-histological remission defined as follows: histological remission - peak eosinophil count <16 eos/mm^2 hpf (corresponding to <5 eos/hpf), clinical remission - symptom severity of ≤2 points on each 0-10 numerical rating scale, for dysphagia and odynophagia, respectively on each day in the week before end of treatment

**Histological remission defined as per primary outcome definition

Abbreviations: CI, confidence interval; ODT, orodispersible tablet

Source: CS, tables B.2.10 and B.2.11, figure B.2.4

BUU-2/EEA trial results: histological remission at week 2

Outcome	**Budesonide ODT 1 mg twice daily (N=19)**	**Placebo (N=19)**	**Odds ratio (95% CI)**	**P value**
Histological remission*	19 (100%)	0 (0%)	NR	p<0.0001

*Histological remission defined as mean of <16 eos/mm^2 hpf)

Abbreviations: CI, confidence interval; ODT, orodispersible tablet

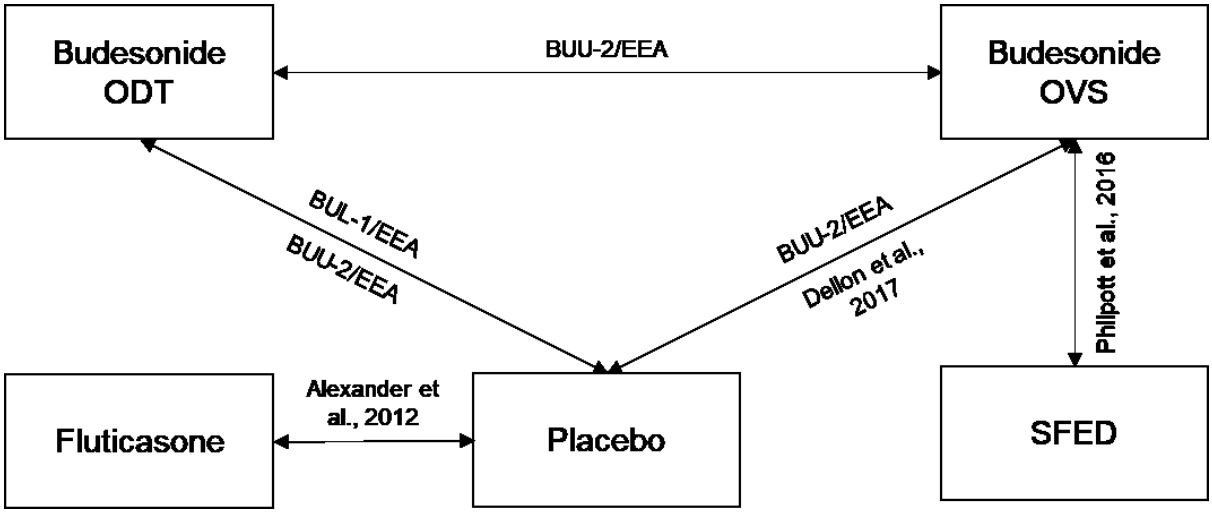
Source: CS, tables B.2.10 and B.2.11, figure B.2.4

1.5 Indirect treatment comparisons

- The company conducted a systematic literature review to identify evidence relevant to the decision problem (as defined in the CS). No head-to-head trials comparing budesonide ODT to off-label fluticasone or SFED were identified so the company conducted a network meta-

analyses (NMA) to estimate the relative effectiveness of these interventions.

Studies included in the company's network meta-analysis



Source: CS, figure B.2.5

Abbreviations: ODT = oro-dispersible tablet; OVS = oral viscous suspension; SFED = six-food elimination diet

- The company chose histological remission, defined as <16 eos/mm^2 hpf (eosinophils per millimetre squared high power field), as the outcome measure of interest for the NMA. It reported both fixed and random effects results – the results from its random effects NMA were used in the company's economic model to inform its base case.
- At clarification the ERG asked the company to re-run its NMA with a continuity correction to try to reduce the uncertainty in the results that was due to zero remission rates in some of the placebo arms. The company performed the requested analysis, but the ERG identified some further limitations with the updated results. The ERG therefore reran the analysis using a frequentist approach which automatically adds a continuity correction. The ERG used the results of its frequentist analysis (random effects model) to inform the ERG base case.

Company NMA results for histological remission

Budesonide ODT 1 mg BID versus:	Random effects NMA		Fixed-effect NMA	
	OR	95% CrI	OR	95% CrI
Budesonide OVS	NR	NR	14.71	1.212, 428.800
Fluticasone	8.657	0.009, 7,508.000	9.62	0.116, 494.800
SFED	81.840	0.109, 63,620.000	52.86	3.683, 1,760.000

Abbreviations: CrI, credible interval, OR, odds ratio

Source: ERG report, table 16

ERG frequentist NMA results for histological remission (includes continuity correction)

Budesonide ODT 1 mg BID versus:	Random effects NMA		Fixed-effect NMA	
	OR	95% CI	OR	95% CI
Placebo	475.19	39.58, 5705.32	437.02	47.42, 4207.86
Fluticasone	6.96	0.11, 441.71	6.40	0.16, 253.31
SFED	23.24	0.85, 635.07	24.72	1.83, 333.94

Abbreviations: CI, confidence interval, OR, odds ratio

Source: ERG report, table 17

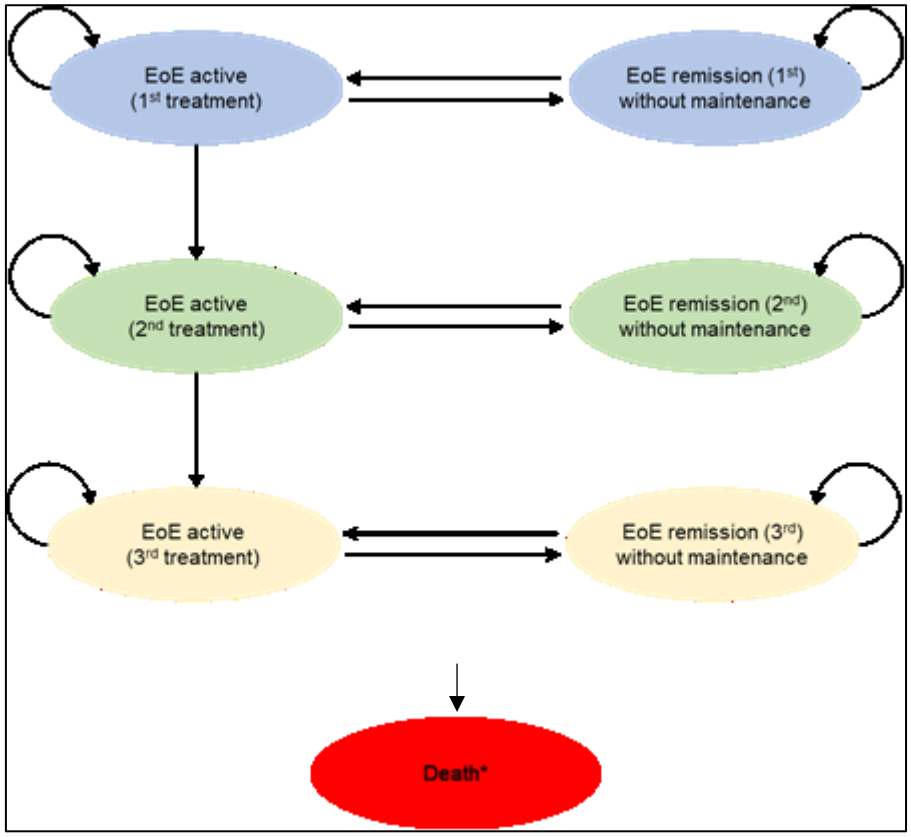
1.6 Model structure

- The company modelled the cost effectiveness of budesonide ODT using a Markov model with 7 health states and a 40-year time horizon.
- The health states are primarily defined by disease status: patients either have active disease or are in histological remission. Patients enter the model in active disease and in this health state receive treatment (for 6-12 weeks) with either budesonide ODT or a comparator. The probability of transitioning from the first active disease state to the first remission health state following induction therapy is informed by the company's NMA results.
- No further treatments are received at any stage in the model; the probability of transitioning from the subsequent (2nd or 3rd) active

disease states to the subsequent (2nd or 3rd) remission states was calculated in the NMA using the placebo arms of the trials .The probability of transitioning from a remission health state back into an active disease state (the relapse rate) is assumed to be the same across all treatments – an 88% relapse rate after 1 year/22% per 12-week cycle was applied based on data from the placebo arm of BUL-2/EEA

- Death is an absorbing state that patients can transition to from any of the above health states. The CS argues that EoE has no impact on mortality; therefore, this health state reflects general population mortality. The company model is illustrated below.

Cost-utility model - Markov model structure



Source: CS, figure B.3.1

1.7 Other key model assumptions

Population	Adults with EoE pre-treated with proton pump inhibitors. Average starting age of the cohort 30 years, 53.8% of individuals are male
Intervention	Budesonide ODT for 6 or 12 weeks
Perspective, time horizon and discounting	NHS and PSS, 40 years, 3.5% per annum for costs & health effects
Treatment effectiveness and extrapolation	Remission rates for the treatments were defined as the histological remission rate. The odds ratios (ORs) for achieving histological remission for the different treatments were calculated through the NMA. The absolute remission rate, referred to in the CS as the response rate, for each treatment was calculated based on the response rate for budesonide ODT and each comparator's corresponding ORs. The relapse rates used in the model for those not on maintenance therapy are assumed to be same as observed in the placebo arm of the company's BUL-2/EER maintenance study, i.e. 88% relapse in one year. The relapse rate per cycle is calculated from the study by assuming that events occur at a constant rate over time, i.e. 22% per 12-week cycle.
Adverse events	• Budesonide ODT: Oral candidiasis, oesophageal candidiasis, headache, gastrointestinal disorders, pharyngitis, irritation in nose and/or throat • Fluticasone: Oral candidiasis, oesophageal candidiasis, headache, irritation in nose and/or throat • SFED: None • No treatment: none
Health related quality of life	For patients with Active EoE, the utility of GORD (gastro-oesophageal reflux disease) patients with average symptoms was selected (u=0.70). For patients in remission, the utility value was taken from UK general population norms (u=0.85). The CS states that age-adjusted utilities were not used in the model
Resources and costs	• Drug acquisition • Follow-up monitoring and care • Add-on dilation treatments • Adverse event costs

Source: ERG report section 4.3

1.8 **Overview of how quality-adjusted life years accrue in the model**

- The model estimates QALYs by multiplying utility values for the health states by the proportion of the cohort in those states and adding this over time.

2. Summary of the draft technical report

2.1 In summary, the technical team considered the following:

Issue 1 **Are the right comparators included? There is uncertainty in the estimates of treatment effectiveness.** The company's choice of comparators does not reflect all the potential comparators of interest in clinical practice and budesonide ODT's status as the only licensed treatment for EoE.

Issue 2 **Maintenance therapy for patients in remission should not be included in the economic evaluation for budesonide ODT.** NICE can only appraise technologies within their marketing authorisation. The licensed duration of budesonide ODT is treatment for is 6 weeks, which may be extended to 12 weeks for patients who do not respond appropriately. Clinical experts consulted by the technical team have stated that the unlicensed comparator treatments may be used without a specific time limit. The exclusion of a remission with maintenance health state in the model and the exclusion of the maintenance therapy costs reduce the total costs and if maintenance therapy is given in clinical practice, these costs should be considered when evaluating the cost-effectiveness.

Issue 3 **Model structure and time horizon**. The structure and time horizon of the model is inappropriate given that budesonide ODT is only licenced for short term use and the available evidence is limited to short term histological remission outcomes. It would be more appropriate to calculate cost effectiveness based on a

single episode of budesonide ODT treatment and the effect this has on histological remission. It is unclear how long the time horizon would have to be to capture all the benefits and costs associated with a single episode of treatment, but a time horizon of one year may be adequate for comparisons with no treatment or for short term use of 'off-label' formulations.

Issue 4 **The costs for follow up and monitoring have been overestimated.** The costs included in the company's model for follow-up and monitoring do not reflect clinical practice. The ERG's assumptions are difficult to validate but would probably be sufficiently accurate in the context of the shorter time horizon preferred by the technical team.

Issue 5 **The company have assumed that the probability of add-on dilation treatments varies by treatment and health state**. While it is clinically plausible that more effective treatments will reduce the need for these treatments in the long term, evidence to support this assumption is limited. The ERG has chosen to use the same probability across all the model arms, but this is problematic given the time horizon of the ERG model. However, if the time horizon is restricted to a single episode of budesonide ODT treatment then it would not be necessary to incorporate costs for add-on treatments.

Issue 6 **The company's utility values are not robust.** Patients who are in histological remission may still experience symptoms and this should be reflected in the utility value that is applied to the remission health states (currently this is not the case). The company's utility value for active disease is based on patients with gastro-oesophageal reflux disease with heartburn, rather than EoE – the ERG provided a more suitable estimate that is based on patients with EoE that could be used instead. Also, the company's utility values have not been adjusted to reflect the age of the model cohort.

2.2 The technical team recognised that the following uncertainties would remain in the analyses and could not be resolved:

- Both the company's and the ERG's NMA results are very uncertain due to limitations in the underlying data.

2.3 There are no relevant commercial arrangements.

2.4 The intervention does not meet the end-of-life criteria.

2.5 The technology is unlikely to be considered innovative (see table 3).

2.6 No equality issues were identified (see table 3)

3. Key issues for consideration

Issue 1 – Are the right comparators included? There is uncertainty in the estimates of treatment effectiveness.

Background/description of issue	**Comparator choice** The NICE scope stated the comparators as: 'Established clinical management without budesonide, which may include PPIs, other corticosteroid formulations and dietary intervention'. The company has argued that: • budesonide ODT is likely to become the first-line treatment option for EoE • off-label fluticasone and the six-food elimination diet (SFED) are the only first-line treatments currently used the NHS for EoE. The ERG agreed with the company's choice of comparators. One clinical expert of the two consulted by the technical team corroborated the company's view that in practice nearly all patients receive PPIs before receiving an EoE diagnosis. Both clinical experts noted that practice regarding other off-label drug and dietary interventions is very variable. Other corticosteroid formulations currently used include off-label fluticasone delivered by inhaler but swallowed and budesonide in suspension (respules which would ordinarily be used as a nebulizer - swallowed and mixed with food). Both clinical experts stated that these treatments are given on an on-going basis (no treatment time limit). They further stated that dietary interventions are not consistently implemented and are not limited to the SFED. Budesonide ODT is the first licensed drug therapy for EoE. The current General Medical Council Ethical Guidance indicates that unlicensed therapies should only be used in specific circumstances. This means that while budesonide ODT has the potential to displace other off-label corticosteroids in the treatment pathway, these are not like-for-like comparators. These considerations do not apply to dietary interventions because diets are not subject to the same regulatory process and GMC guidance. However, dietary interventions are arguably not a like-for-like comparison either because they may not be tolerable for all patients. **Uncertainty in the estimates of treatment effectiveness** • There are no UK patients in either of the pivotal RCTs included in the NMA (BLU-1/EEA and BUU-2/EEA) and it is unclear whether the patients recruited from other countries are representative of those treated for

	EoE in the NHS. It is also unclear whether the outcome definitions used in the key trials are generalisable to the NHS. • Uncertainties in the results of the network meta-analyses due to the small number of included studies and differences in the study populations and designs • The response rates (rate at which a person transitions between the EoE active health state to the remission health state) for budesonide ODT and the alternative treatments in the company's economic model were derived from an NMA: Budesonide ODT – 94.9%; Fluticasone – 68%; SFED – 18%; No treatment – 4%. • There are no head-to-head trials of the comparators of interest so all the estimates of effect for the comparisons of interest are based on indirect data alone. • SFED has not been studied in a randomised controlled trial. The only study identified by the company was a prospective observational study comparing SFED to budesonide OVS. • The following variables are known to differ across the studies included in the company's NMA: o mean symptom duration ranged from 1 to 8 years o mean time since diagnosis ranged from 0 to 4 years o the proportion of patients pre-treated with PPIs ranged from 30% to 100% Furthermore, smoking status, associated atopic disease, severity of inflammation and presence of established fibro stenotic disease have all been identified by the ERG's clinical experts as effect modifying variables but it is unknown whether these baseline characteristics differed across the study populations. The impact of the differences in the study populations on the results of the NMA are unknown. Consequently, caution should be exercised in the interpretation of the results. The ERG believes the random effects model is the appropriate choice given the clinical heterogeneity between the studies in the NMA. The ERG states that NMA has been implemented correctly, however there is potential differences in effect modifying variables in the studies included in the NMA.
Why this issue is important	In the absence of head-to-head comparative data, the NMA was the next best alternative in terms of evidence. However, any limitations of the NMA will feed into the cost-effectiveness analysis. The results of the NMA directly inform the response rates (rate at which a person transitions between the EoE active health state to the remission health state). These transitions are a major driver of the cost effectiveness estimates. As the NMA results are uncertain, the cost effectiveness estimates are also uncertain.

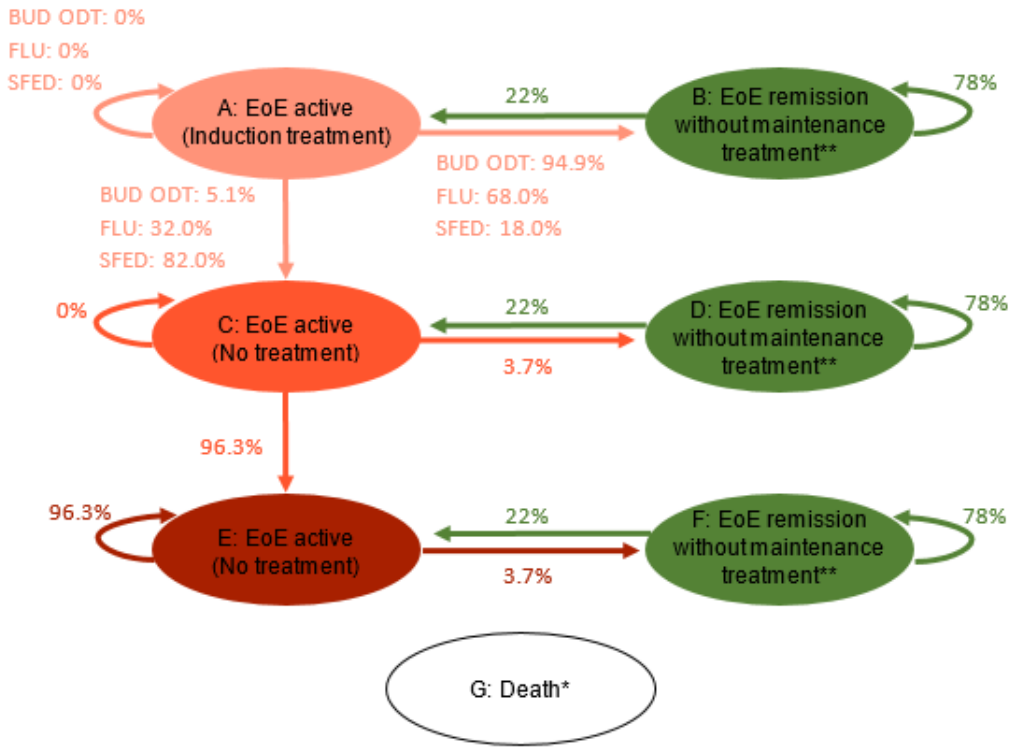
Questions for engagement	a) Are symptom duration and time since diagnosis important prognostic factors? b) Are the key trials for budesonide ODT (BLU-1/EEA and BUU-2/EEA) generalisable to NHS practice, particularly are the patients included representative of those treated with EoE in the NHS? c) Can the following additional comparisons be justified for the reasons outlined in the background section of this table: i. Budesonide ODT versus swallowed off-label budesonide in suspension ii. Budesonide versus no treatment
Technical team preliminary judgement and rationale	The technical team agree with the company and ERGs that it is reasonable to exclude PPIs as a comparator. A comparison of the cost effectiveness of budesonide ODT with swallowed off-label budesonide in suspension is justified, despite the wording of the NICE scope, because this intervention is still in use in NHS practice. It should be feasible to perform this comparison because the company's NMA already includes two studies where patients in one arm received budesonide oral viscous solution (OVS). In one of these studies, budesonide ODT was compared directly with budesonide OVS. A comparison of the cost effectiveness of budesonide ODT with no treatment can be justified on the grounds that budesonide ODT is the first licensed treatment for EoE. A comparison against no treatment is also likely to provide a more certain result given the limitations with the current NMA

Issue 2 –Maintenance therapy for patients in remission should not be included in the economic evaluation

Background/description of issue	**Maintenance therapy for patients in remission** The company excluded maintenance therapy for patients in remission in their model. The company assumes that patients who respond to induction treatment do not then receive maintenance treatment. The ERG heard from its clinical experts that this does not reflect clinical practice and assumed that patients would receive maintenance treatment. The intervention under appraisal is budesonide orodispersible tablet (ODT) (dose 1 mg, taken orally twice daily). The licensed duration of treatment is 6 weeks, which may be extended to 12 weeks for patients who do not respond appropriately. Maintenance treatment with budesonide ODT is being studied in an ongoing clinical trial but is not currently licenced. In the ERG base case, patients who are in remission and are treated with maintenance budesonide OTD or fluticasone are assumed to have a dosage of 50% of that used for induction treatment. **Transition from remission to active heath state: relapse rates** In the company model patients in remission may relapse and return to active EoE. The CS comments that there are limited data on the relapse rate of EoE in remission. The relapse rates used in the model for those not on maintenance therapy are assumed to be same as observed in the placebo arm of the company's phase II BUL-2/EEA study, i.e. 88% relapse in one year. The relapse rate per cycle is calculated from the study by assuming that events occur at a constant rate over time, i.e. 22% per 12-week cycle. Expert clinical advice to the ERG is that EoE patients in remission would typically relapse if they stopped treatment but those who continue on maintenance therapy would mostly remain in remission. Furthermore, in the study by Straumann et al, (reference 26 in the ERG report) all patients in the placebo arm (i.e. not receiving maintenance therapy) relapsed. 'Lucendo et al (reference 1 in the ERG report) commented "When pharmacological treatment for EoE is stopped, symptoms and/or oesophageal eosinophilia typically recur over a 3–6-month period".
Why this issue is important	NICE can only appraise technologies within their marketing authorisation. The licensed duration of budesonide ODT is treatment for is 6 weeks, which may be extended to 12 weeks for patients who do not respond appropriately. Clinical experts consulted by the technical team have stated that the comparator treatments have no treatment time limit. The exclusion of a remission with maintenance health state in the model and the

	exclusion of the maintenance therapy costs reduce the total costs and if maintenance therapy is given in clinical practice, these costs should be taken into account when evaluating the cost-effectiveness. The ERG base case (shown in section 4, table 1) includes maintenance treatment (with the same intervention as induction treatment) and a relapse rate following maintenance treatment of 11% for all treatments. Adding in maintenance treatment increases the ICER for budesonide ODT versus both fluticasone and SFED but changing relapse rate from 22% to 11% had the opposite effect of lowering the ICER. The ERG conducted scenario analyses on its base case exploring the impact of varying these inputs further (see ERG report table 45). These exploratory analyses demonstrate that the company's base case is sensitive to changes in the assumptions regarding maintenance treatment and relapse rates.
Questions for engagement	a) When pharmacological treatment for EoE is stopped, typically when do symptoms and/or esophageal eosinophilia recur? b) In practice, would patients responding to fluticasone or other corticosteroid formulations be likely to continue receiving these as maintenance therapy?
Technical team preliminary judgement and rationale	NICE can only appraise a technology within its marketing authorisation and currently budesonide ODT is not licensed for maintenance therapy. The technical team prefer an economic model that reflects the marketing authorisation for budesonide ODT which is currently allows a maximum of 12 weeks treatment.

Issue 3 – Model structure and time horizon

Background/description of issue	The company model is described in section 1 (Topic background). The figure below is adapted from the company diagram and shows the transition probabilities per 12-week cycle. **Company model with per cycle transition probabilities (cycle length 12 weeks)**  * Patients can transition to the death health state from any other health state ** After 1 year all patients in remission relapse Source: adapted from CS, figure B.3.1

The company model has a time horizon of 40 years. During this time patients undergo several rounds of episodic treatment.

Number of rounds of treatment received by patients in each arm of the company's model (throughout total model time horizon)

Budesonide ODT	16.9
Fluticasone	3.1
SFED	1.3

Source: These values were confirmed by the ERG by email. They reflect the number of rounds of treatment patients received after a mistake in the company model was corrected by the ERG. The error in the company model related to how the half cycle correction had been implemented. This error is commented on by the ERG in Table 40 of the ERG report. The equivalent values in the company's original model were 16.4, 2.6 and 0.7 respectively. These are presented on table 38 of the ERG report.

The subsequent health states do not differ in description and have the same utility values as the initial active disease and remission states; in other words, the model does not attempt to capture any clinical outcomes or reductions in health-related quality of life related to disease progression or long-term complications.

The ERG stated that the absence of reporting on complications such as stricture formation may be because the two key trials, BUU-2/EEA and BUL1/EEA had a relatively short duration (BUU-2/EEA two weeks of treatment, BUL1/EEA six weeks double blind treatment with optional further six week open-label induction and four week follow-up for those not in remission at the end of the double blind phase, giving a maximum period of 16 weeks).

One of the experts consulted by the technical team who is using budesonide ODT in line with the marketing authorisation in their practice confirmed that they prescribe it episodically and there is no maximum number of times a patient can receive it. These comments align with the company's decision to allow repeat prescriptions of the licensed dose of budesonide ODT. However, both clinical experts said that other off-label steroid treatments are not used episodically but on an on-going basis, although maintenance treatment practice varies. The dietitian explained that SFED is a complex intervention that involves systematically eliminating food groups and monitoring changes in symptoms and histology to identify allergens. If diets are successful and patients can eliminate the allergenic foods on a sustained basis, remission can often be maintained and there is no need to continue or repeat the initial intervention. Dietary interventions are difficult to adhere to for many patients.

	Both the clinical experts also said that it was reasonable to assume that increasing the time in remission would slow disease progression and reduce the risk of long-term poor outcomes such as oesophageal strictures and fibrosis occurring. One expert stated that it was likely to take between 5 and 10 years for patients with active disease to develop strictures, the other gave a very similar range of 5 to 9 years. However, both recognised that there is currently very little evidence on the natural history of the disease or how budesonide ODT affects long-term outcomes. They noted that some patients present with established disease that has remained untreated for several years. Some patients have strictures and fibrotic disease at presentation.
Why this issue is important	The time horizon of the company's model, plus the structure which allows patients to receive the same induction therapy multiple times increases the overall costs in the model for all treatments. This is important because in the short term (that is, after the first round of treatment alone) the overall costs associated with budesonide ODT are much higher than for fluticasone or SFED due to the difference in the procurement costs, but over the extended time horizon patients receiving fluticasone and SFED spend more time in the active disease states where they accrue costs related to follow-up and monitoring (issue 3), and add-on treatments (issue 4) until they eventually become more expensive than budesonide ODT. The structure and time horizon of the model is therefore very important for assessing cost effectiveness because this is what determines whether budesonide ODT is more or less costly than the comparators. It is also problematic to model treatment effects over such a long time horizon without taking into account outcomes and QALY losses related to disease progression.
Questions for engagement	a) Would it be more appropriate to model the cost effectiveness of budesonide ODT using a time horizon that captures the costs and benefits associated with a single episode of treatment? b) What is the appropriate time horizon for the model considering that the treatment under consideration can be given continuously for a maximum of 12 weeks according to the licence? c) What time frame adequately captures the true costs and benefits of budesonide ODT as it is licensed? Would this be different for different comparators? d) If a shorter time horizon is required, would a different model structure be appropriate?
Technical team preliminary judgement and rationale	Neither the company's 40-year nor the ERG's 20-year time horizon is well justified. Given that the only available evidence for budesonide ODT relates to short term histological remission outcomes and the lack of evidence regarding the natural history of the disease, using a time horizon that reflects the costs and benefits of a single episode of treatment to model the cost effectiveness is appropriate.

Issue 4 – The costs for follow up and monitoring have been overestimated

Background/description of issue

The follow-up and monitoring costs in the company's model fall into two categories

- Costs relating to monitoring procedures, specifically upper endoscopy with biopsy sampling
- Costs relating to routine consultations with clinicians, specifically gastroenterologists and dietitians

Dietician visits	Only patients receiving dietary therapy (i.e. SFED) visit a dietician - 1.8 visits per active disease cycle, 0 during remission.
Gastroenterologist visits	1 visit per active disease cycle, 0 during remission.
Endoscopies	Frequency of endoscopies during active disease health states is 0.47 for all treatments except SFED. For SFED, the frequency of endoscopies during active disease health states is 1.3. Patients do not receive endoscopies during remission

Source: ERG report table 31-32

The ERG has argued that the company's assumptions result in unrealistic costs being accrued over the 40-year time horizon.

Number of resources used in the company's model

	Clinician visits	Endoscopy
Budesonide ODT	102	48
Fluticasone	139	65
SFED	144	68

Source: ERG report table 38

The company assumed that all clinical consultations would be with gastroenterologists (and dieticians for those on SFED) and that frequency and type of monitoring visits and procedures would remain constant throughout out the time horizon. Conversely, the ERG argue that the programme of health care professional visits proposed by the company would only be relevant for the first 6 months of treatment. The ERG argues that after 6 months patients in remission would then be discharged to be monitored by primary care. If they had a disease relapse,

	they would have the following health care resource uses: 1 GP visit / cycle, 0.5 gastroenterologist appointment / cycle, 0.25 endoscopies / cycle. The ERG also argues that the company's assumption that the second line and third line treatments (which are assumed to be "No treatment") have the same follow-up and monitoring costs as treatment with budesonide ODT and fluticasone results in unrealistically high health resources being incurred. They argue that a better approach is to have no health resources associated with the 'no treatment' Active EoE health states. Clinical experts consulted by the technical team stated that EoE treatments are generally prescribed and monitored in secondary care. The expert that is already using budesonide ODT in practice explained that patients receive a follow-up endoscopy 12 weeks after treatment is initiated, and then treatment outcomes are assessed through clinical review 2 to 3 weeks later (i.e. at week 15), by which point the biopsy results would be available. When treatment is successful patients are usually then offered a routine review 9 to 12 months later, and annually thereafter, with the option to return sooner if symptoms reoccur. The experts said that monitoring for other off-label steroid preparations would be similar, with the additional need for patients to collect repeat prescriptions from primary care. Both experts noted that initially monitoring for SFED is considerably more intensive requiring multiple endoscopies. Neither expert was able to say definitively how many repeat endoscopies would be required – the dietitian stated it would be a minimum of 4 procedures but did not specify the timeframe over which these would occur. Both experts noted that practice is likely to vary between centers.
Why this issue is important	The company's assumptions about healthcare resource use relating to follow-up and monitoring do not reflect clinical practice and this means that these costs are overestimated in the company model. The company's assumptions combined with time horizon contribute to why the costs of fluticasone and SFED increase over time relative to budesonide ODT. The ERG base case (shown in section 4, table 1) includes its preferred assumptions regarding follow-up and monitoring. Using the ERG's assumptions increases the ICER for budesonide ODT versus both fluticasone and SFED. The ERG conducted scenario analyses on its base case exploring the impact of varying these inputs further (see ERG report table 45). These exploratory analyses demonstrate that the company's base case is sensitive to changes in the assumptions for follow-up and monitoring.
Questions for engagement	a) Are the ERG's assumptions about follow-up and monitoring costs sufficiently realistic given the feedback received from clinical experts? b) In clinical practice would the rate of monitoring visits and procedures be constant, or would there be more monitoring in the initial treatment period?

Technical team preliminary judgement and rationale	The ERG's assumptions are considerably more realistic than the company's. The technical team agree with the ERG that applying follow-up and monitoring costs at a constant rate throughout the model time horizon is inappropriate. The technical team also agree with the ERG that patients receiving any EoE treatment would be initially monitored in secondary care and that resource use would be more intense for dietary interventions than drug interventions. The ERG's assumption that patients will be monitored in primary care once in remission was not validated by the clinical experts consulted by the technical team, although patients using off-label corticosteroids may have to make visits to primary care to get repeat prescriptions. Overall, the impact of any uncertainties in the ERG's assumptions is likely to be minimised by reducing the time horizon of the model . The technical team therefore consider that if the time horizon is restricted to a single episode of budesonide ODT treatment, the ERG assumptions may be sufficiently accurate for the purposes of decision making.

Issue 5 – Endoscopic dilation rates

<table>
<tr>
<td>Background/description of issue</td>
<td>The company has included costs for add-on dilation treatments for managing emergency food bolus removal and oesophageal strictures in its base case. The company assumed that the probability of add-on dilation treatments varied according to the treatment patients received and by health state as follows:
<table>
<tr><th>Treatment</th><th>Health state</th><th>Probability of strictures/bolus impaction per 12-week cycle</th></tr>
<tr><td rowspan="2">Budesonide ODT</td><td>Active disease</td><td>0.00</td></tr>
<tr><td>Remission (without maintenance)</td><td>0.15 (60% at 48 weeks)</td></tr>
<tr><td rowspan="2">Fluticasone</td><td>Active disease</td><td>0.14 (9.5% at 8 weeks)</td></tr>
<tr><td>Remission (without maintenance)</td><td>0.41 (27.0% at 8 weeks)</td></tr>
<tr><td rowspan="2">SFED</td><td>Active disease</td><td>0.01 (8.0% in 24.9 months)</td></tr>
<tr><td>Remission (without maintenance)</td><td>0.15 (60% at 48 weeks)</td></tr>
<tr><td rowspan="2">No treatment</td><td>Active disease</td><td>0.14</td></tr>
<tr><td>Remission (without maintenance)</td><td>0.41</td></tr>
</table>
Source: ERG report table 33
The ERG have argued that

approach taken to estimate add-on dilation treatment is not representative of clinical practice
the estimates used by the company produces more than 25 dilation treatments per person over the time horizon and this appears to be a large overestimation

</td>
</tr>
</table>

<table>
<tr><td></td><td>
Number of add-on dilation treatments received by treatment arm in company's model
<table>
<tr><td>Intervention</td><td>Number of dilation treatments over 40 years</td></tr>
<tr><td>Budesonide ODT</td><td>25.1</td></tr>
<tr><td>Fluticasone</td><td>30.9</td></tr>
<tr><td>SFED</td><td>29.3</td></tr>
</table>
Source: ERG report table 38

the evidence is not strong enough to differentiate by treatment
a more realistic probability of add-on treatment is 2% per 12-week cycle for those in active disease and remission (which has the same effect as not including any costs for add-on dilation treatments)

Comments from clinical experts consulted by the technical team regarding the outcomes these add on treatments are used for (oesophageal strictures and fibrosis) are summarised in the background section of issue 2 above. The experts said it was reasonable to assume that maintaining remission would reduce risk of the outcomes occurring but there are currently no data to support this.
</td></tr>
<tr><td>Why this issue is important</td><td>
The company's assumptions about add-on dilation treatment costs combined with time horizon of the model contribute to why the costs of fluticasone and SFED increase over time relative to budesonide ODT.

The ERG base case (shown in section 4, table 1) assumes the probability of add-on treatment is 2% per 12-week cycle for those in active disease and remission. Using the ERG's assumptions increases the ICER for budesonide ODT versus both fluticasone and SFED. The ERG conducted scenario analyses on its base case exploring the impact of varying these inputs further (see ERG report table 45). Together these exploratory analyses demonstrate that the company's base case is sensitive to changes in the assumptions for add-on treatments.

</td></tr>
<tr><td>Questions for engagement</td><td>
a) Should the costs for add-on treatments be removed from the company model?
b) Should the number of add-on dilation treatments received vary depending on the induction treatment received or be assumed the same across all arms of the model?
c) Is it reasonable to assume that patients in remission have the same probability of requiring treatment for emergency food bolus removal/endoscopic dilation as those in the active disease state?
</td></tr>
</table>

Technical team preliminary judgement and rationale	The technical team recognise that over the 40- and 20-year time horizons considered by the company and ERG respectively, some patients are likely to undergo add-on dilation treatments to deal with complications of EoE. The technical team consider that it is clinically plausible that more effective EoE treatments will reduce the need for add-on treatments in the long term but acknowledge the lack of evidence to support this. The technical team is aware of the difficulty in extrapolating treatment effectiveness regarding long-term complications given the short duration of the clinical trials and paucity of available data. If the time horizon is restricted to a single episode of budesonide ODT treatment, then it would not be necessary to incorporate costs for add-on treatments.

Issue 6 – Choice of utility data

<table>
<tr><td>Background/description of issue</td><td>The utility values in the economic model for Active EoE are taken from a study of patients with a disease considered to be a proxy for EoE (GORD). The ERG considers an alternative study of EoE patients provides a better source of utility values. The utility value for patients in remission is taken from UK population norms, however the incorrect value has been used for this population. Age-adjusted utilities have not been included in the economic model.
The company and ERG base case utility estimates are summarised below.
<table>
<tr><th>Health state</th><th>Mean utility value</th><th>Standard deviation</th><th>Source (description)</th></tr>
<tr><td colspan="4">Company base-case analysis</td></tr>
<tr><td>Active EoE</td><td>0.70</td><td>0.24</td><td>Kartman et al. 2004
(Swedish/German data for gastro-oesophageal reflux disease with heartburn)</td></tr>
<tr><td>EoE in Remission</td><td>0.85</td><td>0.24</td><td>Kind et al. 1999
(UK population norms for EQ-5D, unadjusted for age)</td></tr>
<tr><td colspan="4">ERG base-case analysis</td></tr>
<tr><td>Active EoE</td><td>0.86</td><td>Not reported</td><td>Hewett et al. 2017 and Kind et al. 1999
(Age-adjusted UK population norms minus the disutility for EoE observed in Hewett et al. 2017)</td></tr>
<tr><td>EoE in Remission</td><td>0.93</td><td>Not reported</td><td>Kind et al. 1999
(Age-adjusted UK population norms for EQ-5D)</td></tr>
</table>
Source: CS Table B.3.6</td></tr>
<tr><td>Why this issue is important</td><td>The ERG base case (shown in section 4, table 1) includes its preferred utility values. Using the ERG's values increases the ICER for budesonide ODT versus both fluticasone and SFED. The ERG conducted scenario analyses on its base case exploring the impact of varying these inputs further (see ERG report table 45). Together these exploratory analyses demonstrate that the company's base case is sensitive to changes in the utility values.</td></tr>
</table>

Questions for engagement	a) Is gastro-oesophageal reflux disease with heartburn a good proxy for active EoE, how similar are the conditions in terms of health-related quality of life? b) It is appropriate to use a utility value that is based on the population norm (that is for an average person without EoE) for the remission health states given that the data informing this heath state relates to histological remission?
Technical team preliminary judgement and rationale	The technical team agree with age-adjusting the utility values because age impacts QoL and should be reflected in the utility values of the population in the model. The technical team think that the utility values for the EoE remission health state are likely to be optimistic given that patients in this state have only achieved histological remission and may still have symptoms. The technical team would welcome clinical feedback on the appropriateness of the utilities for active disease health state.

4. Issues for information

Tables 1 to 4 are provided to stakeholders for information only and not included in the technical report comments table provided.

Table 1: Cumulative impact of ERG preferred assumptions on the company's base case

Parameter	Value	Total costs			Total QALYs			ICER vs Fluticasone	ICER vs SFED
		Budesonide	Fluticasone	SFED	Budesonide	Fluticasone	SFED		
Company's base case		£24,020	£27,122	£27,657	16.12	15.30	15.14	Budesonide dominates	Budesonide dominates
+ Apply corrections	See Table 40 of ERG report	£24,248	£27,174	£27,657	16.12	15.30	15.14	Budesonide dominates	Budesonide dominates
+ Time horizon	20 years	£15,922	£18,351	£18,834	11.13	10.45	10.29	Budesonide dominates	Budesonide dominates
+ Remission	From ERG's random effects NMA	£15,963	£18,328	£18,712	11.12	10.47	10.32	Budesonide dominates	Budesonide dominates
+Maintenance therapy	Include maintenance therapy after all induction treatments	£26,411	£18,730	£18,712	11.12	10.47	10.32	£11,780	£9,555
+ Endoscopic dilation rate	2% per cycle	£23,211	£13,725	£14,585	11.12	10.47	10.32	£14,548	£10,706
+ Health care resources	No health state resources in active EoE if patients receive 'no treatment'.	£17,642	£2,098	£1,540	11.12	10.47	10.32	£23,840	£19,986

Parameter	Value	Total costs			Total QALYs			ICER vs Fluticasone	ICER vs SFED
		Budesonide	Fluticasone	SFED	Budesonide	Fluticasone	SFED		
	Initial health care costs applied for a short time period (6 months), including remission health states.								
+ Utility	(0.93 for remission, 0.86 for relapse)	£17,642	£2,098	£1,540	12.81	12.51	12.43	£51,086	£42,826
	Include age adjusted utility	£17,642	£2,098	£1,540	12.76	12.49	12.43	£58,023	£47,907
+ Relapse rate	11% for remission with maintenance	£17,939	£2,181	£1,546	12.82	12.52	12.43	£52,796	£42,897
+ Relapse rate after 1 year	Same relapse rate as other cycles*	£18,595	£2,539	£1,528	12.99	12.64	12.48	£45,735 (ERG base case)	£33,630 (ERG base case)

Source: ERG report addendum 3rd January 2020

Table 2: Technical team preferred assumptions

Alteration	Technical team rationale	ICER vs fluticasone	ICER vs SFED	ICER vs budesonide OVS	ICER vs placebo
Company base case	–	Budesonide ODT dominates	Budesonide ODT dominates	NA	NA
1. Include swallowed off-label budesonide in suspension and placebo as comparators in the economic analyses	The company's choice of comparators does not reflect all the comparators of interest [issue 1]	Budesonide ODT dominates	Budesonide ODT dominates	TBC	TBC
2. ERG correction of minor errors	Technical team agreed with ERG's amendments. See table 40 of ERG report	Budesonide ODT dominates	Budesonide ODT dominates	TBC	TBC
3. Apply ERG frequentist random-effects NMA results	The ERG's analysis included a continuity correction that reduces some of the uncertainty in the NMA results	Budesonide ODT dominates	Budesonide ODT dominates	TBC	TBC
4. Reduce time horizon to reflect a single round of budesonide ODT treatment	Reflects the available evidence	TBC	TBC	TBC	TBC
5. Apply ERG assumptions regarding follow-up and monitoring costs	The ERG's assumptions are sufficiently accurate in the context of the revised time horizon [issue 3]	TBC	TBC	TBC	TBC
6. Remove add-on treatment costs	The model does not include outcomes related to these treatments, so the costs are not relevant [issue 4]	TBC	TBC	TBC	TBC

Alteration	Technical team rationale	ICER vs fluticasone	ICER vs SFED	ICER vs budesonide OVS	ICER vs placebo
7. Adjust utility values for remission health states to reflect quality of life associated with histological remission, apply the ERG utility values for active disease and adjust all the utilities to reflect the age of the patient cohort in the model	The evidence included in the model for remission relates to histological remission. Patients who are in histological remission may still experience symptoms and this should be reflected in the utility value. The ERG choice of utility for active disease is more robust than the company's because it is based on patients with EoE. Age impacts quality of life and should be reflected in the utility values of the population in the model [issue 5]	TBC	TBC	TBC	TBC
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate	**–**	TBC	TBC	TBC	TBC

Table 3: Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
The company's NMA has several limitations that cannot be resolved due to limitations in the underlying data.	The results of the NMA directly inform the transitions between health states A and B in the economic model. These transitions are a major driver of the cost effectiveness estimates. Because the NMA results are uncertain, the cost effectiveness estimates are also uncertain	The exact impact is unknown. The ERG have tested the impact of using different estimates of relative effectiveness to inform the transitions between health states A and B in the economic model but as these alternative estimates are based on data from the same underlying trial set, it is unclear whether these analyses demonstrate the full range of uncertainty relating to limitations in the trial data. The impact of the wide credible intervals (company's NMA) and wide confidence intervals (ERG frequentist analysis) on the cost effectiveness estimates is unknown because reliable probabilistic sensitivity analyses (PSA) results are not currently available.

Table 4: Other issues for information

Issue	Comments
Implementation of company model	The ERG highlighted two errors in the company model (relating to calculating errors in the drug acquisition costs and transition matrix – see ERG report table 40 for more details). Correction of these errors did not change the cost effectiveness results (budesonide ODT still dominates [is cheaper and more effective] compared with fluticasone or SFED)
Proportion of patients receiving budesonide ODT for 6 versus 12 weeks	The recommended dose for budesonide ODT is 1 mg BID for six or 12 weeks. Based on the company's BUL1/EEA trial, 57.6% of patients receive budesonide ODT for six weeks and the remainder receive budesonide ODT for 12 weeks. The ERG accepted this assumption
Fluticasone dosing	Fluticasone is used off-label and there is no fixed dose for use on patients with EoE. The company notes that the recommended daily dose for asthma is 100 – 1000 mcg twice daily for adults and children over 16 years old. The company assumes the dose used was the midpoint of this range for asthma, i.e. 550 mcg twice daily. The ERG suggests that the cost of fluticasone should be using the larger inhaler with 250mcg doses (120 doses = £36.14), rather than 50 mcg doses, as this is more consistent with the recommended dosage. Further the dose of fluticasone should be 1 mg per day (rather than 1.1 mg per day), i.e. 2 x 250mcg / dose, twice a day. The ERG tested making these changes to the dose for fluticasone and found that it had minimal effect on the model results and did not include these changes in its base case analyses
Innovation	The company considers the drug to be innovative. However, the technical team considers that all relevant benefits associated with the drug are adequately captured in the model.
Equality considerations	No equalities issues were identified by the company, consultees and their nominated clinical experts and patient experts.

Authors

Brian Shine

Appraisal committee chair

Juliet Kenny

Technical lead

Rufaro Kausi

Technical adviser

Janet Robertson

Associate director

With input from the lead team:

Andrew Champion

Lead team member

Stephen Sharp

Lead team member

Richard Ballerand

Lead team member

NICE National Institute for Health and Care Excellence

Technical engagement response form

Budesonide for treating active eosinophilic oesophagitis [ID1202]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments 5pm, Wednesday 11 March 2020

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- **Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.**
- **Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.**
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- **Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised**

data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	Dr Falk Pharma UK Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Questions for engagement

Issue 1: Are the right comparators included? There is uncertainty in the estimates of treatment effectiveness	
a) Are symptom duration and time since diagnosis important prognostic factors?	Retrospective studies have demonstrated that the duration (and severity) of eosinophilic oesophagitis (EoE) symptoms prior to diagnosis is predictive of treatment response.[1-3] This reflects the chronic, progressive nature of EoE – persistent symptoms and inflammation eventually lead to fibrosis and oesophageal remodelling,[4] with increasing duration of diagnostic delay being significantly associated with the prevalence of fibrotic features ($p=0.02$) and oesophageal strictures ($p<0.001$).[5] In a medical record review of 35 adults with EoE, diagnostic delay was significantly associated with the risk of refractory disease ($p=0.03$).[2] In addition, an extreme narrow-calibre oesophagus has been identified as a treatment-resistant sub-phenotype of EoE characterised by longer symptom duration in a cohort of 513 patients with newly diagnosed EoE,[1] and the need for oesophageal dilation at baseline examination was predictive of non-response to steroid therapy in a retrospective cohort of 221 patients.[3] Unless fibrosis and oesophageal remodelling have become established at the time of diagnosis, and assuming appropriate management of EoE following diagnosis, there is no evidence to suggest that increased time since diagnosis would be an important prognostic factor. However, compliance with current off-label corticosteroids and dietary therapies is typically poor.[6] Therefore, in patients who do not achieve adequate control of inflammation following diagnosis, ongoing symptoms and the potential for the development of fibrotic complications may be expected to contribute to poorer outcomes. As such, increasing time since diagnosis may be a prognostic factor in some patients.
b) Are the key trials for budesonide ODT (BLU-1/EEA and BUU-2/EEA) generalisable to	Although no patients from the UK were included in BUL-1/EEA and BUU-2/EEA, it is expected that patients were representative of those treated in the NHS. Both studies were conducted in Western

NHS practice, particularly are the patients included representative of those treated with EoE in the NHS?	Europe, and all patients were Caucasian,[7,8] reflecting the majority of the UK population. Patient demographics reflected the epidemiology of EoE;[9] in both studies, the majority of patients were male (83.0% in BUL-1/EEA and 82.9% in BUU-2/EEA) with a mean age of 37.0 and 39.7 years in BUL-1/EEA and BUU-2/EEA, respectively.[7,8] Furthermore, the inclusion/exclusion criteria of each study mirrored the consensus criteria for EoE,[7,8] and patients selected for the pivotal phase III study were all non-responsive to proton-pump inhibitors (PPIs).[7] This reflects current UK clinical practice, in which patients are typically treated unsuccessfully with PPIs prior to receiving a diagnosis of EoE.[10]
c) Can the following additional comparisons be justified for the reasons outlined in the background section of this table: i. Budesonide ODT versus swallowed off-label budesonide in suspension ii. Budesonide versus no treatment	**Budesonide orodispersible tablet (ODT) versus swallowed budesonide in suspension** While evidence for the clinical efficacy of budesonide in suspension (budesonide oral viscous suspension [OVS]) is available from clinical studies, including the phase II BUU-2/EEA study, oral budesonide suspensions used in clinical trials are not equivalent to those used in clinical practice in the UK.[8] In BUU-2/EEA, patients received a pre-prepared, consistent formulation of budesonide OVS, with clear instructions for administration and storage.[11] However, in UK clinical practice, patients treated with oral budesonide suspensions are prescribed formulations intended for nebulisation (e.g. Pulmicort® Respules®), which must be mixed with a carrier, such as apple sauce, yoghurt, honey or sucrose. As such, preparation may be inconsistent and/or inaccurate, leading to variable active drug concentrations.[12,13] In addition, adherence in a clinical trial setting is likely better than that in clinical practice. Therefore, any comparison based on budesonide OVS administered in clinical trials would not be representative of clinical practice in the UK. In addition, in order to obtain information on the treatment of EoE in the UK, seven UK clinicians with expertise in EoE were consulted via telephone interview. The feedback from the clinical experts was that oral budesonide suspensions would typically only be used as a first-line treatment in exceptional cases, but may be used as a second-line treatment by some clinicians.[10] Therefore, given the differences between oral budesonide suspensions used in clinical trials and those used in clinical practice, along with the lack of use as a first-line treatment in the UK, Dr Falk

	Pharma does not consider off-label budesonide in suspension to be an appropriate comparator for budesonide ODT. **Budesonide ODT versus no treatment** Due to the variation in current UK clinical practice, and lack of knowledge of EoE among healthcare professionals (HCPs), Dr Falk Pharma recognises that many patients do not receive any treatment for EoE, and that those who undergo endoscopic dilation and/or emergency food bolus removal may not receive any anti-inflammatory treatment. Therefore, given that budesonide ODT is the first licensed treatment for EoE, Dr Falk Pharma agrees that no treatment may be an appropriate comparator, and is therefore included in additional economic analyses conducted in response to technical engagement (see page 15).
Issue 2: Maintenance therapy for patients in remission should not be included in the economic evaluation	
a) When pharmacological treatment for EoE is stopped, typically when do symptoms and/or oesophageal eosinophilia recur?	Guidelines for the diagnosis and management of EoE state that, when pharmacological treatment for EoE is stopped, symptoms and/or oesophageal eosinophilia typically recur over a 3–6-month period.[4,14] This is confirmed by data from the phase III BUL-2/EER study of budesonide ODT maintenance treatment, which enrolled patients who achieved clinico-pathological remission following treatment with budesonide ODT in BUL-1/EEA. In the placebo arm of BUL-2/EER (i.e. up to 12 weeks budesonide ODT in BUL-1/EEA, followed by no treatment), the median time to clinical or histological relapse (including the need for endoscopic dilation or endoscopic intervention for food impaction) was 86 days (interquartile range: 29–333).[15]
b) In practice, would patients responding to fluticasone or other corticosteroid formulations be likely to continue receiving these as maintenance therapy?	Other than budesonide ODT, no topical corticosteroid formulations are licensed for the treatment of EoE. Therefore, UK clinical practice varies, with no standardised dose used across the NHS. However, expert clinical opinion suggests that corticosteroids such as fluticasone are typically prescribed continuously, with a lower maintenance dose often used following induction of remission (e.g. 1 mg twice daily [BID], followed by 0.5 mg BID or 1 mg once daily).[6,10] Consequently, the additional analyses (see page 15) assume maintenance (or continuous) treatment for fluticasone

	and dietary therapy (six-food elimination diet [SFED], which requires the avoidance of the six food types that are most commonly associated with allergy [typically milk, wheat, eggs, soy, nuts and seafood][16-18]).
Issue 3: Model structure and time horizon	
a) Would it be more appropriate to model the cost effectiveness of budesonide ODT using a time horizon that captures the costs and benefits associated with a single episode of treatment?	In order to model a single episode of treatment with budesonide ODT, the time horizon would need to be very short (~24 weeks), as the majority of patients relapse after stopping treatment (88% within one year in BUL-2/EER)[15] and receive subsequent treatment with budesonide ODT. As this happens throughout the year (median time to relapse of 86 days in BUL-2/EER),[15] some patients will receive a second treatment course of budesonide ODT in cycle 3 (i.e. after 24 weeks). Hence, a time horizon longer than 24 weeks is required to include costs associated with subsequent treatment with budesonide ODT. Dr Falk Pharma does not believe that such a short time horizon fully captures the costs and benefits associated with treatment with budesonide ODT. In particular, the main benefit of budesonide ODT is its high response rate (94.9% histological response in BUL-1/EEA).[7] Therefore, as not all patients relapse, a proportion of patients will still be in remission after one year.
b) What is the appropriate time horizon for the model considering that the treatment under consideration can be given continuously for a maximum of 12 weeks according to the licence?	Budesonide ODT is expected to be prescribed episodically (i.e. patients will receive multiple treatment courses over a period of time). In the original company submission (January 2019) and cost-utility model, a time horizon of five- years was used, as EoE is a rare disease and there is a lack of data to populate the model beyond this time horizon. Upon request from the Evidence Review Group (ERG) for a time horizon of up to 40 years (Clarification Question B8 [March 2019]), the time horizon was increased to 40 years in the September 2019 company submission. However, this required the assumption that the parameters originally used in the model would apply over a much longer time horizon. Given the paucity of data and uncertainty involved, particularly around the lack of data on relapse rates, subsequent response rates and adherence to treatment, Dr Falk Pharma believes that a shorter time horizon is more

	appropriate. Therefore, time horizons of one and two years have been used in the additional analyses conducted in response to technical engagement (see page 15).
c) What time frame adequately captures the true costs and benefits of budesonide ODT as it is licensed? Would this be different for different comparators?	Given the dearth of data for both budesonide ODT and the comparators, Dr Falk Pharma accepts that a shorter time horizon is more appropriate. The main benefit of budesonide ODT is its high histological response rate (94.9%).[7] Whilst it is expected that the majority of these patients (88%)[15] will relapse within one year of stopping treatment, the rest (12%) will remain in remission. Patients in remission incur lower costs and have improved quality of life (QoL) compared with those in the active disease health state. However, there are no data on subsequent relapse rates. The costs for budesonide ODT are driven by health state (active disease or remission). Hence, the impact of the time horizon on costs is largely driven by the response and relapse rates. In the case of fluticasone, patients receive maintenance (or continuous) treatment, which is associated with a lower relapse rate. Consequently, the majority of patients adhering to treatment remain in remission (once the correct dose is established), which is associated with lower costs and higher QoL than active disease. As with budesonide ODT, the costs of fluticasone are driven by health state (active disease or remission). Hence, the impact of the time horizon on costs is largely driven by the response and relapse rates. In the case of SFED, patients who have their food trigger identified and adhere to the diet will continue to respond. Those that adhere will thus remain in remission, which is associated with lower costs and higher QoL than active disease. In terms of costs, patients receiving SFED require 5–6 endoscopies in the first year as well as visits to a dietician. Otherwise, costs are driven by health state as for budesonide ODT and fluticasone. The additional analyses (see page 15) use a time horizon of 1-2 years, which is considered long enough to capture the costs and benefits of treatment, while accounting for the uncertainty surrounding longer-term treatment of EoE

d) If a shorter time horizon is required, would a different model structure be appropriate?	Dr Falk Pharma believes that the model structure should not change with a shorter time horizon. The model structure adequately captures patients as they move from active disease to remission health states and back again. This allows for differences in costs and QoL between the active disease and remission health states. Using a different model structure is also complicated by the fact that, in the additional analyses conducted in response to technical engagement (see page 15), patients receiving budesonide ODT are treated episodically (i.e. receive treatment for a maximum of 12 weeks), whilst patients receiving fluticasone and SFED are treated continuously (i.e. receive induction treatment followed by maintenance, or a continuous dietary intervention).
Issue 4: The costs for follow up and monitoring have been overestimated	
a) Are the ERG's assumptions about follow-up and monitoring costs sufficiently realistic given the feedback received from clinical experts?	**Gastroenterologist visits** Dr Falk Pharma does not agree that patients with EoE are managed in primary care. Seven UK clinical experts interviewed by Dr Falk Pharma all stated that patients with EoE would be managed by a gastroenterologist, and GP involvement would be limited to repeat prescriptions. This was confirmed at an advisory board meeting organised by Dr Falk Pharma on 6th March 2020.[6] Similarly, one of the clinical experts engaged by NICE stated that EoE is a disease that requires management in secondary care because GPs do not see enough patients to have the relevant experience to manage the disease. There are no shared care protocols and patients are currently treated with off-licence products which makes management in primary care challenging. Clinical experts also cited difficulties with patients obtaining repeat prescriptions, being dispensed different asthma inhalers to the one recommended or being given inappropriate guidance on inhaler use based on asthma guidelines. Therefore, while the additional analyses (see page 15) assume management in secondary care, scenario analyses have also been conducted using the same healthcare resource utilisation (HRU) as the ERG. Dr Falk Pharma believes that one gastroenterologist visit per 12-week active disease cycle is representative of clinical practice. Both clinical experts engaged by NICE stated that all patients

	should return if symptoms recur (i.e. relapse). This is represented by patients returning to the active disease health state in the model. Dr Falk Pharma agrees that patients receiving no treatment should have a lower rate of gastroenterologist visits per 12-week active disease cycle, as these patients spend the majority of their time in the active disease health states. However, it is unlikely that these patients would not receive any gastroenterologist visits, as they would be symptomatic and may require endoscopic dilation, emergency food bolus removal, or endoscopies for disease assessment. This is particularly relevant given the much shorter time horizon (1 and 2 years) used in the additional analyses (see page 15). **Endoscopies** Endoscopies are conducted for the diagnosis of EoE and ongoing disease assessment. Seven UK clinical experts interviewed by Dr Falk Pharma stated that patients with EoE would receive one to three endoscopies per year (average of two per year).[10] The ERG agreed with the frequency of endoscopies but stated that they should only be applied to an initial treatment period of six months. As the additional analyses use a much shorter time horizon (one and two years), Dr Falk Pharma believes that the frequencies used are relevant throughout this time horizon. Thus, in the additional analyses (see page 15), a value of 0.47 endoscopies per active disease cycle is used for all treatment regimens except SFED (0.25 per cycle). However, the majority of patients receiving budesonide ODT will only spend two cycles in the active disease health state per year. Similarly, most patients receiving maintenance (continuous) treatment with fluticasone will only spend one or two cycles in the active disease health state per year. Therefore, in the additional analyses (see page 15), the total number of endoscopies is small for patients receiving budesonide ODT or fluticasone. For patients receiving no treatment, additional analyses assume that endoscopies will still be conducted to monitor/assess disease, but with a lower frequency used in order to limit the number of endoscopies to one per year.

b) In clinical practice would the rate of monitoring visits and procedures be constant, or would there be more monitoring in the initial treatment period?	As noted above, time horizons of one and two years have been used in the additional analyses (see page 15) in order to account for the uncertainty surrounding longer-term treatment of EoE. Dr Falk Pharma expects that monitoring will be constant over this much shorter time horizon, compared with the 40-year time horizon in the September 2019 company submission.
Issue 5: Endoscopic dilation rates	
a) Should the costs for add-on treatments be removed from the company model?	Dr Falk Pharma believes that add-on treatment, which includes emergency food bolus removal and endoscopic dilation, should be included in the model, in order to represent clinical practice. Oesophageal dilation may be considered an independent treatment option in EoE, with studies conducted of dilation versus other treatment options for EoE. For example, a 2014 cost analysis compared the costs of swallowed fluticasone with those of upper endoscopy with oesophageal dilation,[19] based on a study in which 63 patients with EoE were treated with dilation alone.[20] The oesophageal dilation arm of this analysis is therefore equivalent to no treatment with add-on dilation in the additional analyses (see page 15). It is accepted that patients receiving no treatment would have a higher rate of add-on treatment than patients receiving pharmacological treatment or dietary intervention, as dilation is generally reserved for patients who have oesophageal strictures or rings, and/or have failed to respond to medical therapy. As no treatment is included as a comparator in the additional analyses (see page 15), and there is a difference in dilation rates between active disease and remission health states (see response to Q5c), it is therefore important to include add-on treatment in the model. While the costs of add-on treatment can be estimated, there are no published data on the disutility of emergency food bolus obstruction or oesophageal strictures requiring dilation. However, both recurrent food impaction and strictures will both impact QoL, and emergency food bolus removal/endoscopic dilation are associated with rapid symptomatic improvement.[20,21] Given the dearth of data, the disutility for emergency food bolus obstruction or strictures is assumed to be zero

	in the additional analyses (see page 15). While this is considered a conservative assumption, scenario analyses have also been conducted which exclude the costs of add-on treatment.
b) Should the number of add-on dilation treatments received vary depending on the induction treatment received or be assumed the same across all arms of the model?	The probability of requiring endoscopic dilation is reduced by effective control of the underlying eosinophilic inflammation; in a retrospective cohort study the likelihood and frequency of oesophageal dilation was reduced by 65% in those who received swallowed topical steroids and achieved histologic remission.[21] As such, therapies which more effectively induce and maintain histological remission are likely to be associated with lower rates of endoscopic dilation. Although some commentators believe that dilation rates will vary by treatment, there is no evidence to support this. However, it is generally accepted that patients receiving no treatment will undergo endoscopic dilation due to the lack of treatment of the underlying mechanisms of disease, and consequent disease progression.
c) Is it reasonable to assume that patients in remission have the same probability of requiring treatment for emergency food bolus removal/endoscopic dilation as those in the active disease state?	There are data to suggest that patients in remission will still require add-on treatment, though at a lower rate than during active disease. Lucendo & Molina-Infante (2018) reviewed the current position of oesophageal dilation in the therapeutic algorithm for EoE, including effectiveness and safety issues. They concluded that 'as dilation has no effect on the underlying eosinophil inflammation, repeated procedures are usually needed to maintain symptoms in remission. Adding an effective drug or dietary-based EoE therapy reduces the need of further dilation'.[21] Thus it is expected that patients will have a lower rate of emergency food bolus removal and endoscopic dilation during remission.
Issue 6: Choice of utility data	
a) Is gastro-oesophageal reflux disease with heartburn a good proxy for active EoE, how similar are the conditions in terms of health-related quality of life?	In the absence of utility values for EoE, gastro-oesophageal reflux disease (GORD) with heartburn is considered an appropriate proxy. In a literature review of cost-effective care in EoE, Dellon (2019)[22] identified three published economic analyses in EoE (Miller et al., 2011; Cotton et al, 2017; Kavitt et al., 2014),[19,23,24] two of which were cost-utility analyses (Cotton et al., 2017 and Miller et

	al., 2011).[23,24] None of these studies used EoE-specific utility values, with GORD utilities used as a proxy for EoE in all three. The ERG based its utility value for the active disease health states on a UK study comparing 36-Item Short Form Survey (SF-36) scores for patients with EoE to a control group (Hewett et al., 2017).[25] The ERG mapped the SF-36 scores in this study to the EuroQol 5-Dimension (EQ-5D) instrument, leading to utility values of 0.88 and 0.95 for EoE patients and controls respectively (corresponding to a disutility of 0.07 for those with EoE). This disutility was applied to the age-adjusted utility value for the general population (0.93), to obtain a utility value for EoE of 0.85. However, Dr Falk Pharma does not accept that this utility value for active disease health states is appropriate. Hewett et al., 2017 was a cross-sectional study that took place between May 2013 and June 2014, with study participants recruited while attending outpatient gastroenterology clinics in the UK. The study included patients treated with PPIs (20.5%) and topical corticosteroids (25.7%),[25] and as such would be expected to include those in both the active disease and remission health states in a single EoE cohort. No attempt was made to differentiate these patients or make a comparison between patients with EoE in active disease or remission health states. Instead, patients with EoE were compared with age- and gender-matched healthy controls recruited from the local population.[25] Due to the inclusion of patients in remission, the utility value used by the ERG overestimates the QoL of patients in the active disease health states. The utility values in the company submission were derived from a study by Kartman et al. (2004),[26] which recruited a total of 1,011 patients from Germany (n=507) and Sweden (n=504) with GORD with heartburn (37% mild, 54% moderate and 9% severe). The overall utility value for the pooled group of patients (with all severities of disease) was 0.70. The utility values for mild, moderate and severe disease were 0.78, 0.67 and 0.49, respectively.[26] Following the initial interviews with seven UK clinical experts conducted by Dr Falk Pharma, five experts responded to an additional question about the utility values used in the model. The assessment of the clinical experts was that QoL for patients with EoE was similar to, if not worse than, that for GORD, due to increased levels of functional impairment (e.g. dysphagia), more limited treatment options with no symptomatic 'quick fix' (e.g. antacids/alginates), and increased complication rates. One clinical expert stated that EoE

	was similar to chronic oesophagitis in terms of QoL. Clinical experts all agreed that QoL for EoE patients in the UK would be similar to that for EoE patients in Sweden and/or Germany.[10] In terms of the impact of severity on QoL, one expert stated that QoL in EoE varies depending on the severity of disease, with patients with mild EoE experiencing symptoms less than once per week and usually able to compensate well by adapting their food consistency to avoid eating foods that 'stick' (estimated to be 50% of patients); patients with moderate EoE experiencing symptoms at least once per week and suffering food 'sticking' or short lived bolus obstruction despite food adaptation (approximately 25% of patients); and patients with severe EoE unable to swallow any solid foods without symptoms occurring on a daily basis, despite adaptation (approximately 25% of patients), and liable to severe bolus obstructions, dietary insufficiency and marked psychosocial restrictions. This expert estimated utilities of 0.85, 0.67 and 0.3 for mild, moderate and severe EoE, respectively.[10] Dr Falk Pharma therefore believes that the use of GORD utility values as a proxy for EoE is appropriate and in line with published economic analyses in EoE. Based on expert clinical opinion, the utility values used in the company submission (and additional analyses) may be considered conservative for budesonide ODT, as they potentially overestimate the QoL associated with active disease. However, scenario analyses have also been conducted using the same utility values as the ERG.
b) It is appropriate to use a utility value that is based on the population norm (that is for an average person without EoE) for the remission health states given that the data informing this heath state relates to histological remission?	In the absence of utility data in EoE, it was considered appropriate to use a utility value based on the population norm (for an average person without EoE) for the remission health state in the company submission. The ERG agreed with this approach. There are also limited data on the correlation between histological measures and QoL in EoE. One study (Safroneeva et al., 2015)[27] was identified, which assessed the relationship of QoL with clinical, endoscopic and histological activity. This study demonstrated that the variation in severity of symptoms, endoscopic and histological findings alone explained 38%, 35% and 22% of the variability in EoE-related QoL, respectively. Taken together, the severity of these findings explained

	60% of the variation in EoE-related QoL.[27] In a prospective observational study (Safroneeva et al., 2016), the accuracy of symptoms in detecting endoscopic and histological remission in adults with EoE was assessed. In a sample of 269 adults, 111 (41.3%) were in clinical remission (based on symptom score), 79 (29.7%) were in endoscopic remission and 75 (27.9%) and were in histological remission. The authors concluded that endoscopic or histological remission can be identified with only modest accuracy based on symptoms alone, and that HCPs cannot rely on a lack of symptoms to make assumptions about lack of biological disease activity.[28] This supports the use of data on histological remission to inform the remission health states, as more patients would be expected to be in clinical remission (i.e. lack of symptoms) than in histological remission. Hence, patients in histological remission are unlikely to have significant clinical symptoms.

Additional economic analyses

In response to the technical engagement, additional analyses were conducted in March 2020. As per the company submission, the model is a Markov state transition model with nine health states and an additional health state for death. The nine disease health states are active disease (three health states), remission without maintenance (three health states) and remission with maintenance (three health states). The intervention is budesonide ODT as episodic treatment and the comparators are fluticasone as continuous treatment, SFED as continuous treatment, and no treatment. No treatment is used for second and third treatment lines for all treatment arms. Analyses were conducted with one- and two-year time horizons. A summary of inputs and assumptions is provided in Table 1.

Table 1. Summary of variables used in the additional economic analyses (conducted March 2020)

Variable	Value	Rationale
Intervention/comparators		
Budesonide ODT	1 mg BID for 6 weeks (57.6%) or 12 weeks (42.4%)	Licensed budesonide dose,[29] with treatment duration based on BUL-1/EEA[7]
Fluticasone	1 mg BID (induction) and 0.5 mg BID (maintenance)	• Based on a study of high-dose swallowed fluticasone (1,760 µg daily) for induction followed by a lower maintenance dose (880 µg daily) in patients with complete remission[30] • Due to the high dose, clinicians prescribe the 250 µg strength Flixotide Evohaler. As doses can only be given in increments of 250 µg, patients would receive 1 mg BID for induction and 0.5 mg BID for maintenance. The assumption is that patients would receive the lowest possible dose as maintenance therapy (50% of induction dose), and is in line with feedback from one of the clinical experts engaged by NICE and confirmed by clinical experts at a Dr Falk advisory board on 6th March 2020[6] • Patients who relapse on fluticasone 0.5 mg BID are assumed to have the dose increased to 1 mg BID and will stay on this dose in remission
SFED	Continuous	Patients who have their food trigger identified and adhere to the diet are assumed to continue with dietary therapy
No treatment	Continuous	N/A
Response rates (transition from active disease to remission)		
Budesonide ODT	94.9% (first and subsequent treatment episodes)	As per company submission (based on NMA)
Fluticasone	68.1% for first treatment, thereafter 100%	• Initial response rate based on NMA • 100% for subsequent treatments, based on the assumption that all patients that initially respond to fluticasone will continue responding over the short-

Variable	Value	Rationale
		term on the higher dose (confirmed by clinical experts at a Dr Falk advisory board on 6th March 2020)[6]
SFED	18.5%	As per company submission (based on NMA)
No treatment	4.2% (first and subsequent treatments)	Based on NMA
Relapse rates (transition from remission to active disease)		
Budesonide ODT	88% after 1 year (22% per 12-week cycle)	Based on the placebo arm of BUL-2/EER[15]
Fluticasone	61% after 1 year (15% per 12-week cycle)	• Maintaining the lowest effective dose of medication possible in EoE makes intuitive sense given the potential long-term side effects of corticosteroids (e.g. adrenal suppression, oropharyngeal candidiasis). Hence, a lower dose is used for maintenance treatment. However, for some patients, the dose will be too low and they will relapse. Therefore, patients who relapse will be treated with the higher dose thereafter. • The relapse rate for fluticasone was derived from a retrospective study of 55 patients with EoE who had initially responded to swallowed/topical fluticasone: 61% had histological loss of response at follow-up (median 11.7 months). Patients who maintained their initial dose were less likely to relapse than those in whom the dose was reduced[31]
SFED	0% after 1 year	Patients relapse because they are non-adherent and thus instead transition to subsequent treatment
No treatment	88% after one year	Based on the placebo arm of BUL-2/EER[15]
Relapse rates (transition from remission to subsequent treatment)		
Budesonide ODT	N/A	
Fluticasone	N/A	
SFED	50% after one year (at end of year)	Patients relapse due to non-adherence and thus transition to subsequent treatment. The rate of relapse is based on a study assessing adherence to diet; 50% of patients who responded to diet at the end of year 1 were not followed up at the end of year 2.[32] It is assumed that these patients stopped adhering to dietary intervention
No treatment	N/A	
Utility values		
EoE (active disease)	0.78	• Due to a lack of appropriate utility values for EoE, the values for the active disease health state was derived from a study of GORD with heartburn.[26] This was considered an appropriate proxy (and a conservative estimate, based on expert clinical opinion). In this study, the utility value for these patients (mean age 51) was 0.7. The corresponding utility value for the

Variable	Value	Rationale
		general population (ages 45-54) is 0.85.[33] This represents a disutility of 0.15 for active disease (versus remission) • Applying this disutility to the general population utility value for a 30 year old (0.93) results in a utility value for active disease of 0.78
EoE (remission)	0.93	General population utility value (ages 25-34)[33]
Food bolus obstruction	N/A	Due to a lack of appropriate utility values, no disutility was applied. This was considered a conservative assumption
Oesophageal strictures requiring dilation		
Drug acquisition costs		
Budesonide ODT	£429.29 per 12-week cycle	• List price of £323.00 per pack of 90 tablets[34] • Wastage is excluded from the analysis as most patients respond to treatment (94.9%) and 88% of these relapse after one year. Hence, the majority of patients will continue treatment with budesonide ODT
Fluticasone	£202.38 (1 mg BID) and £101.19 (0.5 mg BID) per 12-week cycle	• List price of £36.14 per 250 mcg Flixotide Evohaler (120 doses)[35] • Wastage is excluded from the analysis as the majority of patients respond to treatment (68.1%) and receive subsequent maintenance treatment with fluticasone. Hence, the majority of patients will continue treatment with fluticasone
HCP visits		
Gastroenterologist, following visits (budesonide ODT, fluticasone, SFED)	Active EoE: 1.0 per cycle Remission: 0.0 per cycle	As per the company submission, except: • A lower rate of gastroenterologist visits is used for no treatment (active disease) • Includes dietician visits for patients receiving SFED in remission in the first year
Gastroenterologist, following visits (no treatment)	Active EoE: 0.5 per cycle Remission: 0.0 per cycle	
Dietitian (SFED)	Active EoE: 1.8 per cycle Remission: 1.8 per cycle for first year, 0.0 thereafter	
Dietician (budesonide ODT, fluticasone, no treatment)	0.0 per cycle	
Endoscopies		
Endoscopies (budesonide ODT, fluticasone)	Active EoE: 0.47 per cycle Remission: 0.0 per cycle	As per the company submission, except:

Variable	Value	Rationale
Endoscopies (no treatment)	Active EoE: 0.25 per cycle Remission: 0.0 per cycle	• A lower rate of endoscopies is used for no treatment for active disease in order to cap the number at one per year • Includes endoscopies for patients receiving SFED in remission in the first year
Endoscopies (SFED)	Active EoE: 1.3 per cycle Remission: 1.3 per cycle for first year, 0.0 thereafter	
Add-on treatment (emergency food bolus removal or endoscopic dilation)		
Add-on treatment (budesonide ODT, fluticasone, SFED)	Active EoE: 0.06 per cycle Remission: 0.03 per cycle	• There is a dearth of data on the number of patients receiving endoscopic dilation and/or emergency food bolus removal by treatment regimen or by health state. One retrospective study found that 67% of patients had symptoms requiring repeat dilation every 15 months.[20] This equates to 0.125 per 12-week disease cycle. • It is assumed that this applies to patients receiving no treatment in the active disease health states and that patients receiving treatment (budesonide ODT, fluticasone, SFED) would have a lower rate (assumed to be 50% lower [0.06]). • For patients in the remission health states, it is assumed that patients would receive 50% of that received in the active disease health states
Add-on treatment (no treatment)	Active EoE: 0.125 per cycle Remission: 0.06 per cycle	

Abbreviations: BID = twice daily; EoE = eosinophilic oesophagitis; HCP = healthcare professional; GORD = gastro-oesophageal reflux disease; N/A = not applicable; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; ODT = orodispersible tablet; SFED = six-food elimination diet

Results of the additional economic analyses are presented in Table 2 (1-year time horizon) and Table 3 (2-year time horizon).

Table 2. Results for 1-year time horizon

	Budesonide ODT	Fluticasone	No treatment	SFED
Drug costs	£766	£585	£0	£0
Co-medications (dilation)	£94	£132	£253	£211
Medical costs	£364	£401	£605	£968
AE costs	£0	£0	£0	£0
TOTAL COSTS	**£1,224**	**£1,117**	**£858**	**£1,179**
Incremental costs (budesonide ODT versus comparator)	-	£107	£367	£45
TOTAL QALYS	**0.99**	**0.97**	**0.89**	**0.91**
Incremental QALYs (budesonide ODT versus comparator)	-	0.02	0.10	0.08
ICER - cost per QALY gained; budesonide ODT versus comparator)	**-**	**£4,780**	**£3,574**	**£563**

Abbreviations: AE = adverse event; ICER = incremental cost-effectiveness ratio; ODT = orodispersible tablet; QALY = quality-adjusted life year; SFED = six-food elimination diet

Table 3. Results for 2-year time horizon

	Budesonide ODT	Fluticasone	No treatment	SFED
Drug costs	£1077	£1003	£0	£0
Co-medications (dilation)	£170	£231	£444	£394
Medical costs	£599	£611	£1,050	£1,391
AE costs	£0	£0	£0	£0
TOTAL COSTS	**£1,846**	**£1,844**	**£1,494**	**£1,785**
Incremental costs (budesonide ODT versus comparator)	-	£2	£352	£61
TOTAL QALYS	**1.76**	**1.73**	**1.58**	**1.61**
Incremental QALYs (budesonide ODT versus comparator)	-	0.03	0.18	0.15
ICER - cost per QALY gained; budesonide ODT versus comparator)	**-**	**£62**	**£1,958**	**£405**

Abbreviations: AE = adverse event; ICER = incremental cost-effectiveness ratio; ODT = orodispersible tablet; QALY = quality-adjusted life year; SFED = six-food elimination diet

In addition to the above analyses, the following scenario analyses were conducted (with both 1- and 2-year time horizons):

- Excluding costs of add-on treatment (emergency food bolus removal and endoscopic dilation)
- Using the same utility values as the ERG
- Using the same HRU as the ERG for the whole time horizon (the resource utilisation for active treatment is 0.5 gastroenterologist visits per cycle, one GP visit per cycle [£37.40 per visit] and 0.25 endoscopies per cycle. There is no resource utilisation

associated with remission and no treatment. Dietician visits and endoscopies for SFED do not change)

Table 4. Scenario analysis excluding add-on treatment costs (1-year time horizon)

	Budesonide ODT	Fluticasone	No treatment	SFED
Drug costs	£766	£585	£0	£0
Co-medications (dilation)	£0	£0	£0	£0
Medical costs	£364	£401	£605	£968
AE costs	£0	£0	£0	£0
TOTAL COSTS	**£1,131**	**£986**	**£605**	**£968**
Incremental costs (budesonide ODT versus comparator)	-	£145	£526	£162
TOTAL QALYS	**0.99**	**0.97**	**0.89**	**0.91**
Incremental QALYs (budesonide ODT versus comparator)	-	0.02	0.10	0.08
ICER - cost per QALY gained; budesonide ODT versus comparator)	**-**	**£6,482**	**£5,127**	**£2,032**

Abbreviations: AE = adverse event; ICER = incremental cost-effectiveness ratio; ODT = orodispersible tablet; QALY = quality-adjusted life year; SFED = six-food elimination diet

Table 5. Scenario analysis excluding add-on treatment costs (2-year time horizon)

	Budesonide ODT	Fluticasone	No treatment	SFED
Drug costs	£1077	£1003	£0	£0
Co-medications (dilation)	£0	£0	£0	£0
Medical costs	£599	£611	£1,050	£1,391
AE costs	£0	£0	£0	£0
TOTAL COSTS	**£1,677**	**£1,614**	**£1,050**	**£1,391**
Incremental costs (budesonide ODT versus comparator)	-	£63	£627	£286
TOTAL QALYS	**1.76**	**1.73**	**1.58**	**1.61**
Incremental QALYs (budesonide ODT versus comparator)	-	0.03	0.18	0.15
ICER - cost per QALY gained; budesonide ODT versus comparator)	**-**	**£2,075**	**£3,485**	**£1,891**

Abbreviations: AE = adverse event; ICER = incremental cost-effectiveness ratio; ODT = orodispersible tablet; QALY = quality-adjusted life year; SFED = six-food elimination diet

Table 6. Scenario analysis using ERG utilities (1-year time horizon)

	Budesonide ODT	Fluticasone	No treatment	SFED
Drug costs	£766	£585	£0	£0
Co-medications (dilation)	£94	£132	£253	£211
Medical costs	£364	£401	£605	£968
AE costs	£0	£0	£0	£0
TOTAL COSTS	**£1,224**	**£1,117**	**£858**	**£1,179**
Incremental costs (budesonide ODT versus comparator)	-	£107	£367	£45
TOTAL QALYS	**1.02**	**1.00**	**0.96**	**0.97**
Incremental QALYs (budesonide ODT versus comparator)	-	0.01	0.05	0.04
ICER - cost per QALY gained; budesonide ODT versus comparator)	**-**	**£8,962**	**£6,701**	**£1,056**

Abbreviations: AE = adverse event; ICER = incremental cost-effectiveness ratio; ODT = orodispersible tablet; QALY = quality-adjusted life year; SFED = six-food elimination diet

Table 7. Scenario analysis using ERG utilities (2-year time horizon)

	Budesonide ODT	Fluticasone	No treatment	SFED
Drug costs	£1077	£1003	£0	£0
Co-medications (dilation)	£170	£231	£444	£394
Medical costs	£599	£611	£1,050	£1,391
AE costs	£0	£0	£0	£0
TOTAL COSTS	**£1,846**	**£1,844**	**£1,494**	**£1,785**
Incremental costs (budesonide ODT versus comparator)	-	£2	£352	£61
TOTAL QALYS	**1.80**	**1.79**	**1.71**	**1.72**
Incremental QALYs (budesonide ODT versus comparator)	-	0.02	0.10	0.08
ICER - cost per QALY gained; budesonide ODT versus comparator)	**-**	**£116**	**£3,672**	**£760**

Abbreviations: AE = adverse event; ICER = incremental cost-effectiveness ratio; ODT = orodispersible tablet; QALY = quality-adjusted life year; SFED = six-food elimination diet

Table 8. Scenario analysis using ERG resource utilisation (1-year time horizon)

	Budesonide ODT	Fluticasone	No treatment	SFED
Drug costs	£766	£585	£0	£0
Co-medications (dilation)	£94	£132	£253	£211
Medical costs	£221	£151	£0	£518
AE costs	£0	£0	£0	£0
TOTAL COSTS	**£1,081**	**£867**	**£253**	**£730**
Incremental costs (budesonide ODT versus comparator)	-	£214	£828	£351
TOTAL QALYS	**0.99**	**0.97**	**0.89**	**0.91**
Incremental QALYs (budesonide ODT versus comparator)	-	0.02	0.10	0.08
ICER - cost per QALY gained; budesonide ODT versus comparator)	**-**	**£9,553**	**£8,066**	**£4,391**

Abbreviations: AE = adverse event; ICER = incremental cost-effectiveness ratio; ODT = orodispersible tablet; QALY = quality-adjusted life year; SFED = six-food elimination diet

Table 9. Scenario analysis using ERG resource utilisation (2-year time horizon)

	Budesonide ODT	Fluticasone	No treatment	SFED
Drug costs	£1077	£1003	£0	£0
Co-medications (dilation)	£170	£231	£444	£394
Medical costs	£345	£196	£0	£1,518
AE costs	£0	£0	£0	£0
TOTAL COSTS	**£1,592**	**£1,429**	**£444**	**£913**
Incremental costs (budesonide ODT versus comparator)	-	£162	£1148	£679
TOTAL QALYS	**1.76**	**1.73**	**1.58**	**1.61**
Incremental QALYs (budesonide ODT versus comparator)	-	0.03	0.18	0.15
ICER - cost per QALY gained; budesonide ODT versus comparator)	**-**	**£5,343**	**£6,383**	**£4,491**

Abbreviations: AE = adverse event; ICER = incremental cost-effectiveness ratio; ODT = orodispersible tablet; QALY = quality-adjusted life year; SFED = six-food elimination diet

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Budesonide for treating eosinophilic oesophagitis

Evidence Review Group's comments on the company's response to the technical report

Commissioned by the
NIHR Systematic Reviews Programme on behalf of NICE

Produced by	Southampton Health Technology Assessments Centre (SHTAC)
Authors	Dr Keith Cooper, Senior Research Fellow, SHTAC Dr Jonathan Shepherd, Principal Research Fellow, SHTAC Mrs Neelam Kalita, Research Fellow, SHTAC
Correspondence to	Dr Jonathan Shepherd Southampton Health Technology Assessments Centre (SHTAC) Wessex Institute Alpha House Enterprise Road, University of Southampton Science Park Southampton SO16 7NS www.southampton.ac.uk/shtac
Date completed	1st April 2020

1 Introduction

This document is the ERG's critique of the response by the company (Dr Falk Pharma UK Ltd) to the draft technical report for technical engagement issued by NICE to stakeholders on 12th February 2020. The ERG received the company's response to technical engagement on 12th March 2020. The company responded to each of the issues for technical engagement and updated the cost-effectiveness analyses from their submission to NICE (in September 2019).

In this report we present the following:

- Our commentary on the company's response to the issues raised in technical engagement (with the exception of Issue 1 for which the ERG has no further comments to make).
- Our validation of the results of the company's updated cost-effectiveness analysis.
- The results of an updated ERG analyses, incorporating some of our original preferred assumptions (as detailed in the ERG report dated 27th November 2019), and revised assumptions reflecting our current position following discussions with the NICE technical team and the company during technical engagement.

2 ERG commentary on the company's response to technical engagement

Issue 2 – Maintenance therapy for patients in remission should not be included in the economic evaluation for budesonide

Question	ERG comments
a) When pharmacological treatment for EoE is stopped, typically when do symptoms and/or esophageal eosinophilia recur?	The ERG has no further comments to make.
b) In practice, would patients responding to fluticasone or other corticosteroid formulations be likely to continue receiving these as maintenance therapy?	Expert clinical advice to the ERG suggests that this is the case. In current practice patients typically begin EoE treatment with fluticasone, the majority of whom respond to and are maintained on this treatment in the long term to prevent relapse. The company's expert opinion agrees with this.
c) Additional ERG comments on maintenance therapy	In their response to technical engagement the company updated their analyses to compare budesonide ODT induction therapy (6 to 12 weeks duration, with repeat episodes for patients who relapse), versus fluticasone induction therapy which is continued in responders (i.e. maintenance therapy) and versus SFED (six-food elimination diet) comprising an initial dietary intervention to identify and eliminate symptom-triggering foods, and thereafter the maintenance of that diet by the patient. The company justifies not modelling continued budesonide ODT in patients responding during the induction episode (i.e. maintenance therapy) because the marketing authorisation permits treatment for a maximum duration of 12 weeks. The ERG acknowledges that NICE are unable to issue guidance on the use of a treatment outside its

	marketing authorisation. However, expert clinical advice to the ERG suggests that clinicians would prefer to continue treating patients who respond to induction treatment beyond 12-weeks, to maintain symptom control and prevent relapse. Thus, modelling repeated budesonide ODT treatment episodes of up to 12-weeks of whilst permitted by the marketing authorisation, does not necessarily reflect clinician preference. In section 4 below we investigate different treatment options regarding the use of induction and maintenance treatment.

Issue 3 – Model structure and time horizon

Question	**ERG comments**
a) Would it be more appropriate to model the cost effectiveness of budesonide ODT using a time horizon that captures the costs and benefits associated with a single episode of treatment?	In their response to technical engagement the company did not model the cost effectiveness of a single episode of budesonide ODT treatment. They state that budesonide ODT is expected to be prescribed episodically, given that the majority of patients relapse after completing a course of treatment. As discussed above (Issue 2), they model induction treatment with budesonide ODT (6 to 12 weeks duration), and patients who subsequently relapse receive repeat episodes of budesonide ODT. The ERG acknowledges that episodic budesonide ODT treatment may become standard practice in some areas. However, our clinical experts (consulted before technical engagement) did not discuss episodic treatment. As discussed above, they favoured continued therapy with budesonide ODT in responding patients, possibly because a similar approach is currently used for fluticasone.
b) What is the appropriate time horizon for the model considering that the treatment	In their response, the company proposes a time horizon spanning one year, and two years (NB. This is based on their approach of modelling repeat budesonide ODT

under consideration can be given continuously for a maximum of 12 weeks according to the licence?	episodes, rather than just a single episode). They consider that a longer time horizon would increase uncertainty due to paucity of data on model parameters, specifically for relapse rates, subsequent response rates and adherence to treatment.
c) What time frame adequately captures the true costs and benefits of budesonide ODT as it is licensed? Would this be different for different comparators?	An appropriate time horizon depends upon the assumptions used in the model. According to the NICE reference case, the time horizon should be "*Long enough to reflect all important differences in costs or outcomes between the technologies being compared".* In this appraisal this means differences in costs and outcomes between treatments in the number of people in remission or in active EoE receiving treatment. Where a single episode of budesonide ODT treatment is to be modelled we consider that a time horizon of between 5-10 years would be sufficient. The proportion of patients in remission in the fluticasone arm would be between 6% and 0.5%, at 5 years and 10, respectively.
d) If a shorter time horizon is required, would a different model structure be appropriate?	The technical report states the technical team's preference for a model structure that reflects the marketing authorisation for budesonide ODT (i.e. a maximum of 12 weeks treatment). The company's view is that the model structure remains appropriate for the shorter time horizon they use for modelling episodic budesonide ODT treatment. The ERG's view is that a single episode of budesonide ODT is a treatment option that should be included, with a time horizon appropriate to this. The existing model structure, which is for episodic budesonide ODT treatment, would need to be altered. In section 4 below we present an ERG analysis based on a single episode of budesonide ODT treatment.

Issue 4 – The costs for follow up and monitoring have been overestimated

Question	ERG comments
a) Are the ERG's assumptions about follow-up and monitoring costs sufficiently realistic given the feedback received from clinical experts?	The company's view is that patients with EoE would be managed by a gastroenterologist, with any general practitioner involvement limited to providing repeat prescriptions. The technical report stated that clinical experts consulted did not validate the ERG's assumption that patients will be monitored in primary care once in remission. The ERG accepts that GPs would only be required for repeat prescriptions. We maintain the view that health care resources would not be maintained at a constant rate throughout the model's time horizon. This may be less important if a short time horizon is used. The company has agreed that patients not receiving treatment would have a lower rate of gastroenterologist visits and endoscopies, per 12-week cycle. They contend that these patients would still receive gastroenterologist visits as they would be symptomatic and so may require endoscopic dilation or emergency food bolus removal. We raised concerns in the ERG report about the unrealistically high levels of resource use which was driven by the resource use for those not receiving treatment. As discussed above, these concerns are more substantial if a longer time horizon is used. The company's assumptions are more reasonable for their shorter time horizon of one and two years used in their updated analyses.
b) In clinical practice would the rate of monitoring visits and procedures be constant, or would there be more	The company state they would expect that the rate of monitoring visits will be constant over the updated shorter time horizon of one to two years, compared with the 40-year time horizon in the company submission. We consider that the rate of monitoring visits is unlikely to be constant over a long time horizon, however for a shorter time horizon the

monitoring in the initial treatment period?	company's assumption of constant rate of monitoring visits may be reasonable.

Issue 5 – The company have assumed that the probability of add-on dilation treatments varies by treatment and health state

Question	ERG comments
a) Should the costs for add-on treatments be removed from the company model?	The ERG agrees, in principle, with the company's rationale for the inclusion of endoscopic dilation add-on treatment in the model. In clinical practice, repeated endoscopic dilation would be required to resolve oesophageal strictures caused by food-bolus obstructions in untreated patients or patients who have not responded adequately to active treatment. These would be required to a lesser extent in patients responding to existing available therapies. The company's updated analyses retains the costs of add-on treatment, but, as in their previous analyses it does not include the outcomes. These outcomes could include the adverse impact of emergency food bolus removal and dilation treatment on health-related quality of life (HRQoL). The company justifies this omission by noting the lack of available data on HRQoL to inform utility estimates. The ERG notes that both costs and outcomes should be Included in an economic evaluation. However, like the company, we have not identified any evidence that could inform utility estimates or assumptions. It is difficult to predict with certainty the impact on cost effectiveness if disutility estimates for dilation and food bolus removal were included. This therefore remains an area of uncertainty. The company include a scenario analysis in which the costs of add-on treatment are removed (Table 4 and Table 5 of the company's response document). The results show an

	increase in the ICERs for budesonide versus comparators, all of which remain under £10,000 per QALY. In common with the company we have reduced the add-on treatment costs for patients in remission to half of those used for patients in the active EoE health state receiving treatment.
b) Should the number of add-on dilation treatments received vary depending on the induction treatment received or be assumed the same across all arms of the model?	Expert clinical advice to the ERG is that, due to lack of available evidence, it is unclear whether dilation rates would vary between treatments. Furthermore, the ERG also notes that there is likely to be little evidence on dilation rates following a single episode of induction treatment (with no subsequent maintenance treatment), or repeat episodes of the same treatment (which reflects the company's expectation for the prescribing pattern for budesonide ODT once available and therefore their updated analysis). The ERG considers that, in the absence of evidence, it is reasonable to assume the number of add-on endoscopic dilations would be similar between treatments. We therefore retain this assumption in our analyses. We also assume that the no treatment arm would have a higher dilation rate, as would reasonably be expected. The company's updated analyses assumes the same rate of dilation for all treatments (previously they assumed rates differed between treatments). They also assume that patients in the no treatment arm would receive twice the number of dilations, based on a retrospective database study of patients who received endoscopic dilation, by Schoepfer et al (2010)[1] (NB. this study was not cited in the company submission). This study reported that 67% of patients required a repeat dilation every 15 months (equating to 0.125 per 12-week disease cycle).
c) Is it reasonable to assume that patients in remission have	The company's original base case used different dilation rates for the active treatment and remission health states. In

the same probability of requiring treatment for emergency food bolus removal/endoscopic dilation as those in the active disease state?	their updated analyses they retain this assumption, but they use a different probability per 12-week cycle than in the original analyses. This is based on dilation rates estimated in a retrospective study by Schoepfer et al (2010)[1] mentioned above. The company assumes that in the remission health state the rates would be 50% lower than in active disease. The ERG considers this to be a reasonable approach. The estimates are 6% per model cycle for active disease, and 3% per cycle for remission. In our original analyses we assumed the same rate of dilation in the active disease and remission health states, with a probability of add-on treatment of 2% per 12-week model cycle. This probability was based on a retrospective cohort study of patient database records from 2002-2014 in a US hospital, by Runge et al (2016)[2]. We retain this source in our updated ERG analyses, and we use the same assumption as the company of a 50% lower dilation rate for remission (1%) than for active disease (2%). We note that our dilation rate estimates are lower than those of the company in their updated analyses (i.e. 6% and 3% (company); 2% and 1% (ERG) per cycle for the active and remission health states, respectively). As we will report in section 4 below, this has relatively little impact on ICERs in the ERG analyses.

Issue 6 – The company's utility values are not robust

Question	**ERG comments**
a) Is gastro-oesophageal reflux disease with heartburn a good proxy for active EoE, how similar are the conditions in terms of health-related quality of life?	The company disagrees with the ERG's utility value for the active disease health state, which was based on a UK study of patients with EoE, comparing their SF-36 scores to those of a control group (Hewett et al. 2017)[3]. In their response the company *states that "The study included patients treated with PPIs (20.5%) and topical corticosteroids*

	(25.7%), and as such would be expected to include those in both the active disease and remission health states in a single EoE cohort. No attempt was made to differentiate these patients or make a comparison between patients with EoE in active disease or remission health states. Instead, patients with EoE were compared with age- and gender-matched healthy controls recruited from the local population. Due to the inclusion of patients in remission, the utility value used by the ERG overestimates the QoL of patients in the active disease health states." (page 12) The ERG considers the company's objection to the use of this study to be reasonable. However, we still consider that utility values taken from a population of patients with EoE is preferable to utility values from a proxy population (in this case patients with gastro-oesophageal reflux disease (GORD)). As data on the numbers of patients in remission or with active disease are not reported in the study by Hewett et al[3] it is not possible to adjust the quality of life values to ascertain the values for only those with active disease. We have therefore investigated alternative health related quality of life evidence sources. A study by Larsson et al (2015)[4] of 47 Swedish patients with EoE collected SF-36 scores before and after two months treatment with topical corticosteroids, and again at long-term follow-up of 23 months. We had previously considered this study in our review of quality of life studies, but we did not discuss it in the ERG report. We mapped SF-36 scores to EQ-5D using the mapping algorithm described by Ara and Brazier.[5] The mapped EQ-5D scores are as follows: • at study inclusion 0.85, • post-treatment 0.91, • long term follow-up 0.89.

	The difference in utility between study inclusion (i.e. active disease) and post-treatment is 0.053. Assuming the same proportion of responders from the ERG's network meta-analysis (NMA) for fluticasone (described in the ERG report) (i.e. 73%), the adjusted post-treatment utility for responders is 0.927, i.e. difference to active disease of 0.072. This value is similar to the value used in the ERG base case (0.07).
b) It is appropriate to use a utility value that is based on the population norm (that is for an average person without EoE) for the remission health states given that the data informing this heath state relates to histological remission	The company maintains their justification for use of population norms for an average person without EoE to estimate utility for the remission health state. They cite evidence suggesting that clinical symptoms have modest accuracy in predicting endoscopic or histological remission. The ERG is not aware of any evidence to the contrary.

3. ERG validation of the results of the company's additional cost-effectiveness analysis

The company's updated economic analysis compares budesonide ODT induction therapy of 6 to 12 weeks duration (with repeat episodes for patients who relapse), versus induction therapy with fluticasone which is continued in responders (i.e. maintenance therapy) and versus SFED (comprising an initial dietary intervention to identify and eliminate symptom-triggering foods, and thereafter the maintenance of that diet by the patient to maintain remission). A no treatment comparator arm has also been added as recommended in the technical report.

The updates to the parameter values are shown in Table 1 of the company's response document. Briefly, they made changes to:

- The time horizon (reduced from 40 years to a set of two shorter term time horizons - one and two years)
- The cost of budesonide and fluticasone;

- The response (remission) rates for budesonide ODT;
- The relapse rates for fluticasone and SFED;
- The health care resources used in the no treatment arm, and
- The rate of add-on treatment (emergency food bolus removal and endoscopic dilation)

In addition, the company has corrected errors in the model as follows:

- Calculation of relapse rate per 12-week remission cycle. For example, in the case of budesonide ODT, 22% of all patients who initially respond will relapse each 12-week cycle, not 22% of the patients still in remission. Thus, 88% over four 12-week remission cycles.
- Calculation of patients who remain in remission i.e. those who don't relapse at the end of the year (i.e. 12% of patients for budesonide ODT) remain in remission.'

The ERG disagrees with the first correction made above. The correction has the effect of increasing the probability of relapse every 12-week cycle, as shown in Table 1 below. As can be seen, the probability of relapse increases from 0.22 to 0.65. The company has not justified why the probability of relapse increases in this way and we suggest a better approach is to use a constant probability which can be calculated using the formula: 1-(1-0.88)^(1/4), where 0.88 is the proportion of patients who relapse over a year and the number of cycles is four. However, in the company's updated analyses the effect of this correction is likely to be relatively small.

Table 1 The company's relapse probability using original and revised methods

Cycle	Company's original relapse probability	Company's revised relapse probability	ERG suggested relapse probability
2	0.22	0.22	0.411
3	0.22	0.28	0.411
4	0.22	0.39	0.411
5	0.22	0.65	0.411

The results of the company's updated analyses are shown in their response document in Tables 2 and 3, for one-year and two-year time horizons, respectively. They also report results of scenario analyses exploring the impact of excluding the costs of add-on treatment (Table 4 and 5); analyses using the same utility values as the ERG (Table 6 and 7); and analyses using the same health care resource use assumptions as the ERG (Table 8 and 9).

Each of these scenarios is repeated for a one-year and two-year time horizons. The ERG has checked the updated analyses by making the changes described above in the original model and successfully verified the results.

In the company's submission to NICE, budesonide ODT dominated all comparators (i.e. it was cheaper and more effective). In the company's updated cost effectiveness analyses with the ICER for budesonide ODT ranged from £62 - £4780 per QALY versus fluticasone, £1,958 - £3,574 per QALY versus no treatment and £405 – 563 per QALY versus SFED, for the one and two-year time horizons, respectively.

4. Results of updated ERG analyses following technical engagement

We have updated our analyses to model the cost effectiveness of budesonide ODT using the company's updated model (section 4.1). We also report ERG analyses based on the company's model from their submission to NICE (September 2019), to explore different scenarios regarding the use of maintenance treatment (section 4.2).

4.1 ERG analyses based on the company's updated model following technical engagement

In these analyses we model the same episodic treatment approach as the company in their updated analyses: budesonide ODT induction therapy (with repeat episodes for patients who relapse), versus induction therapy with fluticasone which is continued in responders (i.e. maintenance therapy) and versus SFED (patient-maintained diet following initial dietary intervention).

Table 2 shows the company's and the ERG's preferred parameter estimates, some of which have been updated following technical engagement. The results of the ERG's analyses are shown in Table 3 and 4 below for time horizons of one year and two years, respectively. The model results are most sensitive to changes in the cost of the treatments, the utility values used and the resource use for the no treatment active EoE health state. The combined effect of all changes is a large change in the ICERs for all treatments compared to those of the company's updated analyses. The changes have the biggest impact in the two-year time horizon, with the combined assumptions resulting in budesonide ODT becoming dominated by SFED and the ICER for budesonide ODT compared to fluticasone increasing to £105,391 per QALY.

Table 2 Summary company's and ERG's revised parameter estimates

Parameter	Company's revised estimate	ERG preferred estimate
Cost of budesonide, fluticasone	Cost of budesonide £429 per cycle; cost of fluticasone £202 per cycle (dose of 1 mcg per day)	Cost of budesonide £460 per cycle; cost of fluticasone £104 per cycle (dose of 2 mcg per day)
Utility values	Active EoE 0.78; remission 0.93	Active EoE 0.86; remission 0.93
Relapse values	Fluticasone 15.3% per cycle, SFED 50% after end of year	Fluticasone 11% per cycle; SFED 11% per cycle
Remission odds ratio	Company's NMA	ERG's NMA (with continuity correction)
Endoscopic dilation rate	Active EoE 0.06 per cycle; remission 0.03 per cycle (budesonide ODT, fluticasone, SFED) Active EoE 0.125 per cycle, remission 0.06 per cycle (no treatment)	Active EoE 0.02 per cycle; remission 0.01 per cycle (budesonide ODT, fluticasone, SFED) Active EoE 0.125 per cycle, remission 0.06 per cycle (no treatment)
No resource use for the active EoE health state (no treatment)	Active EoE (no treatment) half resources of treatment with budesonide, fluticasone	Active EoE (no treatment) no health care resources
Remission rate after 1 year	Assumes all who have remission at 1 year remain in remission	Assumes individuals in remission continue to relapse after 1 year

EoE = eosinophilic oesophagitis; NMA = network meta-analysis; ODT = oral dispersible tablet; SFED = six-food elimination diet.

Table 3 ERG analyses for budesonide ODT vs comparators, time horizon 1 year

	ICER (£/QALY) for budesonide vs		
	Fluticasone	**No treatment**	**SFED**
Company's updated base case	*£4,780*	*£3,574*	*£563*
Cost of budesonide, fluticasone	£20,275	£4,104	£1,243
Utility using ERG estimates	£10,242	£7,659	£1,206
Relapse	£8,665	£3,574	£371
Remission odds ratio	£6,244	£3,468	BUD Dominates
Dilation rate	£5,915	£4,609	£1,542
No resource use for the active EoE health state (no treatment)	£11,102	£8,440	£5,764
All changes above	£107,827	£21,166	£12,571

Table 4 ERG analyses for budesonide ODT vs comparators, time horizon 2 year

	ICER (£/QALY) for budesonide vs		
	Fluticasone	**No treatment**	**SFED**
Company's updated base case	*£62*	*£1,958*	*£406*
Cost of budesonide, fluticasone	£19,065	£2,383	£911
Utility using ERG estimates	£133	£4,196	£869
Relapse	£5,913	£1,958	£356
Remission odds ratio	BUD dominates	£1,857	£43
Dilation rate	£1,404	£2,976	£1,396
No resource use for the active EoE health state (no treatment)	£7,766	£6,934	£5,622
Remission rate after 1 year	BUD dominates	£2,299	£646
All changes above	£105,391	£18,614	Dominated by SFED

We conducted scenario analyses to assess the impact of changes in the following parameters:

1. **Fluticasone dose.** The company's updated model uses a dosage of 2µg day for fluticasone. The ERG notes that the recommended dose is 440-880 µg BID.[6] The mean recommended dose is 1.32 µg per day and the higher recommended dose is 1.76 µg per day.
2. **Resource use estimates for patients not receiving treatment.** The company assumed the resource use for the no treatment arm would be half of that used for fluticasone or budesonide ODT treatment arms. We change the resource use in the no treatment arm to a quarter of that used by patients with active EoE receiving fluticasone or budesonide.
3. **Excluding add-on treatment costs.** We ran an analysis where add-on treatment costs (emergency food bolus removal and endoscopic dilation) were excluded (see Issue 5 above).

All other ERG-preferred assumptions as reported in Table 2 above are included. We have focused on the two-year time horizon, as we consider this is more appropriate than a one-year horizon for the reasons we discussed above (Issue 3c).

The results are shown in Table 5, and the ICERs are most sensitive to changes in the dose of fluticasone used.

Table 5 ERG scenario analyses for budesonide ODT vs comparators, time horizon 2 years

		ICER (£/QALY) for budesonide vs		
		Fluticasone	**No treatment**	**SFED**
Company base case		*£62*	*£1,958*	*£406*
ERG analyses based on all changes made in Table 2 above		*£105,391*	*£18,614*	*Dominated by SFED*
ERG scenario 1	Dose of fluticasone, 1.3 µg per day.	£85,571	£18,614	Dominated by SFED
	Dose of fluticasone, 1.76 µg per day.	£58,319	£18,614	Dominated by SFED
ERG scenario 2	Treatment resource use for active EoE when receiving no treatment (1/4 the health care resource used by patients with active EoE receiving fluticasone or budesonide)	£82,728	£7,824	Dominated by SFED
ERG scenario 3	Add-on treatment costs excluded	£107,253	£19,708	Dominated by SFED

4.2 ERG analyses based on previous version of economic model submitted to NICE

4.2.1 A single episode of budesonide ODT (ERG scenario 4)

The technical report recommended that a single episode of budesonide ODT treatment would be preferable given that it reflects the marketing authorisation. As we discussed earlier, the company has chosen not to include this in their updated analyses. To inform the NICE appraisal committee's decision making we have modelled a single episode of budesonide ODT induction treatment with no maintenance treatment for responders and no further treatment episodes for relapsers, versus induction therapy with fluticasone which is continued in responders (i.e. maintenance therapy), and versus SFED.

We conducted these analyses using the version of the company's model accompanying their submission to NICE in September 2019 (retaining the preferred assumptions which informed our analyses in the ERG report, November 2019). Our intention was to use the company's updated model. However, the model is structured for episodic budesonide ODT and adaptations are required to model a single treatment episode. It was not possible for the ERG to make the necessary adaptions within the time available. Furthermore, we have not included a comparison to no treatment as this version of the model did not include no treatment as formal comparator (its inclusion as a comparator in the appraisal was a recommendation at technical engagement – see Issue 1 of the technical report).

We used a time horizon of five years, which as discussed earlier, we consider more appropriate for a single episode of budesonide ODT (see Issue 3c 'Model structure and time horizon' above). We also changed the endoscopic dilation rate so that it was half the rate for patients in remission compared to the rate for patients receiving treatment in the active EoE health state. All other parameters and assumptions are as reported in the ERG report (section 4.4.5). We report the results of this scenario below in section 4.2.3.

4.2.2 Budesonide induction and maintenance treatment (ERG scenario 5)

In our discussion of Issue 2 above ('Maintenance therapy for patients in remission'), we noted the variations in clinical practice regarding the use of induction and maintenance therapy, and likely clinician treatment preferences if budesonide ODT is available on the NHS. We therefore report, for illustration, the results of a scenario analysis of budesonide ODT induction treatment, maintained in responders, versus fluticasone induction treatment maintained in responders, and versus SFED. We reiterate that budesonide ODT is not

licenced for use as maintenance treatment and therefore cannot be included in NICE guidance recommendations.

4.2.3 Results of ERG scenario analyses

In both scenarios, fluticasone is more cost effective than budesonide ODT. For the scenario modelling a single episode of budesonide ODT (scenario 1), budesonide dominates SFED, i.e. it is cheaper and more effective.

Table 6 ERG scenario analysis 4. One cycle budesonide ODT induction therapy with no maintenance treatment, versus induction and maintenance fluticasone treatment, and versus SFED, 5-year time horizon.

	Total costs (£)	Total QALYs (£)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY) Pairwise BUD vs each treatment
SFED	£ 874	4.05	-£136	0.01	BUD dominates
Fluticasone	£948	4.09	-£209	-0.02	£9,219[a]
Budesonide ODT	£ 738	4.06			

[a] Fluticasone vs budesonide ODT

Table 7 ERG scenario analysis 5. One cycle budesonide ODT induction therapy then budesonide ODT maintenance treatment, versus induction and maintenance fluticasone treatment, and versus SFED, 5-year time horizon.

	Total costs (£)	Total QALYs (£)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY) Pairwise BUD vs each treatment
SFED	£ 874	4.05	£2,584	0.06	£45,617
Fluticasone	£948	4.09	£2,511	0.02	£ 100,893
Budesonide ODT	£ 3,459	4.11			

5. Summary

In the company's updated analyses the ICERs for budesonide ODT compared to alternative options lie within conventional cost per QALY thresholds that decision makers would consider acceptable. The updated analyses conducted by the illustrate that there is considerable uncertainty in cost per QALY estimates based on alternative assumptions on the time horizon, the use of maintenance therapy, treatment costs, utility values and health care resource use.

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Evidence Review Group Report commissioned by the NIHR Evidence Synthesis Programme on behalf of NICE

Budesonide orodispersible tablet (ODT) for treating eosinophilic oesophagitis ID1202

Addendum to the Evidence Review Group's comments on the company's response to the technical report

Produced by	Southampton Health Technology Assessments Centre (SHTAC)
Authors	Dr Keith Cooper, Senior Research Fellow, SHTAC
	Dr Joanna Picot, Senior Research Fellow, SHTAC
	Mrs Neelam Kalita, Senior Research Fellow, SHTAC
	Dr Jonathan Shepherd, Principal Research Fellow, SHTAC

Date completed 17th March 2021

1 Introduction

Following technical engagement for this STA (between February to April 2020) and a pause in the appraisal due to the COVID-19 pandemic, NICE have re-scheduled the appraisal committee discussion of this topic for April 2021. In preparation for the discussion NICE requested additional information from the ERG with regard to the following economic evaluation parameters:

- An appropriate time horizon for the model
- Relapse rates
- Endoscopic dilation rates
- Costs of budesonide orodispersible tablet (ODT) and fluticasone

NICE also requested analyses of budesonide ODT as a single induction treatment episode and as a multiple induction episode therapy, to be modelled over appropriate time horizons, based on the review of the parameters.

In this document we provide a brief review of the available evidence relating to the above parameter values, and we propose revised parameter estimates where appropriate. We use these estimates to inform two exploratory scenario analyses of budesonide ODT single episode induction treatment, the results of which are presented for consideration by the NICE appraisal committee.

2 Technical engagement issue 3 – time horizon

We refer to the comments made in our response to technical engagement in Issue 3. These are reproduced in part below:

An appropriate time horizon depends upon the assumptions used in the model. According to the NICE reference case, the time horizon should be “Long enough to reflect all important differences in costs or outcomes between the technologies being compared”. In this appraisal this means differences in costs and outcomes between treatments in the number of people in remission or in active EoE receiving treatment.

We consider the time horizon can be estimated as the time at which the proportion of patients in these health states is low enough that significantly changes to the estimates of cost effectiveness are unlikely. Using these criteria, we recommend a time horizon of:

- 3 years where a single budesonide ODT induction treatment is modelled
- 5 years where a single induction treatment followed by with maintenance treatment is modelled
- 30 years where multiple induction episodes of budesonide ODT and fluticasone induction and maintenance treatment are modelled.

2.1 Should SFED be included as a comparator if budesonide ODT is modelled only as an induction treatment?

Our view has been that SFED should be included as a comparator as it is in the NICE scope, and therefore we modelled SFED to reflect its real-world use, i.e. as a long-term (maintenance) treatment. Our approach to modelling fluticasone was similar, as our clinical experts advised us that patients responding to an induction episode of fluticasone would then be maintained on this drug in the long-term.

However, we agree that it would not be appropriate to include SFED as a comparator in an analysis based on a single budesonide ODT induction episode. We provide a scenario analysis comparing budesonide ODT induction only versus fluticasone induction only, in which SFED is excluded as a comparator. See Table 3 in Section 6 of this document.

2.2 Should single or multiple induction episodes be modelled?

The company's revised analyses following technical engagement includes modelling of multiple budesonide ODT induction episodes. When patients who respond to the initial induction treatment relapse, they receive further repeat induction episodes over time. The company assumes that for those patients re-treated with budesonide ODT, the response rate will be the same as the first episode and all patients who responded to the initial induction treatment with fluticasone will respond to subsequent induction treatment. The ERG notes that the response rate for subsequent induction therapy is based on an assumption. rather than any clinical effectiveness evidence.

Given that the short-term nature of the trials for the treatments, making assumptions over the long-term may be problematic. The ERG's preference is to model budesonide ODT as a single induction treatment episode.

3 Relapse rates

The model includes relapse rate estimates for those on maintenance treatment and those in the no treatment comparator arm. In their technical engagement response, the company assumed a relapse rate for no treatment of 88% after 1 year, based on the placebo arm of the BUL-2/EER[1] trial. This has been included within the model with non-constant relapse probabilities of 22%, 28%, 39% and 65% for the first four cycles respectively. They assumed a relapse rate of 15% per cycle for fluticasone maintenance, based on the study by Eluri et al[2] and assumed 50% of patients with SFED relapsed after one year due to non-adherence.

We conducted a targeted search in Pubmed to explore the published evidence on relapse rates, initially in October 2019 and updated in February 2021. We found seven studies that reported relapse rates for patients on maintenance therapy. Four studies were in adults and three studies were in children. The relapse rates for those on maintenance therapy is shown in Table 1.

Table 1 Relapse rates for EoE patients on maintenance therapy

Study	Maintenance treatment	Population	Sample size	Number remaining in remission	Months
Reed et al.[3]	SFED	Adults	21	10	24.9
Eluri et al.[2]	Fluticasone / Budesonide OVS	Adults	33	13	23
Straumanm et al.[4]	Budesonide OVS	Adults	14	5	12
Greuter et al.[5]	Fluticasone / Budesonide[a]	Adults	82	27	26.4
Total / Average			**150**	**55**	**24.1**
Oliva et al.[6]	Budesonide OVS	Children	20	17	5.5
Andraea et al.[7]	Fluticasone	Children	43	30	20.4
Butz et al.[8]	Fluticasone	Children	15	11	3.0

OVS = oral viscous solution

[a] Formulation of budesonide unclear / not reported

Using only the four studies for adults, the average relapse rate for patients on maintenance therapy is 63.3% over an average 24.1 months, i.e. 11.7% per cycle. (Note: the original ERG relapse rate for maintenance treatment calculated as 11% by a different method).

Clinical advice to the ERG suggests that the relapse rate seen in clinical practice is considerably lower than reported in the clinical trials (<10% per year; i.e. <2.5% per cycle).

In our revised analyses we use a relapse rate of 11.7% per cycle for maintenance therapy and provide sensitivity analyses with alternative relapse rates (Section 8).

With respect to the relapse rate for patients not receiving maintenance, we found a recent published study by Dellon et al.(2019)[9] which reported the relapse rate for patients who were initially treated with budesonide OVS or fluticasone and responded but did not receive maintenance therapy. This study found no difference in the relapse rates for those initially treated with budesonide OVS or fluticasone. Patients were followed up for one year and 78% of patients had a histologic relapse (i.e.31.5% per 12-week cycle). Dellon's study, published in a peer reviewed journal, specifically investigated relapse following induction treatment and we consider it highly relevant to this appraisal. We therefore use this relapse estimate for the no treatment comparator in our analyses (section 6).

4 Endoscopic dilation rates

We conducted a search in Pubmed for studies that report endoscopic dilation rates (initial search conducted in October 2019 and updated in February 2021). We discuss the studies of most relevance in more detail below.

Moawad et al.[10] conducted a systematic review and meta-analysis to assess the efficacy and safety of endoscopic dilation in children and adults with EoE. There were 27 studies describing 845 EoE patients, who underwent a total of 1820 oesophageal dilations. The median number of dilations was 3 (range: 1-35). Of the studies included, the most relevant studies were by Runge et al (2016)[11] and Schoepfer[12] et al and these are discussed below.

Runge et al. (2016)[11] followed patients with EoE for a median follow-up of 15.1 months. 164 of 507 patients (32.2%) required dilation and had an average of 2.96 dilations. Sixty per cent of those receiving planned dilations were receiving medications for EoE.

In the study by Schoepfer et al.[12] 207 out of 681 (30.3%) EoE patients underwent esophageal dilation in two cohorts. Cohort 1 consisted of 63 patients treated with dilation alone, whereas cohort 2 included 144 patients treated with a combination of dilation and anti-eosinophilic medication. Patients from cohort 1 underwent a prospective histological re-examination and an evaluation using a questionnaire. After dilation, dysphagia recurred after 23 ± 22 months in cohort 1 and 20 ± 14 months in cohort 2. The total number of dilations completed is unclear. The study reports the number of dilation sessions performed until clinically successful was 2 in both cohorts.

From the two studies above the proportion of patients who had dilations was about 30% and the dilation rate ranged from every 5 months to 2 years.

Clinical advice to the ERG suggests that the proportion of patients who have dilations is considerably lower (5-10%) and that the time between dilations would be in excess of 2 years. Further, our clinical expert commented that in their experience repeat dilation was uncommon. Therefore, based on the figures above, this corresponds to a dilation rate of <1% per cycle.

4.1 Assumptions regarding dilation rate for those on active treatment and maintenance

Runge et al. 2017[13] conducted a retrospective cohort study to investigate whether histologic response to topical steroid treatment decreases the likelihood and frequency of subsequent esophageal dilation. The 55 EoE patients who received dilation included 27 responders and 28 non-responders who underwent a mean of 3.0 dilations over a median follow-up of 19 months. Responders required fewer dilations than non-responders (1.6 vs. 4.6, P = 0.03), after adjusting for potential confounders. The authors concluded that inflammation control is an important goal in patients with fibrostenotic changes of EoE.

Schupack et al.[14] assessed the relationship between short-term histologic remission and maintenance therapy on the need for repeat dilation in eosinophilic esophagitis. A total of 77 patients with EoE were included. Fifty-one patients achieved histologic remission and 42 of these remained on maintenance therapy (23 PPIs, 14 topical steroids, and 5 dietary therapy). A significantly lower proportion of patients on maintenance therapy required repeat dilation (12/42) compared with patients not on maintenance therapy (8/9) (hazard ratio 0.12; p < 0.001). The difference in need for repeat dilation in patients who achieved histologic remission on therapy (14/26) versus those who did not (20/51) was not statistically significant (hazard ratio 1.34; p = 0.45). The authors concluded that a significantly lower proportion who received maintenance therapy (PPIs, steroids, or dietary exclusions) required repeat dilation.

In their technical engagement response, the company assume that patients in the no treatment comparator arm had a repeat dilation rate of 12.5% per cycle, those with active disease receiving treatment would have a lower rate (assumed to be 50% lower, i.e. 6% per cycle). For patients in the remission health states, it was assumed that patients would receive 50% of the dilations of those in the active disease health states.

Clinical advice to the ERG commented that it was reasonable to assume that dilation rate would be lower for those on treatment and in remission than those not on treatment.

In our revised our analyses we continue to use a dilation rate of 2% for those on induction treatment and 1% for those in remission, as this is in line with clinical advice. We agree with the company's assumption that patients on no treatment would have a dilation rate double that of patients on treatment. Therefore, we use a dilation rate for those on no treatment of 4% for those not in remission and 2% for those in remission. Analyses with alternative dilation rates are shown in section 6.

5 Budesonide ODT and fluticasone cost

5.1 Cost of budesonide ODT

In their response to technical engagement, the company reduced the cost of budesonide ODT from £460 per cycle (original cost) to £430 per cycle. They assumed drug wastage in the original analysis but no wastage in the revised analysis.

The ERG considers that the cost of budesonide ODT should include wastage, as induction treatment is for a period of up to 12 weeks (i.e. a total 84 days) and the budesonide ODT pack size is 90 tablets.

5.2 Cost of fluticasone

At technical engagement the company increased the daily dosage of fluticasone for the induction period from 1.1 mg per day to 2mg per day, based on a study of high-dose swallowed fluticasone (1.76mg per day) by Butz et al.[8] The company assumed that patients would receive 2mg for induction and 1 mg for maintenance, as doses can only be given in increments of 250mcg.The company also changed the formulation of fluticasone used, as suggested in the ERG report. The original cost per pack (6 mg) is £6.53 and the revised cost per pack (30 mg) is £36.14. These changes increase the cost of fluticasone from £104 (original cost) to £202 per cycle for the induction period, and from £54.48 (original cost) to £104 per cycle for the first maintenance phase.

We note a published recommended dose of fluticasone is 0.88 mg BID.[15] However, the dose given in clinical practice may vary. One of the ERG's clinical experts stated that the dose used in their practice for fluticasone was 1.5 mg/day for induction therapy and 1 mg/day for maintenance therapy.

In our revised analyses we adopt the fluticasone doses used by our clinical expert, i.e. 1.5 mg/day for induction therapy and 1 mg/day for maintenance therapy. Analyses with alternative costs for fluticasone are shown in the analyses in section 6.

6 ERG pre-appraisal committee meeting (ACM) revised analyses (March 2021)

The following analyses were conducted by the ERG using the company's original (pre-technical engagement) model. This was because the company's revised model (submitted at technical engagement) does not allow adjustments to extend the time horizon beyond 2 years.

Table 2 summarises our revised parameter estimates informed by the above evidence, review alongside the estimates used by the company at technical engagement in March 2020.

Table 2 Summary of selected parameters for the economic analyses

Parameter	Company estimates (technical engagement)	ERG Pre-ACM revised analyses
Relapse rate for fluticasone with maintenance	15% per cycle based on a retrospective study[2]	11.7% per cycle based on updated ERG review
Relapse rate for budesonide ODT with maintenance[a]	3%	11.7% per cycle based on updated ERG review
Relapse rate for SFED with maintenance	0% after 1 year, but 50% start on a new treatment per cycle after 1 year	11.7% per cycle based on updated ERG review
Relapse rate for all treatments with no maintenance	41%[b] per cycle based on: BUL-2/EER placebo – new calculation applied for TE	31.5% per cycle based on Dellon 2019
Endoscopic dilation rate	• 12% active EOE and 6% remission for no treatment, • 6 % active EOE and 3% remission for active treatments	• 4% active EoE and 2% remission for no treatment, • 2% active EOE and 1% remission for active treatments
Dose of fluticasone	2 mg/day induction; 1 mg/day maintenance – induction based on dose in Butz 2014 (1.76 mg) rounded up to 2 mg as only increments of 0.25mg are possible.	1.5 mg/day induction; 1 mg/day maintenance based on ERG's clinical experts
Cost of budesonide ODT	£430 per cycle – not including wastage	£460 per cycle – including wastage
Remission rate after 1 year	Assumes all in remission at 1 year remain in remission	Assumes all in remission relapse after 1 year

[a] Maintenance with budesonide ODT not used in company or ERG analyses

[b] Company uses different relapse rates for no maintenance of 22%, 28%, 39%, 65% for first four cycles respectively. This is equivalent to a constant relapse rate of 41% per cycle.

The results, shown in the following tables, use these parameter values, unless stated otherwise.

Table 3 shows the results of the scenario (scenario 1) with one cycle of budesonide ODT induction therapy compared with induction and maintenance treatment with fluticasone or SFED. The time horizon is 5 years.

Table 3 Scenario 1. One cycle budesonide ODT induction therapy with no maintenance treatment, versus induction and maintenance fluticasone, and versus SFED, 5-year time horizon.

	Total costs (£)	Total QALYs (£)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY) Incremental
No treatment	£436	4.00			
Budesonide ODT	£887	4.04	£451.4	0.04	£11,587
SFED	£1,015	4.05	£127.96	0.01	Extendedly dominated
Fluticasone	£1,405	4.08	£517.64	0.04	£ 14,012

Table 4 shows the results of the scenario (scenario 2) with one cycle budesonide ODT induction therapy and no maintenance treatment, versus fluticasone induction and no maintenance treatment. SFED is not included as, due to the long-term nature of this intervention, it is not appropriate to model it as a short-term induction therapy. The time horizon is 3 years.

Table 4 Scenario 2. One cycle budesonide ODT induction therapy with no maintenance treatment, versus fluticasone induction with no maintenance, 3-year time horizon

	Total costs (£)	Total QALYs (£)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY) Incremental
No treatment	£ 318	2.63	-	-	-
Fluticasone	£501	2.66	£183.20	0.03	£ 6,177
Budesonide ODT	£ 770	2.67	£268.43	0.01	£27,078

6.1 Sensitivity analyses

We varied the parameter values for the time horizon, relapse rate, dilation rate and dose of fluticasone. Table 5 shows the sensitivity analyses results for the comparison between one cycle of budesonide ODT induction therapy with no maintenance treatment, versus induction

and maintenance fluticasone treatment, and versus SFED (i.e. based on scenario 1). Results are most sensitive to time horizon, relapse rate and the utility values.

Table 6 shows the sensitivity analyses results for the comparison between one cycle of budesonide ODT induction therapy with no maintenance treatment, versus fluticasone induction and no maintenance (i.e. based on scenario 2). Results are most sensitive to the relapse rates for patients in remission after 1 year and the utility values.

Table 5 Sensitivity analyses: One cycle budesonide ODT induction therapy, versus fluticasone induction and maintenance treatment, and versus SFED, 5-year time horizon.

Parameter	Treatment	Total costs	Total QALYs	ICER (£/QALY) Incremental
Revised ERG base case	No treatment	£ 436	4.00	-
	Budesonide ODT	£ 887	4.04	£11,587
	SFED	£ 1,015	4.05	Extendedly dominated
	Fluticasone	£1,405	4.08	£ 14,012
2-year time horizon	No treatment	£ 240	1.72	-
	Budesonide ODT	£ 693	1.76	£11,629
	SFED	£ 832	1.75	Extendedly dominated
	Fluticasone	£1,061	1.78	£ 22,020
10-year time horizon	No treatment	£ 722	7.35	-
	Budesonide ODT	£ 1,173	7.39	£12,212
	SFED	£ 1,299	7.40	Extendedly dominated
	Fluticasone	£1,722	7.43	£ 13,250
Relapse rate for all treatments with no maintenance 41% (company estimate)	No treatment	£ 438	4.00	
	Budesonide ODT	£ 897	4.03	Extendedly dominated
	SFED	£ 1,017	4.04	Extendedly dominated
	Fluticasone	£1,406	4.08	£ 12,523
Relapse rate for fluticasone and SFED maintenance 15% (company estimate)	No treatment	£ 436	4.00	-
	Budesonide ODT	£ 887	4.04	£11,587
	SFED	£ 1,018	4.04	Extendedly dominated
	Fluticasone	£1,307	4.06	£ 18,705
Relapse rate 2.5% for fluticasone and SFED (ERG estimate)	No treatment	£ 436	4.00	-
	Budesonide ODT	£ 887	4.04	Extendedly dominated
	SFED	£ 983	4.10	£5,668
	Fluticasone	£1,963	4.16	£ 8,842

Dilation rate: • 12% active EOE and 6% remission for no treatment • 6% active EOE and 3% remission for active treatments (company estimate)	No treatment	£ 1,124	4.00	-
	Budesonide ODT	£ 1,494	4.04	£9,503
	SFED	£ 1,612	4.05	Extendedly dominated
	Fluticasone	£1,948	4.08	£ 12,286
Fluticasone treatment dose: 2 mg/ day active treatment, 1 mg/day maintenance (company estimates)	No treatment	£ 436	4.00	
	Budesonide ODT	£ 887	4.04	£11,587
	SFED	£ 1,015	4.05	Extendedly dominated
	Fluticasone	£1,455	4.08	£ 15,371
Utility estimates Active EoE 0.78; remission 0.93 (company estimates)	No treatment	£ 436	3.30	
	Budesonide ODT	£ 887	3.38	£5,235
	SFED	£ 1,015	3.39	Extendedly dominated
	Fluticasone	£1,405	3.46	£ 6,539
Patients on remission do not relapse after 1 year (company assumption)	No treatment	£ 432	4.01	
	Budesonide ODT	£ 853	4.08	£5,560
	SFED	£ 984	4.08	Extendedly dominated
	Fluticasone	£1,773	4.14	£ 16,819

Table 6 Sensitivity analyses: One cycle budesonide ODT induction therapy with no maintenance treatment, versus fluticasone induction with no maintenance, 3-year time horizon

Parameter	Treatment	Total costs	Total QALYs	ICER (£/QALY)
Revised ERG base case	No treatment	£ 318	2.63	-
	Fluticasone	£501	2.66	£ 6,177
	Budesonide ODT	£ 770	2.67	£27,078
2-year time horizon	No treatment	£ 240	1.72	-
	Fluticasone	£425	1.75	£ 6,288
	Budesonide ODT	£ 693	1.76	£27,820
10-year time horizon	No treatment	£ 722	7.35	-
	Fluticasone	£905	7.38	£ 6,779
	Budesonide ODT	£ 1,173	7.39	£26,939
Relapse rate for all treatments with no maintenance 41% (company estimate)	No treatment	£ 319	2.62	-
	Fluticasone	£509	2.65	£ 8,259
	Budesonide ODT	£ 779	2.66	£34,514
Relapse rate for fluticasone maintenance 15% (company estimate)	No treatment	£ 318	2.63	-
	Fluticasone	£501	2.66	£ 6,177
	Budesonide ODT	£ 770	2.67	£27,078

Relapse rate for fluticasone maintenance 2.5% (ERG clinical expert estimate)	No treatment	£ 318	2.63	-
	Fluticasone	£501	2.66	£ 6,177
	Budesonide ODT	£ 770	2.67	£27,078
Dilation rate: 12% active EOE and 6% remission for no treatment 6% active EOE and 3% remission for active treatments (company estimate)	No treatment	£ 771	2.63	-
	Fluticasone	£891	2.66	£ 4,030
	Budesonide ODT	£ 1,142	2.67	£25,349
Fluticasone treatment dose: 2 mg/ day active treatment, 1 mg/day maintenance (company estimates)	No treatment	£ 318	2.63	-
	Fluticasone	£537	2.66	£ 7,386
	Budesonide ODT	£ 770	2.67	£23,461
Utility estimates Active EoE 0.78; remission 0.93 (company estimates)	No treatment	£ 318	2.16	-
	Fluticasone	£501	2.23	£ 2,803
	Budesonide ODT	£ 770	2.25	£12,637
Patients on remission do not relapse after 1 year (company assumption)	No treatment	£ 316	2.63	-
	Fluticasone	£489	2.67	£ 4,088
	Budesonide ODT	£ 754	2.69	£18,677

6.2 Update of the ERG critique of the company analyses at technical engagement

In this section we update the ERG analyses, shown in Tables 3-5 of the ERG's critique of the company's technical engagement response (April 2020), using the company's model submitted at technical engagement. These tables show the company's technical engagement analyses adjusted with ERG's preferred assumptions. These analyses model repeat episodes of budesonide ODT induction treatment, and fluticasone induction treatment with maintenance.

We have updated the ERG assumptions based on the review of the parameters in this document and the changes to the company's revised estimates, shown in Table 7.

Note we have not changed the relapse rate for patients in the 'no treatment' comparator arm (from 41% to 31.5% when it is considered without maintenance) as it is not possible to change these values in the company's model submitted at technical engagement (without significant recoding of the model).

Table 7 Summary of company's and ERG's revised parameter estimates

Parameter	Company's revised estimate	ERG preferred estimate
Cost of budesonide ODT, fluticasone	Cost of budesonide ODT £429 per cycle; dose of fluticasone 2 mg per day for induction, 1 mg per day for maintenance.	Cost of budesonide ODT £460 per cycle dose of fluticasone 1.5 mg per day for induction, 1 mg per day for maintenance.

Utility values	Active EoE 0.78; remission 0.93	Active EoE 0.86; remission 0.93
Relapse values	• Fluticasone 15.3% per cycle, SFED 50% per cycle onto a new treatment after end of year • without maintenance (budesonide and fluticasone) 41% per cycle[a]	• Fluticasone 11.7% per cycle; SFED 11.7% per cycle • without maintenance all treatments 31.5% per cycle
Remission odds ratio	Company's NMA	ERG's NMA (with continuity correction)
Endoscopic dilation rate	Active EoE 0.06 per cycle; remission 0.03 per cycle (budesonide ODT, fluticasone, SFED) Active EoE 0.125 per cycle, remission 0.06 per cycle (no treatment)	Active EoE 0.02 per cycle; remission 0.01 per cycle (budesonide ODT, fluticasone, SFED) Active EoE 0.04 per cycle, remission 0.02 per cycle (no treatment)
No resource use for the active EoE health state (no treatment)	Active EoE (no treatment) half resources of treatment with budesonide ODT, fluticasone	Active EoE (no treatment) no health care resources
Remission rate after 1 year	Assumes all in remission at 1 year remain in remission	Assumes all in remission relapse after 1 year

EoE = eosinophilic oesophagitis; NMA = network meta-analysis; ODT = oral dispersible tablet; SFED = six-food elimination diet.

[a] Company uses different relapse rates for no maintenance of 22%, 28%, 39%, 65% for first four cycles respectively. This is equivalent to a constant relapse rate of 41% per cycle.

The incremental analyses with the ERG's preferred analyses are shown in Table 8 and Table 9 for time horizons of one and two years, respectively. (Note the results for the 2-year time horizon we have not changed the remission odds ratio as results for SFED were counter-intuitive).

Table 8 Company technical engagement analyses with ERG preferred assumptions. Multiple budesonide ODT induction episodes, time horizon of 1 year

	Total costs (£)	Total QALYs (£)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY) Incremental
No treatment	£155	0.97			
SFED	£ 893	1.00	£738	0.03	Dominated by SFED
Fluticasone	£689	1.01	£534	0.04	£12,665
Budesonide ODT	£ 1,182	1.02	£492	0.01	£77,990

Table 9 Company technical engagement analyses with ERG preferred assumptions. Multiple budesonide ODT induction episodes, time horizon of 2 year

	Total costs (£)	Total QALYs (£)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY) Incremental
No treatment	£220	1.72			
SFED	£ 718	1.76	£498	0.04	Extendedly dominated
Fluticasone	£1,125	1.79	£905	0.07	£13,049
Budesonide ODT	£ 1,783	1.81	£658	0.01	£49,385

The summary of effect of each of the ERG assumptions on the model results are shown in Table 10 and Table 11 for time horizons of one and two years, respectively.

Table 10 Summary of ERG changes to company technical engagement analyses. Multiple budesonide ODT induction episodes, time horizon of 1 year

	ICER (£/QALY) for budesonide ODT vs		
	Fluticasone	No treatment	SFED
Company's updated base case	*£4,780*	*£3,574*	*£563*
Cost of budesonide ODT, fluticasone	£13,742	£4,104	£1,243
Utility using ERG estimates	£10,242	£7,659	£1,206
Relapse	£7,925	£3,574	£356
Remission odds ratio	£6,244	£3,468	BUD Dominates
Endoscopic dilation rate	£5,915	£4,609	£1,542
No resource use for the active EoE health state (no treatment)	£11,102	£8,440	£5,764
All changes above	£77,990	£21,166	£12,373

Table 11 Summary of ERG changes to company technical engagement analyses. Multiple budesonide ODT induction episodes, time horizon of 2 years

	ICER (£/QALY) for budesonide ODT vs		
	Fluticasone	No treatment	SFED
Company's updated base case	*£62*	*£1,958*	*£406*
Cost of budesonide ODT, fluticasone	£10,820	£2,383	£911
Utility using ERG estimates	£133	£4,196	£869
Relapse	£4,732	£1,958	£343
Dilation rate	£1,404	£2,976	£1,396
No resource use for the active EoE health state (no treatment)	£7,766	£6,934	£5,622
Remission rate after 1 year	BUD dominates	£2,299	£646
All changes above	£49,385	£18,905	£23,627

We have updated table 5 of the ERG response to technical engagement which contains scenario analyses varying the dose of fluticasone, treatment resource use and excluding the add-on treatment costs. The updated table is shown in Table 12.

Table 12 Updated ERG scenario analyses for budesonide ODT vs comparators, multiple induction episodes, time horizon 2 years,

		ICER (£/QALY) for budesonide ODT vs		
		Fluticasone	**No treatment**	**SFED**
Company base case		*£62*	*£1,958*	*£406*
		£49,385	£18,905	£23,627
ERG scenario 1	Dose of fluticasone, 1.3 µg per day.	£56,863	£18,905	£23,627
	Dose of fluticasone, 1.76 µg per day.	£39,663	£18,905	£23,627
ERG scenario 2	Treatment resource use for active EoE when receiving no treatment (1/4 the health care resource used by patients with active EoE receiving fluticasone or budesonide ODT)	£41,002	£14,185	£15,532
ERG scenario 3	Add-on treatment costs excluded	£50,894	£20,008	£25,249

7 Summary

In February 2021 we did a further literature search for evidence on relapse rates and on endoscopic dilation rates in EoE,and we spoke again with our clinical experts. We examined the evidence in relation to the company's and the ERG's parameter estimates, as used in technical engagement a year earlier (March 2020). In the light of this we revised some of the estimates and applied them to two ERG scenario analyses modelling a single episode of budesonide ODT induction treatment. The results are most influenced by whether the analysis includes maintenance therapy for the comparator treatments or not. We would like to stress that these results may not be fully applicable to clinical practice, given clinician preference for an induction-maintenance approach to treatment.

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Factual error check by Company of the Evidence Review Group's Addendum to Evidence Review Group's comments on the company's response to the technical report.

Issue number	Company comments	ERG response
General		
1	Throughout the report, the Evidence Review Group (ERG) refers to consultation with clinical experts. The number of clinical experts consulted/responding should be included for transparency.	Not a factual inaccuracy, no change required.
2	It is important to refer to budesonide (Jorveza®) as budesonide orodispersible table (ODT) to distinguish it from other formulations of budesonide.	Text has been revised to distinguish between different formulations of budesonide, as suggested.
Section 2		
3	The ERG report states 'We consider the time horizon can be estimated as the time at which the proportion of patients in these health states is low enough that significant changes to the estimates of cost-effectiveness are unlikely.' The meaning of 'low enough' is subjective and has not been provided.	Not a factual inaccuracy, no change required.
4	The ERG report refers to a time horizon of '30 years where multiple induction episodes of budesonide ODT and fluticasone induction and maintenance treatment are modelled (as used in the company's original submission and technical engagement).' This is incorrect, as the company submission (CS) used a time horizon of 40 years.	The phrase in brackets has been deleted as it is misleading.
Section 2.1		
5	The ERG report states that 'it would not be appropriate to include SFED [six-food elimination diet] as a comparator in an analysis based on a single budesonide induction episode' due to SFED being used as a long-term (maintenance) treatment. Yet, the report also states that advice from clinical experts was that 'patients responding to an induction dose of fluticasone would then be maintained on this drug in the long-term.' Therefore, the reason for excluding SFED also applies to fluticasone.	Not a factual inaccuracy, no change required.

Section 2.2		
6	The ERG report states that 'the focus of the appraisal since technical engagement […] has been on induction therapy without maintenance therapy.' However, the focus of the appraisal has always been on induction therapy, as the remit/appraisal objective within the final scope was 'to appraise the clinical and cost effectiveness of budesonide within its marketing authorisation for treating eosinophilic oesophagitis.' At the time of issuing the final scope (and submission of the CS), the marketing authorisation for budesonide ODT was for the treatment of adults with eosinophilic oesophagitis for up to 12 weeks (i.e. induction of remission). Multiple induction treatment episodes are not excluded by the marketing authorisation.	This sentence has been deleted to avoid confusion.
7	The report states that 'The ERG's preference is to model budesonide as a single induction treatment episode'. However, it should also be highlighted in the report that this does not represent the licensed indication for budesonide ODT. In addition, restricting budesonide ODT to a single treatment episode would not be representative of clinical practice.	Not a factual inaccuracy. This is the ERG's preference, based on discussion expert clinicians
Section 3		
8	The ERG report states that relapse rates are shown in Table 1, but this is not the case. Data relating to relapse are shown in the Table 1, but not relapse rates per se.	Not a factual inaccuracy, no change required.
9	Table 1 does not differentiate between the different formulations of budesonide. This is important as the method of delivery of budesonide impacts outcomes.	This has been revised as per our response to Issue 2 above.
10	There are multiple errors in the totals/averages in Table 1, which also affect the numbers in the paragraph below (and used in the model):	Our response to these specific issues are detailed below, 10a – 10d.
10a	For sample size, the total should be 137, not 150	The values from Reed et al were incorrect and these have now been corrected.
10b	The total number remaining in remission should be 50, not 55	See above (10a)
10c	The average months should 21.6, not 24.1	We disagree, these values have been calculated as a weighted average, using study sample sizes.

10d	Based on a. and b. above, the average relapse rate in the paragraph below Table 1 should be 63.5% ([137-50]/137) over an average 21.3 months. This correction also impacts the relapse rate of 11.7% per cycle	See above (10a).
11	The ERG report states that 'the model includes relapse rate estimates for those on maintenance treatment and those in the no comparator treatment arm.' However, the model also included a relapse rate estimate of 88% after one year for budesonide ODT.	Not a factual inaccuracy, no change required.
12	The ERG report states that 'the company assumed a relapse rate for no treatment of 88% after 1 year, based on the placebo arm of the BUL-2/EER trial.' The cited reference incorrectly refers to the Phase 2 BUU-2/EEA (Miehlke et al., 2016)[1,2] study, whereas the relapse rate in the CS was based on the Phase 3 BUL-2/EER (Straumann et al., 2020)[3,4] study.	Not a factual inaccuracy, no change required. We used the same citation as used by the company in their technical engagement response.
Section 4.1		
13	The ERG report states 'For patients in remission states, it was assumed that patients would receive 50% of the dilations of those in the active disease health states (i.e. 3% per cycle).' This should be 3% for budesonide ODT, fluticasone and SFED; 6% for no treatment.	Not a factual inaccuracy. We have removed the wording in the bracket to avoid confusion.
Section 5.1		
14	It should be noted that not all patients receive budesonide ODT for 12 weeks. According to the summary of product characteristics, the usual duration of budesonide treatment is 6 weeks;[5] therefore, patients who achieve a response during this time will only receive treatment for 6 weeks (in the pivotal, phase III BUL-1/EEA study, 93.2% and 57.6% of patients achieved histological and clinico-histological remission at week 6, respectively).[6,7]	Not a factual inaccuracy, no change required.
Section 6		
15	The second row of Table 2 includes estimates for 'relapse rates for budesonide ODT with maintenance.' However, this is not included in the analysis and this row should be removed from the table.	Not a factual inaccuracy, no change required.
16	The third row of Table 2 presents the relapse rate for SFED maintenance treatment. The text for the company estimates should read '50% after one year due to non-	Not a factual inaccuracy, no change required.

<table>
<tr><td></td><td>adherence.' The value for 'relapse rate' used in the model is 0%, because the model only allows for one relapse rate (i.e. it is the same for each cycle); for SFED, it was intended that relapse occurs only at the end of the year, therefore the model was amended in a different way in order to avoid significant recoding. Only 18.5% of patients initially responded to SFED, and it was assumed that those patients that responded continue adhering to SFED for the first year.</td><td></td></tr>
<tr><td>17</td><td>The fourth row of Table 2 presents relapse rate for all treatments with no maintenance (i.e. budesonide ODT and no treatment). The ERG report states in footnote b: 'Company uses different relapse rates for no maintenance of 22%, 28%, 39%, 65% for first four cycles respectively. This is equivalent to a constant relapse rate of 41% per cycle.'

The values in the updated model for technical engagement were changed as it was realised that the model applied the relapse rate to the number of patients in remission at the end of the previous cycle (the model submitted with the CS was initially developed by others, and it was thought that the model applied the relapse rate to patients who are in remission at the beginning of cycle 1). The model should have used a relapse of 88% after one year (i.e. 22% per cycle), so changing the values in the updated model for technical engagement allowed the number of patients who relapse each cycle to be constant over time (see table below). Using a constant relapse rate of 41% as suggested by the ERG would also provide a relapse rate of 88% at one year, but the number of patients relapsing is higher in the first cycle, and decreases over time; this may not reflect what would be expected in clinical practice. It should be noted that this change was made for all treatments in the model (not just no treatment). The change was highlighted in cell C50 in 'Model Settings' in the updated model for technical engagement.

<table>
<tr><th></th><th colspan="3">Number of patients</th><th rowspan="2">Formula used in model</th></tr>
<tr><th></th><th>Total</th><th>Relapsed</th><th>Not relapsed</th></tr>
<tr><td>Start</td><td>100</td><td>0</td><td>100</td><td></td></tr>
</table>
</td><td>Not a factual inaccuracy, no change required. We do not agree that the company's method for calculating varying relapse rates is plausible.</td></tr>
</table>

	Cycle 1	100	22	78	100*22% =22*
	Cycle 2	100	44	56	78*28% =22*
	Cycle 3	100	66	34	56*39% = 22*
	Cycle 4	100	88	12	34*65% = 22*
	*22 patients relapsed each cycle, 88 patients relapsed at end of 4 cycles.				
18	The eighth row of Table 7 shows remission rate after 1 year. Whilst the text in the table is correct, the calculation in the model is not. The label for cell E14 in 'Model Settings' incorrectly states 'relapse rate after 1 year no relapse'. This should be 'remission rate after 1 year no relapse'. This was later corrected. It was also highlighted in cell C53 in 'Model Setting' in the updated model for technical engagement. Thus, the results in the ERG report are incorrect.				Not a factual inaccuracy, no change required. We do not consider the results to be incorrect as suggested.
19	Based on the above errors, it seems that the ERG has used the first version of the model. As previously highlighted, this model was not validated for maintenance as the functionality was not used at the time of the CS. In addition, as detailed above, some corrections were made to the model during the appraisal process.				Not a factual inaccuracy, no change required. We do not agree with this point as the model was used for maintenance in the CS (submitted October 2019). Further, It was not possible to use the model submitted at technical engagement for time horizons longer than 2 years.
Section 6.2					
20	The third row of Table 7 shows relapse rates. For the company estimate for SFED, the text should read '50% after one year due to non-adherence.' The value for 'relapse rate' used in the model is 0%; this is because the model only allows for one relapse rate (i.e. it is the same for each cycle) and for SFED, it was intended that relapse occurs only at the end of the year (see above). Consequently, the model was amended in a different way, in order to avoid significant recoding. Only 18.5% of patients initially responded to SFED, and it was assumed that those patients that responded continue adhering to SFED for the first year.				Not a factual inaccuracy, no change required.

21	The 'relapse rate per cycle' is used differently by the company and the ERG. The company applies this to patients who are in remission at the beginning of cycle 1, whereas the ERG applies this to patients in remission at the end of the last cycle. As detailed above, the values used in the model were amended during technical engagement to be constant over time. Although using a constant relapse rate of 41% as suggested by the ERG would also provide a relapse rate of 88% at one year, the number of patients relapsing be higher in the first cycle and then decrease over time (unlike the company model, which has a constant relapse rate of 22% per cycle). Consequently, there are differences in how the relapse rates per cycle are interpreted and calculated by the company and ERG. As the ERG has used the model that was amended by the company, this means that the results in the ERG report are incorrect.	Not a factual inaccuracy, no change required. We have applied relapse rate in the same way as the company.
22	It is not clear from the report what values the ERG is using for response rates for fluticasone and SFED. The updated company model for technical engagement uses 68.1% for fluticasone and 18.5% for SFED for one cycle only, with a response rate of 100% thereafter. As the model only allows for one value for response rate, this change was made in a such a way so as to avoid significant recoding. The ERG did not change this, so it seems that they are in agreement with this assumption. However, this is not clear.	Not a factual inaccuracy, no change required. We are not in agreement with these values and prefer those produced by the ERG in the ERG report.