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Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy: An Evidence Review Group perspective of a NICE Single Technology Appraisal

Short Title: Vedolizumab for the Treatment of Moderate-to-Severe Crohn's Disease

Corresponding author: Rachid Rafia, MSc, Research Fellow, School of Health and Related Research (ScHARR), University of Sheffield, Regent Court, 30 Regent Street, Sheffield, UK, S1 4DA.

Tel: +44 (0) 114 222 0739, Fax: +44 (0) 114 272 4095, Email: r.rafia@sheffield.ac.uk

Rachid Rafia, ScHARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA

Alison Scope, ScHARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA

Sue Harnan, ScHARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA

John W Stevens, ScHARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA

Matt Stevenson, ScHARR, University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA

Alan Lobo, Consultant Gastroenterologist and Honorary Professor of Gastroenterology, Sheffield Teaching Hospitals NHS Foundation Trust, University of Sheffield

Abstract

As part of its single technology appraisal (STA) process, the National Institute for Health and Care Excellence (NICE) invited the manufacturer of vedolizumab (Takeda UK) to submit evidence of the clinical effectiveness and cost-effectiveness of vedolizumab for the treatment of patients with moderate-to-severe active Crohn's disease. The School of Health and Related Research (ScHARR) at the University of Sheffield was commissioned as the Evidence Review Group (ERG) and produced a critical review of the evidence for the clinical effectiveness and cost-effectiveness of the technology, based upon the company's submission to NICE. The GEMINI II and GEMINI III trials formed the main supporting evidence for the intervention. Both studies were Phase III, multicentre, randomised, double-blind, placebo-controlled trials designed to evaluate the efficacy and safety of vedolizumab. They included patients who were naïve to tumour necrosis factor-alpha antagonist (anti-TNF-α), and patients who had an inadequate response to, loss of response to, or intolerance to immunomodulators or anti-TNF-α. The GEMINI II trial was designed to evaluate the efficacy and safety of vedolizumab as an induction treatment (dosing at weeks 0 and 2 with assessment at week 6) and maintenance treatment (weeks 6 to 52). In contrast, the GEMINI III trial was designed to evaluate the efficacy and safety of vedolizumab as an induction treatment only with doses at weeks 0, 2 and 6 with assessment at weeks 6 and 10. In the absence of any direct head-to-head randomised controlled trials comparing vedolizumab with other relevant biologic therapies (adalimumab and infliximab) for the treatment of moderate to severe Crohn's disease, the company conducted a network meta-analysis (NMA) which compared vedolizumab, adalimumab, infliximab and placebo for the outcomes of: clinical response, enhanced clinical response, clinical remission, and discontinuation due to adverse events.

The company model estimated the incremental cost-effectiveness ratio (ICER) for vedolizumab compared with standard of care (consisting of 5-aminosalicylic acid [5-ASAs], corticosteroids and immunosuppressants) to be £21,620 per QALY gained within the anti-TNF-α failure population (which included a confidential Patient Access Scheme for vedolizumab). The ICERs were above £30,000 per QALY gained for the mixed intention to treat (ITT) population (including both anti-TNF-α naïve and failure population) and in patients who were anti-TNF-α naïve only. The ERG identified a number of limitations which were believed to limit the robustness of the results presented by the company. These limitations could not be addressed by the ERG without major restructuring of the economic model. Therefore, the ERG concluded that results from the company's model needed to be interpreted with caution and that it was unclear whether the ICERs would increase or decrease following amendment of the identified structural issues.

Key Points for Decision Makers

- Vedolizumab appears to be more effective in both the induction and maintenance phase compared with placebo in patients with moderate-to-severe active Crohn's disease who have had an inadequate response to, loss of response to, or intolerance to conventional therapy or TNF-α inhibitor. However, it is noted that the primary endpoint (clinical remission at week 6) in GEMINI III was not met, but was met at week ten.
- The effectiveness of vedolizumab compared with adalimumab and infliximab is unknown and uncertain in the absence of a head-to-head randomised controlled trial and differences between studies included the network meta-analysis.
- The ERG identified a number of limitations with the company's model which were believed to limit the robustness of the results presented by the company.
- The National Institute for Health and Care Excellence Appraisal Committee recommended vedolizumab as an option for treating moderately to severely active Crohn's disease only in patients for whom TNF-α antagonists has failed (that is the disease has responded inadequately or has lost response to treatment) or cannot be tolerated or is contra-indicated on the condition that the company provides vedolizumab with the discount agreed in the patient access scheme.

1. Introduction

In order to be recommended for use within the National Health Service (NHS) in England, health technologies must be shown to be clinically effective and to represent a cost-effective use of NHS resources. The National Institute for Health and Care Excellence (NICE) is an independent organisation which provides national guidance and advice to improve health and social care. The NICE single technology appraisal (STA) process covers a single technology in a single indication, and is usually conducted soon after a UK marketing authorisation is granted [1]. The manufacturer of the technology submits a written submission to NICE, which details the company's estimates of the clinical effectiveness and cost-effectiveness of the technology, together with an executable health economic model which provides estimates of cost per QALY. An independent external organisation (the Evidence Review Group [ERG]) reviews the submission in consultation with clinical specialists and produces an ERG report. The NICE Appraisal Committee then meets to make a decision based on the company's submission, the ERG report and testimony from experts and other stakeholders. Where the Committee decide to recommend a technology without restrictions a Final Appraisal Determination (FAD) is issued. Where the initial decision is to restrict or not recommend a technology, an Appraisal Consultation Document (ACD) is produced. Stakeholders are then invited to comment on the ACD and on the submitted evidence, after which a subsequent ACD may be produced or a FAD issued, which is open to appeal.

This paper presents a summary of the ERG report [2, 3] for the STA of vedolizumab for the treatment of adults with moderate-to-severe active Crohn's disease (CD) and the subsequent development of the NICE guidance for the use of this drug in England. Full details of all relevant appraisal documents, can be found on the NICE website.[4]

2. The Decision Problem

The prevalence of CD is approximately 50-100 per 100,000 patients with CD estimated to affect approximately 60,000 patients in the UK in total [5]. CD is characterised by a chronic relapsing inflammation that mainly affects the gastrointestinal tract and is often accompanied by: abdominal pain, diarrhoea, weight loss, malaise, and anorexia [6, 7]. CD may also be complicated by stricturing (leading to intestinal obstruction), fistulae (often perianal), or abscesses [7].

The diagnosis of CD combines patient history, physical symptoms, and evidence from imaging and laboratory studies [6]. Disease activity, in combination with phenotypic and endoscopic features, allows stratification of patients and selection of appropriate therapeutic strategies [6]. In clinical trials, the CD Activity Index (CDAI) has been widely used to describe disease activity [8] – though the index is based on symptoms and does not capture intestinal mucosal activity or healing. A simplified form, the Harvey Bradshaw Index may be used in trials and clinical practice.

The aim of drug treatment in CD is to induce and maintain remission and mucosal healing, with the optimal outcome of maintaining corticosteroid-free-remission and reducing complications and the need for hospitalisations and surgery [5].

Existing guidelines [5, 7] suggest a standard 'step-up approach' for the treatment of CD in the UK. This involves the initial use of monotherapy with a conventional or locally released glucocorticosteroid to induce remission, escalating to the addition of azathioprine, mercaptopurine or methotrexate in those who do not respond.

Infliximab and adalimumab are currently recommended as treatment options for adults with severe active CD whose disease has not responded to conventional therapy, or who are intolerant of or have contraindications to conventional therapy [9].

Vedolizumab (brand name Entyvio®, Takeda UK) is a humanized monoclonal antibody that binds exclusively to the α4β7 integrin on gut-homing T helper lymphocytes and selectively inhibits adhesion of these cells to mucosal addressing cell adhesion molecule-1 (MAdCAM-1) and fibronectin, but not vascular cell adhesion molecule-1 (VCAM-1) [5]. Vedolizumab has a therapeutic indication for the treatment of adult with moderately to severely active CD who have had an inadequate response with, lost response to, or were intolerant to conventional therapy including anti-TNF-α [10]. The recommended dosage of vedolizumab is 300 mg given by intravenous infusion at 0, 2 and 6 weeks and then every 8 weeks thereafter. In patients who have not shown a response by Week 10, an additional dose should be considered at that point resulting in a 0, 2, 6, 10 and 14 schedule. The licensing states that treatment should be stopped if no evidence of therapeutic benefit is observed by Week 14 [10]. Finally, the licensing states that dose could be increased to every 4 weeks in patients who have experienced a decrease in their response.

NICE issued a final scope [11] to appraise the clinical effectiveness and cost-effectiveness of vedolizumab, within its licensed indication, for the treatment of moderate-to-severe active CD in adults in whom the disease has responded inadequately to, or is no longer responding to, either conventional therapy or an anti-TNF-α, or who are intolerant to either.

3. The Independent ERG Review

The company provided a submission to NICE on the clinical and cost-effectiveness of vedolizumab for the treatment of patients with moderate-to-severe active CD [5]. The company submission (CS) [5] included a systematic review and network meta-analysis (NMA) of the clinical effectiveness literature and a model-based health economic analysis.

In line with the STA process, the ERG critically reviewed the evidence presented in the company's submission by assessing (i) whether the submission conformed to NICE methodological guidelines; (ii) whether the company's interpretation and analysis of the evidence were appropriate; and (iii) the presence of other evidence or alternative interpretations of the evidence. In addition, the ERG identified areas requiring clarification, for which the company provided additional evidence.

3.1. Clinical Effectiveness Evidence Submitted by the Company

The company [5] presented a systematic review of the clinical effectiveness and safety of vedolizumab for the treatment of moderately to severely active CD in adults in whom the disease has responded inadequately to, or is no longer responding to, either conventional therapy or an anti-TNF-α, or who are intolerant to either of them. The systematic review aimed to assess the best available evidence to evaluate the efficacy and safety of all biological treatments (vedolizumab, adalimumab and infliximab) in patients with moderate to severe CD to inform a NMA.

Two trials, GEMINI II [12] and GEMINI III [13] formed the main supporting evidence for the intervention. Both studies were Phase III, multicentre (GEMINI II 39 countries; GEMINI III 19 countries), randomised, double-blind, placebo-controlled trials designed to evaluate the efficacy and safety of vedolizumab and included patients who were naïve to an anti-TNF-α, and patients who had an inadequate response to, loss of response to, or intolerance to immunomodulators or an anti-TNF-α.

The GEMINI II trial [12] was designed to evaluate the efficacy and safety of vedolizumab as an induction treatment (dosing at weeks 0 and 2 with assessment at week 6) and maintenance treatment (weeks 6 to 52, every 4 or 8 weeks). In contrast, the GEMINI III trial [13] was designed to evaluate the efficacy and safety of vedolizumab as an induction treatment only, with a dosing regimen of weeks 0, 2 and 6 with assessment at weeks 6 and 10. In general, efficacy analyses in the GEMINI II and III trials [12, 13] were conducted according to the intention-to-treat (ITT) principle whereby patients who withdrew prematurely were considered as treatment failures.

For the 6 week induction phase of the GEMINI II trial [12], 368 individuals were randomised (3:2 ratio) to receive 300mg vedolizumab i.v. or placebo (as saline) at Weeks 0 and 2 (Cohort 1). In order to fulfil sample size requirements for the maintenance study, an additional 748 individuals were enrolled in an open-label group (Cohort 2), which also received 300mg vedolizumab i.v. For the maintenance phase, patients from both cohorts (Cohort 1 and Cohort 2) who had a clinical response (defined as > 70 point decrease in the CDAI score) to vedolizumab at week 6 were randomised (1:1:1 ratio) to double-blind treatment with vedolizumab 300mg i.v.

every 8 weeks (with placebo administered every other visit to preserve blinding), vedolizumab 300mg i.v. every 4 weeks or placebo every 4 weeks for up to 52 weeks. Randomisation was stratified by three factors: (1) cohort; (2) concomitant use/non-use of glucocorticoids; and (3) concomitant use/non-use of immunosuppressive agents or prior use/non-use of anti-TNF-α or both. The two primary endpoints in the induction trial phase were enhanced clinical response at week 6 (defined as ≥100-point decrease in CDAI score), and clinical remission at week 6 (defined as a CDAI score of ≤150 points). The primary endpoint for the maintenance trial phase was clinical remission at week 52. Secondary outcome measures included enhanced clinical response at 52 weeks, glucocorticoid-free remission at week 52 in patients receiving glucocorticoids at baseline, and durable clinical remission (defined as clinical remission at ≥ 80% of study visits, including the final visit). The proportion of patients meeting these end points was analysed.

During the 10 week induction phase of the GEMINI III trial [13], 416 individuals were enrolled. 315 individuals had a previous inadequate response to, loss of response to, or intolerance of one or more anti-TNF-αs and 101 individuals were naïve to an anti-TNF-α. Patients were randomly assigned to receive intravenous vedolizumab (300mg) or placebo (as saline) at week 0, week 2, and week 6, with three stratification factors: (1) the presence or absence of previous anti-TNF-α failure; (2) concomitant use/non-use of glucocorticoids; and (3) by concomitant use/non-use of immunosuppressive agents. The primary endpoint in the GEMINI III trial [13] focussed on patients for whom an anti-TNF-α has failed (i.e., an inadequate response to, loss of primary response to, loss of secondary response to, or intolerance of ≥1 anti-TNF-α)), and was the proportion of patients in clinical remission (CDAI score ≤150 points) at week 6. A secondary analysis evaluated an overall population which included patients who were naïve to anti-TNF-α, and pre-specified exploratory analyses examined the group naïve to an anti-TNF-α.

Key efficacy data for both trials are presented in Table 1. Only results for the primary outcomes are summarised here. Further efficacy data can be found in the company submission [5] and the ERG report [2, 3].

In GEMINI II [12], patients treated with vedolizumab had significantly higher rates of clinical remission (CDAI score ≤150 points) at week 6 compared with placebo (14.5% versus (vs) 6.8%, treatment difference of 7.8% (95% CI 1.2, 14.3; p = 0.0206)) in the ITT population. In the anti-TNF-α failure population of GEMINI III [13], there was no statistically significant difference in the proportion of patients achieving clinical remission at week 6 between vedolizumab and placebo (15.2% vs 12.1%, treatment difference 3.0% (95% CI -4.5 to 10.5, p=0.433), and thus vedolizumab was not statistically significantly better than placebo with respect to the primary outcome. Therefore, statistical evaluations of all remaining endpoints in GEMINI III were considered exploratory. For the full recruited population of GEMINI III, the exploratory analysis reported a statistically significant difference in favour of vedolizumab (19.1% vs 12.1%, treatment difference 6.9% (95% CI 0.1 to 13.8, p=0.0478) for clinical remission at week 6. Only GEMINI III reported results at 10 weeks, and both the anti-TNF-α failure population and the whole recruited population reported statistically significant differences in clinical remission in the exploratory analyses (14.4% (95% CI 5.7 to 23.1, p=0.0012) and 15.5% (95% CI 7.8 to 23.3, p< 0.0001) respectively).

Table 1: Summary of key efficacy outcomes.

Phase	Treatment schedule	N	CR			ECR		
			n (%) (95% CI)	Comparison Adjusted % difference (95% CI, P value)	RR (95% CI)	n (%) (95% CI)	Comparison Adjusted % difference (95% CI, P value)	RR, (95% CI)
Induction phase	**Gemini II, Mixed ITT, 6 weeks**							
	Vedolizumab, wk 0, wk 6	220	32 (14.5) (9.9 to 19.2)*	7.8 (1.2 to 14.3, p=0.0206)*	2.1 (1.1 to 4.2)*	69 (31.4) (25.2 to 37.5)*	5.7 (-3.6 to 15.0, p=0.2322)*	1.2 (0.9 to 1.7)*
	Placebo	148	10 (6.8) (2.7 to 10.8)*			38 (25.7) (18.6 to 32.7)*		
	Gemini III, Prior TNR- α-failure, 6 weeks							
	Vedolizumab, wk 0, 2 and 6	158	24 (15.2) (9.6 to 20.8)*	3.0 (-4.5 to 10.5, p=0.433)*	1.2 (0.7 to 2.2)*	62 (39.2) (31.6 to 46.9)	16.9 (6.7 to 27.1, n/a)**	2.2 (1.3 to 3.6)**
	Placebo	157	19 (12.1) (7.0 to 17.2)*			35 (22.3) (15.8 to 28.8)		
	Gemini III, Mixed ITT, 6 weeks							
	Vedolizumab, wk 0, 2 and 6	209	40 (19.1) (13.8 to 24.5)**	6.9 (0.1 to 13.8, p=0.0478) **	1.6 (1.0 to 2.5) **	82 (39.2) (32.6 to 45.9) **	16.4 (7.7 to 25.2, p=n/a) **	1.7 (1.3 to 2.3) **
	Placebo	207	25 (12.1) (7.6 to 16.5) **			47 (22.7) (17.0 to 28.4) **		
	Gemini III, Prior TNF-α-failure, 10 weeks							
	Vedolizumab, wk 0, 2 and 6	158	42 (26.6) (19.7 to 33.5) **	14.4 (5.7 to 23.1, p=0.0012) **	2.2 (1.3 to 3.6) **	74 (46.8) (39.1 to 54.6) **	22 (11.4 to 32.6, p=n/a) **	1.9 (1.4 to, 2.6)
	Placebo	157	9 (12.1) (7.0 to 17.2) **			39 (24.8) (18.1 to 31.6) **		
	Gemini III, Mixed ITT, 10 weeks							
	Vedolizumab, wk 0, 2 and 6	209	60 (28.7) (22.6 to 34.8) **	15.5 (7.8 to 23.3, p< 0.0001) **	2.2 (1.4 to 3.3) **	100 (47.8) (41.1 to 54.6) **	23.7 (14.5 to 32.9, p=n/a) **	2.0 (1.5 to 2.6)
	Placebo	207	27 (13.0) (8.5 to 17.6) **			50 (24.2) (18.3, 30.0) **		
Maintenance phase	**Gemini II, Mixed ITT, 52 weeks**							
	Vedolizumab, Q8W	154	60 (39.0) (31.3 to 46.7)*	**Vedolizumab, Q8W*** 17.4 (7.3 to 27.5, p=0.0007)	**Vedolizumab, Q8W*** 1.8 (1.3, 2.6)	67 (43.5) (35.7, 51.3)	**Vedolizumab, Q8W** 13.4, (2.8 to 24.0), p=0.0132)	**Vedolizumab, Q4W*** 1.4 (1.1, 1.9)
	Vedolizumab, Q4W	154	56 (36.4) (28.8 to 44.0)*			70 (45.5) (37.6, 53.3)		
	Placebo	153	33 (21.6) (15.1 to 28.1)*	**Vedolizumab, Q4W*** 14.7 (4.6 to 24.7, p=0.0042)	**Vedolizumab, Q4W*** 1.7 (1.2 to 2.4)	46 (30.1) (22.8, 37.3)	**Vedolizumab, Q4W** 15.3, (4.6 to 26.0, p=0.0053)	**Vedolizumab, Q4W** 1.5 (1.1 to 2.0)

CR, Clinical remission defined as CDAI score ≤ 150 points; ECR, Enhanced clinical response defined as a ≥100-point reduction in CDAI score from baseline; SCR, Sustained clinical remission defined as CDAI score ≤ 150 points at both week 6 and week 10; Vedo, vedolizumab; CI, confidence interval; RR, relative risk; Q8W, vedolizumab treatment every 8 weeks; Q4W, vedolizumab treatment every 4 weeks; NR, not reported; N/A, not available; TNF, tumour necrosis factor

* Primary outcomes

** These outcomes were classified as exploratory analyses as the primary outcome (CR at 6 weeks for the prior TNF-α-failure population) was not met.

There was no significant difference between the vedolizumab and placebo groups for the second primary outcome in GEMINI II [12] which analysed the number of patients achieving enhanced clinical response (defined as a 100-point reduction from baseline in CDAI score) at week 6.

In the maintenance phase of the GEMINI II trial [12], 48% (242/461) of patients discontinued from the study. Patients treated with vedolizumab every 8 weeks and every 4 weeks, had significantly higher rates of clinical remission at week 52 compared with placebo (treatment difference 17.4% (95% CI 7.3 to 27.5, p = 0.0007) and 14.7% (95% CI 4.6, 24.7; p = 0.0042) respectively).

In the absence of any direct head-to-head randomised controlled trials comparing vedolizumab to other relevant biologic therapies (adalimumab and infliximab) for the treatment of moderate to severe CD, the company conducted an NMA [5]. The NMA, as reported in the CS [5], compared vedolizumab, adalimumab, infliximab and placebo for the outcomes of: clinical response, enhanced clinical response, clinical remission, and discontinuation due to adverse events (AEs). Data were from the trials GEMINI II [12], GEMINI III [13], CLASSIC I [14], Targan et al(1997) [15], NCT00105300 [16], NCT00445939 [17] EXTEND [18], ACCENT I [19], CLASSIC II [20], NCT00445432 [17], and CHARM [21]. The size of the network for each outcome varied depending on the availability of the data in each study.

In the induction phase for the anti-TNF-α naïve population, for clinical response (drop in CDAI ≥70) all treatments were statistically significantly effective versus placebo. Infliximab was statistically significantly better than vedolizumab. For clinical remission, all treatments except adalimumab 40/20mg (dose not licensed in the UK) were statistically better than placebo. In pairwise comparisons, infliximab was statistically significantly better than vedolizumab at 10 and 6 weeks; vedolizumab had a better odds ratio (OR) versus placebo than adalimumab 80/40mg dose, but worse OR versus placebo than adalimumab 160/80mg, but neither comparison was statistically significant. For discontinuations due to AEs, adalimumab 160/80mg dose was significantly better (lower) than vedolizumab; there were no data available for infliximab.

In the maintenance phase for the anti-TNF-α naïve population, vedolizumab every 4 weeks was only statistically different to placebo for the outcome of clinical remission. Vedolizumab every 8 weeks was statistically significantly better than placebo for both clinical response and clinical remission. Infliximab was statistically different from placebo in all three outcomes (clinical remission, clinical response, discontinuation due to AEs). The statistical significance of the difference in clinical response between vedolizumab and infliximab was not reported for the standard dose (5mg) of infliximab licenced in the UK, but infliximab 10mg was statistically significantly better than vedolizumab every 4 weeks. The clinical response OR for infliximab 5mg versus placebo was better than that for both vedolizumab every 4 weeks and every 8 weeks (dose every 4 weeks is licensed in the UK for patients who have experienced a decrease in their response only. It was not clear if patients in this analysis met this criteria). The difference between vedolizumab and infliximab for the outcome clinical remission was not statistically significant. There was a high OR for discontinuation due to AE's compared to placebo for infliximab; vedolizumab was significantly better than infliximab for discontinuations due to AEs.

No statistically significant differences were observed for most outcomes between vedolizumab and adalimumab in the induction phase for anti-TNF-α experienced/failure network. A network for anti-TNF- α failure subgroups was not possible for maintenance due to lack of data.

3.1.1. Critique of Clinical Effectiveness Evidence and Interpretation

The ERG considered the systematic review process followed by the company to be satisfactory, although the details were not reported fully in the CS [2] but provided in a separate document (commercial in confidence). Despite minor limitations in the company's search strategy, the ERG was confident that all relevant studies of vedolizumab were included in the CS [2]. The specified inclusion and exclusion criteria appeared generally appropriate, though lacking in detail in places, and reflected the information given in the decision problem. The validity assessment tool used to appraise the included studies, as suggested by NICE's Specification For Company/Sponsor Submission Of Evidence template [22], was based on the quality assessment criteria for RCTs and was considered appropriate by the ERG [2].

The efficacy and safety of vedolizumab was positively demonstrated in GEMINI II [12]. Owing to the high discontinuation rates in the maintenance phase of the GEMINI II trial, estimates of treatment effects (including magnitude) may be affected. The imputation of missing patients as failures should, however, limit the impact of attrition on estimates of efficacy to underestimation of treatment effects, though the effect of attrition may be more problematic for safety outcomes and lead to underestimates of AEs. The trials assess response in the induction phase earlier than would be done in the UK, at six weeks compared to ten weeks. As such, the population entering the maintenance phase in GEMINI II [12] may not fully be representative of the UK spectrum, as patients who take longer to respond are excluded. This could conceivably lead to an overestimation of maintenance treatment effect, if these patients are also less likely to maintain a response when in remission. In addition, the trial of maintenance therapy was not of sufficient size or duration to estimate the risk of uncommon AEs. The primary endpoint was not achieved in GEMINI III [13]; therefore, statistical evaluation of the secondary endpoints was acknowledged as exploratory by the company.

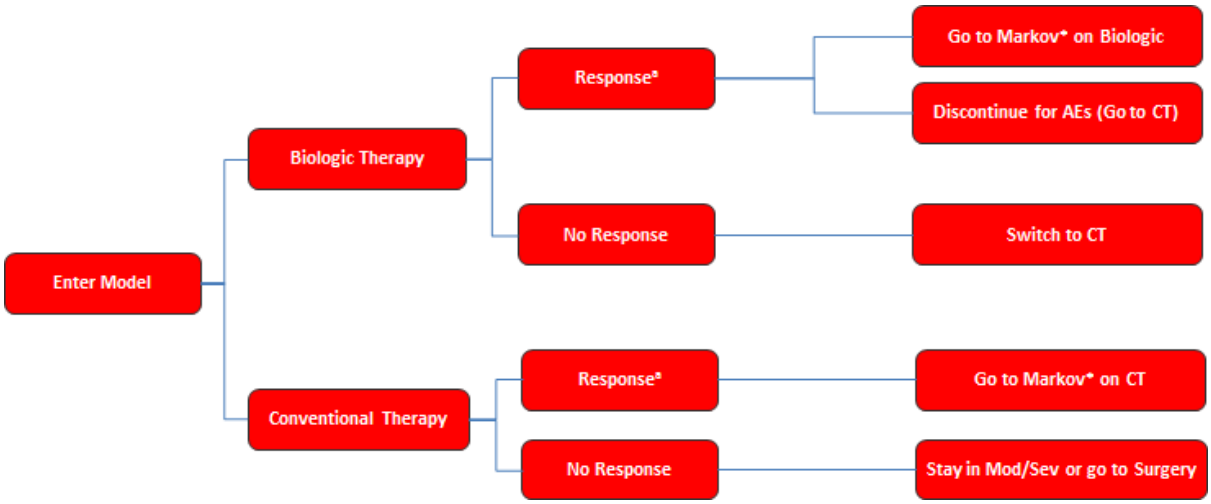
The ERG considered that the results presented in the company's NMA may have underestimated the uncertainty in treatment effects since fixed effects models were used [5]. The networks included in the CS [5] were of varying quality and relevance. The results of the "entire population" networks were thought to be difficult to interpret, as study populations were too heterogeneous in terms of potentially important treatment modifying effects [2]. The anti-TNF-α failure network may have overestimated efficacy for adalimumab as primary anti-TNF-α failure patients were excluded from the adalimumab study but not the vedolizumab studies. Several studies across the evidence base excluded patients with strictures, meaning generalisation to this population is problematic, and most did not report the proportion of patients with fistulising disease, so it is unclear whether all studies were representative of UK populations in this respect [2]. Similarly no studies included patients with CDAI>450, meaning generalisation to severe patients (if defined as CDAI 450 to 600) is problematic. Uncertainty remains around how the comparator "usual care" provided in studies compares with UK practice. No analysis for serious AEs was provided for the anti-TNF-α naïve networks. Additionally, for the induction networks, there were limitations with the induction schedule used in the trials included, with fewer doses than recommended being provided, and/or assessments taking place earlier than would be done in UK practice or than stated in the licence. Maintenance networks were subject to potential bias from the recruitment of patients on the basis of assessment at earlier time points that would commonly be done in the UK.

3.2. Cost-Effectiveness Evidence Submitted by the Company

The company submitted a model-based health economic analysis as part of their submission to NICE, which was subsequently revised. The analysis was undertaken from the perspective of the NHS over a 10-year time horizon. All costs and health outcomes were discounted at a rate of 3.5% per annum in accordance with NICE guidance. The company's analysis was presented for three populations: (1) the mixed-ITT population, which is comprised of patients who have previously received anti-TNF-α therapy and those who are anti-TNF-α naïve; (2) patients who are anti-TNF-α naïve only and; (3) patients who have had anti-TNF-α only. Within all three analyses, comparators included conventional non-biologic therapies (a combination of 5-ASAs, immunomodulators and corticosteroids). Other anti-TNF-α agents (infliximab, adalimumab) were included only in the analysis of the anti-TNF-α naïve subgroup; these are excluded from the analyses of the mixed-ITT and anti-TNF-α failure subgroups.

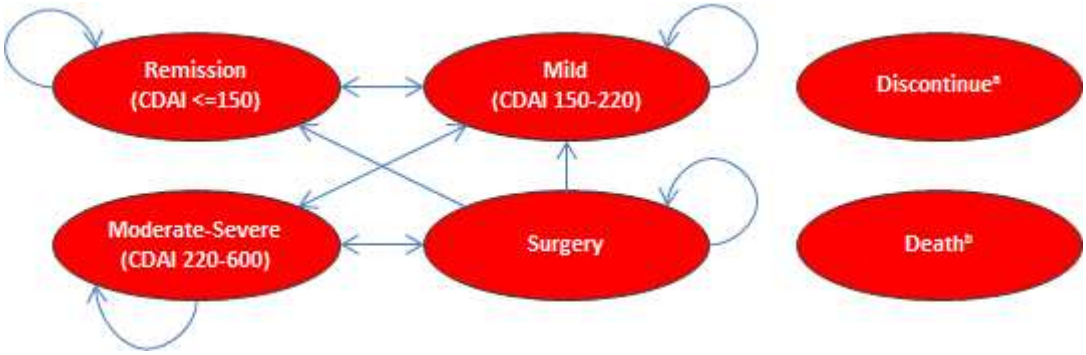
The company's model structure was based on the structure published by Bodger et al [23] and adopted a hybrid approach whereby a decision tree is used to evaluate outcomes at the end of the initial induction therapy during which all patients receive initial treatment to induce response. The induction period is assumed to be 6 weeks for all biologic and non-biologic therapy. A Markov structure (8-week cycle) is used afterward to evaluate subsequent outcomes. The model is composed of a total of 12 mutually exclusive and exhaustive health states, according to the treatment received, severity of the condition and surgery.

Figure 1 Decision-tree for induction treatment (reproduced from company's submission)



[a] Response is defined as a drop in CDAI of 70 points or more; * The Markov structures; AE = adverse event; CDAI = Crohn's Disease Activity Index; CT = conventional therapy.

Figure 2 Markov model schematics for CD maintenance phase and beyond (reproduced from company's submission)



[a] Reasons for discontinuation include lack of response and adverse events. Discontinuation due to adverse events is applicable only to responders on biologic treatments, because non-responders on biologics switch to conventional therapy and continue receiving such until the end of the model's time horizon.

[b] Patients may transition to death from any health state during any cycle.

Key efficacy parameters used within the company's model were either (i) observed or (ii) derived and taken from the two pivotal trials (GEMINI II & III [12, 13]) for vedolizumab and from the NMA for the anti-TNF-α [5]. Key parameters are the transition probabilities in the maintenance phase. These were 'calibrated' using the Solver function within Excel so that (a) the proportion of patients in remission at the end of the maintenance treatment (approximately at one-year) predicted by the model matches the 'expected' proportion of patients in remission at the end of the maintenance phase and (b) the proportion of patients with mild disease at the end of the maintenance phase predicted by the model matches the 'expected' percentage of responders to the induction phase with a drop of 70 points of more in the CDAI score and not in remission at the end of the maintenance phase. AEs were included in the model and the EQ-5D utility scores from the GEMINI trials [12, 13] were used to represent the utility values for the disease health states. Management costs (healthcare resource use associated with inpatient, outpatients visits, investigations and medications) for the different health states were taken from Bodger et al [23] and uplifted to 2012.

Key results provided by the company are presented here. The full list of results are available in the CS [5]. Within the anti-TNF-α naïve subgroup, the company reported the ICER for vedolizumab versus adalimumab to be £758,344 per QALY gained and infliximab versus vedolizumab to be £26,580 per QALY gained [5]. Based on a fully incremental analysis (performed by the ERG), vedolizumab was subject to extended dominance [2].

Within the anti-TNF-α failure subgroup, the company reported the ICER for vedolizumab versus conventional non-biologic therapy to be £98,452 per QALY gained in its original submission to NICE [5]. Following the publication of the appraisal consultation document (ACD) [24], the company submitted a revised economic model which included the following modifications:

- focusing on patients for whom a TNF-α antagonist has failed (i.e., an inadequate response to, loss of response to, or intolerance of >1 TNF-α antagonist),
- employing a lifetime horizon,
- using an assessment time of response in line with its licensing [10],

- inclusion of a revised patient access scheme,
- amendment of inputs and assumptions including assumptions around mortality and updating the health state costs using resource use estimated through a survey conducted amongst 8 clinical experts rather than the costs reported from Bodger et al (2009) [23],
- amendments to the Markov trace and calculations.

These had the effect of reducing the company's base case deterministic (probabilistic) ICER from £98,452 (not reported) per QALY gained [5] to £21,620 (£27,428) per QALY gained [25] within the anti-TNF-α failure population.

3.2.1. Critique of Cost-Effectiveness Evidence and Interpretation

The ERG [2, 3] critically appraised the company's health economic analyses and the models upon which these analyses were based. In summary, the ERG identified a number of limitations with the main limitations described below. The ERG noted that the combination of all these issues leads to discrepancies between the model prediction and trial data in terms of the proportion of patients in remission in the placebo arm and responders to vedolizumab to the induction phase remaining on treatment and discontinuing treatment.

3.2.1.1. Limitations regarding the model structure/key structural assumptions

Whilst the model structure is based on a previous economic evaluation by Bodger et al [23], the ERG [2] noted the following: (a) the company's model captures two key aspects of the condition: changes in disease severity (measured by the CDAI score) and the risk of surgery. The model ignores a key aspect of the condition in that CD is relapsing (exacerbation) and remitting (some patients may improve spontaneously), (b) surgery is modelled as a single health state representing a mix of procedures (c) the difficulty associated with parameterising the company's chosen structure which led the company to make a series of assumptions and adjustments that are not adequately justified by the evidence, and (d) debatable key structural assumptions. These debatable structural assumptions include the assumption that non-responders have moderate to severe disease; the lack of distinction between responders and non-responders with moderate to severe CD; the assumption of the same induction phase duration for all therapy; the relevance to clinical practice of drop of 70 or more in CDAI score to identify patients going onto receive maintenance treatment; end of scheduled maintenance at approximately 1-year; potentially optimistic assumption following discontinuation whilst on biologics and omission of discontinuation due to lack of efficacy.

3.2.1.2. Generalisability of the population

The ERG [2] further noted that the population included in the economic model was based on the GEMINI trials [12, 13] which only included patients with a CDAI score between 220 and 450 and therefore may not be representative of clinical practice in England. The trial recruited from a large number of centres worldwide and therefore, conventional non-biologic therapy may not be generalizable to England. The ERG noted that interpretation of results and the relevance of the mixed-ITT population to the decision problem was open to

debate. The ERG believed that patients who have previously received anti-TNF-α agents and those who are anti-TNF-α naïve are two distinct, defined patient groups, with different characteristics and propensities to respond to treatment, as demonstrated in the GEMINI trials [12, 13]. The appropriate comparators as chosen by the company are also different within these two populations. As such the ERG believes that the use of vedolizumab in these groups represents two separate decisions.

3.2.1.3. Comparators and treatment regimens

The company's analysis within the anti-TNF-α failure subgroup excludes all other biologic therapy. However, the use of a second anti-TNF-α agent following the failure of a first anti-TNF-α agent may be possible particularly where loss of response has occurred due to development of antibodies to the first anti-TNF-α therapy; however, the ERG recognises the limited efficacy evidence available.

The ERG had concerns with the treatment regimens assumed in the company's model. Notably, despite biologics having different treatment regimens, the company assumed the same induction phase duration for all therapies (6 weeks in the original model and 10 weeks in the revised model), adjusting the cost accordingly leading to discrepancies in the company's model (in terms of costing, cycle length and efficacy).

3.2.1.4. Parameterisation of the company's model

The ERG [2] discussed the efficacy data that were used in the economic model, notably the comparability of data for the different biologics at the maintenance phase, the efficacy data used for conventional non-biologic treatment, the partial use of the NMA and lack of clarity of the derivation of inputs - in particular, the derivation of the transition probabilities during the maintenance phase which were 'calibrated'. The ERG observed that the calibration approach was complex and may have been unnecessary as patient-level data from the GEMINI II trial [12] were available and could have been used to estimate the transition probabilities in the maintenance phase in patients treated with conventional non-biologic therapy and vedolizumab. The ERG identified a number of limitations with the calibration approach used by the company, notably that the target data-points used in the fitting process seemed inconsistent with the data point the model was fitted to and that the derivation of the transition probabilities was dependent on structural assumptions and input parameters. Transition probabilities were assumed to be constant and applied for the remainder of the model which was uncertain given the lack of evidence after one year.

Whilst the ERG [2, 3] recognised that there may be limitations with health state costs taken from Bodger et al (2009) [23], using costs estimated from the clinician survey conducted by the company may also have been inaccurate. This is particularly important given that this amendment to health state costs had a considerable impact on the ICER. The revised base-case ICER estimated by the company was £21,620 per QALY gained using the updated cost for the CD health states based on the clinician survey. Using the original management cost for the CD health states from Bodger et al (2009) [23] increased the ICER to £46,025 per QALY gained.

3.3. Additional work undertaken by the ERG

The key issues described above could not be addressed by the ERG [2, 3] without major restructuring of the economic model which was not achievable with the time frame for this STA. Incorporating changes to the model was challenging given the structure of the model and lack of transparency. As a result, the ERG was not able to amend the economic model structure.

However, the ERG [2, 3] conducted additional scenarios analyses where possible which included removing AEs, change utility values associated with the surgery health state, amendments to the cost of adalimumab, assuming the same efficacy in the maintenance phase between the different biologics, accounting for lack of efficacy and assuming the same excess mortality rate for each CD health state. In summary, the additional exploratory analyses conducted by the ERG had a limited impact on the ICER in isolation (variation in the ICER less than 5%).

3.4. Conclusion of the ERG Report

Compared with placebo, the addition of vedolizumab to standard care in patients with moderately to severely active CD who had an inadequate response to, loss of response to, or intolerance of conventional therapy or anti-TNF-α was significantly more effective in terms of remission (defined as CDAI $\leq$150) at week 6 in the induction phase of GEMINI II [12]. However, in GEMINI III [13] there was no statistically significant difference between vedolizumab and placebo in the primary endpoint of the proportion of patients achieving clinical remission at week 6 (CDAI score ≤150 points) in the anti-TNF-α failure population.

In the maintenance phase of GEMINI II [12] patients treated with vedolizumab every 8 weeks and every 4 weeks, had significantly higher rates of clinical remission at week 52 (defined as CDAI score of $\leq$ 150 points) compared with placebo.

There are, however, a number of limitations and uncertainties in the evidence base which warrant caution in its interpretation. Key issues relate to the high attrition rates in the maintenance phase of the GEMINI II [12] trial, the uncertainty on the long-term treatment effect, the duration of optimal therapy and how and when withdrawal should be introduced. The primary endpoint was also not achieved in GEMINI III; therefore, statistical evaluation of the secondary endpoints is exploratory. Results presented in the NMA are highly uncertain.

Changes made by the company in the revised economic model following the ACD had the effect of reducing the company's base case deterministic (probabilistic) ICER from £98,452 (not reported in the CS) to £21,620 (£27,428) per QALY gained for the anti-TNF-α failure population [25]. It should be noted that most of the changes were attributable to two amendments that are subject to uncertainty: increasing the time horizon from 10 years to a lifetime; and updating the health state costs using resource use estimated through a survey conducted amongst clinical experts.

The ERG [2, 3] identified a number of limitations which were believed to limit the robustness of the results presented by the company. These limitations could not be addressed by the ERG without major restructuring of the economic model. Therefore, the ERG concluded that results from the company's model needed to be

interpreted with caution and that it was unclear whether the ICERs would increase or decrease following amendment of the identified structural issues.

4. Key Methodological Issues

The NMAs included in the CS [5] were also of varying quality and relevance. There was heterogeneity in the population and outcomes included in the studies that participated to the network. The company's NMA is also likely to have underestimated the uncertainty in treatment effects since fixed effects models were used.

The health economic model submitted by the company was subject to a number of methodological issues which limited the credibility of the company's results [2] including: the potential omission of key aspects of the condition such as the relapsing-remitting nature of CD; simplifying and debatable assumptions regarding surgery; the difficultly associated with parameterising the company's chosen model structure; most notably the derivation of the transition matrices; and debatable key structural assumptions. The combination of all these issues led to some discrepancies between the model prediction and observed trial data. These issues could not addressed by the ERG without major restructuring of the economic model.

5. National Institute for Health and Care Excellence Guidance

The Appraisal Committee reviewed the data available on the clinical and cost-effectiveness of vedolizumab, having considered evidence on the nature of moderate-to-severe active CD and the value placed on the benefits of vedolizumab by patients with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

In December 2014, the Appraisal Committee produced a preliminary negative recommendation [24] for the use of vedolizumab within its marketing authorisation, i.e in adults whose disease has responded inadequately to, or has lost response to, either conventional therapy or a anti-TNF-α, or who cannot tolerate either of these treatment types.

As part of the appraisal consultation process, the company provided further analyses of the GEMINI II [12] and GEMINI III [13] trials on patients for whom a TNF-α antagonist has failed (i.e., an inadequate response to, loss of response to, or intolerance of >1 TNF-α antagonist) [25] and submitted a revised economic model focusing on the anti-TNF-α failure population including a revised patient access scheme.

Following consideration of the evidence presented on the clinical and cost-effectiveness of vedolizumab in patients for whom a TNF-α antagonist has failed [25], NICE issued its final guidance [4] in August 2015 and recommended the use of vedolizumab as an option for treating moderately to severely active CD only if:

- an anti-TNF-α has failed (that is the disease has responded inadequately or has lost response to treatment) or
- an anti-TNF-α cannot be tolerated or is contra-indicated.
- only if the company provides vedolizumab with the discount agreed in the patient access scheme.

The guidance [4] also states that vedolizumab should be given as a planned course of treatment until it stops working or surgery is needed, or until 12 months after the start of treatment, whichever is shorter. The guidance recommends that at 12 months, patients should be reassessed to determine whether treatment should continue and that treatment should only continue if there is clear evidence of ongoing clinical benefit. The guidance [4] recommends that for patients in complete remission at 12 months, the cessation of vedolizumab should be considered, with treatment being resumed if there is a relapse. The guidance recommends that patients receiving vedolizumab should be reassessed at least every 12 months to decide whether continued treatment is justified.

The guidance [4] further states that patients whose treatment with vedolizumab is not recommended, but was started within the NHS before this guidance was published, should be able to continue treatment until they and their NHS clinician consider it appropriate to stop

5.1. Consideration of Clinical and Cost-Effectiveness Issues

This section discusses the key issues considered by the Appraisal Committee. The full list can be found in the Appraisal Committee's final appraisal document (FAD) [4].

5.1.1. Generalisability of the GEMINI trials [12, 13] to the likely use and population to receive vedolizumab in clinical practice in England

The Committee [4] considered the generalisability of the populations enrolled in the GEMINI II [12] and III [13] to the populations that would be eligible to receive vedolizumab in clinical practice in England. The Committee heard from clinical experts that only a few number of patients seen in clinical practice have a CDAI above 450 and therefore considered the spectrum of disease activity of patients included in the trial broadly comparable to that seen in clinical practice. The Committee also discussed the induction regimens used in the GEMINI trials [12, 13] and heard from the clinical experts that induction response would usually be assessed later than observed in the trials. The Committee considered that the two populations (anti-TNF-α naïve and failure) needed to be evaluated separately and that assessing response at week 6, as in the GEMINI trials would not detect all patients whose disease respond to therapy.

5.1.2. Clinical effectiveness of vedolizumab

The Committee [4] discussed the efficacy estimates for vedolizumab from the GEMINI II trial [12] at the induction phase compared with placebo and noted that vedolizumab was more effective at week 6 in inducing clinical remission in the ITT mixed population, patients who had not had an anti-TNF-α, and patients in whom an anti-TNF-α had failed. The Committee considered the efficacy estimates for vedolizumab from the GEMINI III trial [13] at the induction phase compared with placebo and noted that whilst vedolizumab did not meet the primary outcome for inducing a better clinical remission compared with placebo at week 6 in patients in whom anti-TNF-α had failed, a statistically significant benefit was observed in week 10. The Committee then discussed the efficacy estimates for vedolizumab at the maintenance phase compared with placebo and noted that only GEMINI II provided 52 weeks evidence for this outcome. The Committee noted that vedolizumab showed higher remission rates than placebo in the mixed ITT population, patients who had never had anti-TNF-α, and patients in whom anti-TNF-α has failed. The Committee also heard from the clinical experts that even a small absolute treatment effect would be perceived as beneficial given the absence of alternative treatment options. After consideration of the clinical evidence, the Committee concluded that vedolizumab improved clinical remission at the induction phase and that vedolizumab was more effective compared with place in maintaining response up to 52 weeks in patients who had never had anti-TNF-α and patients in whom anti-TNF-α has failed.

The Committee [4] also considered the results from the NMA to estimate the relative effectiveness of vedolizumab compared with adalimumab and infliximab but concluded that results from the NMA were too uncertain in light of the ERG's comments and testimony from the clinical experts.

Finally, the Committee considered the evidence presented on the impact of vedolizumab on health-related quality of life and identified discrepancies on the reporting of the EQ-5D. These discrepancies could not be explained by the company and therefore the Committee was not able to conclude whether vedolizumab would have an effect on the EQ-5D value but noted that results using other assessment tools suggested that vedolizumab could improve quality of life.

5.1.3. Uncertainties around the model structure and plausibility of assumptions and inputs used in the economic model

The Committee [4] considered the model structure used by the company and concluded that it was uncertain whether the model was structurally sound in light of the number of concerns expressed by the ERG, but that, overall, it was acceptable to inform its decision-making. The Committee then went on to discuss the dosing assumptions and assessment of response used in the economic model and considered that the dosing assumptions used in the revised economic model was appropriate.

The Committee discussed the discontinuation rule assumed by the company whereby biologic treatments would be stopped after a maximum of one year. The Committee heard from the clinical experts that patients at high risk of relapse or surgery are likely to remain on treatment after one year but that they would try to stop treatment if it was not needed. The Committee considered that the assumption made by the company was not unreasonable, but that in clinical practice, patients could be treated for longer.

The Committee [4] considered whether the time horizon used in the original model (10 years) was appropriate and concluded that, whilst there was uncertainty in the long-term extrapolation given the short amount of data available, the use of a lifetime horizon in the revised economic model was more appropriate.

The Committee considered the modelling of long-term AEs and noted that AEs associated with the long-term use of corticosteroids such as diabetes and osteoporosis were not included and were likely to improve the cost-effectiveness for vedolizumab compared with conventional non-biological treatments.

Finally, the Committee considered the modelling of surgery, health state costs, mortality rate and was generally satisfied with the assumptions used in the revised economic model but highlighted that there was some uncertainties.

6. Conclusion

Vedolizumab appears to be more effective in both the induction and maintenance phase compared with placebo in patients with moderate-to-severe active Crohn's disease who have had an inadequate response to, loss of response to, or intolerance to conventional therapy or anti-TNF-α. The effectiveness of vedolizumab compared with adalimumab and infliximab is unknown and uncertain in the absence of head-to-head randomised controlled trial and differences between studies included the network meta-analysis. The ERG identified a number of limitations which were believed to limit the robustness of the results presented by the company. These limitations could not be addressed by the ERG without major restructuring of the economic model. Therefore, the ERG concluded that results from the company's model needed to be interpreted with caution and

that it was unclear whether the ICERs would increase or decrease following amendment of the identified structural issues. Nevertheless, the Committee considered that, on balance, after taking into account the uncertainty in the modelling of the long-term treatment effect of vedolizumab and structural assumptions, the absence of modelling of long-term AEs associated with corticosteroids and the high unmet need in patients in whom anti-TNF-α has failed, vedolizumab could be considered cost-effective and recommended vedolizumab in this population, providing the company provides vedolizumab with the discount agreed in the patient access scheme [4]. The Committee [4] also considered the high unmet need of a subgroup of patients who cannot take anti-TNF-α and in whom vedolizumab would provide the only medical alternative to conventional non-biological therapy and concluded that vedolizumab could be prescribed for this population providing the company provides vedolizumab with the discount agreed in the patient access scheme. The Committee [4] did not recommend the use of vedolizumab in patients who had never had anti-TNF-α and were able to receive them.

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Compliance with Ethical Standards

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Conflicts of interest

Professor Alan Lobo acted as a paid member of an Advisory Board for Takeda UK, who manufacture vedolizumab – after work on this project had been completed. Other authors declare no non-financial conflict of interest.

Contributions made by each author

Alison Scope and Sue Harnan summarised and critiqued the clinical effectiveness data reported by the company. John W Stevens critiqued the statistical analyses undertaken by the company. Anthea Sutton and Kath Dickinson undertook the literature searches run by the ERG and critiqued the searches by the company. Rachid Rafia and Matt Stevenson critiqued the health economic analysis submitted by the company. Professor John Mayberry, Professor Alan Lobo and Dr. Miles Parkes provided clinical advice to the ERG throughout the project. All authors were involved in drafting and commenting on the final document.

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