Vedolizumab for the Treatment of Adults with Moderate-to-Severe Active Ulcerative Colitis: An Evidence Review Group perspective of a NICE Single Technology Appraisal

Short Title: Vedolizumab for the Treatment of Moderate-to-Severe Ulcerative Colitis

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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 ulcerative colitis (UC). The Evidence Review Group (ERG) 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 evidence was derived mainly from the GEMINI1 trial, which is a Phase III, multicentre, randomised, double-blind, placebo-controlled trial designed to evaluate the efficacy and safety of vedolizumab as an induction and maintenance treatment in patients with moderate-to-severe active UC who had an inadequate response to, loss of response to, or intolerance to conventional therapy or anti-Tumour necrosis factor-alpha (TNF-α). The clinical evidence showed that vedolizumab performed significantly better than placebo in both the induction and maintenance phases. In the post-hoc subgroup analyses, patients with or without prior anti-TNF-α therapy, vedolizumab performed better then placebo (p-value not reported). In addition, a greater improvement in health-related quality of life was observed in patients treated with vedolizumab and the frequency and types of adverse events were similar between the vedolizumab and placebo group but the evidence was limited to short-term follow-up. There were a number of limitations and uncertainties in the clinical evidence base which warrant caution in its interpretation. In particular, the post-hoc subgroup analyses and high dropout rates in the maintenance phase of the GEMINI1 trial. The company also presented a network meta-analysis of vedolizumab versus other biologics therapies indicated for moderate-to-severe UC. However, the ERG considered that the results presented may have underestimated the uncertainty in treatment effects since fixed effects models were used, despite clear evidence of heterogeneity amongst the trials included in the network. Results from the company's economic evaluation (which included price reductions to reflect the proposed Patient Access Scheme for vedolizumab) suggested that vedolizumab is the most effective option compared with surgery and conventional therapy in the following three populations: (i) mix intention to treat population, including patients who have previously received anti-TNF-α therapy and those who are anti-TNF-α naïve; (ii) patients who are anti-TNF-α naïve only and; (iii) patients who have previously failed anti-TNF-α therapy only. The ERG concluded that the results of the company's economic evaluation could not be considered robust, because of errors in model implementation, the omission of relevant comparators, deviations from the NICE Reference Case and questionable model assumptions. The ERG amended the company's model and demonstrated that vedolizumab is expected to be dominated by surgery in all three populations.

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 ulcerative colitis who have had an inadequate response to, loss of response to, or intolerance to conventional therapy or TNF-α inhibitor. However, the subgroup analyses for patients with or without prior TNF-α inhibitor therapy were post-hoc and the study was not powered for these assessments.
- The findings of the network meta-analysis of vedolizumab versus TNF-α inhibitor are limited due to a number of uncertainties in treatment effects. In addition, there is currently no head-to-head randomised

controlled trial comparing vedolizumab to other biologic therapies indicated for moderate-to-severe ulcerative colitis.

- The National Institute for Health and Care Excellence (NICE) Appraisal Committee recommended vedolizumab within its licence indication but only if the company provides vedolizumab with the discount agreed in the patient access scheme.

1. Introduction

Health technologies must be shown to be clinically effective and to represent a cost-effective use of National Health Service (NHS) resources in order to be recommended for use within the NHS in England and Wales. The National Institute for Health and Care Excellence (NICE) is an independent organisation responsible for providing national guidance on promoting good health and preventing and treating ill health in priority areas with significant impact. The NICE single technology appraisal (STA) process usually covers new technologies within a single indication, soon after they have received UK marketing authorisation [1]. Within the STA process, the company provides NICE with a written submission which summarises the company's estimates of the clinical effectiveness and cost-effectiveness of the technology, together with an executable health economic model. This submission is reviewed by an external organisation independent of NICE (the Evidence Review Group [ERG]), which consults with clinical specialists and produces an ERG report. After consideration of the company's submission, the ERG report and testimony from experts and other stakeholders, the NICE Appraisal Committee formulates the preliminary guidance, the Appraisal Consultation Document (ACD), which indicates the initial decision on whether or not to recommend the intervention. Stakeholders are then invited to comment on the submitted evidence and the ACD, after which a subsequent ACD may be produced or a Final Appraisal Determination (FAD) is issued, which is open to appeal. An ACD is not produced when the intervention is recommended without restriction; in that instance, a FAD is produced directly.

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

2. The Decision Problem

UC is a relapsing-remitting form of inflammatory bowel disease (IBD) [4] with inflammation typically occurring in the colon and rectum. Symptoms include the development of bloody diarrhoea with or without mucus, abdominal pain, weight loss, fatigue, rectal urgency and tenesmus [5-7]. The onset of symptoms and diagnosis of UC usually occurs in young-middle aged working adults. Peak incidence is between 15 and 25 years of age, with a potential second peak between 55 and 65 years [8]. Over two-thirds of patients describe interference with work and three-quarters describe interference with leisure activities [9]. The unpredictable nature of relapse in UC and the significant symptom burden also has a negative effect on patients' psychological well-being and quality of life [10]. UC is recognised as the most common form of IBD in the UK. The

incidence of UC is approximately 10 per 100,000 population per year, whilst the prevalence of the disease is approximately 240 per 100,000 population [8]. The majority (approximately 80%) of incident cases are reported to be of mild or moderate severity. An estimated 132,600 people in England and Wales have been diagnosed with UC [8].

2.1 Current Treatment

At present, there is no agreed pathway for the management of patients with treatment refractory (second-line conventional therapy) moderate-to-severe active UC. The main aim of treatment is to resolve symptoms and maintain remission. Conventional therapy for UC may include aminosalicylates (mesalamine, sulfasalazine, balsalazide and olsalazine), corticosteroids (beclomethasone, or prednisolone), thiopurines (mercaptopurine or azathioprine) and calcineurin inhibitors. Tumour necrosis factor-alpha (TNF-α) inhibitors (infliximab, adalimumab and golimumab) may be used for disease refractory to conventional therapy [8]. Choice of treatment may be influenced by the severity of symptoms, the extent and location of inflammation, and is based on clinical expertise and individual patient choice. Patients who fail both conventional and TNF-α inhibitor therapy typically have no other medical therapeutic options available to them and up to 40% [11] may progress to surgery [12]. However, people may be reluctant to consider surgery due to the potential serious post-surgery complications such as bleeding, faecal incontinence, depression, distorted body image, sexual dysfunction, female infertility, pouchitis, pouch leakage, pelvic abscesses, pouch fistulae, small bowel obstruction and anastomotic stricture [13]. Current treatment options are also associated with safety concerns associated with long term use of corticosteroids, immunomodulators and TNF-α inhibitors including immunosuppression, osteoporosis and lymphoma [14;15].

Vedolizumab ((Entyvio®), Takeda) is a humanised monoclonal antibody. It targets α4β7 integrin, which is expressed in certain white blood cells that are found in the gut. α4β7 integrin is responsible for recruiting these cells to inflamed bowel tissue. Vedolizumab therefore offers gut-selective targeted therapy without systemic immunosuppression. On 22 May 2014, the European Medicines Agency (EMA) [16] granted marketing authorisation for the medicinal product Entyvio "for the treatment of adult patients with moderate-to-severe active UC who have had an inadequate response with, or lost response to, or were intolerant to either conventional therapy or a TNF-α inhibitor. The recommended dosage of vedolizumab is 300 mg given by intravenous infusion at 0, 2 and 6 weeks and then every 8 weeks thereafter. Continued therapy for people with UC should be carefully reconsidered if no evidence of therapeutic benefit is observed by week 10. Some patients with decreased response may benefit from an increase in dosing frequency to 300mg every four weeks."

NICE issued a final scope [17] in June 2014 to appraise the clinical effectiveness and cost-effectiveness of vedolizumab, within its licensed indication, for the treatment of moderate-to-severe active UC in adults who are intolerant of, or whose disease has had an inadequate response or loss of response to conventional therapy or a TNF-α inhibitor.

3. The Independent Evidence Review Group Review

The company (Takeda UK) provided a submission to NICE on the clinical and cost-effectiveness of vedolizumab for the treatment of patients with moderate-to-severe active UC [3;18]. 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's submission [3;18] included a systematic review and network meta-analysis (NMA) of the clinical effectiveness evidence. The aim of the review was to demonstrate the efficacy and safety of vedolizumab for the treatment of adult patients with moderate-to-severe active UC who are intolerant of, or whose disease has had an inadequate response or loss of response to conventional therapy (immunosuppressants and/or corticosteroids) or a TNF-α inhibitor compared with established clinical treatment without vedolizumab. The GEMINI1 trial [19] (ClinicalTrials.gov identifier NCT00783718), which forms the main supporting evidence for the intervention, was a Phase III, multicentre (34 countries including 2 sites in the UK), randomised, double-blind, placebo-controlled trial designed to evaluate the efficacy and safety of vedolizumab as an induction treatment (Weeks 0 to 6) and maintenance treatment (Weeks 7 to 52) in patients with moderate-to-severe active UC who had an inadequate response to, loss of response to, or intolerance of conventional therapy or TNF-α inhibitor.

In the 6-week induction phase, 374 patients were randomised (3:2 ratio) to receive 300mg vedolizumab intravenous (i.v.) or placebo (as saline) at Weeks 0 and 2, with two stratification factors: (1) concomitant use or non-use of glucocorticoids and (2) by concomitant use or non-use of immunosuppressive agents or prior use or non-use of anti-TNF-α agents. In order to fulfil sample size requirements for the maintenance study, an additional 521 patients were enrolled in an open-label group, who received the same treatment regime. The primary endpoint was clinical response at week 6 (defined as a reduction in the Mayo Clinic score of at least 3 points and a decrease of at least 30% from the baseline score, with a decrease of at least 1 point on the rectal bleeding subscale or an absolute rectal bleeding score of ≤1). In the double-blinded cohort, patients treated with vedolizumab had significantly higher rates of clinical response, clinical remission and mucosal healing compared with placebo (Table 1). Additional post-hoc subgroup analyses showed that compared with placebo, treatment with vedolizumab improved clinical response and remission rates at 6-weeks in patients with no prior anti-TNF-α exposure, and to a lesser extent in those with prior anti-TNF-α failure (p-values were not provided as the company stated that 'multiple testing adjustments were not made'). A post-hoc 'delayed responder' exploratory analysis in patients who failed to demonstrate clinical response at Week 6 in the induction phase found that the percentage of patients achieving clinical response (using partial Mayo scores) at Week 10 and Week 14 in vedolizumab-treated patients was 32% (102/322) and 39% (126/322), respectively, compared with placebo (15% (12/82) and 21% (17/82), respectively).

Table 1: Efficacy endpoints at week 6 in induction phase of GEMINI1 trial [19]

Endpoint	Vedolizumab 300mg i.v. at weeks 0 and 2	Placebo	Percentage difference (95% CI)	p-value
Double blinded cohort	n=225	n=149		
Clinical response[a], No. (%) (primary end point)	106 (47.1)	38 (25.5)	21.7 (11.6 to 31.7)	<0.001
Clinical remission[b], No. (%)	38 (16.9)	8 (5.4)	11.5 (4.7 to 18.3)	0.001
Mucosal healing[c], No. (%)	92 (40.9)	37 (24.8)	16.1 (6.4 to 25.9)	0.001
Open-labelled cohort	n=521			
Clinical response[a], No. (%)	231 (44.3)			NR
No prior anti-TNF-*α naive*	n=130	n=76		
Clinical response[a], No. (%)	69 (53.1)	20 (26.3)	26.8 (13.7 to 39.9)	NR
Clinical remission[b], No. (%)	30 (23.1)	5 (6.6)	16.5 (2.4 to 30.2)	NR
Mucosal healing[c], No. (%)	64 (49.2)	19 (25.0)	24.2 (11.2 to 37.2)	NR
Prior anti-TNF-*α failure*	n=82	n=63		
Clinical response[a], No. (%)	32 (39.0)	13 (20.6)	18.4 (3.9 to 32.9)	NR
Clinical remission[b], No. (%)	8 (9.8)	2 (3.2)	6.6 (-9.8 to 22.8)	NR
Mucosal healing[c], No. (%)	25 (30.5)	13 (20.6)	9.9 (-4.3 to 24.0)	NR

CI - confidence interval; NR - not reported

[a] Clinical response is defined as reduction in complete Mayo score of ≥ 3 points and ≥ 30% from baseline (Week 0) with an accompanying decrease in rectal bleeding subscore of ≥ 1 point or absolute rectal bleeding subscore of ≤ 1 point.
[b] Clinical remission is defined as complete Mayo score of ≤ 2 points and no individual subscore > 1 point.
[c] Mucosal healing is defined as Mayo endoscopic subscore of ≤ 1 point.

Patients with a clinical response at Week 6 from both the blinded and non-blinded cohort (n=373) were randomised (1:1:1 ratio) in the maintenance phase to a 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. The primary endpoint was clinical remission at 52 weeks (defined as a Mayo score ≤2 points with no individual score >1). According to the company's submission, randomisation was stratified by three factors: (1) cohort; (2) concomitant use or non-use of glucocorticoids; and (3) concomitant use or non-use of immunosuppressive agents or prior use or non-use of anti-TNF-α. Patients in the induction study who did not have a clinical response at Week 6 continued to receive their assigned study drug (vedolizumab or placebo) every 4 weeks and were followed through until Week 52 separately from the maintenance study.

In the maintenance phase higher rates of efficacy were observed in both the vedolizumab (300mg i.v.) 4-weekly and 8-weekly groups compared with the placebo group at Week 52 (Table 2). In addition, no clear differences in efficacy were observed between the two vedolizumab regimens.

Table 2: Efficacy endpoints in maintenance phase of GEMINI1 trial [19]

Study Endpoint	Vedolizumab every 8weeks	Vedolizumab every 4weeks	Placebo	Between group percentage difference[g]			
				Vedolizumab every 8weeks vs placebo (95% CI)	p-value	Vedolizumab every 4weeks vs placebo (95% CI)	p-value
ITT patients[a]	n=122	n=125	n=126				
Clinical remission[b] at Wk, 52, No. (%)	51 (41.8)	56 (44.8)	20 (15.9)	26.1 (14.9 to 37.2)	<0.001	29.1 (17.9 to 40.4)	<0.001
Durable clinical response[c], No. (%)	69 (56.6)	65 (52.0)	30 (23.8)	32.8 (20.8 to 44.7)	<0.001	28.5 (16.7 to 40.3)	<0.001
Durable clinical remission[d], No. (%)	25 (20.5)	30 (24.0)	11 (8.7)	11.8 (3.1 to 20.5)	0.008	15.3 (6.2 to 24.4)	0.001
Mucosal healing at Wk 52[e], No. (%)	63 (51.6)	70 (56.0)	25 (19.8)	32.0 (20.3 to 43.8)	<0.001	36.3 (24.4 to 48.3)	<0.001
Corticosteroid-free clinical remission at Wk 52[f], No. (%)	22/70 (31.4)	33/73 (45.2)	10/72 (13.9)	17.6 (3.9 to 31.3)	0.01	31.4 (16.6 to 46.2)	<0.001
Anti-TNF-*α naïve*	n=72	n=73	n=79				
Clinical remission[b], No. (%)	33 (45.8)	35 (47.9)	15 (19.0)	26.8 (12.4 to 41.2)	NR[h]	29.0 (14.6 to 43.3)	NR[h]
Durable clinical response[c], No. (%)	47 (65.3)	41 (56.2)	21 (26.6)	38.7 (24.0 to 53.4)	NR[h]	29.6 (14.6 to 44.6)	NR[h]
Durable clinical remission[d], No. (%)	16 (22.2)	21 (28.8)	10 (12.7)	9.6 (-2.5 to 21.6)	NR[h]	16.1 (3.4 to 28.8)	NR[h]
Mucosal healing[e], No. (%)	43 (59.7)	44 (60.3)	19 (24.1)	35.7 (20.9 to 50.4)	NR[h]	36.2 (21.6 to 50.9)	NR[h]
Prior Anti-TNF-*α failure patients*	n=43	n=40	n=38				
Clinical remission[b], No. (%)	16 (37.2)	14 (35.0)	2 (5.3)	31.9 (10.3 to 51.4)	NR[h]	29.7 (7.4 to 49.4)	NR[h]
Durable clinical response[c], No. (%)	20 (46.5)	17 (42.5)	6 (15.8)	30.7 (11.8 to 49.6)	NR[h]	26.7 (7.5 to 45.9)	NR[h]
Durable clinical remission[d], No. (%)	9 (20.9)	5 (12.5)	1 (2.6)	18.3 (-3.8 to 38.9)	NR[h]	9.9 (-13.0 to 31.5)	NR[h]
Mucosal healing[e], No. (%)	18 (41.9)	19 (47.5)	3 (7.9)	34.0 (12.6 to 53.2)	NR[h]	39.6 (18.1 to 58.5)	NR[h]

CI - confidence interval; NR - not reported; ITT, intention-to-treat; Wk - week

[a] Patients with insufficient diary entries were imputed as not achieving clinical response

[b] Clinical remission is defined as complete Mayo score of ≤ 2 points and no individual subscore >1 point at Week 52

[c] Durable clinical response is defined as reduction in complete Mayo score of ≥3 points and ≥ 30% from baseline (Week 0) with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point at both Weeks 6 and 52.

[d] Durable clinical remission is defined as complete Mayo score of ≤ 2 points and no individual subscore >1 point at both Weeks 6 and 52.

[e] Mucosal healing is defined as Mayo endoscopic subscore of ≤ 1 point.

[f] Corticosteroid-free clinical remission is defined as patients using oral corticosteroids at baseline (Week 0) who have discontinued corticosteroids and are in clinical remission at Week 52.

[g] Between-group differences in percentage points were adjusted for three stratification factors: cohort, concomitant use or non-use of glucocorticoids, and concomitant use or non-use of immunosuppressive agents or prior use or non-use of TNF-α antagonists.

[h] p-values are not provided because multiple testing adjustments were not made.

Clinical response and remission rates were generally favourable for vedolizumab compared with placebo in both the anti-TNF-α naïve and anti-TNF-α failure subgroups. However, efficacy was greater in the anti-TNF-α naïve group compared with the anti-TNF-α failure group (see Table 2). In addition, a greater health-related quality of life (HRQoL) improvement was observed in patients treated with vedolizumab in both the induction and maintenance phase compared with the placebo group.

In general, all efficacy analyses in the GEMINI1 trial [19] were conducted according to the intention-to-treat (ITT) principle whereby patients who withdrew prematurely were considered as treatment failures. In the induction phase, 6% (57/895) of the total population prematurely discontinued from the study. In contrast, a larger proportion of patients discontinued during the maintenance phase (44% (164/373) of the total population i.e. responders to vedolizumab during the induction phase that were re-randomised to maintenance therapy at Week 6). The main reasons for discontinuation in the vedolizumab and placebo groups were lack of efficacy or disease-related adverse events (AEs).

The frequency of AEs was similar between the vedolizumab and placebo groups in the GEMINI1 trial [19]. The most commonly occurring AEs during the maintenance phase in the combined vedolizumab group compared with the combined placebo group were nasopharyngitis (12.9% versus 9.5%), headache (12.9% versus 10.2%), arthralgia (9.0% versus 9.1%) and upper respiratory tract infections (8.4% versus 7.6%), respectively. The majority of infusion-related reactions in the induction and maintenance phases were mild to moderate in severity with only 3 cases resulting in drug discontinuation. Although no cases of anaphylaxis, serum sickness or progressive multifocal leukoencephalopathy (PML) were observed, one patient died during the GEMINI1 trial [19]; this was considered by the study investigators to be unrelated to treatment. Supplementary safety evidence from an ongoing GEMINI Long Term Safety trial (LTS) [20;21] (ClinicalTrials.gov identifier NCT00619489) and two separate pooled safety analyses (not meta-analysed) were also provided by the company [22;23]. In general, the overall safety profile of vedolizumab appeared to be similar between patients with UC and Crohn's disease (CD) with slightly higher rates of AEs in the CD patients. As of June 2013, no cases of PML had been reported in any of the >2,700 patients treated with vedolizumab, including approximately 900 patients with ≥24 months exposure. In addition, a total of 26 vedolizumab-treated patients in the integrated safety population had been diagnosed with malignancy, of which 18 met serious adverse event (SAE) criteria. Tuberculosis (TB) was reported in a total of 4 patients (3 with CD, 1 with UC), and 13 deaths occurred across all controlled and uncontrolled studies in UC (n=4) and CD (n=9). None of the UC deaths were considered by the study investigators to be treatment-related.

In the absence of any direct head-to-head randomised controlled trials (RCTs) comparing vedolizumab and other relevant biologic therapies for the treatment of moderate-to-severe UC, the company conducted an NMA. The NMA compared vedolizumab, adalimumab, golimumab, infliximab and placebo for the outcomes; clinical response, durable clinical response, clinical remission, mucosal healing, discontinuation due to AEs, SAEs and corticosteroid-free (CSF) remission using data from the trials: GEMINI1 (vedolizumab) [19], ULTRA1 (adalimumab) [24], ULTRA2 (adalimumab) [25], ACT1 (infliximab) [26], ACT2 (infliximab) [26], PURSUIT-

SC (golimumab) [27], PURSUIT-M (golimumab) [28] and Suzuki 2014 (adalimumab) [29]. The size of the network for each outcome varied depending on the availability of the data in each study.

The fixed effects NMA suggested that in the induction phase for anti-TNF-α naïve patients, infliximab provided the largest treatment effect on clinical response, remission and mucosal healing compared with placebo, and vedolizumab was associated with the lowest rate of discontinuations due to AEs compared with placebo. In the induction phase for patients who had previously had TNF-α inhibitors, only the treatment effects of adalimumab and vedolizumab were analysed relative to placebo. Each had positive effects in term of clinical response, remission and mucosal healing, but only the effect of vedolizumab compared with placebo for the outcome of response was statistically significant. For the maintenance phase, vedolizumab was associated with the largest treatment effect compared with placebo in both the anti-TNF-α naïve and anti-TNF-α failure patient subgroups. However, only those patients who responded to vedolizumab in the induction phase entered the GEMINI1 [19] maintenance phase hence there is no data available to compare the effect/efficacy of vedolizumab against placebo in the maintenance phase in patients who responded to placebo in the induction phase.

3.1.1. Critique of Clinical Effectiveness Evidence and Interpretation

The systematic review process followed by the company was comprehensive. Despite minor limitations in the company's search strategy, the ERG was confident that all relevant studies of vedolizumab were included in the company's submission. The specified inclusion and exclusion criteria appeared generally appropriate and reflect the information given in the decision problem. The validity assessment tool used to appraise the included studies, as suggested by NICE [30], was based on the quality assessment criteria for RCTs and was considered appropriate by the ERG.

Although the efficacy and safety of vedolizumab was positively demonstrated (compared with placebo) in the GEMINI1 study [19], there were a number of limitations and uncertainties which warrant caution in the interpretation of the available evidence. Owing to the high discontinuation rates in the maintenance phase of the GEMINI1 trial [19], estimates of treatment effects (including magnitude) may be confounded. The subgroup analyses undertaken to determine the efficacy of vedolizumab in patients who were anti-TNF-α failure and in patients who were anti-TNF-α naïve were exploratory and the study was not powered for these assessments. The duration of treatment of vedolizumab in the GEMINI1 trial [19] was 52 weeks, followed by enrolment in the ongoing GEMINI LTS study [20;21]. As a result, the long-term efficacy and safety of vedolizumab is unknown and the optimum duration of therapy remains unclear. There are no data on strategies for withdrawal of the drug in those on maintenance therapy or how to predict instances in which this can be successfully achieved. Furthermore, the safety and efficacy of vedolizumab has not been established in children aged below 17 years, in pregnant women, in women of childbearing potential, lactating mothers, patients with renal or hepatic impairment, or in concomitant use with biologic immunosuppressants. Finally, of the 211 study sites from which patients were recruited, only two were UK-based and 63 were US-based. With the exception of the US sites, where permitted immunosuppressants were discontinued after induction, all other sites maintained

immunosuppressants at stable doses throughout the induction and maintenance period. As such, there is some uncertainty regarding the generalisability of the evidence to the clinical population of England and Wales.

Despite considerable differences between the trials included in the NMA, the company's NMA used a fixed-effect model. As a result, the ERG believes that the results presented may have underestimated the uncertainty in treatment effects. Moreover, the main differences between the studies in both the induction phase and maintenance phase related to the following: patient characteristics, study design (randomisation at baseline or re-randomisation of biologic induction-responders) and study duration. Only GEMINI1 [19] and ULTRA2 [25] included patients with prior anti-TNF-α experience and anti-TNF-α naïve patients, whilst ACT1 [26], ACT2 [26], PURSUIT-SC [27], Suzuki 2014 [29] and ULTRA1 [24] included only patients who were anti-TNF-α naïve. Within PURSUIT-M [28], all recruited patients were golimumab induction-responders [27]. It is noteworthy, that patients with prior anti-TNF-α experience may be a more difficult to treat population than those who are anti-TNF-α naïve. Furthermore, the inclusion criteria between GEMINI1 [19] and ULTRA2 [25] differed. In GEMINI1 [19], failure to anti-TNFs was defined as inadequate response (i.e. primary non-responders to induction therapy with anti-TNF therapy), loss of response (i.e. secondary non-response/loss of response to anti-TNFs over time following initial response) or patients were intolerable to anti-TNFs. Whereas ULTRA2 [25] included people whose disease had lost response to, or who could not tolerate another anti-TNF, before starting adalimumab (i.e. this study does not appear to have included primary non-responders to anti-TNFs). In terms of study design, the adjustments made by the company in the maintenance phase to the trials without re-randomisation at the end of the induction phase inflate estimates of treatment effects in both the placebo and experimental treatment groups. The impact of this adjustment on the relative treatment effect in these trials was not clear. It was also unclear if the large relative treatment effect observed for vedolizumab compared with placebo in the GEMINI1 [19] maintenance phase was due to the low event rates for placebo, which included only prior vedolizumab induction-responders. Whilst the placebo arm in ULTRA2 [25] maintenance phase included both induction-responders and non-responders as patients were randomised to induction and maintenance regimes at baseline. Hence, it was not clear if the placebo groups in these two trials [19;25] are comparable in the NMA for the anti-TNF-α failure/experience subgroup. The anti-TNF-α naïve subgroup also has this comparability issue in the maintenance phase. The results of the NMA for clinical response and remission should be interpreted with further caution because these were estimated without considering the dependence/correlation between response and remission i.e. remission is a subset of response and the data are ordered categorical in nature, but the NMA was binary and considered only response or no response, or remission or no remission. Use of these results in the economic model ignores this dependence and may generate inappropriate samples for probabilistic sensitivity analysis (PSA).

3.2 Cost-Effectiveness Evidence Submitted by the Company

The company submitted a model-based cost-utility analysis as part of their submission [3;18]. The analysis was undertaken from the perspective of the NHS over a 10-year time horizon. 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 previously failed anti-TNF-α therapy only. Within all three analyses, comparators included conventional non-biologic therapies (a combination of 5-aminosalicylic acids, immunomodulators and corticosteroids) and surgery as separate options. Other anti-TNF-α agents (infliximab, adalimumab and golimumab) were included only in the analysis of the anti-TNF-α naïve population. Calcineurin inhibitors (tacrolimus and ciclosporin) were not included in the economic analysis. All analyses included price reductions to reflect the proposed Patient Access Scheme (PAS) for vedolizumab. The company's model adopted a hybrid approach whereby a decision tree was used to evaluate outcomes at the end of induction therapy and a Markov structure was used to evaluate subsequent maintenance treatment outcomes (including subsequent induction treatment using conventional therapies for patients who discontinue biologic treatments). Pre-colectomy health states were defined according to Mayo score (remission, mild, moderate-to-severe UC); additional states were included to reflect surgery, post-surgical complications and post-surgical remission and death.

The company's results were presented as pairwise comparisons of vedolizumab versus each comparator and were thus difficult to interpret appropriately. Based on a fully incremental analysis of all treatment options undertaken by the ERG (see Table 3), within the mixed ITT population, the company's model suggests that surgery is dominated as it produces fewer health gains and is more costly than both conventional therapy and vedolizumab. Vedolizumab is expected to be the most effective option. Compared with conventional therapy, vedolizumab is expected to produce an additional 0.15 quality adjusted life years (QALYs) at an incremental cost of £5,131; the incremental cost-effectiveness ratio (ICER) for vedolizumab versus conventional therapy is estimated to be £33,297 per QALY gained. Within the anti-TNF-α naïve population, surgery is expected to be dominated by medical therapies. Vedolizumab is expected to be the most effective option. Infliximab and golimumab are expected to be dominated by vedolizumab. The ICER for adalimumab versus conventional therapy is estimated to be £3,664 per QALY gained, whilst the ICER for vedolizumab versus adalimumab is estimated to be £6,634 per QALY gained. Within the anti-TNF-α failure population, surgery is expected to be dominated. Vedolizumab is expected to be the most effective option. Compared with conventional therapy, vedolizumab is expected to produce an additional 0.09 QALYs at an incremental cost of £5,839; the ICER for vedolizumab versus conventional therapy is estimated to be £64,999 per QALY gained.

Table 3: Company's cost-effectiveness results

Option	QALYs	Costs	Incremental QALYs	Incremental costs	Pairwise ICER (vedolizumab versus comparator)
Mixed ITT population					
Vedolizumab	5.55	£77,056	-	-	-
Conventional therapy	5.40	£71,925	0.15	£5,131	£33,297
Surgery	4.28	£107,831	1.27	-£30,775	dominating
Anti-TNF-*α naïve population*					
Vedolizumab	5.90	£69,075	-	-	-
Infliximab	5.82	£73,952	0.08	-£4,877	dominating
Golimumab	5.79	£70,387	0.11	-£1,312	dominating
Adalimumab	5.76	£68,157	0.14	£918	£6,634
Conventional therapy	5.56	£67,406	0.34	£1,669	£4,862
Surgery	4.28	£107,831	1.67	-£38,756	dominating
Anti-TNF-*α failure population*					
Vedolizumab	5.46	£78,409	-	-	-
Conventional therapy	5.37	£72,570	0.09	£5,839	£64,999
Surgery	4.28	£107,831	1.182	-£29,422	dominating

3.2.1 Critique of Cost-Effectiveness Evidence and Interpretation

The ERG critically appraised the company's health economic analysis and the model upon which this analysis was based.

The ERG partially re-built part of the model to check for technical programming errors; one serious programming error was found; in the anti-TNF-α naïve population, the maintenance transition matrix for conventional therapy incorrectly draws on the transition matrix for infliximab. Fixing this error, however, did not have a significant impact on the results. The broader critical appraisal of the company's model highlighted a number of concerns and uncertainties. The most notable of these related to (i) the deviations from the NICE Reference Case [31] and final NICE scope [17]; (ii) questionable assumptions regarding continuation/discontinuation of vedolizumab and other biologic therapies; (iii) highly pessimistic assumptions regarding the use, costs and benefits of colectomy, and; (iv) considerable uncertainty regarding the methods used to calibrate and extrapolate the pre-colectomy maintenance transition matrices.

(i) Deviations from the NICE Reference Case

The company's economic analysis deviated from the NICE Reference Case [31] and the final NICE scope [17] due to (a) missing biologic comparators in the mixed ITT population and the anti-TNF-α failure populations, (b) the use of a 10-year (rather than lifetime) time horizon and (c) the use of pairwise comparisons rather than a fully incremental analysis. These issues hindered the interpretation of the company's results against the decision problem specific in the NICE scope [17]. Whilst the ERG was able to re-analyse the company's results using a fully incremental framework over a lifetime horizon, it was not possible to address issues surrounding missing comparators.

(ii) Questionable assumptions regarding continuation/discontinuation of vedolizumab and other biologic therapies

The company's health economic model assumed that all patients who are still receiving anti-TNF-α therapy at 1-year will discontinue and subsequently receive non-biologic therapies, irrespective of whether they are currently responding to treatment. Whilst there is uncertainty with respect to the long-term efficacy of vedolizumab, infliximab, adalimumab and golimumab as the randomised phases of trials of these therapies adopted a maximum follow-up of 54 weeks, the wording of the marketing authorisations for the biologics does not stipulate if or when responding patients should discontinue therapy [16;32-35]. The ERG had concerns that the discontinuation rule adopted in the company's model would not be adhered to in routine practice as it may not be preferable to patients and clinicians to withdraw biologic therapy when a patient is still obtaining clinical benefit from it.

(iii) Pessimistic assumptions regarding the use, costs and benefits of colectomy

A number of assumptions used in the calculation of the surgery and post-surgery health states were likely to bias against surgery and towards medical interventions by overestimating the costs and reducing the health gains of surgery. The surgery health state represents a patient undergoing a colectomy and any further routine surgery associated with the procedure. By returning patients to the surgery health state, to reflect that a proportion of patients undergo further unplanned surgeries, the model assumed these patients undergo a further colectomy and all associated surgeries. In total the model assumed that over a 10 year period a patient would cycle through the surgery health state 4.3 times and over a lifetime horizon would cycle through the surgery health state up to 19 times. The model was also likely to have overestimated the rate of post-surgical complications. Data from the literature on rates of complications up to 30 days and up to six months following surgery were converted to constant transition probabilities [36;37]. These may have overestimated the long term probabilities of complications as the likelihood of complications decreases as the time from surgery increases [38;39]. The health utilities used were also likely to bias against surgery as the utility for post-surgical remission is lower than that for moderate-to-severe UC indicating that it would be illogical for any patient to opt for surgery.

(iv) Uncertainty surrounding pre-colectomy maintenance transition matrices

The method for deriving the pre-colectomy transition matrices adopted by the company was unconventional. The company's model used the Microsoft Excel Solver add-in to determine pre-colectomy transition probabilities (response, remission and active UC) by comparing the model-predicted proportion of patients in remission or response at 1-year against the observed proportion of patients in remission or response at 1-year in GEMINI1 [19], or against the predicted proportion based on the manufacturer's NMAs of induction and maintenance therapies (note - the target datapoints and their derivation depend on the population considered in the analysis). The ERG had concerns that (i) the company's calibration approach discarded the empirical GEMINI1 trial data [19] that could have been used to directly estimate transition probabilities; (ii) the initial starting matrix of transitions used in the optimisation approach appeared to be largely arbitrary; (iii) the constraints imposed in the optimisation approach appeared to be largely arbitrary (for example, no more than 99.5% of patients remain in remission over each 8-week cycle); (iv) fitting seven unknown parameters to two known datapoints is likely to result in overfitting and many combinations of transition probabilities could have

fitted the two target datapoints, and; (v) the fitting process ignored those patients who achieved response but had moderate-to-severe disease. This issue could have been better addressed by using the observed transitions between moderate-to-severe UC, response and remission states using the individual patient data from the GEMINI1 trial [19]. The ERG requested but did not receive these data from the company.

3.3 Additional work undertaken by the Evidence Review Group

In light of the problems identified during the critical appraisal, the ERG undertook a number of additional analyses to explore the impact of likely biases on the cost-effectiveness of vedolizumab. Nine sets of additional analyses were undertaken in each of the three modelled populations; these included correcting the mistake in the maintenance transition matrix for conventional management in the anti-TNF-α naïve population, the use of alternative sources of HRQoL values i.e. using utilities for patients with UC in various health states (remission, response, moderate-to-severe UC and post-surgery), based on data reported by Woehl et al. [40] and Swinburn et al. [39], amending the surgery and post-surgical transition probabilities to better reflect clinical reality, removing assumptions regarding biologic treatment discontinuation, removing assumptions regarding the lower use of conventional therapies whilst patients are also receiving biologics, and improving the cost estimates used in the model to better reflect the costs borne by the NHS. The ERG also produced a preferred base case which combines most of these additional analyses. The results of these additional analyses did not consistently favour one particular option but indicated that these issues have the propensity to dramatically shift the ICER for vedolizumab versus other therapies in all three populations. The ERG-preferred base case indicated that surgery was likely to dominate all medical treatments in all three populations analysed. However, surgery may not be an acceptable option for all patients. Where surgery is not an acceptable option in the mixed ITT population, the ICER for vedolizumab versus conventional therapy was estimated to be £53,084 per QALY gained. Where surgery was not an acceptable option in the anti-TNF-α naïve population, vedolizumab is expected to be dominated by adalimumab. Where surgery is not an acceptable option in the anti-TNF-α failure population, the ICER for vedolizumab versus conventional therapy was estimated to be £48,205 per QALY gained.

3.4 Conclusion of the Evidence Review Group Report

On the basis of the evidence submitted by the company, the ERG concluded that vedolizumab was clinically more effective than placebo for the treatment of moderate-to-severe active UC, in patients who had an inadequate response to, loss of response to, or intolerance of conventional therapy or TNF-α. However, there are a number of limitations and uncertainties in the evidence base which warrant caution in its interpretation. In addition, the results presented in the NMA may have underestimated the uncertainty in treatment effects.

The ERG believed that robust estimates of the likely cost-effectiveness of vedolizumab could not be made on the basis of the original version of the company's economic model. However, on the basis of the ERG's amended version of the company's model based on lifetime horizon including the revised patient access scheme, surgery was more effective and less costly than vedolizumab. In the whole population, the ICER for vedolizumab compared with conventional therapy was £53,084 per QALY gained. In the population who have not had prior treatment with TNF-α inhibitors, vedolizumab is dominated by adalimumab. In the population in

whom treatment with a prior TNF-α inhibitor has failed, the ICER for vedolizumab compared with conventional therapy is £48,205 per QALY gained.

4. Key Methodological Issues

Several methodological issues in the cost-effectiveness evidence and uncertainties in the clinical effectiveness of vedolizumab were highlighted during the appraisal. The subgroup analyses to determine the efficacy of vedolizumab in patients with prior TNF-α inhibitor failure and in patients who were TNF-α inhibitor naïve were exploratory and the study was not powered for these assessments. Furthermore, there are no data on strategies for withdrawal of the drug or optimum duration and the trial was not large enough or of sufficient duration to estimate the risk of uncommon AEs.

The ERG considered that the results of the NMA may underestimate the uncertainty in treatment effects since fixed effects models were used, and there was clear evidence of heterogeneity among the trials included. There are also issues regarding the adjustment of data to account for re-randomisation which may lead to bias in the model's results.

The health economic model submitted by the company was subject to a number of issues which limited the credibility of the company's results. These include errors in model implementation, the omission of relevant comparators, deviations from the NICE Reference Case and questionable model assumptions. Whilst the company's economic analysis suggests that the ICER for vedolizumab is below £7,000 per QALY gained within the anti-TNF-α naïve population, the ERG-preferred base case indicates that vedolizumab is expected to be dominated by surgery in all three populations

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 UC and the value placed on the benefits of vedolizumab by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources. In November 2014, the Appraisal Committee produced preliminary recommendation, recorded in the ACD, which stated the following:

Vedolizumab is recommended within its marketing authorisation as an option for treating moderately to severely active UC in adults only if: the person has not had a TNF-α inhibitor or the person has had a TNF-α inhibitor but could not tolerate it and the company provides vedolizumab with the discount agreed in the patient access scheme. However, vedolizumab is not recommended for treating moderately to severely active UC in people who have not had a response to, or have lost response to, treatment with a TNF-α inhibitor. People currently having treatment initiated within the NHS with vedolizumab that is not recommended for them by NICE, should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

In response to the consultation, the company requested NICE to reconsider its preliminary recommendation regarding the use of vedolizumab in patients who have failed anti-TNF-α inhibitor. The company submitted

supportive evidence detailing the unmet need associated with anti-TNF-α failure, the limited current options (high dose steroids, anti-TNF-α cycling or surgery) available for this patient group, highlighted the clinical evidence from GEMINI1 trial [19], the limitations of the QALY approach in UC and submitted a revised cost-effectiveness analysis using the ERG/NICE suggested base case parameters for the analysis of the anti-TNF-α failure population.

Following further consultation, in June 2015, NICE issued its final guidance and recommended the use of vedolizumab within its marketing authorisation, as an option for treating moderately to severely active UC in adults who had an inadequate response to, loss of response to, or intolerance of conventional therapy or TNF-α inhibitor but only if the company provided vedolizumab with the discount agreed in the patient access scheme. Vedolizumab should be given until it stops working or surgery is needed. At 12 months after the start of treatment, people should be reassessed to see whether treatment should continue. Treatment should only continue if there is clear evidence of ongoing clinical benefit. For people who are in complete remission at 12 months, consideration should be given in stopping vedolizumab therapy. However, if patients relapse, treatment should be resumed. People who continue vedolizumab should be reassessed at least every 12 months to see whether continued treatment is justified [41].

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 FAD [41].

5.1.1 Generalisability to the UK population

The Committee considered the generalisability of the population in GEMINI1 to the population who would have received vedolizumab in clinical practice in England. It understood that GEMINI1 [19] was an international study and 2 of the centres were in the UK. It was aware that there were differences in the study entry criteria between the USA and other centres. These differences related to which previous treatments had failed and the use of immunosuppressants during the study. The Committee heard from the clinical experts that the population included in the trial broadly reflected the population who would be treated with vedolizumab in England. It also heard that differences in immunosuppressant use between trial centres were unlikely to affect the trial's generalisability to clinical practice in England. The Committee concluded that the clinical efficacy results from GEMINI1 [19] were generalisable to clinical practice, but that there was uncertainty about whether the proportion of people who had previous TNF-α inhibitor treatment in GEMINI1 [19] would be the same as in the population considered for vedolizumab treatment in England.

5.1.2 Estimate of the size of the clinical effectiveness

The Committee discussed the efficacy estimates for vedolizumab from GEMINI1 [19]. The Committee noted that in GEMINI1 [19] people had vedolizumab at Weeks 0 and 2 and response was assessed at Week 6, but the marketing authorisation for vedolizumab states that people should have 3 doses before response is assessed at Week 10. The Committee concluded that, although the efficacy of vedolizumab had been shown in GEMINI1 [19], it may have underestimated the proportion of people who would have a response to induction treatment in

clinical practice, and that data on the outcome for those who responded after 6 weeks were not available from the trial.

5.1.3 Uncertainties generated by the evidence

The Committee considered the NMA presented by the company to estimate the relative effectiveness of vedolizumab [19] compared with adalimumab [25], infliximab [26] and golimumab [27]. It noted that clinical data for infliximab [26] and golimumab [27] were not available for people who had previously had a TNF-α inhibitor. Therefore, for this subgroup a comparison could only be made between vedolizumab [19] and adalimumab [25]. The Committee understood that the company had presented NMA for the subgroups rather than the whole population. The Committee noted the ERG's concerns that there were differences between the trials included in the meta-analyses, and the company had presented results from a fixed-effect model which was less suitable than a random-effects model in these circumstances. The Committee understood that a NMA for the whole population would include data from studies that included people who had, and had not, taken a TNF-α inhibitor, and that these differences in patient characteristics may affect the results. Therefore, the Committee recognised that the relative effectiveness of vedolizumab compared with the TNF-α inhibitors, obtained from a mixed treatment comparison of the whole population, would be subject to considerable uncertainty.

5.1.4 Uncertainties around plausibility of assumptions and inputs in the economic model

The Committee discussed the uncertainty around cost and frequency of surgery. The Committee noted that when the company's model was run over 10 years, people would have 4 operations, and over a lifetime time horizon up to 19 operations. The ERG considered that the total number of operations, and therefore the costs was overestimated by the company. The clinical experts highlighted that that surgery for UC was normally carried out in 3 stages in separate operations, and a person could have further surgery if there were complications or further problems. The ERG considered the cost of surgery from Buchanan 2011 [42], which were used by the company and represented the total cost of multiple operations. The clinical expert argued that the costs reported by Buchanan 2011 [42] only accounted for the cost of one operation. The Committee concluded that the total costs of surgery in the company's base case were too high due to the number of operations included and those in the ERG exploratory base case were too low.

6. Appraisal Committee's Key Conclusion

The Committee considered that taking into account the uncertainty of the utility values, and the costs of surgery and post-surgery care, the ICER of vedolizumab for people who had not had TNF-α inhibitors before was well within the range normally considered to be cost-effective. It was concerned that the plausible ICERs for people in whom treatment with a TNF-α inhibitor had failed were around the upper limit of the range normally considered to be a cost-effective use of NHS resources. The Committee recommended vedolizumab, within its marketing authorisation, as an option for treating moderately to severely active UC in adults only if the company provides vedolizumab with the discount agreed in the patient access scheme.

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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 – on 29th January 2015 after work on this project had been completed. Munira Essat, Paul Tappenden, Shejie Ren, Alice Bessey, Rachel Archer, Ruth Wong and Sami Hoque declare no non-financial conflict of interest.

Contributions made by each author

Munira Essat and Rachel Archer summarised and critiqued the clinical effectiveness data reported by the manufacturer. Shijie Ren critiqued the statistical analyses undertaken by the manufacturer. Ruth Wong undertook the literature searches run by the ERG. Paul Tappenden and Alice Bessey critiqued the health economic analysis submitted by the manufacturer. Sami Hoque and Alan Lobo provided clinical advice to the ERG throughout the project. All authors were involved in drafting and commenting on the final document. Munira Essat acts as the guarantor of the manuscript.

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