Takeda UK NICE Appraisal Consultation Document Response:

Vedolizumab for treating moderately to severely active ulcerative colitis [ID691]

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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

(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

	1st line infliximab
Primary non-response	19.0–58.3% [1-2]
Secondary non-response	17.0–22.2% [2-3]

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.[4,5]

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:[6,7]

Duration of exposure	Examples of toxicities/serious side effects due to steroid use
Short-term use	Hypertension, infection, moon face, acne, ecchymoses, hirsutism, petechial bleeding, striae
Prolonged use	Hypertension, infection, new onset diabetes mellitus, ostenecrosis, steroid associated osteoporosis, myopathy, psychosis, cataracts, glaucoma

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.[8]

(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[9] 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.

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 <u>exposed</u> 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[11], 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.

(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)[11]

	Induction Cohort 1 (ITT Population)	
Medication Use/ Failure Category	PLA (N=149)	VDZ (N=225)
Prior anti-TNF use, n(%)	73 (49)	95 (42)
No Prior anti-TNF use, n (%)	76 (51)	130 (58)
Any prior anti-TNF failure, n(%)	63 (42)	82 (36)
Inadequate response	29 (46)	44 (54)
Loss of Response	26 (41)	32 (39)
Intolerance	8 (13)	6 (7)

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)[11]

Study Endpoint	Patients With Prior TNFα Antagonist Failure*		
	Vedolizumab (n=82)	**Placebo (n=63)**	**Between Group Difference (95% CI)‡**
Clinical Remission (%)	9.8	3.2	6.6 (-9.8 to 22.8)
Clinical Response (%)	39.0	20.6	18.4 (3.9 to 32.9)

CI=confidence interval; TNF=tumour necrosis factor; Wks=weeks. *Treatment failure (inadequate response, loss of response, or intolerance) defined as follows: inadequate response to TNF antagonist=persistently active disease despite induction treatment with specified agents; loss of response to TNF antagonist=recurrence of symptoms during maintenance dosing following prior clinical benefit; intolerance=occurrence of treatment-related protocol-defined toxicities. A small number of patients (9 placebo, 7 VEDO every 8 weeks, and 12 VEDO every 4 weeks) had prior anti-TNF exposure without documented evidence of anti-TNF failure; these patients are not included in this table. ‡Confidence interval for difference from placebo. Although these endpoints were pre-specified, p-values are not provided because multiple testing adjustments were not made.

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.[11]

Table 4: Key maintenance results at Week 52 for the Anti-TNFα failure patients (GEMINI 1)[11]

Study Endpoint	Patients With Prior TNFα Antagonist Failure*				
	VEDO Every 8 Wks (n=43)	VEDO Every 4 Wks (n=40)	Placebo (n=38)	Between Group Difference (95% CI)‡	
				Every 8 Wks vs. Placebo	Every 4 Wks vs. Placebo
Clinical Remission (%)	37.2	35.0	5.3	31.9 (10.3 to 51.4)	29.7 (7.4 to 49.4)
Durable Clinical Response (%)	46.5	42.5	15.8	30.7 (11.8 to 49.6)	26.7 (7.5 to 45.9)

CI=confidence interval; TNF=tumour necrosis factor; Wks=weeks. *Treatment failure (inadequate response, loss of response, or intolerance) defined as follows: inadequate response to TNF antagonist=persistently active disease despite induction treatment with specified agents; loss of response to TNF antagonist=recurrence of symptoms during maintenance dosing following prior clinical benefit; intolerance=occurrence of treatment-related protocol-defined toxicities. A small number of patients (9 placebo, 7 VEDO every 8 weeks, and 12 VEDO every 4 weeks) had prior anti-TNF exposure without documented evidence of anti-TNF failure; these patients are not included in this table. ‡Confidence interval for difference from placebo. Although these endpoints were pre-specified, p-values are not provided because multiple testing adjustments were not made.

(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.

(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.

(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

Source of Utilities	Incremental Cost-Effectiveness Ratio Cost per QALY gained
Basecase	£42,958
Woehl et al.	£35,767
Swinburn et al.	£31,872

(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).[10]

In Sections 4.73 and 4.74 of this FAD,[10] 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".[10]

Takeda UK would argue that the variables listed in Section 4.78 of the recently published FAD[10] 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[12].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.

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.

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