NICE National Institute for Health and Care Excellence

For committee, projector and public – no ACIC

Budesonide orodispersible tablet for treating eosinophilic oesophagitis

Premeeting briefing

Andrew Champion, Stephen Sharp, Richard Ballerand
ERG/AG: Southampton Health Technology Assessments Centre (SHTAC)
Technical team: Brian Shine, Marcela Haasova, Janet Robertson
Company: Dr Falk Pharma

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Timelines and MA wording

Invitation to participate: December 2018

- Budesonide orodispersible tablet (ODT) marketing authorisation (MA) was received in January 2018 for treating adults with eosinophilic oesophagitis:
  - **At this stage MA only included induction** (1mg twice daily) of up to 6 to 12 weeks duration

Technical engagement: February to March 2020

- Due to COVID 19 this topic was paused after technical engagement responses were received.

MA was updated in June 2020 with an extension of indication to include maintenance treatment of people in remission:

- Induction (1mg twice daily) and maintenance treatment (0.5 mg or 1 mg twice daily). The duration of maintenance is determined by the treating physician.

The company was offered the opportunity to restart with a new submission to include this indication, but it preferred to continue with induction only.

- Therefore, the company's submission focuses on the use of budesonide ODT as an induction treatment.

Budesonide orodispersible tablet (ODT)

Mechanism of action	Budesonide is a non-halogenated glucocorticosteroid, that inhibits antigen-stimulated secretion of pro-inflammatory molecules in the oesophageal epithelium
Marketing authorisation (MA)	Indicated "for the treatment of eosinophilic oesophagitis (EO) in adults" • **Induction:** MA received in 2018 • **Maintenance treatment:** MA extension received in June 2020 – post technical engagement (TE) NOTE: The company's submission focuses on induction only
Posology and administration	• **Induction of remission:** 1mg twice daily for 6 weeks. For patients not appropriately responding it can be extended to up to 12 weeks. • **Maintenance of remission**: 0.5 mg or 1 mg twice daily. Duration is determined by treating clinician. 1 mg twice daily is recommended for patients with a long standing disease history and/or high extent of oesophageal inflammation in their acute disease state. • Delivered orally: ODT is an immediate-release tablet - when placed on the tongue, it begins to dissolve stimulating the production of saliva. The dissolved material is swallowed with saliva, coating the oesophagus and delivering high concentrations of budesonide to the site of inflammation.
Cost	List price: £323 (pack of 90 x 1mg tablets) • Cost for 6 weeks induction: £323 (including wastage) • Cost for 12 weeks induction: £646 (including wastage)

Key clinical issues

1. **Population:** company limits population to adults with eosinophilic oesophagitis who have received prior treatment with post proton pump inhibitors (PPI)
   - Is limiting population to post PPI appropriate?
2. **Intervention:** company's submission focusses on induction only.
   - What do clinicians consider would be the best treatment strategy in clinical practice?
3. **Network metanalyses (NMAs):** results are very uncertain
   - What response rates are expected in clinical practice?
   - Is ERG's or company's NMA suitable for decision making?
4. **Comparators:** no universally accepted dose or mode of delivery for off-label steroids, no definitive dietary intervention, limited evidence available.
   - Are fluticasone and six-food elimination diet (SFED) appropriate comparators?
   - Is a comparison with 'no treatment' appropriate?
5. **Fluticasone and budesonide:** dose and wastage
   - Is the ERG's or company's approach more appropriate?

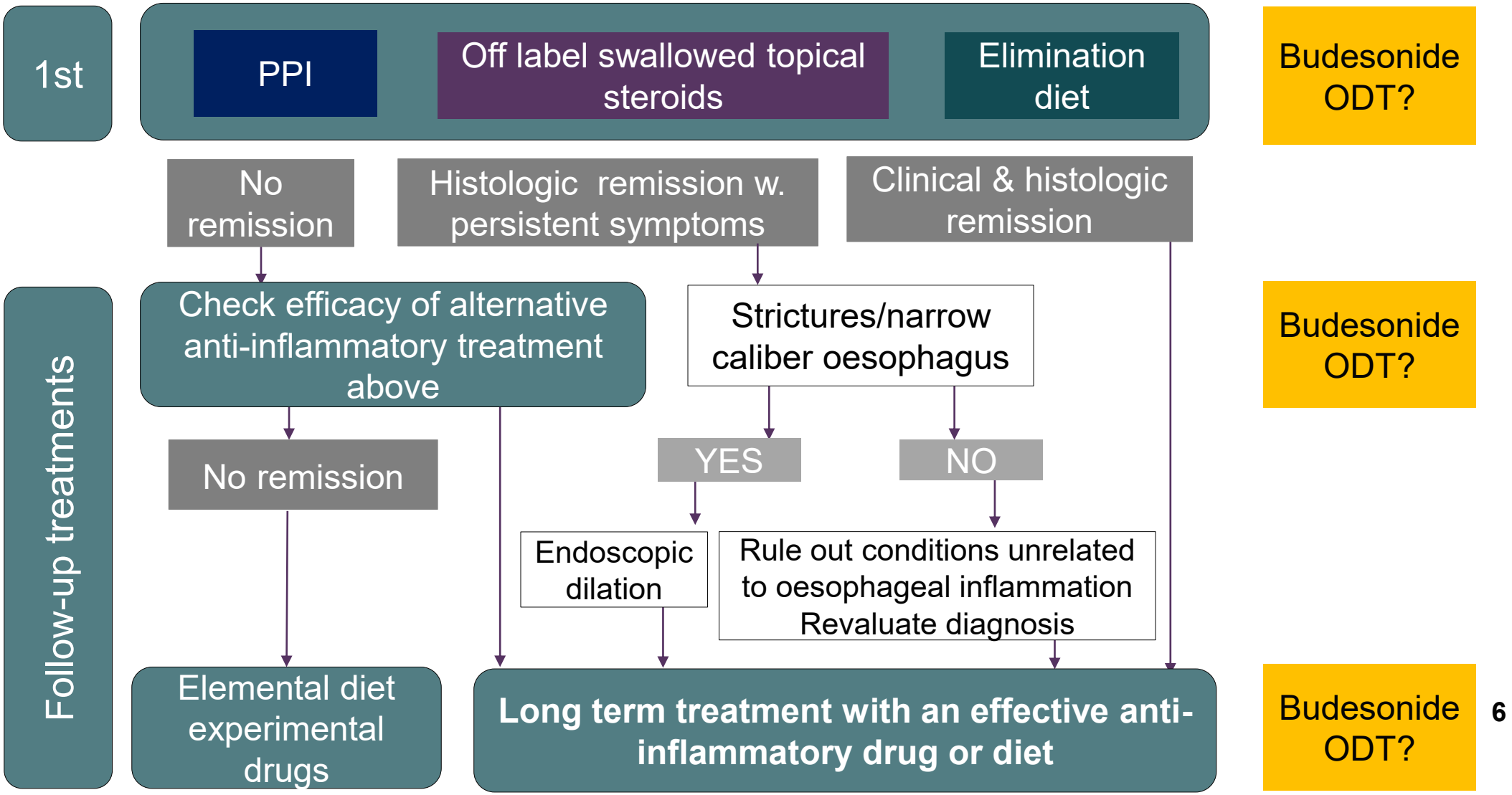
Disease background

- Eosinophilic oesophagitis (EO) is characterised by the chronic inflammation of the oesophagus in which white blood cells called eosinophils infiltrate the lining of oesophagus
- EO is caused by allergen exposure, typically food allergens in milk, egg, wheat, soy, peanuts, beans, rye and beef
- Symptoms can be unpleasant and socially embarrassing, and have a significant impact on quality of life: difficulty in swallowing solid food (dysphagia), obstruction of the oesophagus by swallowed food (food-bolus impaction), swallowing/non-swallowing-associated chest pain…
- If left untreated, EO can lead to oesophageal fibrosis with possible structure formation and functional abnormalities
- No known mortality risk
- Reported throughout the life span but most cases occur in children, adolescents and adults <50 years
- Prevalence: 5,956 adult patients in England and Wales
- Incidence: 963 cases per year based on 2017 Dutch data (no UK-specific data)

Treatment pathway:

Company: budesonide ODT expected to become 1st-line treatment, replacing off-label corticosteroids and SFED - PPIs would be used prior to EO diagnosis

- **Lucendo et al. 2017:** considers these options*:



* In patients with persistent symptoms under anti-inflammatory therapy, endoscopic dilation should be considered

Decision problem

	Final scope issued by NICE	Company submission
Population	Adults with active eosinophilic oesophagitis (EO)	Adults with active EO **who have received prior treatment with a PPI**
Intervention	Budesonide orally dissolving tablet (ODT) • Note: Scope did not explicitly limit the intervention to induction	Budesonide ODT • **Induction treatment only**
Comparators	Established clinical management without budesonide, which may include proton pump inhibitors (PPI), other corticosteroid formulations and dietary intervention.	• **off-label fluticasone (swallowed topical corticosteroid inhaler)** • **six-food elimination diet (SFED)** • **'no treatment' - added post technical engagement (TE)**
Outcomes	• disease activity (remission, response, relapse) – relapse rates not collected in the key RCT • symptoms of oesophagitis • complications such as stricture formation • mortality • adverse effects of treatment • health related quality of life	

Patient and carer perspectives

EOS Network charity

- EO affects every part of patient and carers/family life: home, work, pleasure & social interaction.
- Eating is not just a necessity but a crucial social activity and should be done without the fear of choking and pain. To be able to eat without pain is a human function we normally take for granted.
- Many patients struggle to access knowledgeable dieticians' support.
- People with EO often travel long distances to find appropriate care, this search can sometimes take years.
- Many people struggle with the use of off label steroids. A dispersible tablet would be a simple alternative treatment that dramatically increases the chance of efficacy.

British Society of Allergy and Clinical Immunology

- There is an unmet need for a standardised formulation of budesonide specific for EO.
- Use of off-label corticosteroids is inappropriate.
- Dietary intervention in adults is also highly effective as an alternative treatment.
- The long-term effects on bone mineral density and adrenal suppression are unknown.

Clinical evidence: budesonide

Trial name	Induction		Maintenance – only induction data submitted by company
	BUL-1/EEA	**BUU-2/EEA**	**BUL-2/EER**
Design	Double-blind, multicentre, placebo-controlled Phase III; N=88 (no UK patients)	Double-blind, multicentre, placebo-controlled Phase II; N=76 (no UK patients)	Double-blind (DB), multicentre, placebo-controlled Phase III; N=204 (some UK patients)
Intervention	6 weeks of treatment: • **Budesonide ODT 1mg 2x daily: n=59** • **Placebo: n=29** **+ 6-week open-label induction extension** if no remission: n=51 + 66 patients entered maintenance trial BUL-2/EER (peak eos < 16 eos/mm² hpf and no symptoms)	2 weeks of treatment + 2 weeks follow-up: • **Budesonide ODT 1mg 2x daily: n=19** • Budesonide ODT 2mg 2x daily: n=19 • **Budesonide viscous suspension (2mg 2x daily) n=19** • **Placebo: n=19**	48 weeks with 4 weeks follow-up: • Budesonide ODT (1 mg 2x daily) n=68 • Budesonide ODT (0.5 mg 2x daily) n=68 • Placebo n=68 **+ 6-week open-label induction:** • for patients who did not participate in BUL1-EEA (n=181; 138 entered DB) **+ 6-weeks open label re-induction:** • If clinical or histological relapse or endoscopic intervention (n=82) + 96-weeks optional open-label extension: • If remission (n=105)
Primary outcome	• Clinico-histological remission (peak of <16 eos/mm² hpf + resolution of symptoms) at week 6	• Histological remission (mean of <16 eos/mm² hpf) at week 2 • Change in mean eosinophil load	• Treatment failure at week 48 (including clinical and histological relapse [peak of ≥48 eos/mm² hpf at DB end of treatment])

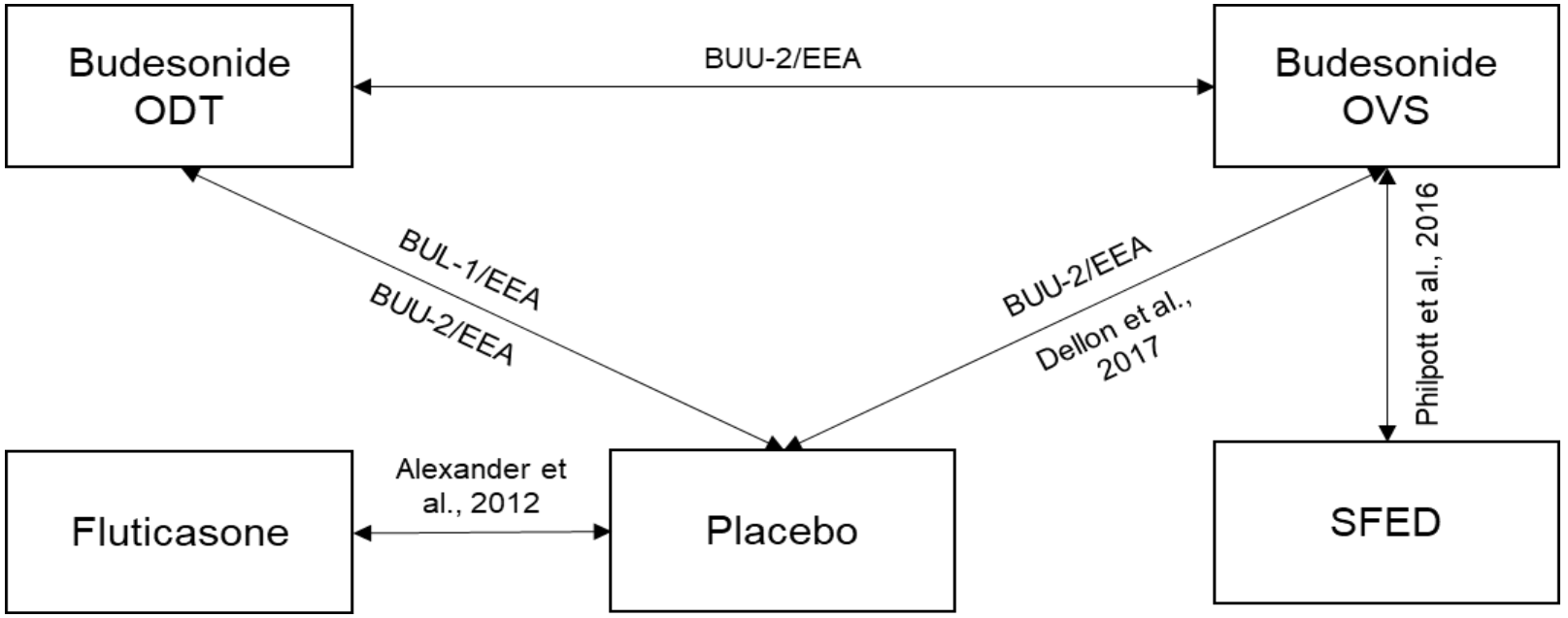
Key trial results: induction 1 mg twice daily

Trial & phase		Clinico-histological remission – primary outcome	Histological remission – peak of < 16 eos/mm² hpf - secondary out.	Histological remission – mean of < 16 eos/mm² hpf - primary out.
BUL-1/EEA trial	**Double blind – 6 weeks of treatment**	• Budesonide 34/59 (57.6%) • Placebo 0/29 (0%)	• **Budesonide 55/59 (93.2%)** • **Placebo 0/29 (0%)**	-
	Open-label extension – 6 weeks treatment (total of 12 weeks)	• Placebo → Budesonide 22/28 (78.6%) • Budesonide → Budesonide 16/23 (69.6%)	• Placebo → Budesonide 25/28 (89.3%) • Budesonide → Budesonide 19/23 (82.6%)	*Note: Values used in network meta-analysis (NMA) are highlighted in **bold***
BUU-2/EEA	**Double blind - 2 weeks of treatment**	-	• Budesonide 16/19 (84.2%) • Placebo 0/19 (0%)	• **Budesonide 19/19 (100%)** • **Placebo 0/19 (0%)**
BUL-2/EER	**Open-label induction - 6 weeks of treatment**	• Budesonide 126/181 (69.6%)	• Budesonide 163/181 (90.1%)	-

Budesonide ODT vs. fluticasone and SFED

- No trial compared budesonide ODT with active treatments

→ **NMA**
network meta-analysis using BUL-1/EEA & BUU-2/EEA and 3 studies:



- **Alexander 2012:** multicentre US RCT of aerosolized *fluticasone* delivered by inhaler twice daily for 6-weeks (n=21) vs *placebo* (n=21)
- **Philpott 2016:** Prospective observational single-center Australian study, patients with no response to PPI choose *six food elimination diet (SFED*) + PPI (n=56) or *budesonide oral viscose solution (OVS*; n=25) for 6 weeks; patients failing SFED were offered budesonide OVS (n=25)
- **Dellon 2017:** multicentre US RCT of 12 weeks treatment with budesonide OVS (n=51) or placebo (n=49)

NMA: Histological remission - induction

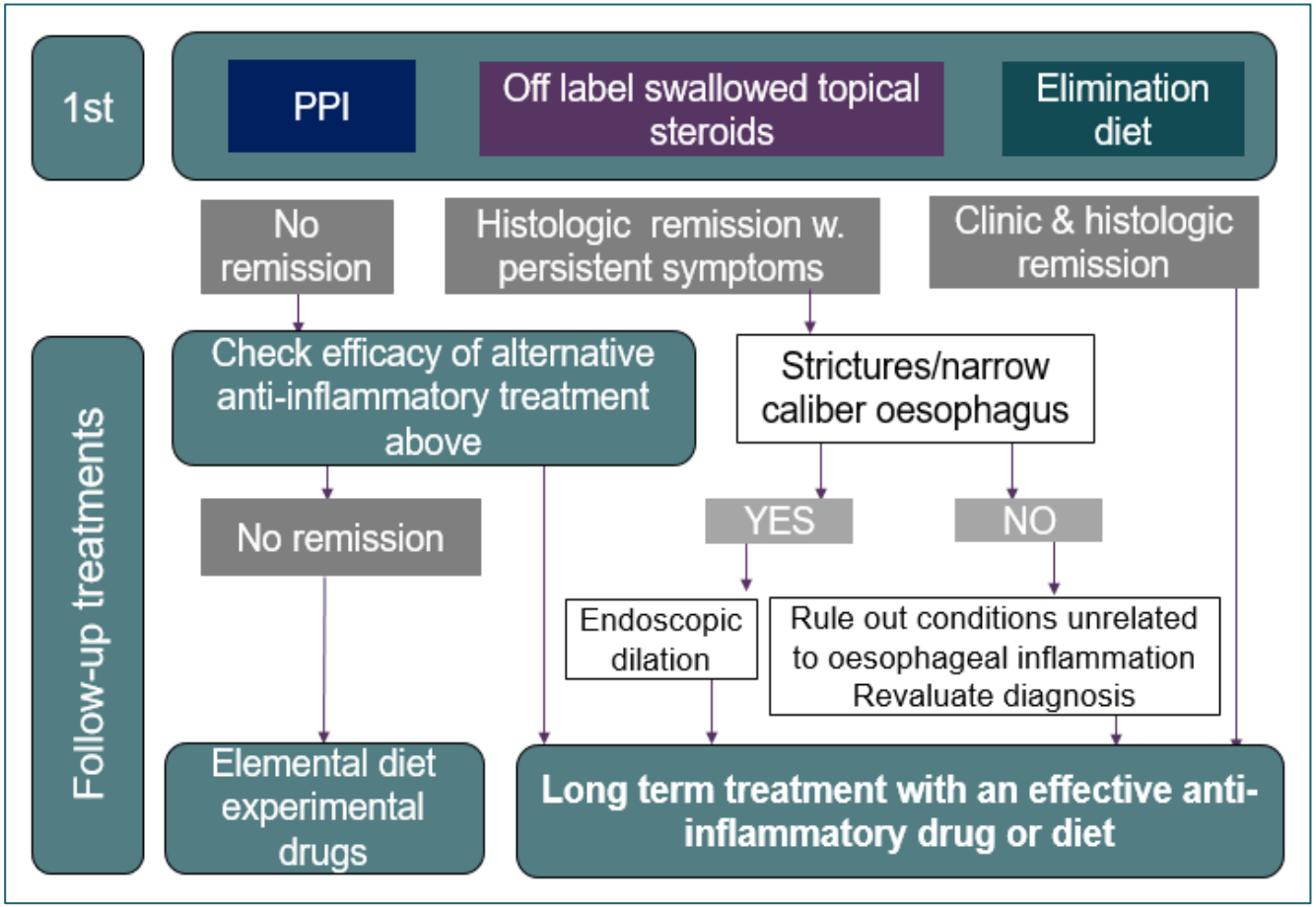
- **Histological remission:** eosinophil count <16 eos/mm² hpf - the company standardised eosinophil counts (eos) reported in studies per high power field (hpf; microscopes' hpf sizes differ) to mm² hpf
- **Sensitivity analyses** provided similar results:
  - Remission defined by eos/hpf thresholds (analysis not standardised by mm² hpf)
  - Remission defined by peak eos/hpf in BUU-2/EEA (secondary outcome)
  - Including RCTs only - excluding Philpott 2016 study → no comparison with SFED

- **Company:** Bayesian random effects (RE) model without continuity correction in base-case
- **ERG:** Frequentist RE model in base-case (automatically correcting for zero events/no remission in placebo). Notes company's Bayesian RE model with continuity correction did not converge when used with uninformative prior.

Budesonide ODT vs.	Company: Bayesian RE without continuity correction		ERG: Frequentist RE with continuity correction	
	OR	95% CrI	OR	95% CI
Fluticasone	8.657	0.009 to 7,508.000	6.96	0.11 to 441.71
SFED	81.84	0.109 to 63,620.000	23.24	0.85 to 635.07
Placebo	NR	NR	475.19	39.58 to 5705.32

Issue 1: Population

Company: budesonide ODT expected to become 1st-line treatment, replacing off-label corticosteroids and SFED - PPIs would be used prior to EO diagnosis



Scope:

- Adults with active EO

ERG:

- Agrees with limiting population to post PPI

Stakeholders comments

- No comments received

Technical team

- Unclear what line of therapy budesonide would be given - company positions treatment post PPIs but believe budesonide to be a first line treatment

Is limiting population to post PPI appropriate? Would PPI be a treatment option for some people with EO?

Issue 2: Intervention

Background

Scope:

- Budesonide orally dissolving tablet (ODT)
- Does not explicitly limit the intervention to induction

MA:

- Includes induction and maintenance treatment

ERG:

- Pre-TE suggested adding maintenance therapy as per feedback from clinicians

Maintenance study BUL2-EER

- Results not included in CS
- Study was ongoing at the time, but results are now available

Stakeholders comments

Company:

- Preferred base-case: budesonide ODT is modelled episodically as a number of 6-12 weeks inductions (instead of maintenance): when patients who respond to initial induction relapse, they receive further repeat induction episodes over time
- + added maintenance treatment for comparators

ERG

- Preferred base-case: single induction budesonide scenarios (with and without maintenance for comparators)
- For episodic inductions: the company assumes that budesonide response rate is the same for all inductions and that responders to initial induction treatment with fluticasone will respond to subsequent inductions

What do clinicians consider would be the best treatment strategy? In the induction phase do patients receive single or multiple inductions?

Issue 3: Response rates - remission NMA

Background

NMA results of histological remission: uncertainty in estimates for induction treatment due to:

- Small number of studies
- No UK participants
- Differences in studies' design and participants baseline characteristics
- Impact of modifying variables is unknown

Post TE

- Company: BUL1/EEA & BUU-2/EEA represent UK practice

Technical team

- As NMA results are uncertain (with very wide confidence intervals), the cost effectiveness estimates are also uncertain.
- Given the limitations of NMA, a comparison with 'no treatment' may provide more certain results

	Company results (Bayesian RE)		ERG results (frequentist RE)	
	1/OR	Response per cycle (%)	1/OR	Response per cycle (%)
Budesonide ODT	-	94.9	-	94.9
Fluticasone	0.116	**68**	0.144	**73**
SFED	0.012	**18**	0.043	**44**
No treatment/placebo	0.002	4	0.002	4

What response rates are expected in clinical practice?
Is the ERG's or company's NMA suitable for decision making?

Issue 4: Comparators

Background

Scope:

- Established clinical management without budesonide, which may include PPIs, other corticosteroid formulations and dietary intervention

Company:

- Six-food elimination diet (SFED) and off-label fluticasone
- PPIs are not considered as they would be used before EO diagnosis

Clinical experts:

- Practice very variable: off-label swallowed topical fluticasone, budesonide in suspension, dietary interventions (not limited to SFED)

Stakeholder comments

Company:

- 'No treatment' comparison added post TE as fluticasone is used off label & SFED is not suitable for all patients
- Off-label budesonide (viscous formulation [OVS]) was not added as it would be used second-line. In addition, the viscous formulation used in the company's trials is different from formulations available in the UK.

ERG:

- Agrees with company's approach
- SFED: not a suitable comparator for single induction scenario with no maintenance because the time period is too short to include dietary interventions

Are fluticasone and SFED the appropriate comparators? Is it appropriate to exclude PPIs and off-label budesonide (viscous formulation)?

Is a comparison with 'no treatment' appropriate?

Issue 5: Fluticasone and budesonide

Fluticasone maintenance dose

Company

- Induction: **2mg/day** (rounded up a dose of 1.76mg/day in Butz et al. 2017)
- Maintenance:1mg/day

ERG

- Induction: **1.5mg/day** (clinical expert advice)
- Maintenance: 1mg/day
- Notes published recommended dose is 0.88 mg twice a day, but dose in clinical practice may vary (Lucendo 2020)
- The difference in cost is £50 per cycle (£202 company estimate - £152 ERG estimate)

Budesonide ODT and wastage

MA induction dose:

- 1mg twice a day for 6 to12 weeks

Company:

- Post TE no longer includes wastage

ERG

- Wastage should be included. Especially for single induction scenarios (84 are needed for 6 weeks induction vs. 90x1mg tablets in budesonide pack)
- Not including wastage decreases budesonide cost from £460 to £430 per cycle

Is the ERG's or company's approach more appropriate?

Key clinical issues

1. **Population:** company limits population to adults with eosinophilic oesophagitis who have received prior treatment with post proton pump inhibitors (PPI)
   - Is limiting population to post PPI appropriate?
2. **Intervention:** company's submission focusses on induction only.
   - What do clinicians consider would be the best treatment strategy in clinical practice?
3. **Network metanalyses (NMAs):** results are very uncertain
   - What response rates are expected in clinical practice?
   - Is ERG's or company's NMA suitable for decision making?
4. **Comparators:** no universally accepted dose or mode of delivery for off-label steroids, no definitive dietary intervention, limited evidence available.
   - Are fluticasone and six-food elimination diet (SFED) appropriate comparators?
   - Is a comparison with 'no treatment' appropriate?
5. **Fluticasone and budesonide:** dose and wastage
   - Is the ERG's or company's approach more appropriate?

Key cost issues

6. **Model structure and time horizon:**

- Is the company's approach allowing multiple budesonide inductions appropriate, or should only a single induction be modelled?
- What is the appropriate time horizon for the model?

7. **Relapse rates:**

- Are the company's or ERG's estimates more appropriate?

8. **Utilities:**

- Can the age-adjusted UK population norm be a proxy for histological remission?
- Which estimate of utility for active disease is more appropriate?

9. **Follow-up and monitoring costs:**

- Are the company's or ERG's assumptions suitable for decision making?

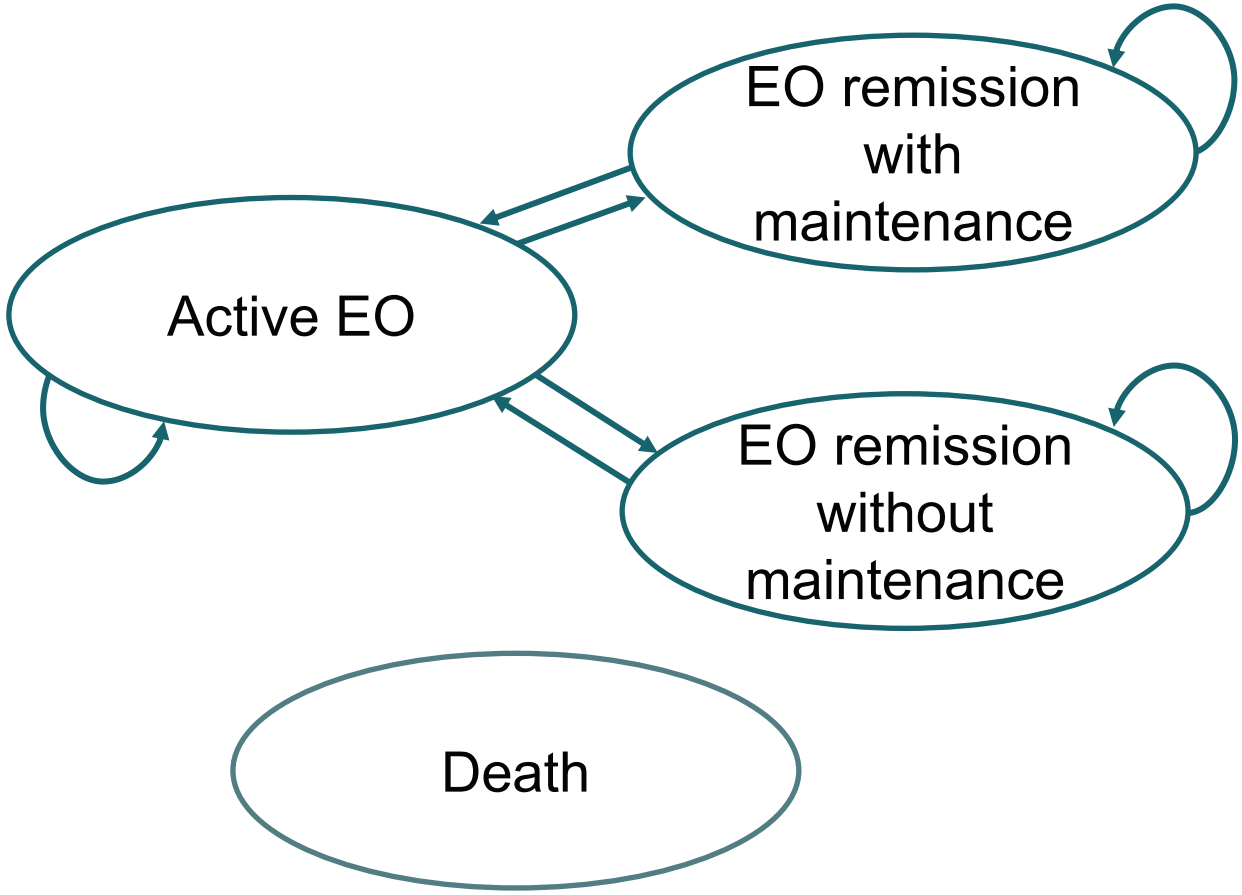
10. **Endoscopic dilation rates**:

- Which estimates are more appropriate?

Company's model

Markov model:

- Time horizon: 1 year / 2 years; cycle length 12 weeks
- Adults with EO post PPIs (age 30 years & 53.8% male)



1. **Budesonide ODT induction modelled episodically:** multiple 6-12 weeks inductions (maintenance is not modelled)
2. **Fluticasone:** 6-12 weeks induction + maintenance
3. **SFED:** 12 weeks of dietitian visits and endoscopies - if response SFED continues for up to 1 year
4. **No treatment**

ERG's approach

1. ERG applied its preferred assumptions to company's post technical engagement (TE) model
2. ERG presented two preferred scenarios of a single induction for budesonide using the company's pre TE model:

- **Time horizon: 5 years**
- Maintenance **included** for comparators
  1. Budesonide ODT: single induction.
  2. Fluticasone: induction + maintenance
  3. SFED: 12 weeks of dietitian visits and endoscopies - if response SFED continues for up to 1 year
  4. No treatment

- **Time horizon: 3 years**
- Maintenance **not included** for comparators
  1. Budesonide ODT: single induction
  2. Fluticasone: induction only (no maintenance)
  3. No treatment

Issue 6: Model structure and time horizon

Note:

- not all inputs in the pre TE and post TE models can be set up in the same way

Time horizon:

- **Company:** 1 & 2 year time horizon are appropriate for multiple inductions due to uncertainty in relapse rates, subsequent response rates and adherence to treatment
- **ERG**: 5-10 year time horizon is appropriate for a single induction because 6% and 0.5% patients would be in remission in the fluticasone arm at 5 years and 10 years respectively. Shorter horizon of 3 years is appropriate when maintenance is not considered as the proportion of patients in remission and active EO is low enough that significant changes to the estimates of cost effectiveness are unlikely.

Is the company's approach allowing multiple budesonide inductions appropriate, or should only a single induction be modelled?

What is the appropriate time horizon for the model?

Company and ERG: models & assumptions

Parameter	Company	ERG
Model & time horizon	Post TE model & 1 year, 2 years (model does not allow longer time horizon)	Pre TE model & 3 years, 5 years
Budesonide	Episodic treatment of 6-12 weeks inductions + no maintenance	Single induction + no maintenance
Comparators	Induction + maintenance	• Induction + maintenance (5 years) • Induction + no maintenance (3 years)
Budesonide and fluticasone	Budesonide - no wastage	Budesonide - includes wastage
	Fluticasone 2mg/day induction	Fluticasone 1.5mg/day induction
Remission rates	Company's NMA	ERG's NMA
	• Individuals who are in remission at 1 year remain in remission	• Individuals in remission continue to relapse after 1 year
Relapse rates per cycle	• Fluticasone 15.3%, SFED 50% non-adherent after 1 year • No maintenance/no treatment: increasing rate for 1st year ~ 41%	• Fluticasone & SFED - 11.7% (pre TE model does not differentiate between treatments) • No maintenance/no treatment: 31.5%
Utility values	Active EO 0.78; remission 0.93	Active EO 0.86; remission 0.93
Resource use for 'no treatment'	Half resources of treatment with budesonide, fluticasone for active EO	No health care resources for active EO
Endoscopic dilation rate per cycle	• No treatment: 12.5% (active EO), 6% (remission) • Active treatments: 6% (active EO), 3% (remission)	• No treatment: 4% (active EO), 2% (remission) • Active treatments: 2% (active EO), 1% (remission)

Company: episodic inductions

Fully incremental ICERs.

2 year time horizon.

	Total costs	QALY	Inc. Cost	Inc. QALY	Inc. ICER (£/QALY)
No treatment	£1,494	1.58	-	-	-
SFED	£1,785	1.61	£291	0.03	Ext dominated
Fluticasone	£1,844	1.73	£59	0.12	Ext dominated
Budesonide ODT	£1,846	1.76	£2	0.03	£1,958 vs no treatment

1 year time horizon.

	Total costs	QALY	Inc. Cost	Inc. QALY	Inc. ICER (£/QALY)
No treatment	£858	0.89			
Fluticasone	£1,117	0.97	£259	0.08	£3,238
SFED	£1,179	0.91	£62	-0.06	Dominated
Budesonide ODT	£1,224	0.99	£45	0.08	£4,780 vs fluticasone

ERG changes to company assumptions

ERG used the company's post TE model and applied its assumptions

- Pairwise ICERs budesonide ODT vs comparator.

2 year time horizon	ICER (£/QALY) for budesonide vs		
	Fluticasone	No treatment	SFED
Company preferred assumptions	**£62**	**£1,958**	**£406**
Budesonide (BUD) wastage included & fluticasone induction 1.5mg/day (not 2mg/day)	£10,820	£2,383	£911
Active EO utility 0.86 instead of 0.78	£133	£4,196	£869
Relapse rates for comparators	£4,732	£1,958	£343
ERG endoscopic dilation rate	£1,404	£2,976	£1,396
No resource use for active EO in "no treatment" group	£7,766	£6,934	£5,622
Remission rates – ERG's NMA	BUD dominates	£2,299	£646
All changes above combined	**£49,385**	**£18,905**	**£23,627**

ERG: single induction with maintenance for comparators (5 year time horizon)

ERG used company's pre TE model:

	Total costs	QALY	Inc. Cost	Inc. QALY	Inc. ICER (£/QALY)
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	**Ext dominated**
Fluticasone	£1,405	4.08	£517.64	0.04	**£14,012 vs budesonide ODT**

Scenario analyses	Incremental ICERs (£/QALY)			
	No treat-ment	Budesonide ODT (BUD)	SFED	Fluticasone
ERG preferred assumptions	-	**£11,587**	**Ext dominated**	**£ 14,012 vs BUD**
2 year time horizon	-	£11,629	Ext dominated	£22,020 vs BUD
Relapse rate for all treatments with no maintenance 41%	-	Ext dominated	Ext dominated	£12,523 vs no treatment
Relapse rate for fluticasone and SFED 2.5 % (rate seen in clinical practice)	-	Ext dominated	£5,668 vs no treatment	£ 8,842
Dilation rate – company estimates	-	£9,503	Ext dominated	£12,286 vs BUD
Fluticasone dose – company estimates	-	£11,587	Ext dominated	£15,371 vs BUD
Utilities – company estimate	-	£5,235	Ext dominated	£6,539 vs BUD
Patients in remission after 1 year do not relapse	-	£5,560	Ext dominated	£16,819 vs BUD

ERG: single induction with NO maintenance for comparators (3 year time horizon)

ERG used company's pre TE model:

	Total costs	QALY	Inc. Cost	Inc. QALY	Inc. ICER (£/QALY)
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**

Scenario analyses	Incremental ICERs (£/QALY)		
	No treatment	Fluticasone	Budesonide ODT
ERG preferred assumptions	-	**£ 6,177**	**£27,078**
2 year time horizon	-	£ 6,288	£27,820
Relapse rate for all treatments with no maintenance 41%	-	£ 8,259	£34,514
Relapse rate for fluticasone and SFED 2.5 % (rate seen in clinical practice)	-	£ 6,177	£27,078
Dilation rate – company estimates	-	£ 4,030	£25,349
Fluticasone dose – company estimates	-	£ 7,386	£23,461
Utilities – company estimate	-	£ 2,803	£12,637
Patients in remission after 1 year do not relapse	-	£ 4,088	£18,677

Issue 7: Relapse rate

Relapse rates per cycle (12 weeks)	Company		ERG	
	Relapse (%)	Source	Relapse (%)	Source
Budesonide ODT	-	-	11.7%	ERG's updated review of maintenance studies.
Fluticasone	15%	Retrospective study of 55 patients with EO		
SFED	50% after one year due to non-adherence	Lucendo et al. 2013 (50% of responders were lost to follow up and assumed that they stopped adhering - relapse is assumed due to non-adherence)		
All treatments (including 'no treatment') when no maintenance	41% (22, 28, 39 & 65% for each of cycles 1-4)	BUL-2/EER placebo (88% in one year)	31.5%	Dellon et al. 2019 - found no difference in the rates for those initially treated with budesonide or fluticasone

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Are the company or ERG estimates more appropriate?

Issue 8: Utilities

Utility	Company	source	ERG	source
Active EO	0.78	Age-adjusted UK population norms (Kind et al. 1999) minus **disutility of 0.15** for **GORD** observed in **Kartman et al. 2004** (0.93-0.15)	0.86	Age-adjusted UK population norms (Kind et al. 1999) minus **disutility of 0.07** for **EO** observed in **Hewett et al. 2017** (0.93-0.07)
Passive EO	0.93	Age-adjusted UK population norms for EQ-5D (Kind et al. 1999)	0.93	Age-adjusted UK population norms for EQ-5D (Kind et al. 1999)

Can the age-adjusted UK population norm be a proxy for histological remission?

Which estimate of utility for active disease is more appropriate?

Issue 9: Follow-up and monitoring costs

Company's assumptions (visits per cycle)	Budesonide ODT and fluticasone		No treatment		SFED	
	Active	Remission	Active	Remission	Active	Remission
Gastroenterologist	1	0	**0.5**	0	1	0
Endoscopy	0.47	0	**0.25**	0	1.3	1.3 for 1st year, 0 thereafter
Dietitian visit	0	0	**0**	0	1.8	1.8 for 1st year, 0 thereafter

Items	Unit cost	Reference
Gastroenterologist - first visit	£188.00	2018/19 National Tariff (WF01B)
Gastroenterologist - following visits	£72.00	2018/19 National Tariff (WF02B)
Upper endoscopy with biopsy sampling:	£391.00	2018/19 National Tariff (FZ61Z)
Dietitian visit	£30.94	2018/19 PSSRU

ERG:

- Company's assumptions are reasonable, but it assumed no resource cost for active EO for 'no treatment'

NICE

Are the company's or ERG's assumptions suitable for decision making?

Issue 10: Endoscopic dilation rates

		Company		ERG	
Dilation rates per cycle		Dilation	Source	Dilation	Source
No treatment	**Active EO**	**12.5%**	Schoepfer 2010	**4%**	Based on clinical advice
	Remission	**6%**	50% of active	**2%**	50% of active
Budesonide ODT fluticasone & SFED	**Active EO**	**6%**	50% of active EO for 'no treatment'	**2%**	Runge 2016
	Remission	**3%**	50% of active	**1%**	50% of active

Which estimates are more appropriate?

Key cost issues

6. **Model structure and time horizon:**

- Is the company's approach allowing multiple budesonide inductions appropriate, or should only a single induction be modelled?
- What is the appropriate time horizon for the model?

7. **Relapse rates:**

- Are the company's or ERG's estimates more appropriate?

8. **Utilities:**

- Can the age-adjusted UK population norm be a proxy for histological remission?
- Which estimate of utility for active disease is more appropriate?

9. **Follow-up and monitoring costs:**

- Are the company's or ERG's assumptions suitable for decision making?

10. **Endoscopic dilation rates**:

- Which estimates are more appropriate?

Back-up slides

ERG's models

Pre TE:

- **Budesonide ODT: Multiple induction + maintenance**
- Horizon: **20 years**
- 3 arms: ERG's NMA:
  1. **Budesonide ODT:** 6-12 weeks induction + maintenance
  2. **Fluticasone:** 6-12 weeks induction + maintenance
  3. **SFED:** 12 weeks induction + maintenance therapy

Post TE scenarios:

- **Budesonide ODT: Single induction + NO maintenance**
- Scenario 1: **Maintenance included for comparators**
  - Horizon: **5 years**
  - 4 arms: ERG's NMA – **budesonide ODT, fluticasone, SFED, 'no treatment'**
- Scenario 2 : **Maintenance for comparators is not included**
  - Horizon: **3 years**
  - 3 arms: ERG's NMA – **budesonide ODT, fluticasone, no treatment**

- For all treatments: patients in remission at 1 year continue to relapse

ERG's pre TE base case

- **Budesonide ODT 6-12 weeks induction + maintenance**
- 20 years time horizon
- No comparison with 'no treatment'
- Fully incremental ICERs are presented

	Total costs	QALY	Inc. Cost	Inc. QALY	Inc. ICER (£/QALY)
SFED	£1,528	12.48			
Fluticasone	£2,539	12.64	£1,012	0.16	£6,466
Budesonide ODT	£18,595	12.99	£16,056	0.35	£45,735

Key trial results: maintenance

BUL-2/EER trial • Double blind phase (DB) – 48 weeks of treatment	Budesonide ODT 0.5 mg twice daily (N=68)	Budesonide ODT 1 mg twice daily (N=68)	Placebo (N=68)	Open-label induction - 6 weeks of budesonide ODT induction (n=181)
Rate of patients free of treatment failure - primary	50/68 (73.5%)	51/68 (75%)	3/68 (4.4%)	**Clinico-histological remission:** 126/181 (69.6%)
Histological relapse – peak of ≥48 eos/mm² hpf	9/68 (13.2%)	7/68 (10.3%)	61/68 (89.7%)	
Clinical relapse	7/68 (10.3%)	5/68 (7.4%)	41/68 (60.3%)	**Histological remission – peak of < 16 eos/mm² hpf:** 163/181 (91.1%)
Deep histological remission- peak of < 15 eos/hpf	27/68 (39.7%)	36/68 (52.9%)	0/68 (0%)	

- All comparisons vs. placebo are $p<0.0001$
- Open-label induction confirms results from BUL1/EEA and BUU2/EEA
- **Open-label re-induction:** 76 of 82 patients (92.7%) showed resolution of their symptoms. Treatment success did not depend on previous treatment received.