NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Vedolizumab for treating moderately to severely active ulcerative colitis

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation.

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment	Response
British Society of Gastroenterology	The BSG has considered the ACD following from the initial STA committee meeting considering vedolizumab treatment in moderate to severe ulcerative colitis (UC). We broadly welcome the recommendation that vedolizumab is used in this condition, recognising that this drug represents a novel treatment modality with gut selectivity that will be a significant advance for the subgroup of patients with UC who have failed conventional therapy.	Comments noted.
	We wish to make the following comments that should be considered in the Final Appraisal Determination, regarding the preliminary recommendation that vedolizumab should not be offered to patients who have failed anti-TNF therapy: **Clinical experience of response to vedolizumab after anti-TNF failure.** The patient expert at the committee on Oct 28th who was on vedolizumab therapy, had previously failed both conventional therapy, and also anti-TNF treatment. It was noted in the committee meeting, that he had had a life-changing response to therapy, enabling him to return to normal life, free of drug side-effects and without having to resort to colectomy. Under the current recommendations in the ACD, this patient would not be offered vedolizumab. Like this patient, there will be a group who have used anti-TNF therapy previously, and who could respond. (This includes patients who have been in clinical trials receiving anti-TNF drugs). They should not be excluded from using this drug without strong evidence	Comments noted. Following consultation, vedolizumab is recommended within its marketing authorisation as an option for treating moderately to severely active ulcerative colitis in adults only if a stopping rule is applied and the company provides vedolizumab with the discount agreed in the patient access scheme (see section 1 and 4.18 in the FAD).
	Scientific rationale for poorer response in anti-TNF failure patients. There is as yet no evidence that patients whose UC fails to respond to anti-TNF drugs, should have a reduced response to vedolizumab. It is recognised that clinical trial patients with IBD who have previously failed anti-TNF drugs are different to those who are anti-TNF naïve. The reasons for this are many, including longer disease duration since diagnosis, and potential for increased presence of symptoms unrelated to inflammation (such as co-existing functional diarrhoea). Careful exclusion of these causes will leave patients with primary or secondary failure of anti-TNF drugs, who have no reason to be more likely to fail vedolizumab than anti-TNF naïve patients.	

Consultee	Comment	Response
	Difference between response and remission rates in anti-TNF naïve and anti-TNF failure patients. It is acknowledged in the ACD (section 4.8) that vedolizumab is effective in both groups. In the maintenance period in GEMINI 1, section 3.5 stated 'In the population who had not had a TNF-alpha inhibitor before, 46% of people having 8-weekly vedolizumab and 19% people having placebo had clinical remission (percentage difference 26.8, 95% CI 12.4 to 41.2). In the population in whom treatment with a TNF-alpha inhibitor had failed, 37% of people having 8-weekly vedolizumab and 5.3% of people having placebo had remission (percentage difference 31.9, 95% CI 10.3 to 51.4). We recognise that there were fewer patients overall in GEMINI 1 who had failed anti-TNF drugs (41% of the total) and the study was not powered to examine end-points for this subgroup. This uncertainty should not exclude this group however, without clear evidence to show this group differs fundamentally.	
	Vedolizumab as first-line biological therapy in moderate to severe UC failing conventional therapy. The implications of the current recommendations in this ACD are to use vedolizumab ahead of anti-TNF drugs in patients failing conventional therapy, in whom surgery is not appropriate. The situation differs in acute severe colitis however. Anti-TNF treatment is approved in acute severe UC (NICE TA163), and the outcome of the MTA on anti-TNF therapy in moderate to severe UC is awaited. Whilst there are no head to head comparisons of the two drug classes, it is clear from the GEMINI 1 data(1), and from the published data on infliximab in UC (2), that the response to infliximab is likely to be much more rapid than vedolizumab. In the acute severe UC situation it seems more appropriate to use infliximab, but responders to anti-TNF therapy in this acute severe situation may subsequently lose response, and it would seem inappropriate then to exclude them from using vedolizumab at some future date, when they have moderate to severe disease non-responsive to conventional therapy. (References not reported here)	

Consultee	Comment	Response
The Royal College of Nursing	**Appraisal Consultation Document – RCN Response** The Royal College of Nursing welcomes the opportunity to review this document. The RCN's response to the questions on which comments were requested is set out below: **Has the relevant evidence has been taken into account?** NICE have recommended the use of Vedolizumab within its licensed indication which is positive in terms of care for UC patients. However we are concerned that the current recommendation implies we can use Vedolizumab first line, but will not be allowed for those who have failed anti-TNF, yet we have evidence for Vedolizumab in this setting (in Gemini 1) but no evidence for anti-TNF in Vedolizumab failures. We feel clinicians will be hesitant to use Vedolizumab first line until there is real time clinical experience and evidence. This means we will use anti-TNF first but then cannot use Vedolizumab if they fail. We have no studies to support using antiTNF following failure of Vedoluzima. Therefore we are concerned that in clinical practice the recommendations within the ACD are not workable as most clinicians will continue to use anti-TNF first due to safety/experience issues. Surgery will then be the only available option, at least until there is evidence of using anti TNF after Vedolizumab failure.	Comments noted. Following consultation, vedolizumab is recommended within its marketing authorisation as an option for treating moderately to severely active ulcerative colitis in adults only if a stopping rule is applied and the company provides vedolizumab with the discount agreed in the patient access scheme (see section 1 and 4.18 in the FAD).
	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? We would ask that the summaries of the clinical and cost effectiveness of this appraisal be aligned to the clinical pathway followed by patients with Ulcerative Colitis. The preliminary views on resource impact and implications should be in line with established standard clinical practice.	Comments noted.

Consultee	Comment	Response
	Are the provisional recommendations sound and a suitable basis for guidance to the NHS? We think that the committee should re think their wording in regards to these particular clauses 1.1 would benefit from the removal of; 'The person has not had a TNF-alpha inhibitor' **or** 1.2 Proposed wording: Vedolizumab is not endorsed for treating moderately to severely active ulcerative colitis in people who have not had a response to, or have lost response to, treatment with a TNF-alpha inhibitor, due to poorer response rates but could be considered with careful pre-treatment counselling and early review. There is evidence for vedolizumab after anti TNF failure, in one study of 895 patients, 32% of the ITT population had prior anti-TNFα failure. Maintenance therapy with VDZ every 8 weeks was significantly more effective than placebo in achieving clinical remission (37%), durable clinical response (46.5%) and remission, mucosal healing, and corticosteroid-free remission in UC patients with a high rate of prior anti-TNF failure (Feagan et al 2012).	Comments noted. Following consultation, vedolizumab is recommended within its marketing authorisation as an option for treating moderately to severely active ulcerative colitis in adults only if a stopping rule is applied and the company provides vedolizumab with the discount agreed in the patient access scheme (see section 1 and 4.18 in the FAD).
	Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief? **Are there any equality-related issues that need special consideration that are not covered in the appraisal consultation document?** We are not aware of any specific issue at this stage. We would ask that any guidance issued should show that an equality impact analysis has been considered and that the guidance demonstrates an understanding of issues relating to all the protected characteristics where appropriate.	Comments noted.

Consultee	Comment	Response
	While we broadly welcome these recommendations as access to biologics for patients with ulcerative colitis is important. However, we have concerns that it will effectively be a first line therapy although TNF alpha inhibitors have been commercially available for many years and there is significant clinical experience with these. Those patients who have previously received TNF alpha inhibitors as rescue therapy, as part of standard management or within the context of a clinical trial will be precluded from receiving Vedolizumab, which appears unfair and illogical in terms of current practice.	Comments noted. Following consultation, vedolizumab is recommended within its marketing authorisation as an option for treating moderately to severely active ulcerative colitis in adults only if a stopping rule is applied and the company provides vedolizumab with the discount agreed in the patient access scheme (see section 1 and 4.18 in the FAD).
RCP	Please take this email as confirmation that the RCP wishes to endorse the comments submitted by Dr Seamus J Murphy/BSG.	Comments noted.
Takeda UK	Takeda UK acknowledge receipt of the Appraisal Consultation Document (ACD) for vedolizumab for treating moderately to severely active ulcerative colitis [ID691] and would like to thank the National Institute for Health and Care Excellence (NICE) Appraisal Committee for its consideration of the evidence in reaching its draft recommendations regarding vedolizumab. We are pleased that NICE has recognised the value of treatment with vedolizumab for patients with moderate to severely active ulcerative colitis who have not had a TNFα antagonist or for patients that have had a TNFα antagonist but could not tolerate it. Having reviewed the NICE ACD, Takeda UK would ask that the NICE Appraisal Committee re-considers its decision regarding the draft recommendation for the use of vedolizumab in patients who have failed anti-TNFα therapy, based on the case we present here and in our main submission to NICE. This response document will lay out supportive evidence for this as follows: (1) Unmet need associated with anti-TNFα failure and the current options for anti-TNFα failure patients (2) Numerically small but clinically significant patient population with anti-TNFα failure (3) Clinical evidence from GEMINI I in anti-TNFα failure patients (4) Revised cost-effectiveness analysis using the ERG/NICE suggested base case parameters for the analysis of the anti-TNFα failure population (5) Limitations of the QALY approach in ulcerative colitis.	Comments noted. Following consultation, vedolizumab is recommended within its marketing authorisation as an option for treating moderately to severely active ulcerative colitis in adults only if a stopping rule is applied and the company provides vedolizumab with the discount agreed in the patient access scheme (see sections 1 and 4.18 in the FAD).

Consultee	Comment	Response
	(1) Unmet need associated with anti-TNFα failure and the current options for anti-TNFα failure patients It is reasonable to assume that patients who are classified as anti-TNFα failure will have been prescribed and failed (i.e. primary and/or secondary failure) at least one of the TNFα antagonists currently licensed in the UK. • Primary failure is usually defined as inadequate response to a TNFα antagonist, meaning persistently active disease despite induction treatment (typically 6–10 weeks) • Secondary failure is defined as loss of response to a TNFα antagonist, meaning a recurrence of symptoms during maintenance dosing following prior clinical benefit. Evidence from the literature demonstrates significant failure rates on TNFα antagonists in ulcerative colitis (see Table 1 below), and highlights the level of unmet need still present despite existing biologic treatments. Table 1: Non-response rates to TNFα antagonist therapy in ulcerative colitis (Not reported here)	
	Despite the lack of NICE recommendation, audit data evidence shows that ulcerative colitis patients are treated with TNFα antagonists in England and Wales (UK IBD audit, 2013), albeit in lower numbers relative to Crohn's disease. Clinical trial evidence and real-world data demonstrate that patients who lose response to one TNFα antagonist have a lower probability of responding to a second TNFα antagonist. Patients who fail TNFα antagonist therapy will most likely progress to severe disease, which may require hospitalisation and for which the only therapeutic options currently are more conventional therapy or surgery with its associated long-term complications. As the NICE Appraisal Committee heard from the clinical experts, conventional therapy at this stage of ulcerative colitis is usually high-dose steroids; however, there are significant risks with both short-term and prolonged use of high-dose steroids.	

Consultee	Comment	Response
	These patients may also progress to acute, severe episodes requiring hospitalisation and treatment with systemic immunosuppressants (e.g. ciclosporin). Takeda UK notes that such patients are not in line with the approved vedolizumab indication, nor the patient population in GEMINI I, which specifically excluded patients who needed any surgical procedure requiring general anaesthesia within 30 days prior to enrolment or were planning to undergo major surgery during the study period. NICE heard from clinical experts that surgery is a 'last resort' option that is considered when all medical treatment options have been exhausted in patients with intractable or poorly controlled ulcerative colitis. Surgery is associated with numerous post-operative complications which have a significant adverse impact on a patient's quality of life. Patients rarely regain normal quality of life after a colectomy, and can suffer from complications such as post-operative bleeding, faecal incontinence, depression, sexual dysfunction, female infertility, pouchitis, pouch leakage, pelvic abscesses and pouch fistulae.	
	(2) Numerically small but clinically significant patient population with anti-TNFα failure There is currently a relatively small but significant population of ulcerative colitis patients in the UK who have been exposed to, and subsequently failed, anti-TNFα treatment. These patients have significant unmet need but limited treatment options, including the use of a second or third anti-TNFα (called "anti-TNFα cycling") or surgery. Vedolizumab is the first medicine to specifically have demonstrated efficacy and safety data in anti-TNFα failure patients and is the only medicine with a marketing authorisation for this specific indication. Market research based on NHS prescribing data suggests that in 2014 approximately 1000 patients are currently treated with anti-TNFα therapy in ulcerative colitis. The incidence of primary non-response to anti-TNFα therapy is 20-40% in trials and 10-20% in real life clinical practice[9] and therefore there is a prevalent population of ulcerative colitis patients who have failed at least one anti-TNFα therapy.	

Consultee	Comment	Response
	Current guidance allows for the use of TNFα antagonist therapy in both anti-TNFα naïve and anti-TNFα failure patients. This cycling of anti-TNFα therapy is likely to become more common in UK practice as access to these agents increases; particularly as a result of the recent NICE FAD for the MTA of anti-TNFα agents in moderate to severe ulcerative colitis[10], in line with clinical practice across Europe. There is limited evidence for the effectiveness of using TNFα antagonists in this way, with no studies available to examine the effect of infliximab in these anti-TNFα failure/exposed patients. The ULTRA 2 trial examined the use of adalimumab in TNFα naïve vs. TNFα exposed patients and showed that prior exposure to infliximab appeared to influence response to adalimumab; the rate of clinical remission in infliximab-naive patients treated with adalimumab was more than double that of patients who had prior exposure to infliximab (Week 8: 21% vs. 9% and Week 52: 22% vs. 10%).[4] At Week 8, the difference in clinical remission rates between the adalimumab and placebo arms was significant among patients who had never been exposed to infliximab (21% vs. 11%; P=0.017). In contrast, the difference in clinical remission rates between the adalimumab and placebo arms at Week 8 in patients who had previously been exposed to infliximab did not reach statistical significance (9% vs. 7%; P=0.559). At Week 52, differences in clinical remission between the active treatment and placebo arms reached statistical significance in relation to both infliximab-naive patients (22% vs. 12%; P=0.029) and infliximab-exposed patients (10% vs. 3%; P=0.039).	
	It was not possible to compare these results to those for vedolizumab in the network meta-analysis due to the different populations studied (ULTRA 2[4] did not include primary TNFα antagonist failure patients which were included in GEMINI I, also ULTRA 2 reported results for TNFα antagonist exposed patients whereas GEMINI I reported data for patients who had specifically failed TNFα antagonist therapy). However, Takeda UK believe these results should be taken into consideration when appraising vedolizumab for use in this group of patients.	

Consultee	Comment	Response
	(3) Clinical evidence from GEMINI I in anti-TNFα failure patients The GEMINI I trial demonstrated the superior efficacy of vedolizumab to conventional therapy/placebo in a patient population that had primary/secondary failure or intolerance to at least one TNFα antagonist,[11] and represents a significant milestone in the evidence base for ulcerative colitis treatment.[7] Vedolizumab is the only biologic medicine that has shown benefit over placebo/conventional therapy in patients who have failed anti-TNFα treatment (primary/secondary failure or intolerance). Adalimumab, which is not licenced for use in anti-TNFα failures, was studied in a Phase 3 trial that included anti-TNFα secondary failures only; primary failures were excluded[4] - a fact noted by the ERG in terms of the comparability of this study to the GEMINI I study which also included patients with more severe disease.[11] Table 2 highlights the types of anti-TNFα failure documented in GEMINI I. It can be seen that approximately 40% of patients had a history of failure to TNFα antagonists and in patients who had failed a TNFα antagonist, approximately half had an inadequate response (primary failure) and approximately 40% had loss of response (secondary failure): Table 2: Categorisation of patients by prior TNFα antagonist use (Induction ITT population in GEMINI 1) Not reported here. Table 3 reports the results in the GEMINI 1 induction study which showed a smaller difference in clinical remission rates between vedolizumab and placebo in the anti-TNFα failure patients (6.6% at week 6) compared with those without prior anti-TNFα failure (16.5%). However, when compared with placebo the results were in favour of vedolizumab treatment in the anti-TNFα failure group. Table 3: Key Induction results at Week 6 for the Anti-TNFα failure patients (GEMINI 1) (Not reported here)	
	In keeping with the induction phase results, although the response and treatment difference in the maintenance phase was less for the anti-TNFα failure group as compared with those without prior anti-TNFα failure, when compared to placebo the results remained in favour of vedolizumab (see Table 4). Hence, in GEMINI 1, the clinical benefits of vedolizumab have been demonstrated in primary and secondary anti-TNFα failure patients. Table 4: Key maintenance results at Week 52 for the Anti-TNFα failure patients (GEMINI 1) Not reported here.	

Consultee	Comment	Response
	(4) Revised cost-effectiveness analysis using the ERG/NICE suggested base case parameters for the analysis of the anti-TNFα failure population The Evidence Review Group (ERG) made eight changes to the model, outlined in the *Technical Appendix for additional ERG analyses*. We have implemented five of those changes and, in addition, used a 10-week response assessment time, in line with the marketing authorisation for vedolizumab. We present here an updated set of analyses based on those changes for patients that have previously failed a TNFα antagonist. The three amendments that were not implemented here were as follows: we did not use the ERG amended transition matrix for surgery and post-surgery states, we did not change the maximum treatment time from one year to 100 years and, lastly, we included different costs for stoma care than the ERG, in line with comments in the ACD. The list of amendments that the ERG made to the model, and as implemented in this update to the model, are listed below. ERG amendments 4 and 5 were not implemented and amendment 8 was changed in line with comments in the ACD.	

Consultee	Comment	Response
	(1) An error in cell referencing in the “Data Store” sheet was corrected. (2) A lifetime horizon was used (3) Three sets of utilities were applied in the model for three scenario analyses: the basecase utilities, as well as those from Woehl and Swinburn. (4) **The transition matrix was not amended.** We believe that the ERG transition matrix for surgery and post-surgical states is too optimistic about the effect of surgery on patient outcomes. Because a Markov model is “memory-less” it is not possible to say how many patients received how many surgeries. However, it is possible to calculate the average number of surgeries that patients are predicted to have by the model. We did that using the original surgery / post-surgery transition matrix, whilst making all other amendments listed here. Patients treated with conventional therapy are predicted to have, on average, 9.1 surgeries over their lifetimes, and patients treated with vedolizumab are predicted to have, on average, 7.3 surgeries. (These results are for the mixed patient population, but are similar in both the TNFα-failure and TNFα-naïve patient populations). By contrast, using the ERG transition matrix for surgery / post-surgery, the model would predict 1.1 surgeries for patients treated with conventional therapy over a lifetime and 0.8 surgeries for patients treated with vedolizumab.	

Consultee	Comment	Response
	(5) In line with the ACD preliminary recommendation (Section 1.3), **we did not change the maximum time on treatment from one year to 100 years**. (6) In line with the ERG amendment, we assumed that all patients treated with vedolizumab also received conventional therapy. (7) NHS Reference Costs were updated using the values provided in the technical appendix. (8) **The ERG cost of stoma care of £72 pounds per cycle was not used. A cost of £307 was applied instead**. The ACD (Section 4.19) states that post-surgery care costs may be £1000-3000 per year. We applied a cost of £2,000 in the updated model, or £307 per 8-week cycle. In addition to these amendments, we used a 10-week response assessment time, in line with the marketing authorisation for vedolizumab. Implementing all of these changes, the incremental cost-effectiveness ratio for vedolizumab, compared with conventional therapy in patients that have failed a TNFα antagonist is outlined in Table 5 below. Because of the uncertainty over the most appropriate set of utilities to use, three values are presented using the basecase utilities, those from Woehl et al. and those from Swinburn et al. Table 5: Revised cost effectiveness results using the ERG/NICE suggested base case parameters for the anti-TNFα failure population (not reported here).	

Consultee	Comment	Response
	(5) Limitations of the QALY approach in ulcerative colitis Takeda UK acknowledges that the ICER for vedolizumab in the anti-TNFα failure population is marginally above the usual thresholds accepted by NICE. However despite applying the changes suggested by the ERG/NICE Appraisal Committee to the base case, we contend that the QALY approach does not adequately capture the full picture in anti-TNFα failure patients and does not fully measure the positive impact that treatment with vedolizumab may offer patients. NICE have noted that the innovative, targeted immunosuppression offered by vedolizumab represents a step-change in the management of ulcerative colitis and that its full benefit may have been under-estimated (see Section 4.21 of the ACD). Vedolizumab is the only proven and licensed treatment in a patient subgroup with a high unmet medical need and inadequate current treatment options, which are typically limited to high-dose steroids or life-altering surgery. The innovation and step-change offered by vedolizumab may not be fully captured in the QALY. It is also evident that the QALY does not capture the full impact of the disease itself and current treatment options on patient's quality of life. This is noted in Section 4.17 of the ACD when the committee reflect on appropriate utility values for surgery related health states in the economic modelling. This discussion is also reflected in NICE's recently published "Final appraisal determination – infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy" (December 2014).	
	In Sections 4.73 and 4.74 of this FAD, the Committee have stated: "The Committee was aware that patients with more severe disease, are likely to experience a greater change in their quality of life from treatment. This, in turn, would generate more QALYs and improve cost-effectiveness." The anti-TNFα failure population is a severe patient population and these patients will have previously been prescribed at least one anti-TNFα agent. There are currently no approved treatments for this subgroup of patients. The NICE Appraisal Committee agree that "it would be difficult to capture all the aspects of the patients quality of life after surgery in the descriptive system of EQ-5D, particularly the emotional aspects and the long term effects such as reduced fertility. The Committee concluded that these are important issues affecting the quality of life of patients with ulcerative colitis which should be taken into account".	

Consultee	Comment	Response
	Takeda UK would argue that the variables listed in Section 4.78 of the recently published FAD for the MTA of the anti-TNFα agents in moderate to severe ulcerative colitis are also relevant when attempting to calculate the cost-effectiveness of vedolizumab in the anti-TNFα failure population. These variables contribute to the uncertainty of ICERs for the anti-TNFα agents, and illustrate that this uncertainty cannot be adequately addressed because of a lack of robust evidence. Therefore, the ICERs currently presented by Takeda UK are likely to underestimate the 'true' value of vedolizumab because of the number of evidence gaps which exist in the management of ulcerative colitis. We would ask the NICE Appraisal Committee to reflect on this when considering the case for vedolizumab in the anti-TNFα failure population, particularly in light of the uncertainties recently identified in the NICE MTA for anti-TNFα agents in moderate to severe ulcerative colitis.	
	Conclusion In Section 4.3 of the ACD, "The Committee concluded that according to its marketing authorisation, vedolizumab may be used after conventional therapy or TNF-alpha inhibitors have failed. However, its lack of systemic immunosuppression, and the subgroup data from the trial, make it more likely to be used before a TNF-alpha inhibitor for treating moderately to severely active ulcerative colitis". Takeda UK acknowledge that the optimal place in therapy for vedolizumab is likely to be in the anti-TNFα naive patient population. However, Takeda UK believe that its novel mechanism of action and lack of systemic immunosuppression make vedolizumab a clinically relevant choice for anti-TNFα failure patients also. Vedolizumab is the only biologic with a licence for use in anti-TNFα failure patients; a licence which is based on evidence from a Phase III trial which included all types of anti-TNFα failure (primary/secondary failure or intolerance to anti-TNFα) and included pre-specified analyses based on prior TNFα antagonist exposure. In addition to its demonstrable efficacy in anti-TNFα failure patients, vedolizumab has a unique gut-selective mechanism of action that differs from that of the TNFα antagonists and translates into a reduced risk of systemic immunosuppression.Therefore, Takeda UK believes that vedolizumab is the clinically rationale choice in anti-TNFα failure patients who are more likely to benefit from a treatment with a different mechanism of action, rather than dose escalation of existing TNFα antagonists or cycling between different TNFα antagonists.	

Consultee	Comment	Response
	In summary, Takeda UK has demonstrated that vedolizumab meets a significant unmet medical need in the anti-TNFα failure population in ulcerative colitis. This is a relatively small but seriously ill patient population with much to gain from a treatment like vedolizumab that is acknowledged as representing a step-change in the management of ulcerative colitis. Cost-effectiveness analyses are likely to underestimate the value of vedolizumab due to the recognised limitations in the ulcerative colitis evidence base, as documented in NICE's FAD[10] for the anti-TNFα agents in moderate to severe ulcerative colitis. Therefore, value judgements are required to adequately assess the potential benefits of vedolizumab for patients with ulcerative colitis who have failed on TNFα antagonist therapy. (References –Not reported here).	
UKCPA	**Response on behalf of the UK Clinical Pharmacy Association (UKCPA)** We welcome the proposed recommendation to use vedolizumab in UC particularly as the drug has of a different mode of action in comparison to the available biologic treatment for UC. We can particularly see the use of vedolizumab in the elderly patient with a higher risk of infection.	Comments noted.

Consultee	Comment	Response
	However we are concerned that the guidance excludes patients previously exposed to anti-TNFs. Current practice uses infliximab (IFX) as rescue therapy in acute sever colitis but has an overall efficacy rate of about 40-50% only. Once failed on anti-TNFs recapturing remission with a second anti-TNF only works in a minority of patients. We feel that the current evidence support the use of vedolizumab in patients previously exposed to anti-TNFs even if the numbers in the trials were not powered enough to show significance (Gemini I)[2]. From the trial data it is clear that vedolizumab is not suitable to treat acute severe colitis and IFX needs to be use as a rescue therapy due to its faster response. It is likely that patients who loose response to anti-TNFs would then respond to vedolizumab as a maintenance treatment avoiding life changing surgery. This would keep it in line with the current draft guidance of anti-TNFs in moderate to severe UC which potentially allows for switching between anti-TNFs although it would make more sense to change class once failed on anti-TNFs. In addition we are currently able to measure antibodies to anti-TNFs to guide therapy decisions which makes for a more individualised optimisation of therapy. Vedolizumab would be a valuable tool in maintaining remission in patients producing antibodies against anti-TNFs avoiding surgery and the following consequences of living without colon (see evidence by Crohn's and Colitis UK and their patients' reports). It is currently not clear if the anti-TNF failure group is different to patients that respond but this should not be a reason to exclude access to an effective treatment for these patients. We are currently in the process of trying to stratify patients according to disease picture and response to treatment, but so far the evidence has been elusive. There are patient reports of effectiveness of vedolizumab after anti-TNF failure with life changing results to their condition (see evidence by Crohn's and Colitis UK and their patients' reports). We have serious concerns that these patients would be denied an effective treatment based on unclear evidence. There is a cohort of patients who had IFX in the past and having active disease would benefit from this novel therapeutic class as pulse treatment produces a higher risk of antibody formation. **We would like to urge the committee to review the decision to exclude patients previously exposed to anti-TNFs from vedolizumab therapy as this may be the only medical alternative to surgery with its life changing impact on the patient.**	Following consultation, vedolizumab is recommended within its marketing authorisation as an option for treating moderately to severely active ulcerative colitis in adults only if a stopping rule is applied and the company provides vedolizumab with the discount agreed in the patient access scheme (see section 4.18 in the FAD).

Comments received from clinical experts and patient experts

Nominating organisation	Comment	Response
Crohn's and Colitis UK	Many thanks for forwarding the ACD document for comment. As a patient expert I am delighted that the committee has taken on board what was said as to how debilitating ulcerative colitis can be, and how desperate we are, as a patient group, for new treatment options. It is fantastic news that vedolizumab is being recommended as a treatment option for moderate to severe UC and this will make a difference for many patients.	Comments noted.
	It is however very disappointing that the committee proposes to restrict access to patients who have not received anti TNF treatment which I do not feel is correct or fair. Although as patient experts we feel that we have been listened to, it is striking that neither myself nor Kameron would be eligible to receive the treatment under these draft guidelines. For Kameron this would have meant missing out on the treatment that has given him six years of remission after all other treatments had failed. The guidelines leave me with no treatment option other than surgery if I lose the exceptional case funding for my infliximab treatment, or if I lose response to this treatment, which could happen within the next year. Yet the committee have accepted that surgery is not an acceptable alternative treatment option. I never had the option to choose vedolizumab before anti TNF because this was not available at the time that I needed it. A number of patients with moderate to severe UC will have received anti TNF at some point, yet they are being prevented from accessing vedolizumab and in my view the evidence does not justify this. The guidelines are also cutting out some of the patients who are most at need. Although we are still awaiting the final outcome of the infliximab/andalimumab/golimumab appraisal, it is looking like these treatments will not be recommended for UC which leaves many patients with no remaining treatment options other than surgery.	Comments noted. Following consultation, vedolizumab is recommended within its marketing authorisation as an option for treating moderately to severely active ulcerative colitis in adults only if a stopping rule is applied and the company provides vedolizumab with the discount agreed in the patient access scheme (see section 4.18 in the FAD).

Nominating organisation	Comment	Response
	Uncertainty of the exception for those who are intolerant to anti-TNF There is some uncertainty as to the significance of the exception in relation to patients who have had anti TNF but could not tolerate this treatment. It is known that anti-TNFs can lead to the development of antibodies against the drug which can either lead to allergic reaction or to loss of response in patients. It appears that some patients have an allergic reaction when the anti TNF treatment is stopped and re-started again. Does the exception in the guidelines cover patients who have had an adverse reaction at any time in their treatment or only at the start? Does this mean that if I have an allergic reaction to my infliximab tomorrow, after 18 months of treatment, then I am eligible to receive vedolizumab, but not if I lose response? What medical evidence is there that I am less likely to respond to vedolizumab in the first, rather than the second scenario? I would consider that in both cases my disease is still classified as amenable to treatment. **Distinction between patients who have had no response to anti TNF, and those who responded to anti-TNF but lost response over time** I note in paragraph 3.8 that '*the company commented that people in whom* **prior treatment with a TNF-alpha inhibitor had failed** *may be less likely to have a successful response to subsequent treatment than people* **whose disease had lost response to, or who could not tolerate a TNF-alpha inhibitor'.** A distinction is drawn between those who have failed, and therefore not responded to anti TNF, and this who had lost response or were intolerant. The draft guidelines however place those who have lost response in the same group as those who did not respond to anti TNF at all. This cannot be correct and contradicts what the company suggested. There is very little evidence to suggest that a distinction should be ade between these subgroups. GEMINI I suggested only a 11% difference in response to vedolizumab between those who had anti TNFs before, and those who had not (paragraph 3.5 36% vs 47%). The committee itself accepted in paragraph 4.8 that GEMINI I was not empowered to test for a statistically significant difference between subgroups yet this is what has been done in these draft guidelines.	

Nominating organisation	Comment	Response
	Distinction between patients who were intolerant to anti-TNF, and those who were tolerant and have responded but lost response over time In paragraph 4.3 the committee accepted that the cost effectiveness of vedolizumab for patients who have had anti TNF but were intolerant, and the cost effectiveness for those who have not had anti TNF were comparable, because we must assume that some patients who were intolerant may have responded to anti TNF if they had been able to continue treatment. However those who have had anti TNFs and have responded well to these, but eventually lost response (which is common due to antibody development) are shut out. This is an incorrect and unfair distinction.	
	Conventional therapy is not a relevant comparator In paragraph 4.9 I note that the committee is referring to conventional therapy as an appropriate comparator. This is a flawed analysis again (as in the other biologics appraisal). Patients who have failed conventional therapy cannot go back to conventional therapy; they have no option other than surgery. Of course patients who lose their other treatment options go back to treatment with high doses of steroids. This is because without them they could die while waiting for surgery; this is not because long term high dose steroid treatment is an option.	
	Innovative treatment I further note that paragraph 4.21 concludes that vedolizumab is an innovative treatment. I completely agree with this, which is why it should be accessible to as many patients as possible. I note that when a treatment is particularly innovative then NICE can recommend this as cost effective even when ICERs are higher than usual. Why was this not done here?	

Nominating organisation	Comment	Response
	Equality and diversity I also welcome NICE's conclusion that there are equality and diversity issues at play for young people who have not yet started a family. It is disappointing that as a 28 year old female, based on these draft guidelines I am still left with surgery as my only alternative treatment option if I lose my infliximab treatment. The reason that vedolizumab is such an exciting treatment option is that it has been proven to work for patients who have failed all other treatment, including anti TNF. It is an additional line of treatment for patients, but under these draft guidelines it is not. It also has less side effects and may enable patients to achieve remission for longer, without the need for concurrent immunosuppressive treatments, but many patients who could gain substantial benefit could miss out under these draft guidelines.	Comments noted.
	I would propose that the draft guidelines be amended to recommend treatment for those who have had anti-TNF treatment and responded to this, but then lost response to treatment. I would also suggest an amendment that enables patients who did not respond to anti TNF, to still access this treatment, but with an earlier review as to whether clinical response has been achieved. This will manage cost effectiveness by only allowing patients who are responding to continue treatment, but without cutting out large groups of patients who could still gain substantial benefit from vedolizumab treatment. The guidelines could provide for a review at week 14, as suggested by the clinical experts, with discontinuation of treatment just before the fourth dose if no clinical response has been achieved.	Comments noted. Following consultation, vedolizumab is recommended within its marketing authorisation as an option for treating moderately to severely active ulcerative colitis in adults only if a stopping rule is applied and the company provides vedolizumab with the discount agreed in the patient access scheme (see section 1 and 4.18 in the FAD).

Nominating organisation	Comment	Response
Crohn's and Colitis UK	I am pleased that the interim guidance for Vedolizumab has recommended this as a treatment option for Ulcerative Colitis. However, I am very concerned that patients who did not previously respond to a TNF- alpha inhibitor are to be prohibited from receiving Vedolizumab. I was previously treated with a TNF- alpha inhibitor (Infliximab) and I did not respond to this. I am currently being treated with Vedolizumab and have been on this treatment for the past six years. I have responded to Vedolizumab and it has kept me in (steroid-free) remission for the entire past six years. Therefore, it is clearly evident that there is no logic to the interim guidance. Not having a response to, or losing response to previous treatment with a TNF-alpha inhibitor does not necessarily have any connection with what may happen with Vedolizumab. As my case clearly shows. I was diagnosed with severe pan-Ulcerative Colitis. It proved to be treatment-refractory and I was steroid dependent. The TNF - alpha inhibitor Infliximab failed to work. Vedolizumab did work. I do not believe there is enough evidence to justify excluding an entire cohort of Ulcerative Colitis sufferers on the (incorrect) judgement that Vedolizumab would not work. These patients will ultimately end up requiring surgery. A huge financial burden on the NHS, as well as having a significant detrimental effect on many aspects of their lives. This clause needs to be removed from the guidance until further and proper investigations can take place.	Comments noted. Following consultation, vedolizumab is recommended within its marketing authorisation as an option for treating moderately to severely active ulcerative colitis in adults only if a stopping rule is applied and the company provides vedolizumab with the discount agreed in the patient access scheme (see section 1 and 4.18 in the FAD).

Comments received from commentators

Commentator	Comment	Response
AbbVie	Please find AbbVie's response to the Appraisal Consultation Document (ACD) for the single technology appraisal (STA) for vedolizumab in treating moderately to severely ulcerative colitis (UC). AbbVie believes that patients in the UK should have the opportunity to receive appropriate treatment for their condition and we welcome the chance to provide our comments in relation to the interpretation of the cost-effectiveness evidence within the ACD. We propose that AbbVie's feedback presented in this document are taken into consideration at the next appraisal meeting in order to ensure the evidence base for the relevant treatments is accurately reflected in the final appraisal of vedolizumab for moderately to severely active UC.	Comments noted.

Commentator	Comment	Response
	Section 1. Has all of the relevant evidence been taken into account? ***1.1*** *Benefit of systemic immunomodulating effect of biologics* AbbVie would like to highlight the systemic benefit of anti-tumour necrosis factor (anti-TNF) treatments in this patient population and that vedolizumab's proposed gut specific mechanism of action means that patients with co-morbid immune-mediated inflammatory diseases (IMIDs) or extra intestinal manifestations (EIM) of UC may not benefit from the extra-gut immunomodulating effect of anti-TNFs. Patients with inflammatory bowel disease (IBD) are at significant risk of developing another autoimmune disease and it has been estimated that between 4-11% of IMIDs such as rheumatoid arthritis, ankylosing spondylitis and psoriasis, co-exist within people with IBD. Furthermore, EIM of IBD have been found in 25-40% of IBD patients and involve the musculoskeletal, dermatological, hepatopancreatobiliary, ocular, renal and pulmonary systems. Within the musculoskeletal system patients present with arthritis and spondylitis (amongst others), dermatological manifestations include psoriatic and reactive lesions such as erythema nodosum and pyoderma gangrenosum and ocular manifestations may present as uveitis. These conditions are chronic and disabling and may present significant socioeconomic burdens, resulting in high healthcare utilisation. Although some of the above mentioned co-morbid conditions or manifestations can be treated with drugs such as analgesics, non-steroidal-anti-inflammatory drugs or steroids, the introduction of anti-TNF based therapies has led to further improvements in these conditions. Vedolizumab's proposed gut specific mechanism of action means that patients with co-morbid IMIDs or EIMs may not benefit from an extra-gut immunomodulating effect, whereas treatment with anti-TNFs may benefit them. These benefits of anti-TNFs have not been taken into account in the appraisal and should be borne in mind by the Committee.	Comments noted. The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of vedolizumab, having considered evidence on the nature of moderately to severely active ulcerative colitis 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.

Commentator	Comment	Response
	2 Are the summaries of clinical and cost-effectiveness reasonable interpretations of the evidence? AbbVie believes that the ACD does not reasonably interpret some elements of the clinical and cost-effectiveness of the vedolizumab compared to anti-TNFs and this is discussed in the points below. **2.1 Appropriateness of the network meta-analysis comparing the efficacy of vedolizumab to anti-TNFs** AbbVie notes that the vedolizumab comparison against adalimumab, infliximab and golimumab is based on a network meta-analysis (NMA). AbbVie believes this is not an appropriate approach as differences in clinical trial design between vedolizumab, adalimumab, infliximab and golimumab trial designs could generate biased results in an indirect comparison of these treatments. Indeed, heterogeneity has been acknowledged in the NMA conducted by the Assessment Group in the recently completed multiple technology appraisal (MTA) for adalimumab, infliximab and golimumab in moderately to severely active UC. Specifically, the vedolizumab GEMINI I study has a different design for assessing outcomes for patients on maintenance therapy than the adalimumab ULTRA 2 study and the infliximab ACT 1 and 2 studies. In the GEMINI I study, initial responders to vedolizumab were re-randomised to either placebo or vedolizumab for the maintenance period outcomes whereas in the adalimumab and infliximab studies, patients were randomised only at baseline and followed throughout the entire study period. Thus, the placebo efficacy during the maintenance period in GEMINI I was measured among patients who were responders to vedolizumab who may or may not respond to placebo whereas in the adalimumab and infliximab studies, the placebo efficacy was evaluated among placebo responders. Therefore, the NMA has estimated the placebo efficacy during the maintenance period in the adalimumab and infliximab studies using placebo responders from the induction period. However, patients responding to vedolizumab in the GEMINI I study and patients responding to placebo (in the adalimumab and infliximab studies) could be inherently different, thus possibly preventing a reliable indirect comparison between these drugs and vedolizumab during the maintenance period using placebo as the common comparator.	Comments noted. The Committee noted the ERG's concerns that there were differences between the trials included in the meta-analyses (See FAD section 4.9).

Commentator	Comment	Response
	Additionally, AbbVie notes that a fixed effect model was used in the NMA presented by the manufacturer. As stated by the Evidence Review Group (ERG), a random effects model would be more appropriate. Using a random effects model would better account for the heterogeneity that exists between studies. As such, results from the NMA based on a fixed effect model does, does not, in AbbVie's view, allow for a reasonable interpretation of the clinical effectiveness of the treatments in the NMA. AbbVie also questions the appropriateness of inclusion of the study by Suzuki et al. in the NMA conducted by the manufacturer. This study was conducted in exclusively Japanese patients aged 15 years and older and was conducted in a Japanese setting. Geographic variations in clinical practice, interpretation of Mayo scores and expectations from clinicians and patients regarding treatment success may influence study results and as such, caution should be exercised when incorporating trials such as Suzuki et al. into a NMA and ideally, the Suzuki trial should not be incorporated into any NMA. Lastly, whilst the point estimates from the NMA may appear plausible, the credible intervals appear wide for some of the results and AbbVie questions the clinical plausibility thereof. AbbVie is concerned that given the combined limitations mentioned above, the efficacy of vedolizumab versus anti-TNFs cannot be fully determined using an NMA framework and any results obtained from the existing NMA would not be a reasonable interpretation of the efficacy of the treatments. As such, results from the NMA should not be relied upon in the cost-effectiveness evaluation and AbbVie requests that careful consideration should be given when evaluating the comparative efficacy of anti-TNFs to vedolizumab and vedolizumab's place in therapy.	The Committee also noted the ERG's concerns that the meta-analyses results were from a fixed effect model which was less suitable than a random effects model in these circumstances (See FAD section 4. 9).

Commentator	Comment	Response
	2.2 Interpretation of the benefit of vedolizumab's mechanism of action As noted in the manufacturer's submission, in the combined studies of UC and Crohn's Disease the adverse reactions that occurred in ≥5% of patients were nausea, nasopharyngitis, upper respiratory tract infection, arthralgia, pyrexia, fatigue, headache and cough. Infections of the upper respiratory and nasal mucosa (nasopharyngitis) occurred more frequently in the vedolizumab than the placebo group (p-values not available) and suggest that vedolizumab might be active in other mucosal tissue. Additionally, vedolizumab's inhibition of leukocyte migration into the gut may increase the risk of systemic infections from enteric pathogens and as such, patients are at potential increased risk of opportunistic infections or infections for which the gut is a defensive barrier. AbbVie notes that the Committee considered that because vedolizumab suppresses immune activity only in the gut, this was a step-change in the management of UC and the Committee therefore concluded that vedolizumab is an innovative therapy. AbbVie questions whether the conclusion that vedolizumab is an innovative technology for which the benefits of targeted immunosuppression might not be fully captured in the model, is a reasonable interpretation of the clinical data.	Comments noted. The Committee concluded that vedolizumab is an innovative technology, and that some of its benefits, such as its targeted immunosuppression, might not be fully captured in the model. The Committee noted that the impact of any such benefits could not be quantified with the available data (See FAD section 4.19).
	3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS? AbbVie has no comments on this point.	Comments noted.
	4. Are there any aspects of the recommendations that need particular consideration to ensure NICE avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? AbbVie has no comments on this point. References (not reported here).	Comments noted.

Commentator	Comment	Response
MSD	MSD thanks NICE for the opportunity to comment on the Appraisal Consultation Document (ACD). We welcome the addition of new treatment options for patients with moderately to severely active UC who have only recently provisionally gained access to any NICE-approved biologic treatments (once conventional therapy has failed or in cases where it is contraindicated or cannot be tolerated) through the Multiple Technology Assessment of the three TNF-alpha inhibitors, Remicade, Simponi, and Humira. However, although we understand that the wording in section 1.1 of the ACD is not meant to recommend a specific treatment pathway (in terms of the order in which biologic therapies are to be used); we are concerned that the wording could be seen to imply this. Through moving the first bullet point ("the person has not had a TNF-alpha inhibitor or") later on in the recommendation, this could resolve this potential for misinterpretation and we believe would not change the intent of the committee. We also believe that the current wording of the recommendation may prejudice against patients who have previously received Remicade for the management of acute severe UC (in line with Technology Appraisal Guidance 163) as is it not clear whether they would then be able to receive vedolizumab for any future treatment of ongoing moderately to severely active UC (not acute).	Comments noted. Section 1 .1 in the FAD has been amended to: Vedolizumab is recommended within its marketing authorisation as an option for treating moderately to severely active ulcerative colitis in adults only if the company provides vedolizumab with the discount agreed in the patient access scheme.

Commentator	Comment	Response
	Through reviewing the material submitted by the manufacturer of vedolizumab and the Evidence Review Group's appraisal of that material, we have noted three key inaccuracies which may impact the cost-effectiveness estimates which have been considered by the appraisal committee: 1. The approved Patient Access Scheme for golimumab has not been included in the manufacturer's cost-effectiveness model 2. The cost-effectiveness model includes a number of induction doses for vedolizumab which is not consistent with its marketing authorisation 3. The network meta-analysis is not a credible reflection of available data from randomised controlled trials and has been inappropriately applied in the cost-effectiveness model Further detail on these three points is provided overleaf, though in summary, the cost-effectiveness results presented by the manufacturer of vedolizumab may not be an accurate reflection of the true cost of vedolizumab in both the TNF-alpha inhibitor-naïve and TNF-alpha inhibitor-failure populations. Finally, please note that MSD has been omitted from the list of commentator organisations in the ACD.	Comments noted. The Committee noted the uncertainties in the modelling, but on balance concluded that vedolizumab should be recommended within its marketing authorisation as an option for treating moderately to severely active ulcerative colitis in adults when the company provides vedolizumab with the discount agreed in the patient access scheme.

Commentator	Comment	Response
	1. <u>Omission of golimumab Patient Access Scheme in cost-effectiveness model</u> The manufacturer of vedolizumab made their submission on the 25th July 2014, which is after the date on which the Patient Access Scheme (PAS) for golimumab was approved by the Department of Health (decision communicated on 16th July 2014). Surprisingly, the PAS for golimumab was not applied in the model although according to the final scope issued by NICE "The availability of any patient access schemes for the comparator technologies should be taken into account." The golimumab PAS gives the opportunity for the NHS to access the 100mg dose at the price of the 50mg dose. Consequently, the number of golimumab doses used in the induction period decreases from six to three and the total drug price for induction with the PAS is £2,289 not £4,578. MSD have explored the impact of including or excluding the golimumab PAS in our own model (developed for the NICE UC MTA) and we would expect the same amendments in the vedolizumab model to have implications on the cost difference between vedolizumab and golimumab. According to Table 103 in the manufacturer's submission, the total incremental difference between vedolizumab and golimumab is £1,312. By applying the PAS price for golimumab, the total cost over 10 years for the golimumab arm in the model would be less than that of vedolizumab. Therefore, it follows that golimumab would not be dominated by vedolizumab.	
	2. <u>Number of vedolizumab induction doses in cost-effectiveness model</u> In the manufacturer's cost-effectiveness analysis, vedolizumab treatment in the induction period is assumed to be administered as a 300mg intravenous infusion at weeks 0 and 2. According to the submission, this dosing assumption is based on the GEMINI I dosing regimen. However, the EMA marketing authorisation for vedolizumab recommends that 300mg is given at 0, 2, and 6 weeks. MSD strongly believes that assumptions adopted in cost-effectiveness models should reflect the way the medicine will be used in UK clinical practice. Additionally, according to the 'Guide to the methods of technology appraisal 2013': "6.1.12 The Appraisal Committee does not normally make recommendations regarding the use of a drug outside the terms of its marketing authorisation, as published in the manufacturer's summary of product characteristics". By increasing the number of vedolizumab infusions in the induction phase to three, the overall drug costs for vedolizumab would be expected to increase.	

Commentator	Comment	Response
	3. <u>Use of network meta-analysis data in cost-effectiveness model</u> We do not believe that the network meta-analysis (NMA) performed by the manufacturer is appropriate to support the cost-effectiveness modelling for a number of reasons. *a) Inconsistencies between effectiveness estimates from NMA and trial data* First, we note that the NMA data have been applied only in the TNF-alpha inhibitor-naïve population while trial data has been used in the other populations. This approach is inconsistent and may be misleading due to the discrepancies between the findings of the NMA compared to the GEMINI I data for vedolizumab which suggests that there may be poor convergence of direct and indirect evidence in the NMA (Table 1 – Not reported here).	
	b) Alternative perspective on relative effectiveness estimates from NMA MSD has incorporated the results from the GEMINI I trial into the NMA that was submitted by MSD as part of the NICE UC MTA. The NMA presented by Takeda stated that for the TNF-alpha inhibitor-naïve population, in induction, infliximab was most effective, followed by vedolizumab, golimumab, and then adalimumab (ranking was the same for clinical response and clinical remission). In maintenance, vedolizumab was found to be most effective, followed by golimumab, adalimumab, and infliximab. While the updated MSD NMA (fixed effects model) found that for induction the ranking of therapies was the same, for maintenance, infliximab moves from being the least effective therapy at maintaining remission (as stated by Takeda) to being the most effective (more effective than vedolizumab) (Table 2 – Not reported here).	

Commentator	Comment	Response
	c) *Inconsistencies between transition probabilities derived from NMA and trial data / lack of clarity around transition probabilities* The inappropriateness of using the NMA to support the TNF-alpha inhibitor-naïve population modelling is further apparent in the transition probabilities that are applied in the cost-effectiveness model. First, it is not clear how these have been derived from the NMA as the equations used were not made available for review (they were included in an appendix to the manufacturer submission). Due to this lack of transparency it is not clear whether the magnitude in the differences between transition probabilities is logically related to the magnitude in the differences between the effectiveness of each biologic therapy according to the NMA. Secondly, there are inconsistencies between the transition probabilities derived from the NMA and those derived from the trial data (Table 3). We note that the manufacturer's model itself states that the NMA data are inappropriate to use for the comparison between vedolizumab and conventional therapy as head to head data exist ("NOTE: Head to head data exist and should be used for comparisons between vedolizumab and conventional therapy"), however, the ICER produced using this inappropriate setting was presented to the appraisal committee as the base case for the TNF-alpha inhibitor-naïve population. Amending the data set that is used has a large impact on the cost-effectiveness estimate, highlighting the considerable uncertainty arising from using the NMA. (Table 3 – not reported here)	
Thanet Clinical commissioning group	I have reviewed the ACD and have the following response for you on behalf of Thanet CCG and South Kent Coast CCG: 1. *Has all of the relevant evidence been taken into account?* Yes, I believe all the relevant evidence has been taken into account.	Comments noted.
	2. *Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?* Yes, I believe the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence	Comments noted.

Commentator	Comment	Response
	3. *Are the provisional recommendations sound and a suitable basis for guidance to the NHS?* Yes, I think the provisional recommendations are sound recognising the trial was not powered to detect differences in sub-groups but given the rationale provided in the document. Vedolizumab appears to be valuable treatment option for patients that have not had a TNF inhibitor or not tolerated a TNF inhibitor. To strengthen the commissioning perspective, is it possible to say 'not tolerated' refers to the TNF inhibitor not being tolerated within the initial loading dose period e.g. for infliximab this would be no later than the first three doses [weeks 0, 2 and 6]? It looks like the guidance will provide a significant treatment option (or opportunity) for patients with moderate-severe UC, particularly new patients that have not had a TNF inhibitor. I think the area of the ACD that is weakest is how long to treat for although I recognise there is a lack of clinical evidence about this. It is probably clear when a drug has not worked or stopped working, and probably also when surgery is needed, but it would be helpful to have clinically objective (as much as it can be) guidance on what is remission and further research recommended on dose/frequency or alternative (i.e. non-biologic) treatment required to maintain response after the initial 12 month period.	Comments noted. Following consultation, vedolizumab is recommended within its marketing authorisation as an option for treating moderately to severely active ulcerative colitis in adults only if the company provides vedolizumab with the discount agreed in the patient access scheme (see FAD section 1.1).
	I could not identify any equality issues.	Comments noted.

Comments received from members of the public

Role*	Section	Comment	Response
General Public	**Comments**	This is a debilitating, distressing and antisocial disease. Any medication is worth a try - lives can be transformed if remission or control is achieved.	Comments noted.

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment	Response
Patient	**Comments**	I personally have acute left sided UC, diagnosed 5 years ago. I have struggled to keep in remission during this time. I have tried asacol, and been on azathioprine for the last 18 months. These have not worked for me and as steroids are not seen as a long term treatment, and with the withdrawal of other biologics for maintenance therapy the only other real course of treatment for me would be surgery. I am a 35 women with a young family. The affects of this disease on my quality of life have been severe. I have been fortunate to have understanding employers and a very supportive network, but there are times when I struggle to function at all. This new drug presents a real opportunity for me to be able to continue in my career and make a positive contribution to the economy, as well as being able to be a proper parent to my children.	Comments noted.
Patient	**Comments**	I am very concerned with the proposal to make Vedolizumab unavailable to those who have not had a response to, or have lost response to treatment with a TNF-alpha inhibitor. I have severe ulcerative colitis (pan-colitis). I have recently come out of hospital, where I was treated with IV steroids and Infliximab. I have finished the three doses funded by the NHS. I have had some response but am not in complete remission. I have not been able to work since July. The only option now is for me to take Azathioprine, with all the risks and nasty side effects this entails. If this does not work, or the side effects/complications are too drastic, I will be looking at surgery. It is not clear whether I would be eligible for Vedolizumab - I was able to tolerate Infliximab and did not lose response; more than 3 doses were simply not funded. I would very much like to try Vedolizumab. I understand that it is expensive, but this would also be making savings in other areas - such as treating the side effects/complications associated with Azathioprine, or the cost of surgery. Not to mention I would be able to return to work, and pay tax once again. Together with Crohns and Colitis UK, I urge NICE to reconsider extending access to vedolizumab to include those - such as myself - most in need.	Comments noted. Following consultation, vedolizumab is recommended within its marketing authorisation as an option for treating moderately to severely active ulcerative colitis in adults only if a stopping rule is applied and the company provides vedolizumab with the discount agreed in the patient access scheme.

Role*	Section	Comment	Response
Patient	**Comments**	I have had UC for 30 years and my son aged 26 has had UC for 5 years. My son is a promising academic at Cambridge University.His academic career has been interrupted on numerous occasions by UC flares and there have been times when it was feared that his career would break down completely because of flares at crucial times eg during exams and periods in hospital. Above all what has been lacking is a drug which can give long term remission. My son has tried Infliximab both in the UK and in France where Infliximab is freely available to UC patients and regarded as a best option. Infliximab was of short term but not long term benefit to my son.He remains steroid dependent and unable to achieve long term remission. To deny the class of UC patients which includes my son ie those who have tried but not gained long term benefit from other mabs the opportunity to try Vedolizumab is both unfair and a poor clinical decision. No patient will wish to continue on a serious drug if it is ineffective. No patient should be forced toward surgery if a promising drug has not been tried no matter what drugs he has tried before.	Comments noted. Following consultation, vedolizumab is recommended within its marketing authorisation as an option for treating moderately to severely active ulcerative colitis in adults only if a stopping rule is applied and the company provides vedolizumab with the discount agreed in the patient access scheme.

Role*	Section	Comment	Response
Patient	**Comments**	I am a patient with ulcerative colitis which has not responded to conventional treatments. I am due to start on infliximab tomorrow and am concerned if this does not work or is unsuitable I will have no other options and no hope for the future. As a father of 3 children I really need more than just surgery that has too many drawbacks for me. I want the chance to live an independent life and be able to earn a living, pay the mortgage, be able to support my family and see my children grow up. I hope this more targeted drug can give myself and others a chance to live a more normal life with fewer side effects. Thank you. I am self-employed and am at risk of losing my business and family home due to the effects of my illness. Please make this drug available to people who desperately need a viable alternative to the other medication available. This illness is very debilitating and we feel that we are running out of options. Our children need their father back in their life again. Please give us some real hope. (Partner of ulcerative colitis sufferer).	Comments noted. Following consultation, vedolizumab is recommended within its marketing authorisation as an option for treating moderately to severely active ulcerative colitis in adults only if a stopping rule is applied and the company provides vedolizumab with the discount agreed in the patient access scheme.

Role*	Section	Comment	Response
Patient	**Comments**	I am 23 years old and I was diagnosed with ulcerative colitis back in 2012 during my 3rd year at university studying dentistry. I had learnt about this condition during my dental studies and never dreamed that I would soon be suffering from it. When I was first diagnosed back in May 2012, I was admitted to hospital for 1 week. I was given medication and prednisolone to taper down on. I did this and had my first relapse in November 2012 where I again had to be admitted to hospital due to having extreme abdominal pain, going to the bathroom over 10x a day and passing blood. I was still working out how to manage this disease and was determined not to let this interfere with my 4th year of dentistry as I was currently in the middle of exams. I was discharged on oral steroids which was to be followed up with the view to starting azathioprine. As soon as I started taking azathioprine I started suffering from extreme abdominal pain at night which I had never experienced to this extent. I was later told to stop taking this and the pain disappeared. I was then given 6-Mercaotopurine but had the same response to the azathioprine which I therefore had to stop. I was offered the AMGEN trial or surgery but at this stage in the middle of my exams and having just gone through the traumatic experience of taking the oral immunosuppressants I declined. I later started infliximab. At the time I started infliximab I was already feeling better and back to normal due to having been tapering on steroids. I felt normal after having my infusions and a month later once I had come off the steroids again, I had another relapse. I then went back on prednisolone and was stable again. I now felt it was time to take control of my health and although only empirical evidence available decided to change my diet. I have since cut out all dairy, grains and try to have a low sugar diet. For the whole of my 5th year at university I stayed on a low dose of 5mg oral prednisolone and stuck to my new lifestyle change. I did not have to be admitted to hospital and if I felt a relapse was starting, I would act fast by using steroid and mesalazine enemas to take control which worked. I have never felt happier and in control of my disease. Knowing I could feel so well again with diet and medication, I could not even think about surgery.	Comments noted.

Role*	Section	Comment	Response
Cont..		I was doing very well and in consultation with my consultant decided to come off steroids with a view to starting the amgen trial. Unfortunately, the trial was no longer accepting patients and I was very angry with myself for missing out on this opportunity earlier. Having come off steroids, I later relapsed and on the 27th June had to be admitted to hospital again due to having severe headaches along with UC symptoms. The severity of the headaches prevented me from controlling my UC symptoms which I would normally do with the use of suppositories and usual medication. Once discharged, I again started tapering the oral steroids but have stayed at a maintenance dose of 10mg steroids. I feel well and know I cannot stay on oral steroids for the rest of my life. I cannot comprehend having surgery which is irreversible unless life-threatening. I feel so well even though steroid dependant but I know if I come off them I will eventually relapse and I will be back in the viscous cycle. Evidence has shown vedolizumab to be efficacious in those who have failed anti-TNF-Î± treatment and could be a last treatment option prior to surgical intervention. Knowing that there a drug which has had success even in those who have had TNF therapy which has failed, at 23 years old I am not prepared to go through such drastic life changing surgery until I have tried every option available. I am managing my condition to my best ability through medication and diet and I will remain strong and positive in the hope that I will be able to receive vedoluzimab one day. I am so grateful for being given the opportunity to express my views to NICE and this could change my life completely no longer living in fear of when I will next relapse.	Comments noted. Following consultation, vedolizumab is recommended within its marketing authorisation as an option for treating moderately to severely active ulcerative colitis in adults only if a stopping rule is applied and the company provides vedolizumab with the discount agreed in the patient access scheme.