NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Premeeting briefing

Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy [ID690]

This premeeting briefing presents:

- the key evidence and views submitted by the company, the consultees and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical effectiveness

- Where in the patient pathway is vedolizumab most likely to be prescribed in clinical practice and what is the biological plausibility of equivalent or different clinical effectiveness before or after failure of TNF-alpha inhibitor treatment?

- The company presented results for 2 randomised controlled trials (GEMINI II and III) that compared vedolizumab with placebo plus conventional therapy. GEMINI II comprised induction and maintenance phases and enrolled a mixed population of TNF-alpha inhibitor-naive and TNF-alpha inhibitor-failure patients (58% of patients across all arms and cohorts had experienced failure of TNF-alpha inhibitor treatments).GEMINI III had an induction phase only, and 76% of patients had

previously experienced failure of TNF-alpha inhibitor treatment. Is the Committee satisfied that, compared with placebo, vedolizumab improves clinical remission in the induction and maintenance phases and what does the Committee consider that these trials show in relation to patients for whom previous TNF-alpha inhibitor treatment had failed, or who had not previously received a TNF-alpha inhibitor?

- GEMINI II and III assessed response in the induction phase at 6 weeks. The marketing authorisation suggests that response can occur after 6 weeks and allows a further dose for non-responding patients at 10 weeks, and assessment at 14 weeks).The ERG considered that the company's approach may have led to an overestimation of maintenance treatment effect. What is the Committee's view on the duration of induction therapy that is most relevant to clinical practice in England and what effect might this have on the effectiveness of vedolizumab in clinical practice compared with that demonstrated in the trials?

- Does the Committee consider that the results of the GEMINI trials are generalisable to the population who would receive vedolizumab for moderately to severely active Crohn's disease in clinical practice in England? The ERG made the following observations:
  - Very few of the study sites were in the UK and the concomitant conventional therapy may not reflect clinical practice in England
  - There was a high proportion of patients with high faecal calprotectin levels indicating possible over-representation of patients with active inflammation
  - Patients with very severe disease (Crohn's Disease Activity Index [CDAI] score greater than 450 points) were excluded, as were patients with strictures or fistulae
  - It was unclear whether the proportions of TNF-alpha inhibitor-failure patients were representative of patients in the NHS
  - High rates of discontinuation (47–58% depending on treatment group) were seen in the maintenance phase of GEMINI II
- In its model, the company identified patients going onto receive maintenance treatment by a drop in CDAI score of 70 points or more in response to induction treatment. The ERG noted that although the CDAI is the gold standard for

classifying disease activity in clinical trials, the Harvey Bradshaw Index is used in clinical practice. Does the Committee consider that the classification of response in the GEMINI trials can be generalised to clinical practice in England?

- The company defined several patient groups with moderately to severely active Crohn's disease, comprising a mixed population (people who have and have not received a TNF-alpha inhibitor), TNF-alpha-naive population and TNF-alpha failure population. Similar groups were presented according to moderate or severe disease. The ERG considered all of these to be relevant but noted difficulties in interpreting results from the mixed population. What is the Committee's view on the clinical relevance and robustness of these patient subgroups? How does the mixed population correspond with the likely patient group considered for vedolizumab in clinical practice?

- No randomised trials have compared vedolizumab with other biological therapies. The company conducted network meta-analyses but was not able to provide all relevant indirect comparisons because of data limitations. What is the Committee's view of trial data incorporated into the network-meta-analyses, the validity of the results of the network meta-analyses, and any conclusions that can be drawn about the clinical effectiveness of vedolizumab compared with other biological therapies?

Cost effectiveness

- The ERG was concerned about a number of structural assumptions in the model:
  - The modelling did not capture the relapsing–remitting nature of the disease
  - The modelling of surgery as a single health state was simplistic because subsequent surgery is likely to depend on the type of surgery originally received.
  - The assumption that all patients whose condition did not respond to treatment had moderate to severe disease for the full duration of the model was not appropriate.

- The assumption that there would be no difference in outcomes, between responders and non-responders for those people in the moderate to severe health state.
- The same treatment duration was assumed for all therapies for the induction phase (6 weeks) which led to discrepancies in costing, cycle length and efficacy.
- The assumption that all responders would stay on therapy for 1 year whether or not disease relapsed, and that biological treatment would stop in all patients at 1 year may not be appropriate (and is inconsistent with the NICE clinical guideline on Crohn's disease).

What are the Committee's views on the structural assumptions used?

- The ERG was concerned about how the company had derived its initial induction vectors in the model (that is, the probabilities of response, remission, surgery or death, and the proportion of responders with moderate to severe disease). Is the Committee satisfied with the company's explanation in its submission?
- The company's model did not allow for relapse in patients in remission or with mild disease after stopping biological treatment. Clinical expert advice received by the ERG indicated this was an optimistic assumption. Does the Committee accept the company's approach to treatment switching after 1 year of maintenance treatment?
- The company used single-arm ACCENT-1 study to estimate the probabilities of remission and response in TNF-naive patients receiving infliximab during induction. The ERG considered it more appropriate to use the Targan study because this is the only placebo-controlled trial assessing the efficacy of infliximab for the induction phase. Which approach does the Committee consider to be more appropriate?

Other issues

- Is vedolizumab an innovative technology?

- Are there any equality-related issues when considering vedolizumab as a treatment for Crohn's disease?

1 Remit and decision problems

1.1 The remit from the Department of Health for this appraisal was: to appraise the clinical and cost effectiveness of vedolizumab within its licensed indication for treating moderately to severely active Crohn's disease in people who are intolerant of, or whose disease has not responded or is resistant to either conventional therapy or a tumour necrosis factor-alpha (TNF-alpha) antagonist.

Table 1 Decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Population	Adults with moderately to severely active Crohn's disease in whom the disease has responded inadequately to, or is no longer responding to, either conventional therapy or a TNF-alpha antagonist, or who are intolerant to either of them	In line with the final scope	None	The ERG considered the GEMINI populations included in the company's submission to reflect broadly the population and subgroups described in the final NICE scope, although it noted that patients with very severe disease were excluded (Crohn's Disease Activity Index [CDAI] score >450). The ERG was unclear whether the proportions of patients who had experienced TNF-alpha inhibitor failure were representative of UK norms
Intervention	Vedolizumab	Vedolizumab	None	The ERG noted that the treatment regimen used in the company's model differs from the recommended licensed dosage and the treatment regimen described in the company's decision problem
Comparators	• Conventional treatment strategies without vedolizumab (including antibiotics,	• Current standard of care, comprising 5-ASAs, corticosteroids and immunomodulators	The company considered the relevant main comparator to be current standard of care. It said that this reflected the	The ERG noted that infliximab and adalimumab are licensed in the UK for treating moderate to severe Crohn's disease.

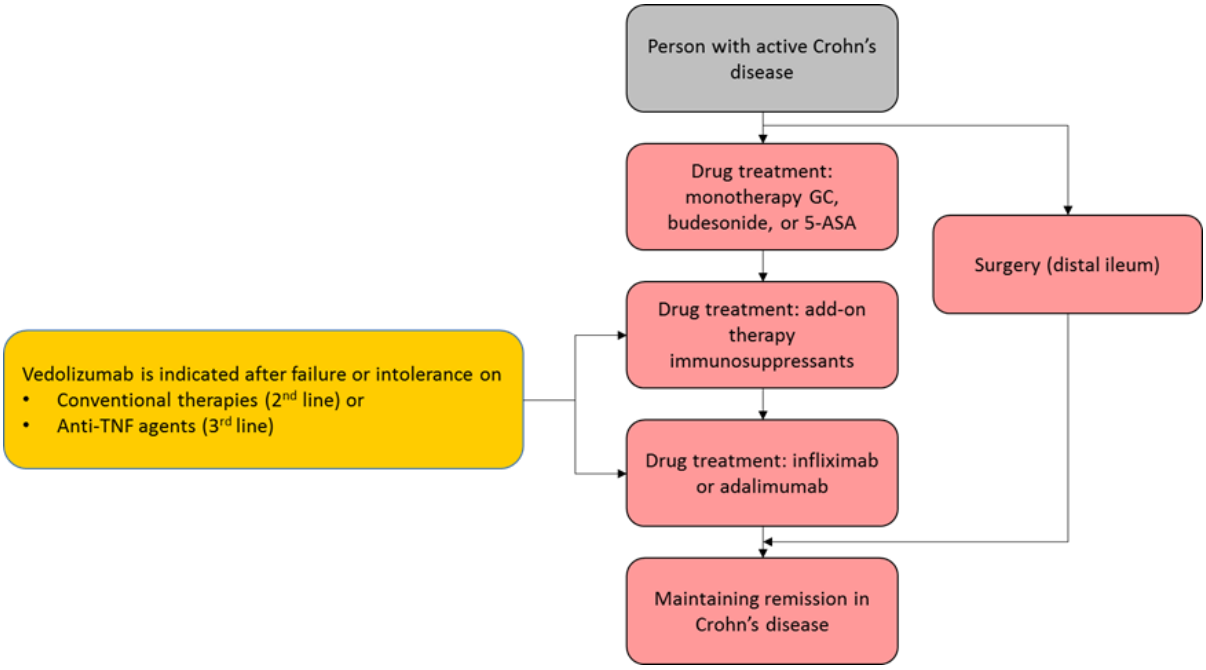
	drug treatment with conventional corticosteroids alone or in combination with azathioprine, mercaptopurine or methotrexate; aminosalicylates; budesonide alone or in combination with azathioprine, mercaptopurine or methotrexate) • TNF-alpha antagonists (infliximab and adalimumab)	• TNF-alpha inhibitor treatments (adalimumab, infliximab) where comparable evidence is available	baseline therapies in the vedolizumab registration studies and was supported by current NICE clinical practice guidelines and UK inflammatory bowel disease patient audit data	Both are recommended by NICE for use in severe disease (they have not been appraised by NICE for moderate disease). The ERG received clinical expert advice that, in clinical practice, they are also used in patients with refractory moderate disease
Outcomes	• Disease activity • Surgery • Adverse effects of treatment • Health-related quality of life	In line with the final scope	None	The ERG noted that the company's submission included data on remission and response rates but not on relapse rates or surgery
Subgroups	If evidence allows, the following subgroups should be considered: • People who have not previously received a TNF-alpha antagonist • People for whom a	Sub-group analyses included: • TNF-alpha inhibitor-naive population • TNF-alpha inhibitor -failure population (those who have previously tried a biologic, including those for whom a-	None	The ERG was unclear whether the proportions of patients in the clinical trials who had experienced TNF-alpha inhibitor failure were representative of UK norms

	TNF-alpha antagonist has failed • People for whom TNF-alpha antagonists are not suitable because of intolerance or contraindication	TNF-alpha inhibitor has failed) • Mixed population (includes patients who are TNF-alpha inhibitor -naive or who have experienced TNF-alpha inhibitor failure)		

2 The technology and the treatment pathway

2.1 Treatment of Crohn's disease aims to reduce symptoms, and to maintain or improve quality of life while minimising short- and long-term adverse effect (Figure 1). Disease severity (including response to treatment) can be assessed using the Crohn's Disease Activity Index (CDAI), which is an index of 8 factors: stool frequency, abdominal pain, assessment of general well-being, complications, medication use to control Crohn's disease, presence of abdominal mass, haematocrit and deviation from standard weight.

Figure 1 NICE pathway for adults with Crohn's disease with company's proposed positioning of vedolizumab



Source: Figure 4.5.1 on page 49 of the company's submission

2.2 NICE clinical guideline 152 recommends monotherapy with a corticosteroid (prednisolone, methylprednisolone or intravenous hydrocortisone) to induce remission in people with a first presentation or a single inflammatory exacerbation of Crohn's disease in a 12-month period. Budesonide or 5-aminosalicylates are considered for some people who decline, cannot tolerate or in whom a conventional corticosteroid is

contraindicated. When 2 or more inflammatory exacerbations are experienced in a 12-month period, azathioprine, mercaptopurine and methotrexate may be considered as add-on treatments to conventional corticosteroids or budesonide to induce remission of Crohn's disease.

2.3 NICE technology appraisal 187 recommends infliximab and adalimumab as treatment options for adults with severe active Crohn's disease whose disease has not responded to conventional therapy (including immunosuppressive and/or corticosteroid treatments), or who are intolerant of or have contraindications to conventional therapy. At the time of NICE technology appraisal 187, marketing authorisations for infliximab and adalimumab did not include treating adults with moderately active Crohn's disease and so moderately active disease is not covered by that guidance. The marketing authorisations for infliximab and adalimumab have subsequently been expanded to include treating people with both moderately and severely active disease that has not responded to conventional therapy (including immunosuppressive and/or corticosteroid treatments).

2.4 For people who choose to have maintenance treatment, NICE clinical guideline 152 recommends azathioprine or mercaptopurine as monotherapy to maintain remission when previously used with a conventional corticosteroid or budesonide to induce remission. Azathioprine or mercaptopurine may also be considered for maintaining remission in people who have not previously received these drugs. Methotrexate may be used to maintain remission only in people who needed methotrexate to induce remission, or in people for whom azathioprine or mercaptopurine maintenance treatment is not suitable.

2.5 In addition to pharmacological treatment, between 50 and 80% of people with Crohn's disease will require surgery during the course of their disease. The main reasons for surgery are strictures (whereby affected areas of the intestines become narrowed and may cause obstructive symptoms), lack of response to medical therapy, and complications such

as fistulae (an abnormal connection that forms between two organs or vessels) and perianal disease.

2.6 Vedolizumab has a marketing authorisation in the UK for ‘the treatment of adult patients with moderately to severely active Crohn’s disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor alpha (TNFα) antagonist’. It is administered by intravenous infusion.

Table 2 Technology

Treatment type	Anti-α4β7 integrin monoclonal antibody	Conventional treatment strategies	TNF-alpha inhibitors
Treatment name(s)	Vedolizumab	• Antibiotics • Conventional corticosteroids ± azathioprine, mercaptopurine or methotrexate • Aminosalicylates • Budesonide ± azathioprine, mercaptopurine or methotrexate	Infliximab and adalimumab
Marketing authorisation	Vedolizumab has a marketing authorisation in the UK 'for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha antagonist'	Not applicable	Infliximab has a marketing authorisation in the UK for 'treatment of moderately to severely active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies'. It is also indicated for 'treatment of fistulising, active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy)'. Adalimumab has a marketing authorisation in the UK for 'treatment of moderately to severely active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies'
Administration method	Intravenous infusion	Oral	• Infliximab is administered by intravenous

			infusion • Adalimumab is administered by subcutaneous injection
Dosing information and cost	The summary of product characteristics recommends that vedolizumab 300 mg is administered by intravenous infusion at 0, 2 and 6 weeks and then every 8 weeks thereafter. It says that patients with Crohn's disease, who have not shown a response may benefit from a dose of vedolizumab at week 10. Continue therapy every 8 weeks from week 14 in responding patients. Therapy for patients with Crohn's disease should not be continued if no evidence of therapeutic benefit is observed by week 14. Some patients who have experienced a decrease in their response may benefit from an increase in dosing frequency to vedolizumab 300 mg every 4 weeks. At the list price (excluding VAT), vedolizumab costs £2050 per 300-mg vial. The manufacturer of vedolizumab has agreed a patient access scheme with the Department of Health that makes vedolizumab available with a discount. The size of the discount is commercial in confidence	The weighted average cost of conventional therapy in the company's updated model was £70.16 per cycle	Infliximab: 5 mg/kg given as an intravenous infusion then a 5 mg/kg infusion 2 weeks later. In responding patients, maintenance may be given as an additional 5 mg/kg infusion 6 weeks after the initial dose then every 8 weeks. Alternatively, a 5 mg/kg infusion may be re-administered if signs and symptoms recur. Limited data suggest dose escalation may cause response to be regained in patients who initially responded to 5 mg/kg but who lost response. Adalimumab's recommended induction dose regimen for adults with moderately to severely active Crohn's disease is 80 mg at Week 0 then 40 mg at Week 2. If a more rapid response is needed, 160 mg at Week 0 and 80 mg at Week 2 can be given. After induction, the recommended dose is 40 mg every other week (may be increased to weekly if response decreases). According to the British national formulary (November 2014), infliximab costs £419.62 per100-mg vial and adalimumab costs £352.14 per 40 mg/0.8-mL vial (both costs excluding VAT).

See summary of product characteristics for details on adverse reactions and contraindications.

3 Comments from consultees

3.1 The 2 professional associations agreed that Crohn's disease is generally treated with a combination of corticosteroids, enteral nutrition, antibiotics and immunosuppressants (azathioprine, mercaptopurine and methotrexate). The professional and patient organisations noted that remission is not achieved or maintained with these treatments in around 30% of patients because of a lack of effect or intolerance. Other treatment options for these patients include biologic drugs or surgery. Although TNF-alpha inhibitors are known to reduce surgery, admission and improve quality of life, 20% experience primary non-response and a further 30% will have lost their response to a TNF-alpha inhibitor after 1 year. A professional organisation also noted a high risk of infection, particularly in older people. The other main alternative is surgery, which is preferred in some circumstances, but considered a last resort when medical treatment has failed. Participating in a clinical trial is another option but this applies to only 0.5% of patients with Crohn's disease in the UK. A professional organisation noted that treatment duration depends on the Clinical Commissioning Group, local stopping or review rules and interpretation of NICE guidance.

3.2 The patient organisation noted that gastrointestinal symptoms, malnutrition and weight loss are common, and that flare-ups can disrupt education, employment, personal relationships, and social and family life. Inflammation can lead to strictures of the bowel, which in severe cases can cause life-threatening complications. The frequent and urgent need for the toilet, together with loss of sleep, pain and fatigue, can severely affect self-esteem and social function. The patient organisation also noted an increased risk of developing colorectal cancer, which is linked to the extent, severity and duration of disease, and age at onset.

3.3 The professional groups described how vedolizumab would require the use of infusion facilities and nursing support. They stated that this could increase the number of infusions given because vedolizumab may replace

adalimumab (which is administered by subcutaneous injection) or create an additional patient group (if it is mainly used after failure of a TNF-alpha inhibitor). This will have resource implications for day case clinical centres and infusion units, as well as a small in-patient resource implication (because first infusions with these types of drug are often preferred as an in-patient).

3.4 A professional group considered that patients with markers of an aggressive course (such as younger age at onset, use of corticosteroids at presentation, penetrating disease and rectal disease) could receive a greater benefit from earlier use of biological treatment by being more likely to avoid complications such as fistulae.

4 Clinical-effectiveness evidence

Overview of the clinical trials

4.1 The company's systematic review identified 2 randomised, double-blind, placebo-controlled trials of vedolizumab, GEMINI II and GEMINI III. No relevant non-randomised controlled trials providing clinical efficacy information were identified.

4.2 The company said the eligibility criteria for GEMINI II and GEMINI III were identical. Both trials enrolled adults with moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] score 220–450) and 1 of the following: C-reactive protein level greater than 2.87 mg/l; colonoscopy with 3 or more large ulcers or 10 or more aphthous ulcers; faecal calprotectin greater than 250 microgram/g stool with evidence of ulcers. All patients had disease that had shown inadequate response to, loss of response to, or intolerance to at least 1 of the following: immunomodulators, TNF-alpha inhibitors, or corticosteroids (outside USA only) within the last 5 years. Therapeutic doses of oral 5-aminosalicylates, oral corticosteroids, probiotics, anti-diarrhoeals, azathioprine or 6-mercaptopurine, methotrexate and antibiotics were permitted. However,

treatment with adalimumab within 30 days and treatment with infliximab or certolizumab pegol within 60 days before enrolment was not permitted.

GEMINI II

4.3 GEMINI II compared the efficacy and safety of vedolizumab with placebo plus conventional therapy for induction and maintenance of moderately to severely active Crohn's disease. It comprised an induction trial (weeks 0–6) and a maintenance trial (weeks 6–52), giving an overall study duration of 52 weeks (Figure 2).

4.4 In the blinded induction trial (cohort 1), patients received vedolizumab 300 mg intravenously (n=220) or placebo (n=148) at weeks 0 and 2. Randomisation was stratified by status according to concomitant use of corticosteroids and status according to concomitant use of immunosuppressive agents, previous use of TNF-alpha inhibitors, or both. The proportion of patients with previous exposure to TNF-alpha inhibitors was limited to 50%. To fulfil sample-size requirements for the maintenance trial, 748 additional patients were assigned treatment in an open-label group (cohort 2), of whom 747 patients received the same active regimen as cohort 1 in the blinded induction trial.

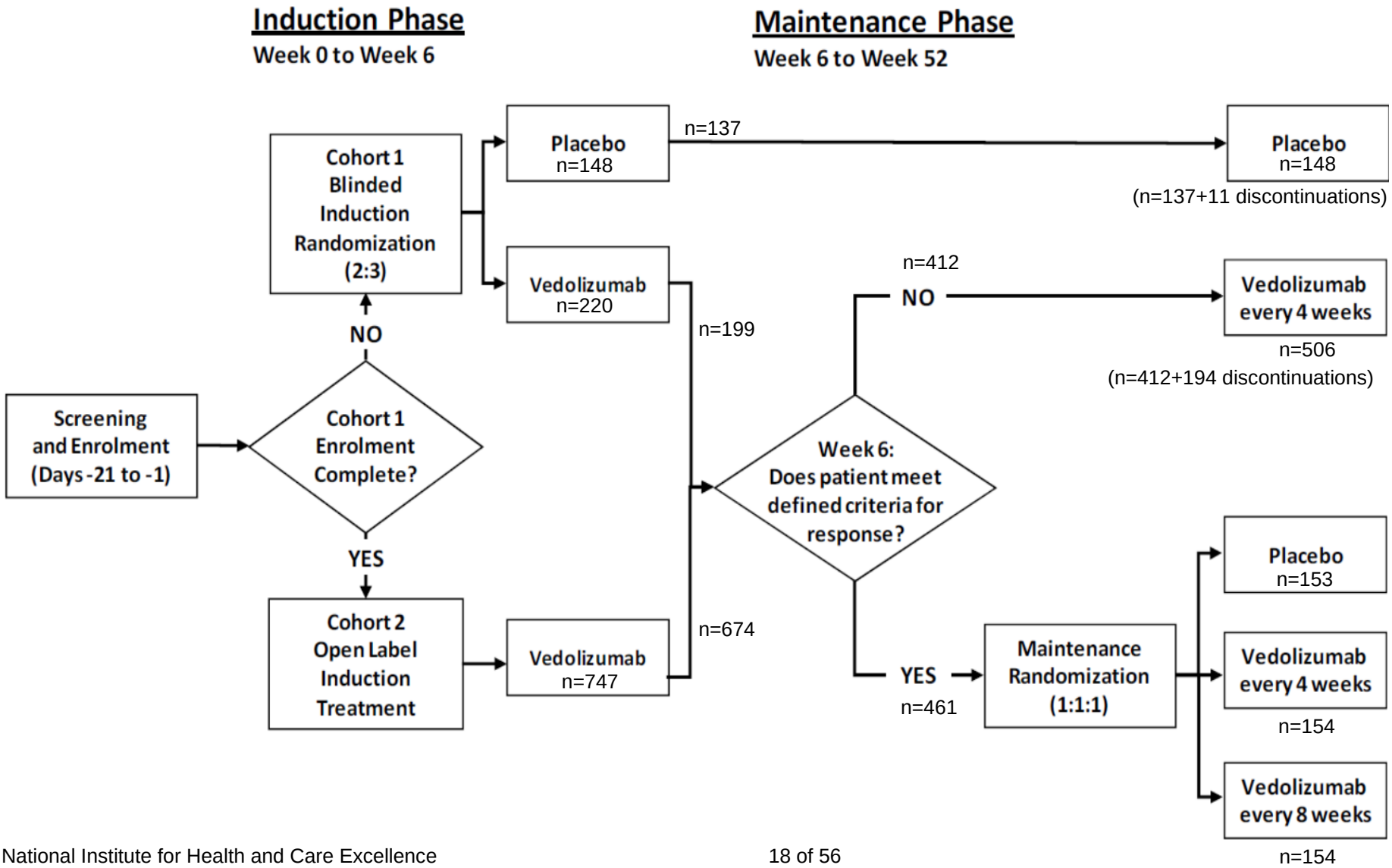
4.5 In the maintenance trial, patients from both cohorts who had a clinical response with vedolizumab at week 6 (that is, ≥70-point decrease in the CDAI score; n=461) were randomly assigned to continue in a blinded fashion to receive vedolizumab every 8 weeks (n=154), vedolizumab every 4 weeks (n=154), or placebo (n=153), for up to 52 weeks. Randomisation was stratified according to (1) participation in cohort 1 or 2 during induction, (2) concomitant use of glucocorticoids and (3) concomitant use of immunosuppressive agents, previous use of TNF-alpha inhibitors, or both. Patients from either cohort who did not have a clinical response at week 6 to vedolizumab induction therapy (n=412) received maintenance treatment with vedolizumab 300 mg every 4 weeks and were followed to week 52. Patients in the placebo group of cohort 1 who completed induction treatment (n=137) continued to receive placebo

and were also followed to week 52. At the end of the study, patients could enrol in GEMINI LTS (an ongoing, single-arm, open-label safety study).

4.6 In GEMINI II, the primary outcomes during induction were clinical remission (CDAI score ≤150 points) at week 6 and enhanced clinical response (≥100-point decrease in the CDAI score) at week 6. During maintenance, the primary outcome was clinical remission at week 52. Secondary outcomes included CDAI-100 response and corticosteroid-free remission at week 52. Safety outcomes were included and quality of life was assessed using the Inflammatory Bowel Disease Questionnaire (IBDQ), SF-36, and EQ-5D questionnaires (at screening and before dosing at weeks 6, 30 and 52.

4.7 The main analyses in the induction study of GEMINI II used the intention-to-treat population, which included all patients in cohort 1 who were randomised and received at least 1 dose of blinded study drug (n=148 in the placebo arm and n=220 in the vedolizumab arm). The maintenance study analyses also used the intention-to-treat population. The non-intention-to-treat population in the maintenance study was included in the safety assessment, comprising 814 patients who received vedolizumab and 301 patients who received placebo. This additionally included patients who received placebo in the induction phase who remained on placebo for the maintenance phase, and patients who did not respond to vedolizumab by week 6 of the induction study.

Figure 2 GEMINI II study design and patient flow



GEMINI III

4.8 GEMINI III is a 10-week study that evaluated the efficacy of vedolizumab compared with placebo. Patients were randomised to receive vedolizumab 300 mg (n=209) or placebo (n=207) at weeks 0, 2 and 6 and stratified according to previous TNF-alpha inhibitor failure (315 patients who had experienced TNF-alpha inhibitor failure and 101 patients who were TNF-alpha inhibitor naive), concomitant use of oral corticosteroids and the concomitant use of immunomodulators (6-mercaptopurine, azathioprine, or methotrexate). At the end of the study, patients could enrol in GEMINI LTS. All randomised patients received at least 1 dose of blinded study drug and were included in the intention-to-treat population.

4.9 The primary analysis of GEMINI III focused on the 315 people for whom a TNF-alpha inhibitor had failed. The primary outcome was clinical remission at week 6 (CDAI score 150 points or less). A secondary analysis evaluated the overall population including patients naive TNF-alpha inhibitor treatment). Secondary outcomes included clinical remission at week 6 in the overall population, clinical remission at week 10 in both the TNF-alpha inhibitor failure and overall populations, sustained clinical remission (CDAI 150 points or less at both week 6 and week 10) in both the TNF-alpha inhibitor failure and overall populations, and safety outcomes. Other outcomes included health-related quality of life, as shown by change from baseline in IBDQ, SF-36, and EQ-5D scores at weeks 6 and 10 in the TNF-alpha inhibitor failure population and in the entire study population.

ERG comments

4.10 The ERG considered the company's methods for performing the clinical effectiveness systematic review to be largely appropriate and was satisfied that all relevant vedolizumab studies had been included in the company's submission.

4.11 The ERG noted that GEMINI II and III assessed response in the induction phase at 6 weeks, and that this did not correspond with the recommended

dosage in vedolizumab's summary of product characteristics. The ERG considered this to be earlier than in routine clinical practice in England because it had received expert clinical advice that response to induction therapy was typically assessed at 10–14 weeks (although it could be earlier, depending on recommended schedules). It considered that this meant the GEMINI II population in the maintenance phase does not fully represent the population expected to receive the treatment in clinical practice in England. It believed that this could lead to an overestimation of maintenance treatment effect, if these patients are also more likely to maintain a response when in remission. The ERG also noted that very few of the study sites in GEMINI II and GEMINI III were in the UK.

Clinical trial results

GEMINI II –induction phase

4.12 The company stated that the demographic and baseline characteristics for patients in GEMINI II in the induction phase were similar in the placebo and vedolizumab groups (see table 6.3.4.1 on page 84 of the company's submission). The results for the primary outcomes of GEMINI II are shown in Table 3. At week 6, clinical remission rates were significantly higher in patients receiving vedolizumab than in patients receiving placebo (14.5% and 6.8%, p=0.02). There was no significant difference between the vedolizumab and placebo groups in enhanced clinical response at week 6 (31.4% compared with 25.7% respectively; p=0.23).

Table 3 GEMINI II induction primary outcomes: clinical remission and enhanced clinical response at week 6 (ITT population)

	Clinical remission[a]		Enhanced clinical response[b]	
	Placebo n=148	Vedolizumab n=220	Placebo n=148	Vedolizumab n=220
Number (%) achieving endpoint 95% CI	10 (6.8) (2.7, 10.8)	32 (14.5) (9.9, 19.2)	38 (25.7) (18.6, 32.7)	69 (31.4) (25.2, 37.5)
Difference from placebo 95% CI for difference from placebo P-value for difference from placebo	7.8 (1.2, 14.3) 0.0206		5.7 (-3.6, 15.0) 0.2322	

Adjusted relative risk (95% CI)	2.1 (1.1, 4.2)	1.2 (0.9, 1.7)

CI, confidence interval
a Clinical remission is defined as CDAI score ≤ 150 points.
b Enhanced clinical response is defined as a minimum 100-point reduction from baseline in CDAI score.

Source: Table 6.5.3.1 on page 103 of the company's submission

4.13 The company undertook pre-specified subgroup analyses for the primary outcomes, investigating the influence of baseline characteristics on treatment effect. For vedolizumab-treated patients compared with placebo-treated patients, the analyses showed a between-treatment difference in clinical remission at week 6 of 8.2% in the TNF-alpha inhibitor-naive subgroup and 6.2% in the TNF-alpha inhibitor-failure subgroup. It stated that, in general, analyses of clinical remission in subgroups of patients according to baseline concomitant corticosteroid or immunomodulator use showed trends that were supportive of the primary efficacy analysis population as a whole.

4.14 The manufacturer presented results for the changes in health-related quality of life from baseline to week 6 in the vedolizumab group (n=211) and placebo group (n=146) in the overall population. The company advised that a decrease of at least 0.3 points in the EQ-5D score represented a clinically meaningful improvement in health-related quality of life. Adjusted mean change in EQ-5D score from baseline (95% confidence interval) was −0.5 (−0.7 to −0.3) in vedolizumab-treated patients and −0.3 (−0.5 to −0.0) in placebo-treated patients, giving a difference in adjusted change of –0.2 (−0.5 to 0.1). The company noted that the 95% confidence interval for the difference between the 2 groups included 0 (that is, the difference was not statistically significant). The company did not present change in EQ-5D scores for the TNF-alpha inhibitor-naive and TNF-alpha inhibitor-failure subgroups. For further health-related quality of life results from the induction phase of GEMINI II, including IBDQ and SF-36 scores, see section 6.5 on pages 106–108 of the company's submission.

GEMINI II – maintenance phase

4.15 In the intention-to-treat population in the maintenance study, there were significantly higher rates of clinical remission (CDAI score 150 points or less) at week 52 in patients treated with vedolizumab every 8 weeks or every 4 weeks, compared with patients treated with placebo (Table 4). In patients receiving vedolizumab every 8 weeks, the treatment difference from placebo was 17.4% (95% CI 7.3 to 27.5, p=0.0007) and in patients receiving vedolizumab every 4 weeks, it was 14.7% (95% CI 4.6 to 24.7, p=0.0042).

Table 4 GEMINI II maintenance primary outcome: clinical remission at week 52 (ITT population)

	Placebo n=153	Vedolizumab Q8W n=154	Vedolizumab Q4W n=154
Number (%) achieving endpoint 95% CI	33 (21.6) (15.1, 28.1)	60 (39.0) (31.3, 46.7)	56 (36.4) (28.8, 44.0)
Difference from placebo 95% CI for difference from placebo P-value for difference from placebo		17.4 (7.3, 27.5) 0.0007	14.7 (4.6, 24.7) 0.0042
Adjusted relative risk 95% CI for relative risk		1.8 (1.3, 2.6)	1.7 (1.2, 2.4)
CI, confidence interval			

Source: Table 6.5.3.4 on page 109 of the company's submission

4.16 Clinical remission rates were higher for patients who received vedolizumab every 4 or 8 weeks compared with those who received placebo regardless of prior exposure to a TNF-alpha inhibitor (Table 5). In the TNF-alpha inhibitor-failure group, the treatment difference was 15.2% (95% CI 3.0 to 27.5) between placebo and vedolizumab every 8 weeks and 14.5% (95% CI 2.0 to 26.9) between placebo and vedolizumab every 4 weeks. In the TNF-alpha inhibitor-naive group, the treatment difference was 24.8% (95% CI 8.9 to 40.6) between placebo and vedolizumab every 8 weeks, and 19.7% (95% CI 4.2 to 35.2) between placebo and vedolizumab every 4 weeks.

Table 5 Clinical remission at week 52 by prior TNF-alpha inhibitor status

Patients with prior TNF-alpha inhibitor failure[a]			
	Vedolizumab every 8 weeks (n=82)	Vedolizumab every 4 weeks (n=77)	Placebo (n=78)
Clinical remission, %	28.0	27.3	12.8
Between-group difference vs Placebo (95% CI)	15.2 (3.0 to 27.5)	14.5 (2.0 to 26.9)	
TNF-alpha inhibitor-naive patients			
	Vedolizumab every 8 weeks (n=66)	Vedolizumab every 4 weeks (n=71)	Placebo (n=71)
Clinical remission, %	51.5	46.5	26.8
Between-group difference vs Placebo (95% CI)	24.8 (8.9 to 40.6)	19.7 (4.2 to 35.2)	
CI, confidence interval; TNF, tumour necrosis factor			

Source: Table 6.5.3.6 on page 112 of the company's submission

4.17 The manufacturer presented results for the changes in health-related quality of life from baseline to week 52 in the groups receiving vedolizumab every 8 weeks (n=79), vedolizumab every 4 weeks (n=92) and placebo (n=81) in the overall population. Adjusted mean change in EQ-5D score from baseline (95% confidence interval) was −1.5 (−1.8 to −1.2) in patients receiving vedolizumab every 8 weeks, −1.4 (−1.7 to −1.1) in patients receiving vedolizumab every 4 weeks and −1.0 (−1.3 to −0.7) in patients receiving placebo. The mean difference in adjusted change from baseline compared with placebo was –0.5 (−0.9 to −0.1) for vedolizumab every 8 weeks and –0.4 (−0.8 to 0.0) for vedolizumab every 4 weeks. The company considered the change in all 3 groups to be clinically meaningful. For further details of these and other health-related quality of life outcomes, see section 6.5 on pages 113–117 of the company's submission.

GEMINI III

4.18 The company noted that most baseline demographics in GEMINI III were similar between the treatment groups (see table 6.3.4.2 on page 86 of the

company's submission).There were 2 exceptions: vedolizumab-treated patients had a slightly higher baseline CDAI score compared with the placebo group (313.9 vs 301.3, p=0.015), and more placebo-treated patients (51%) were under 35 years of age compared with vedolizumab-treated patients (42%). For the primary endpoint of clinical remission at week 6 in people for whom a TNF-alpha inhibitor has failed, no statistically significant difference was observed between the vedolizumab (15.2%) and placebo (12.1%) groups (Table 6). However, an exploratory analysis found a higher proportion of these patients experienced clinical remission at week 10 with vedolizumab compared with placebo (26.6% versus 12.1%, p=0.0012 [nominal p-value]).

Table 6 GEMINI III primary outcome and exploratory analysis: clinical remission in TNF-alpha inhibitor failure population (ITT population)

	Week 6		**Week 10**	
	Placebo n=157	Vedolizumab n=158	Placebo n=157	Vedolizumab n=158
Clinical remission, n (%) 95% CI	19 (12.1) (7.0, 17.2)	24 (15.2) (9.6, 20.8)	9 (12.1) (7.0, 17.2)	42 (26.6) (19.7, 33.5)
Difference from placebo (95% CI) P-value		3.0 (-4.5, 10.5) 0.433		14.4 (5.7, 23.1) 0.0012
Adjusted relative risk 95% CI		1.2 (0.7, 2.2)		2.2 (1.3, 3.6)
CI, confidence interval; TNF, tumour necrosis factor				

Source: Table 6.5.3.11 on page 119 of the company's submission

4.19 An exploratory analysis of the overall population including patients naive to TNF-alpha inhibitors showed that clinical remission occurred in a higher proportion of patients receiving vedolizumab than placebo at week 6 (19.1% versus 12.1%, p=0.0478 [nominal p-value]) and week 10 (28.7% versus 13.0%, p<0.0001 [nominal p-value]) (Table 7).

Table 7 GEMINI III exploratory analysis: clinical remission in overall population (ITT population)

	Week 6		**Week 10**	
	Placebo n=207	Vedolizumab n=209	Placebo n=207	Vedolizumab n=209
Clinical remission, n (%) 95% CI	25 (12.1) (7.6, 16.5)	40 (19.1) (13.8, 24.5)	27 (13.0) (8.5, 17.6)	60 (28.7) (22.6, 34.8)
Difference from placebo 95% CI P-value		6.9 (0.1, 13.8) 0.0478		15.5 (7.8, 23.3) < 0.0001
Adjusted relative risk 95% CI		1.6 (1.0, 2.5)		2.2 (1.4, 3.3)
CI, confidence interval; TNF, tumour necrosis factor				

Source: Table 6.5.3.12 on page 120 of the company's submission

4.20 The manufacturer provided results for change in health-related quality of life from baseline to weeks 6 and 10 for patients in the TNF-alpha inhibitor failure population. At week 6, adjusted mean change in EQ-5D score (95% CI) was −0.4 (−0.6 to −0.2) in patients who received vedolizumab (n=158) and −0.1 (−0.3 to 0.1) in patients who received placebo (n=149), giving a mean difference in adjusted change from baseline of −0.2 (−0.5 to 0.1). At week 10, adjusted mean change in EQ-5D score (95% CI) was −0.6 (−0.8 to −0.4) in patients who received vedolizumab (n=152) and −0.1 (−0.4 to 0.1) in patients who received placebo (n=149), giving a mean difference in adjusted change from baseline of −0.5 (−0.8 to −0.2). The company considered these decreases in the EQ-5D scores to be clinically meaningful improvements and noted that the 95% CI for the difference in the EQ-5D scores between vedolizumab and placebo did not include 0 at week 10, demonstrating improvements in HRQL over placebo. Similar results were seen in the overall study population.

ERG comments

4.21 The ERG observed that although the primary outcomes in GEMINI II had been achieved, this was not the case in GEMINI III and that the company had acknowledged that the statistical evaluation of GEMINI III's secondary endpoints was exploratory.

4.22 The ERG noted high attrition rates in the maintenance phase of GEMINI II, which it considered could limit the robustness of the efficacy and safety data and pose a serious threat to external validity. It highlighted that high rates of discontinuation were seen across all treatment groups (58% [89/153] in the placebo arm, 53% [81/154] in the vedolizumab every 8 weeks arm and 47% [72/154] in the vedolizumab every 4 weeks arm).

4.23 The ERG had concerns about uncertainties in the clinical evidence related to treatment duration and generalisability to the UK population (including prognostic factors that may have affected response):

- There were relatively high levels of faecal calprotectin in both GEMINI II and GEMINI III, indicating that patients may have had significant active inflammation.
- There was a large number of US-based study sites but apparently few UK-based study sites (and therefore few UK patients).
- In the USA, failure of either an immunomodulator (6-mercaptopurine or azathioprine) or a TNF-alpha inhibitor was required, but failure of corticosteroids alone was sufficient for study entry outside the USA.
- The ERG received clinical advice that the concomitant conventional therapy used in the GEMINI trials may not wholly reflect that used in clinical practice in England.
- Response in the induction phase was assessed earlier than in clinical practice in England (see section 4.11).

4.24 The ERG noted that the long-term efficacy and safety of vedolizumab is unknown because treatment duration in GEMINI II was 52 weeks, followed by enrolment in the ongoing GEMINI LTS study.

Network meta-analyses

4.25 In the absence of direct trial evidence, the company undertook a systematic review and network meta-analyses to calculate relative treatment effects for vedolizumab compared with other biological

therapies (that is, adalimumab and infliximab) for treating moderate to severe Crohn's disease. Depending on available data, the company compared outcomes for clinical remission (CDAI score less than 150), clinical response (drop in CDAI score of 70 or greater), enhanced clinical response (drop in CDAI score of 100 or greater) and discontinuation because of adverse events.

4.26 The company identified 10 studies providing information on vedolizumab, infliximab and adalimumab and included 6 of these in its primary analysis (Table 8). It considered that the 4 other studies were not comparable because of lack of detail according to previous TNF-alpha inhibitor exposure or because patients were re-randomised based on remission rather than on response.

Table 8 Trials in the company's network meta-analyses (primary analysis)

Trial	Population	Study phase	Adalimumab	Infliximab	Placebo	Vedolizumab
CLASSIC-I	Naive	Induction	✓	–	✓	–
Sandborn, 2007	Experienced	Induction	✓	–	✓	–
Targan, 1997	Naive	Induction	–	✓	✓	–
GEMINI II	Naive + failure	Induction and maintenance	–	–	✓	✓
GEMINI III	Naive + failure	Induction	–	–	✓	✓
ACCENT I	Naive	Maintenance	–	✓	✓	–

4.27 The company conducted Bayesian fixed-effects and random-effects analyses for the following groups in its primary analysis:

- TNF-alpha inhibitor–naive patients receiving induction treatment
- TNF-alpha inhibitor–naive patients receiving maintenance treatment
- TNF-alpha inhibitor–experienced/failure patients receiving induction treatment.

Network diagrams are presented in figures 6.7.3.1–6.7.3.4 on pages 136–137 of the company's submission. The company validated its Bayesian

analyses by running equivalent frequentist models, and observed that the point estimates and credible intervals closely matched.

4.28 The company advised that it was not able to provide all relevant indirect comparisons, and that caution should be used when interpreting some results because of data limitations:

- It was not possible to construct a network for maintenance treatment in the TNF-alpha inhibitor-experienced/failure group.
- In the network of TNF-alpha inhibitor-failure patients receiving induction treatment:
  - None of the trials included infliximab.
  - The vedolizumab studies included patients with inadequate response (that is, primary non-responders), loss of response or intolerance to a TNF-alpha inhibitor whereas the comparator study included only those who lost response or who were intolerant to TNF-alpha inhibitor therapy.
- Results for the mixed population (that is, all patients regardless of TNF-alpha inhibitor status) were provided as a secondary analysis. The company noted that the placebo response rates in GEMINI II were inexplicably higher than in the other studies and considered that this could bias the results against vedolizumab. It therefore considered it more appropriate to use the sub-population analyses, rather than the mixed population ones that may be affected by confounding factors.

4.29 The company used the results for clinical remission and clinical response from the TNF-alpha inhibitor-naive population network meta-analysis in its economic analyses. The company did not state in its submission if they were results from the Bayesian or frequentist analyses. Results for the TNF-alpha inhibitor-naive population for induction treatment are reported in Table 9. Only results for the doses relevant to the company's economic model are presented.

Table 9 Summary of network meta-analysis for induction treatment: TNF-alpha inhibitor-naive population (odds ratio versus placebo [95% CrI])

		Vedolizumab 300 mg	Adalimumab 80/40	Infliximab 5 mg/kg
Clinical response (drop in CDAI ≥ 70)	Week 6 for vedolizumab	1.8* (1.1, 3.0)	2.5* (1.3, 4.8)	25.0* (6.2, 128.0)
	Week 6 for vedolizumab (Targan et al., 1997 removed)	1.8* (1.1, 3.0)	2.5* (1.3, 5.0)	NA
	Week 10 for vedolizumab	1.9* (1.2, 3.1)	2.5* (1.3, 4.9)	25.0* (6.3, 118.0)
Clinical remission	Week 6 for vedolizumab	2.9* (1.5, 6.0)	2.3* (1.0, 6.2)	26.0* (4.0, 425.0)
	Week 6 for vedolizumab (Targan et al., 1997 removed)	3.0* (1.6, 6.2)	2.4* (1.0, 5.8)	NA
	Week 10 for vedolizumab	2.7* (1.4, 5.4)	2.3* (1.0, 5.9)	25.0* (4.1, 451.0)
Discontinuation due to adverse events		1.4 (0.3, 7.4)	0.4 (0.0, 5.6)	NA

CDAI, Crohn's Disease Activity Index; CrI, credible interval; NA, not applicable
* Significant versus placebo
Source: taken from table 6.7.6.1 on page 142 of the company's submission. The network meta-analysis was based on CLASSIC I, GEMINI II and III, and Targan et al.

4.30 The results for the TNF-alpha inhibitor-naive population receiving maintenance treatment are reported in Table 10. Only results for the dosages relevant to the company's economic model are presented.

Table 10 Summary of network meta-analysis for maintenance treatment: TNF-alpha inhibitor-naive population (odds ratio versus placebo [95% CrI])

Outcome	Vedolizumab every 8 weeks	Infliximab 5 mg/kg
Clinical response (drop in CDAI ≥ 70)	2.6* (1.3, 5.0)	3.4* (1.9, 6.5)
Clinical remission	2.9* (1.4, 6.1)	2.5* (1.3, 5.2)
Discontinuation due to adverse events	0.5 (0.1, 1.8)	6.6* (2.8, 20.0)

CDAI, Crohn's Disease Activity Index; CrI, credible interval; TNF, tumour necrosis factor
* Significant versus placebo
Source: taken from table 6.7.6.2 on page 144 of the company's submission. The network meta-analysis was based on ACCENT 1 and GEMINI II

4.31 For further results of the company's network meta-analyses, including those for the other patient populations, see section 6.7.6 on pages 146–150 of the company's submission.

ERG comments

4.32 The ERG was satisfied that all relevant studies had been included in the network meta-analysis, apart from data from a trial by Watanabe et al. (2012) for the induction period in TNF-alpha inhibitor-naive patients. It believed that the impact of this exclusion was likely to be relatively small because it was a small study (n=57).

4.33 The ERG noted that although the company had stated that Bayesian and frequentist fixed-and random-effects models were conducted, not all models were reported within the company submission. The ERG considered that the results of the network meta-analyses may underestimate the uncertainty in treatment effects because fixed-effects models were used, and that there was clear evidence of heterogeneity among the trials included in the network meta-analyses.

4.34 The ERG noted that there was variation between studies in the inclusion of patients with strictures and a lack of clarity around the proportion of patients with fistulising disease. It also noted that the studies did not include patients with the upper range of severe disease (CDAI score greater than 450) The ERG concluded that the generalisability of the results to these groups of patients was unclear.

4.35 The ERG noted that the mixed population analysis (presented by the company as a secondary analysis) included trials with differential proportions of characteristics that are thought to be treatment-modifying (that is, the proportion of TNF-alpha inhibitor failure populations), making it difficult to interpret the results and to generalise to any particular population. It concluded that the mixed population analyses did not represent a clinically meaningful population.

4.36 The ERG considered that the TNF-alpha inhibitor failure/experienced network may have overestimated efficacy for adalimumab because primary non-responders to TNF-alpha inhibitor therapy were excluded from the adalimumab study but not the vedolizumab studies. It agreed

with the company that the analysis would not give a robust assessment of comparative treatment effects because of differences in patient populations.

4.37 The ERG concluded that the TNF-alpha inhibitor-naive population was the best match to patients presenting after failure of conventional therapy in clinical practice in England. It also concluded the following about the company's network meta-analysis results:

- Induction phase:
  - This group was the best match to patients presenting after failure of conventional therapy
  - When assessing response during induction, the ERG preferred using 10-week data to 6-week data because it had received clinical expert advice that response is typically assessed at 10–14 weeks in clinical practice, and because of the recommended dosing in the marketing authorisation.
  - If the Targan et al. study comparing infliximab with placebo as an induction therapy was included in the network (which the ERG considered to be appropriate), treatment with infliximab led to significantly higher rates of clinical response and clinical remission than vedolizumab.
  - Regardless of the inclusion of Targan et al., there is insufficient evidence to conclude there is a difference in efficacy between vedolizumab and adalimumab.
- Maintenance phase:
  - All of the presented analyses had limitations, for example patients were selected to enter the maintenance phase on the basis of earlier assessment than would commonly be done in clinical practice, which the ERG considered could affect estimates of efficacy and limit generalisation to patients who take longer to respond.
  - The ERG noted that the company had not presented maintenance data including adalimumab in its primary analyses because it had

excluded CLASSIC II (which compared adalimumab with placebo). It considered that the network meta-analyses including CLASSIC II showed that the relative efficacy of vedolizumab and adalimumab was uncertain and that it was likely that vedolizumab was less effective than infliximab.

- In the network meta-analysis excluding CLASSIC II, vedolizumab appeared significantly better than infliximab for discontinuations because of adverse events (though the ERG advised that this should be interpreted with reference to the numbers who discontinued for each treatment in the induction period). The ERG noted that the statistical significance of the difference in response between vedolizumab and infliximab 5 mg was not reported by the company, and that there was no statistically significant difference in remission between vedolizumab and infliximab.
- The ERG was not convinced by the company's argument for excluding CLASSIC II, and believed that networks including and excluding it should be examined. It also considered that a better approach could have been using a random-effects analysis to formally consider heterogeneity, and that it may have been valid to consider that no network was possible because of clinical heterogeneity.

Adverse effects of treatment

4.38 In the 52-week GEMINI II study, 706 patients (87%) taking vedolizumab and 246 patients (82%) taking placebo experienced an adverse event. There was a higher proportion of patients who had a serious adverse event in the vedolizumab group than in the placebo group (24.4% and 15.3% respectively). Serious infection affected 45 patients (5.5%) taking vedolizumab and 9 patients (3.0%) taking placebo. The most common adverse event was exacerbation of Crohn's disease, which occurred in 164 patients (20.1%) in the vedolizumab group and 65 patients (21.6%) in the placebo group.

4.39 In the 10-week GEMINI III study, 117 patients (56%) taking vedolizumab and 124 patients (60%) taking placebo experienced an adverse event. Serious adverse events occurred in 13 patients (6%) taking vedolizumab and 16 patients (8%) taking placebo. Less than 1% of patients taking vedolizumab and 0% of patients taking placebo had a serious infection. Common adverse events in the vedolizumab and placebo groups were Crohn's disease (3% and 10%), headache (5% and 7%), nausea (6% and 2%) and fever (3% and 6%).

4.40 As well as safety data from GEMINI II and III, the company's submission included safety data from 3 additional sources: GEMINI LTS, a pooled safety analysis of GEMINI I (ulcerative colitis) and GEMINI II, and an integrated safety analysis of 6 vedolizumab randomised placebo-controlled trials in inflammatory bowel disease (ulcerative colitis and Crohn's disease). For details of these other safety studies, see section 6.9.2 on pages 162–166 of the company's submission. The company noted that no cases of progressive multifocal leukoencephalopathy had been identified in any of the safety populations.

ERG comments

4.41 The ERG noted that the trial of vedolizumab maintenance therapy was not of sufficient size or duration to estimate the risk of uncommon adverse events.

5 Cost-effectiveness evidence

5.1 The company submitted a de novo economic model that compared vedolizumab with conventional non-biological therapy and with TNF-alpha inhibitors in patients with moderately to severely active Crohn's disease. In its response to clarification, the company provided an updated model that addressed some of the issues and uncertainties that had been identified (see section 5.30 for details).

Model structure

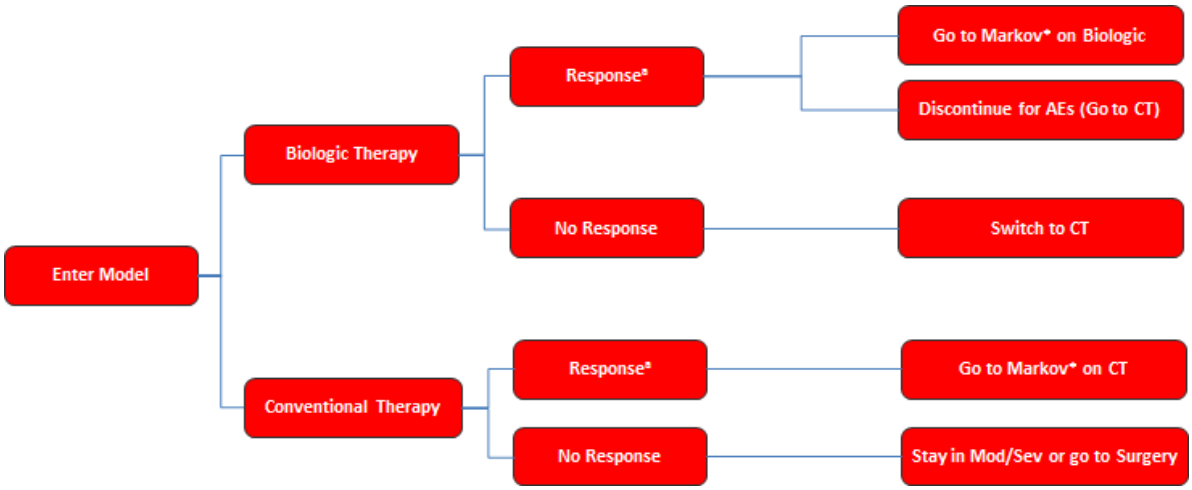
5.2 The company used two-part model to capture the different phases of treatment in the clinical trials: a decision-tree for the induction phase and a Markov model (as a cohort transition model) for the maintenance phase. The Markov model was consistent with a previous model by Bodger et al., 2009 that compared infliximab and adalimumab for treating Crohn's disease. It had a cycle length of 6 weeks in the induction phase and 8 weeks during the maintenance phase (with half-cycle correction) and a time horizon of 10 years. A discount rate of 3.5% was applied to costs and health benefits and the analysis was conducted from an NHS perspective (the company explained that personal social services were expected to be minimal in this population).

5.3 In the induction phase, patients started treatment with vedolizumab, infliximab, adalimumab or conventional non-biological therapy to induce a response (defined as a drop of at least 70 points of the CDAI score) (Figure 3). The company noted that not all of the biological therapies shared the same duration of induction in their trials and advised the 6-week duration phase was chosen to be consistent with the vedolizumab clinical trials. It stated that that the dosages in the induction phase were vedolizumab 300 mg at weeks 0 and 2, infliximab 5 mg/kg at weeks 0 and 2 and adalimumab 80 mg at week 0 followed by 40 mg at week 2, 4 and 6. Conventional non-biological therapy comprised aminosalicylates, corticosteroids and immunomodulators. Standard doses were assumed and the treatment mix was based upon the report of the UK Inflammatory Bowel Disease Audit Steering Group (Royal College of Physicians, 2013).

5.4 Patients who entered the induction phase on a biological therapy (that is, all treatments except conventional non-biological therapy) and responded to treatment at 6 weeks entered the Markov model for maintenance therapy and continued to receive biological therapy (unless they had stopped treatment because of adverse events). If their condition did not respond, or if they had stopped treatment because of adverse events,

they switched to conventional non-biological therapy. Patients who entered the induction phase on conventional non-biological therapy could respond to treatment and enter the Markov model for conventional non-biological therapy. If their condition did not respond, they were assumed to remain in moderate–severe disease for the remainder of the model time horizon or until surgery. Regardless of response status at the end of the induction phase, patients taking conventional non-biological therapy remained on this treatment for the remainder of the model time horizon.

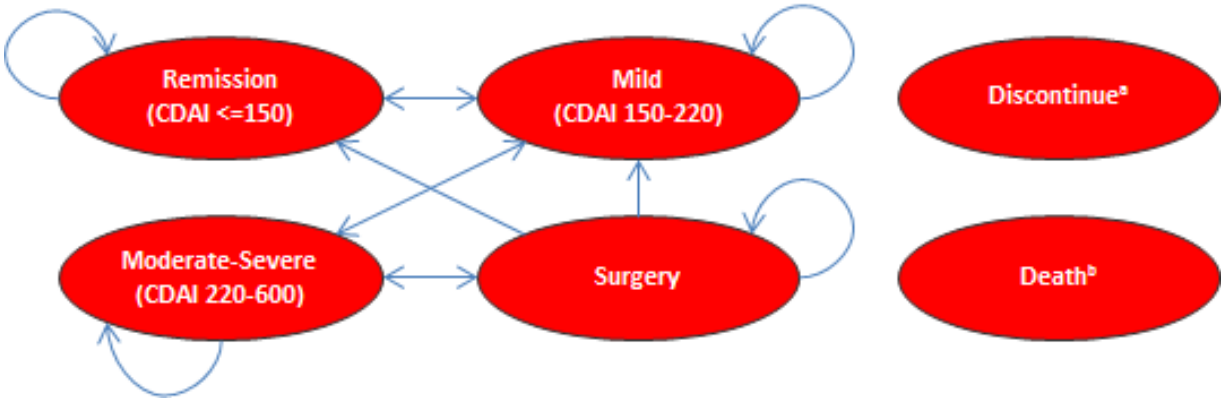
Figure 3 Company's economic model structure for the induction phase



5.5 The modelled health states in the Markov model for maintenance therapy were remission (CDAI score less than 150), mild (CDAI 150–220), moderate–severe (CDAI 220–600), surgery and death (Figure 2). Patients could transition between each of the 4 disease severity health states (remission, mild, moderate-severe, and surgery) or experience death. It was assumed that treatment with a biological therapy was limited to 1 year, when patients switched to conventional non-biological therapy. If patients were having biological therapy, they could stop treatment because of loss of response or adverse events (whereas conventional non-biological therapy was assumed to continue until surgery or the end of the model's time horizon). In the moderate–severe health state, patients stopped treatment after 1 year because of lack of response and switched to conventional non-biological therapy or surgery. After surgery, patients could transition to active treatment in a CDAI-based health state

or remain in the surgery health state. The model used an age- and sex-specific mortality risk, which was adjusted for time spent in each health state.

Figure 4 Company's economic model structure for the maintenance phase



ERG comments

5.6 The ERG was largely satisfied with the company's explanation about why it chose its model structure (adapted from Bodger et al.). However, the ERG considered the quality of the company's model to be generally poor, unnecessarily complex in its implementation and lacking detail on the sources of inputs and the derivation of the transition matrices.

5.7 The ERG expressed concerns about the structure of the company's model in 4 main areas:

- It did not capture that Crohn's disease is a relapsing and remitting condition (that is, patients may experience exacerbations and may improve spontaneously). The company's model assumed that patients who did not respond to conventional non-biological therapy at week 6 remained in the non-responder state and had moderate to severe Crohn's disease until death or surgery, which is overly pessimistic.
- Surgery was modelled as a single health state, which may be overly simplistic because subsequent surgery is likely to depend on the type of initial surgery. However, the ERG recognised the possible lack of data in this area and believed that the impact on results would be minimal.

- There were difficulties associated with parameterising the company's chosen structure, including how the transition probabilities were derived and how the model predictions were calibrated (see section 5.38).
- Some of the key structural assumptions that influenced the derivation of transition probabilities were considered debatable. These included:
  - Non-responders were assumed to have moderate to severe disease, which the ERG considered to be inappropriate. This is because a non-responder could have a drop in CDAI score of less than 70 points that would mean their disease would be re-classified as mild.
  - Except for continuing biological treatment after induction, no distinction was made between responders with moderate to severe Crohn's disease and non-responders. The ERG believed that outcomes would be likely to differ between these groups.
  - The definition of response was taken from the clinical trials, which may have limited relevance to clinical practice in England (because CDAI score is not routinely used).
  - The same treatment duration was assumed for all therapies for the induction phase (6 weeks), which led to discrepancies in costing, cycle length and efficacy in the company's model.
  - All patients still receiving TNF-alpha inhibitor therapy at approximately 1 year were assumed to switch to conventional non-biological therapy. Based on the recommendations in NICE technology appraisal guidance 187, the ERG considered that a discontinuation rule may be appropriate for patients in remission, but not for patients who are not in stable clinical remission.
  - It was assumed that there was no increase in relapse after withdrawal of biological treatment in patients in the remission or mild disease health states, which was not aligned with clinical expert opinion received by the ERG.
  - The efficacy of conventional non-biological therapy was assumed to be independent of previous biological treatment (that is, conventional

non-biological therapy was equally effective in patients who had previously received biological treatment as those who had not). The ERG considered that this would be unlikely.

- Discontinuation owing to lack of efficacy during the maintenance phase was not included in the company's economic model. Based on its interpretation of the data from the GEMINI trials, the ERG believed this should be incorporated.

5.8 The ERG noted that the duration of induction with the biological therapies was not always in line with UK licensing and clinical practice, meaning not all studies delivered a full induction dose:

- Vedolizumab was given in the model in 2 doses at weeks 0 and 6 with assessment at week 6. The ERG considered it more appropriate to follow the marketing authorisation more closely by using the induction regimen from GEMINI III (that is, doses at weeks 0, 2 and 6 with assessment at week 10).
- Adalimumab was administered in the model at 80 mg at week 0, then 40 mg at weeks 2, 4 and 6 with assessment at week 6. The ERG considered it preferable to administer 80 mg at week 0 and 40 mg at week 2, with assessment at week 4, which was more consistent with adalimumab's marketing authorisation.
- The ERG was satisfied with the infliximab induction regimen used in the company's model because this reflected the marketing authorisation and the efficacy data used in the company's model.

Model details

Population

5.9 The company's model included patients with moderately to severely active Crohn's disease (defined as a Crohn's Disease Activity Index [CDAI] score of 220–450) who have had an inadequate response with, lost response to, or are intolerant to either conventional non-biological therapy or TNF-alpha inhibitors. The definition of TNF-alpha inhibitor failure was consistent with that used in GEMINI II and III: persistently active disease

despite at least one 4-week induction regimen of infliximab, or symptom recurrence during maintenance (after previous clinical benefit), or history of intolerance of infliximab. The company defined 3 patient groups in its model:

- Mixed population (includes both TNF-alpha inhibitor–naive and TNF-alpha inhibitor–failure patients, representing the intention to treat trial populations)
- TNF-alpha inhibitor-naive population
- TNF-alpha inhibitor-failure population (both primary failure [no response] and secondary failure [loss of response after initially responding]).

The company compared vedolizumab with conventional non-biological therapy in all of these populations but said it compared vedolizumab with the other biological treatments only in a TNF-alpha inhibitor–naive population because of limitations in the data (see section 4.28). The model also allowed vedolizumab's cost-effectiveness to be assessed based on disease severity at baseline, with moderate and severe disease defined as CDAI score 220–330 and greater than 330 respectively.

ERG comments

5.10 The ERG was unclear how results from the mixed intention-to-treat population could be interpreted. It believed that patients who have previously received TNF-alpha inhibitors and those who are TNF-alpha inhibitor-naive are 2 distinct patient groups with different characteristics and likelihood of responding to treatment and that they should be interpreted separately. The ERG was satisfied that analyses according to disease severity may be informative, despite not being defined in the NICE final scope. However, the ERG was unable to confirm the results of these analyses because it could not verify the calibrated transition probabilities and it was unsure how the clinical data had been estimated in the company's model.

Clinical parameters and transition probabilities

5.11 The company's model was primarily built upon patients transitioning through health states of differing disease severity according to CDAI score. Transition probabilities used in the company's model were calibrated using the percentage of patients in the remission and mild health states after induction and 1 year, which were calibrated with the clinical trial data. Transition probabilities from surgery to other health states were obtained from the study by Bodger et al., 2009. For full details of the transition probabilities used in the company's submission, see tables 7.3.2.1–7.3.2.3 on pages 226–228 of the company's submission.

5.12 The company's model included patient baseline characteristics for age, sex and body weight, which were mean values from the pooled data in the network meta-analyses. Treatment efficacy included response and remission data for the induction phase, and the probability of being in remission or having mild disease at the end of 1 year (the maintenance phase of the GEMINI II study):

- For comparisons between vedolizumab and conventional non-biological therapy in the mixed and TNF-alpha inhibitor-failure populations, the company used head-to-head results of GEMINI II and GEMINI III to estimate treatment efficacy.
- For the comparisons between vedolizumab and the other biological therapies (infliximab and adalimumab) in the TNF-alpha inhibitor-naive population, the clinical parameters in the company's updated model were derived from the network meta-analyses provided in the company's clarification response (see section 5.29). These superseded the original analyses in which the clinical parameters for infliximab and adalimumab were derived from the network meta-analyses and those for vedolizumab (and conventional non-biological therapy) were derived from GEMINI II and III.

The company's economic model defined response as a decrease in CDAI score of 70 or more from baseline and remission as a CDAI score of 150

or less. The company assumed that, for all treatments, there was an equal percentage of patients who responded but did not move out of the moderate–severe health state.

5.13 The company estimated the efficacy of each treatment by estimating odds ratios using the response and remission data from the network meta-analyses (see sections 4.29 and 4.30) or from pooled trial data. These odds ratios were then used to estimate the percentage of patients in each health state at the end of the induction period and at the end of the maintenance period. Table 11 shows the probabilities used for response and remission in the mixed population, TNF-alpha inhibitor-naive population and TNF-alpha inhibitor-failure population. Table 12 shows the patient populations according to disease severity (mixed population with moderate disease, mixed population with severe disease, TNF-alpha inhibitor-naive population with moderate disease, TNF-alpha inhibitor-naive population with severe disease, TNF-alpha inhibitor failure-population with moderate disease and TNF-alpha inhibitor-failure population with severe disease). The probability of surgery was assumed to be the same across the different patient populations in the induction phase (2.03%) and maintenance phase (2.7%).

Table 11 Probability of response and remission in the company's economic model: mixed, TNF-naive and TNF-failure populations

	Induction phase: patients entering the model in moderate–severe disease		End-of-maintenance phase: patients who responded in induction phase	
	Response	Remission	Response	Remission
Mixed population				
Trial-based 6-week data				
Conventional non-biological therapy	33.80%	9.86%	24.93%	15.61%
Vedolizumab	48.02%	16.78%	47.40%	38.96%
TNF-naive population				
Trial-based 6-week data				
Conventional non-biological therapy	38.71%	9.45%	42.25%	26.76%
Vedolizumab	53.75%	22.09%	65.15%	51.52%
Network meta-analysis-based 6-week data				
Conventional non-biological therapy	38.33%	15.63%	39.91%	24.81%
Vedolizumab	53.01%	34.89%	63.45%	49.37%
Infliximab[a]	63.50%	34.50%	69.44%	45.71%
Adalimumab	60.43%	29.92%	49.35%	49.35%
TNF-failure population				
Trial-based 6-week data				
Conventional non-biological therapy	30.97%	10.18%	26.92%	12.82%
Vedolizumab	44.62%	13.08%	29.27%	28.05%

[a] Data derived from ACCENT-1 because the trial by Targan et al. in the network meta-analysis had a small sample size and did not use a standard infliximab dosage

Source: Table 7.3.1.4 and 7.3.6.1 on page 221 and from page 234 in the company's submission (with corrections using the updated model provided at the clarification stage)

Table 12 Probability of response and remission in the company's economic model according to disease severity (trial-based data)

	Induction phase		End-of-maintenance phase: patients who responded in induction phase	
	Response	**Remission**	**Response**	**Remission**
Mixed population				
Moderate disease				
Conventional non-biological therapy	31.88%	7.25%	33.72%	27.91%
Vedolizumab	59.26%	25.00%	46.15%	46.15%
Severe disease				
Conventional non-biological therapy	23.53%	4.41%	25.37%	13.43%
Vedolizumab	38.89%	10.19%	41.33%	30.67%
TNF-naive population				
Moderate disease				
Conventional non-biological therapy	34.21%	7.89%	41.18%	33.33%
Vedolizumab	66.67%	33.33%	56.41%	56.41%
Severe disease				
Conventional non-biological therapy	23.33%	6.67%	37.50%	25.00%
Vedolizumab	43.10%	13.79%	65.63%	43.75%
TNF-failure population				
Moderate disease				
Conventional non-biological therapy	24.14%	6.9%	22.86%	20.00%
Vedolizumab	46.15%	12.82%	35.90%	35.90%
Severe disease				
Conventional non-biological therapy	20.69%	0.00%	18.60%	6.98%
Vedolizumab	35.00%	7.50%	23.26%	20.93%

Source: Table 7.3.6.1 on page 234 in the company's submission (with additional data from the company's updated model provided at the clarification stage). All data are derived from clinical trials.

5.14 The company based the model's starting annual mortality rate on all-cause mortality for the UK general population (0.0015). Assuming an exponential function, the per-cycle (8-week) mortality change factor was estimated to be 1.01385 and relative mortality risk was calculated by health state. Patients in remission were assumed to have the same mortality risk as the general UK population. The health states for mild disease, moderate–severe disease and surgery were assumed to be associated with relative mortality risks of 1.3, 2.3 and 3.2 respectively.

ERG comments

5.15 The ERG noted that the company had provided limited details on the network meta-analyses used in its economic model, how the vedolizumab clinical trial data had been pooled and how the discontinuation rates because of adverse events had been calculated.

5.16 The ERG questioned how the company had used the network meta-analyses for the TNF-alpha inhibitor-naive subgroup. Although the ERG recognised that the Targan trial comparing infliximab with placebo had limitations, it believed that it should have been included in the network meta-analysis for infliximab and used in the base case, potentially adjusting for small sample size. The ERG noted that the company had instead used data for infliximab from the placebo-controlled ACCENT-1 trial (separate from the network meta-analysis), but had not discussed the trial's limitations. The ERG noted that including data for adalimumab from the trial by Watanabe et al. as well as CLASSIC-1 in the primary analysis would likely increase the probabilities of remission and response for adalimumab.

5.17 The ERG was unclear from the company submission and the publication by Bodger et al. (2009) how the transition probabilities for patients undergoing surgery had been calculated. It considered the values used by the company for transitioning from surgery to surgery in the next cycle to be high (33.75%), and was not satisfied by the explanation provided by the company. The ERG was not able to predict how correcting the transition matrix for movement between states after surgery would affect the ICERs.

5.18 The ERG expressed concerns about the assumptions about mortality used in the company's model because of a lack of detail in the company's submission. It noted that because mortality is conditional on the current health states in the company's model, the model predicts greater survival for patients treated with biological therapy compared with patients receiving conventional non-biological therapy. However, the Lichtenstein

study used by the company in its model suggests no statistical differences in the excess mortality rates according to disease severity at baseline, or in mortality between infliximab and non–infliximab-treated patients. The ERG stressed that no increased mortality rate was observed in patients taking placebo in GEMINI II. Given the lack of evidence of a differential mortality rate between treatments, the ERG believed that the same excess risk mortality should be applied to all Crohn's disease health states.

Adverse events and surgical complications

5.19 Annual probabilities of discontinuing biological treatment owing to adverse events were derived from clinical trials for vedolizumab in the mixed population (3.03% and 8.89% during induction and maintenance respectively), TNF-alpha inhibitor-naive subgroup (3.07% and 6.06%) and TNF-alpha inhibitor failure subgroup (2.69% and 8.54%). They were also calculated for adalimumab (1.33% and 5.26%) and infliximab (1.33% and 5.26%) in the TNF-alpha inhibitor-naive subgroup.

5.20 Adverse events to be included in the company's economic model were selected based on clinical expert opinion (Table 13). These were serious infection, tuberculosis, lymphoma, acute hypersensitivity reactions and skin reactions. The probability of each adverse event occurring with each treatment was estimated from clinical trial data included in the mixed treatment comparison. Surgical complications in the model were also based on clinical expert opinion and the probabilities of these occurring were estimated from pooled data from a systematic literature review on surgical intervention.

Table 13 Probability of adverse events, by treatment

Adverse event	Vedolizumab	Infliximab	Adalimumab	Conventional non-biological therapy
Serious infection	1.54%	4.49%	1.80%	1.89%
Tuberculosis	0.00%	0.28%	0.00%	0.00%
Lymphoma	0.00%	0.00%	0.00%	0.08%
Acute hypersensitivity reactions	0.00%	0.00%	0.00%	0.74%
Skin reactions	0.34%	0.00%	0.00%	0.16%

Source: Table 7.3.1.7 on page 224 of the company's submission

ERG comments

5.21 The ERG considered that the inclusion of adverse events and their impact on costs and health-related quality of life was flawed. It was unclear if all or only grade 3 or 4 adverse events had been included and noted the selection was based on the opinion of 2 clinical experts. It found the calculations from the company to be simplistic and likely to be incorrect because they did not account for trial duration. Moreover, the ERG was unsure why data from the network meta-analysis for the incidence of serious adverse events were not used in the company's model. The ERG explored the effect of removing adverse events in its exploratory scenario analyses (see section 5.39).

Utility values

5.22 The company's base case used the observed EQ-5D from GEMINI II and GEMINI III. The company assumed a utility value for the surgery state that was equal to that for the moderate–severe health state because patients in GEMINI II and GEMINI III studies were not followed for surgery. The utility values used in the model were 0.820 for remission, 0.730 for mild disease and 0.570 for both moderate–severe disease and surgery. The company applied disutilities from published literature for the following adverse events: serious infection (0.520), tuberculosis (0.550), lymphoma (0.195), acute hypersensitivity reaction (0.110) and skin reactions (0.030).

ERG comments

5.23 The ERG was largely satisfied with the company's approach to estimating utility values for the different health states in its model. However, it noted that the same utility value was used for patients with moderate to severe disease, regardless of any response to treatment. The ERG considered that this was unlikely to be true because it implied that response (that is, improvement in symptoms) does not improve health.

5.24 The ERG recognised that the GEMINI trials could not inform utility value estimates for patients undergoing surgery. It noted that the company had assumed an equal value for these patients and those with moderate to severe Crohn's disease. It was unsure that this was appropriate, given that the aim of surgery is to improve quality of life.

5.25 The ERG had concerns regarding the approach used by the company to adjust utility weights, noting that limited details were provided in the company's submission and in response to a clarification request. However, it anticipated that any impact on the ICERs would be minimal.

Costs

5.26 Treatment acquisition costs, including the estimated doses and unit costs for conventional non-biological therapy, were taken from the British national formulary (2013). In the induction phase, total treatment acquisition costs were [redacted] for vedolizumab (plus £616 administration costs). The patient access scheme was applied to the cost of vedolizumab as a simple discount on the list price (the level of the discount is confidential). Induction costs for the other biological therapies were £3357 for infliximab (plus £616 administration costs) and £1761 for adalimumab (no administration costs). The weighted average cost of conventional non-biological therapy was £119.49 per cycle in the original model (corrected to £70.16 per cycle in the company's response to clarification) and it was assumed that patients treated with biological therapy, who could additionally receive conventional non-biological therapy, incurred 50% of these costs. In the maintenance phase, treatment acquisition costs per

cycle were [redacted] for vedolizumab and £1678 for infliximab (with £308 costs per administration for both of these) and £1409 for adalimumab (which did not have any administration costs).

5.27 Health-state costs were taken from Bodger et al. (2009) and inflated to 2012 prices. The health-state costs were £110 for remission, £313 for mild disease, £490 for moderate–severe disease and £10,581 for surgery, which included surgical complications. Surgery-related complication costs were estimated by applying NHS reference costs to resource use as reported by the company's clinical experts.

5.28 The company estimated costs of adverse events as weighted averages according to the NHS reference costs and assumed that all affected patients were hospitalised. Costs for treating adverse events were £1470 for serious infection, £2272 for tuberculosis, £14,975 for lymphoma, £3188 for acute hypersensitivity reaction and £1363 for skin reactions.

ERG comments

5.29 The ERG noted that the drug acquisition costs depend on the treatment regimen within the company's model. The ERG had some concerns with the treatment regimens assumed in the induction phase, notably for vedolizumab and adalimumab (see section 5.8). The ERG believed that 3 doses of vedolizumab should be used during induction, rather than the 2 assumed in the company's base case, which would increase the treatment cost to [redacted]. It considered that 3 doses of adalimumab 40 mg should be given in the induction phase rather than 5 doses, which would decrease the costs to £1056. The ERG had concerns about some other aspects of company's approach to calculating costs, including costs of conventional non-biological therapy, and the proportion of costs for conventional non-biological therapy applied to patients receiving biological therapy, but considered that these would have little impact on the ICERs.

Company's updated model

5.30 In response to questions at the clarification stage, the company submitted an updated model, which included:

- results for vedolizumab compared with conventional non-biological therapy using network meta-analysis inputs (instead of clinical trial data) in the TNF-naive population. The company acknowledged that the results based upon the network meta-analysis for all therapies should be presented to allow a fair comparison with infliximab and adalimumab.
- data for the subgroups defined by both prior use of TNF-alpha antagonist and severity of disease at baseline
- correcting the treatment switch at 1 year from biological therapy to conventional non-biological therapy by applying this at cycle 7 (week 54) instead of at cycle 6 (week 46)
- correcting the cost of vedolizumab in the scenario analysis that explored changing the duration of induction to match the marketing authorisation
- updated NHS reference costs
- an amended cost for prednisolone, which decreased the cost of conventional non-biological therapy to £70.16 per cycle.

Company's base-case results and sensitivity analyses

5.31 In its updated model submitted in response to clarification (see section 5.30), the company provided updated base-case results for the mixed population, TNF-alpha inhibitor failure population and TNF-alpha inhibitor-naive population. Results are presented for the company's updated model only because these supersede those from the original model:

- In the mixed population, vedolizumab was associated with greater costs and QALYs than conventional non-biological therapy, giving an ICER of £62,903 per QALY gained.

- In the TNF-failure population, vedolizumab was associated with greater costs and QALYs than conventional non-biological therapy, giving an ICER of £98,452 per QALY gained.
- In the TNF-naive population using vedolizumab trial data, vedolizumab was associated with greater incremental costs and QALYs than conventional non-biological therapy, giving an ICER of £22,718 per QALY gained.
- In the TNF-naive population using mixed treatment comparison data, vedolizumab was associated with lower QALYs and costs than infliximab, giving an ICER for infliximab compared with vedolizumab of £26,580 per QALY gained. Vedolizumab was associated with greater costs and QALYs than adalimumab, giving an ICER for vedolizumab compared with adalimumab of £758,344 per QALY gained.

5.32 The company did not present deterministic sensitivity analyses using the updated model. It concluded that its original model appeared to be most sensitive to transition probabilities (in particular for remission), health state costs and utility values. Using its original model, the company also carried out scenario analyses on time horizon, utility values, response criteria and maximum time on treatment, as well as assessing response at 10 and 14 weeks during the induction phase. It noted that assuming a longer time horizon in the original model made vedolizumab more cost effective in all populations.

5.33 Using its updated model, the company presented ICERs when assuming a 14-week stopping rule in the induction phase. Using clinical-effectiveness estimates derived from the head-to-head clinical trials, the ICERs for vedolizumab compared with conventional non-biological therapy were higher than base-case ICERs in the mixed, TNF-naive and TNF-failure groups. Using clinical-effectiveness estimates derived from the network meta-analysis, vedolizumab was dominated by the other 2 biological therapies in the TNF-naive groups (that is, it cost more but was less effective).

ERG comments

5.34 The ERG noted that the company presented pairwise comparisons rather than a fully incremental analysis for the TNF-alpha inhibitor-naive group and that it had not provided updated cost-effectiveness estimates for all of the patient groups covered by the original model. The ERG therefore extracted this information from the company's updated model (Table 14). In the TNF-naive group, a fully incremental analysis gave ICERs of £19,705 per QALY gained for adalimumab compared with conventional non-biological therapy and £112,882 per QALY gained for infliximab compared with adalimumab. Vedolizumab was extendedly dominated by infliximab (that is, the ICER for vedolizumab compared with adalimumab [£758,344 per QALY gained] was greater than that for infliximab compared with vedolizumab). The ERG could not confirm the results of subgroup analyses according to disease severity for the TNF-alpha inhibitor-naive population because it was unclear how the data for patients treated with infliximab and adalimumab had been estimated in the company's updated model.

5.35 In the mixed and TNF-failure groups, vedolizumab was associated with greater costs and QALYs compared with conventional non-biologic therapy in subgroups according to disease severity, with ICERs of:

- £21,064 per QALY gained for the mixed group with moderate disease
- £77,382 per QALY gained for the mixed group with severe disease
- £55,201 per QALY gained for the TNF-failure group with moderate disease
- £134,330 per QALY gained for the TNF-failure group with severe disease.

The ERG was concerned that the number of patients with moderate to severe disease regularly did not equate to the number of patients with moderate disease plus the number of patients with severe disease. It also had concerns about the validity of the calibrated transition probabilities.

Table 14 Base-case ICERs using the manufacturer's updated model[a]

	Costs	QALYs	Incr. costs	Incr. QALYs	ICER
Mixed population					
Moderate–severe disease (trial data)					
Vedolizumab	£54,195	4.980			
Conventional non-biological therapy	£45,807	4.847	£8338	0.1334	£62,903
Moderate disease					
Vedolizumab	£50,141	5.2536			
Conventional non-biological therapy	£43,693	4.9475	£6447	0.3061	£21,064
Severe disease					
Vedolizumab	£53,652	4.9148			
Conventional non-biological therapy	£45,813	4.8134	£7840	0.1013	£77,382
TNF-naive population (trial data)					
Moderate–severe disease (trial data)					
Vedolizumab	£49,037	5.297			
Conventional non-biological therapy	£42,635	5.015	–	–	£22,718
Moderate–severe disease (network meta-analysis): pairwise comparisons					
Vedolizumab	£51,990	5.145			
Infliximab vs vedolizumab	£52,907	5.179	–	–	£26,580[b]
Vedolizumab vs adalimumab	£48,493	5.140	–	–	£758,344
Moderate–severe disease (network meta-analysis): fully incremental analysis					
Conventional non-biological therapy	£44,347	4.9300			
Adalimumab	£48,493	5.1404	£4146	0.2104	£19,705
Vedolizumab	£51,990	5.1450	Extendedly dominated		
Infliximab	£52,907	5.1795	£4414	0.0391	£112,882
TNF-failure population					
Moderate–severe disease (trial data)					
Vedolizumab	£54,429	4.923			
Conventional non-biological therapy	£45,814	4.836	£8615	0.0875	£98,452
Moderate disease					
Vedolizumab	£53,388	4.9767			
Conventional non-biological therapy	£45,480	4.8335	£7909	0.1433	£55,201
Severe disease					
Vedolizumab	£54,030	4.8485			
Conventional non-biological therapy	£46,104	4.7895	£7926	0.0590	£134,330

[a] Table contains results from the company's updated model that were presented by the company (non-shaded cells) or extracted by the ERG without making any exploratory changes to the company's base case (shaded cells)
[b] Vedolizumab was cheaper and less effective. ICER is for infliximab compared with vedolizumab

Sources: page 31 of the company's clarification response and tables 60–62 on pages 184–186 of the ERG report

5.36 The ERG noted that the company had not re-run its deterministic sensitivity analyses using the updated model. The ERG considered that the parameters that had the largest impact on the ICER would not change between the 2 versions of the model submitted. It agreed with the company that the key drivers of the ICER included many of the transition probabilities, and health state costs and utility values. It considered the ranges used by the company for its deterministic and probabilistic sensitivity analyses to be somewhat arbitrary for most input parameters.

5.37 Using the updated company's model, the ERG reported the results from the scenario analyses presented in the original company submission. It noted that the ICER was sensitive to all the scenarios considered, especially the time horizon and health state utility values.

ERG exploratory analyses

5.38 The ERG had concerns about the validity of the predictions made by the company's model. It considered the company's comparison of the model's prediction of response and remission compared with GEMINI trials to be of limited value, and carried out exploratory analyses to validate the model. The ERG was concerned about several discrepancies between the results generated using the company's model and those from the clinical trials. For the TNF-failure group, it noted that the company's model seemed to under-predict the proportion of patients receiving conventional non-biological therapy who were in remission. Moreover, for patients taking vedolizumab, it under-predicted the proportion discontinuing treatment and over-predicted the proportion who remained on treatment.

5.39 The ERG conducted exploratory analyses to investigate the effect of:

- assuming equivalent safety profiles for treatments by removing costs and disutilities for adverse events
- making the utility value for surgery equal to the utility value for moderate to severe disease for 2 weeks then equal to remission for the remaining 6 weeks of the cycle
- reducing costs for adalimumab in the induction phase to reflect the efficacy data used for the induction phase
- assuming the transitions matrices in the maintenance phase were the same for infliximab and adalimumab as for vedolizumab
- including treatment discontinuation owing to lack of efficacy (using the same rate for all 3 biological therapies)
- assuming the same excess mortality rate (1.7) for each Crohn's disease health state.

Each of these scenarios had little effect on the ICERs for the mixed, TNF-alpha inhibitor-naive and TNF-alpha inhibitor failure groups.

5.40 For transparency, the ERG extracted the probabilistic ICERs using the updated version of the company's model and noted that these were consistent with the deterministic ICERs (see table 64 on page 201 of the ERG report). In a fully incremental comparison, the ERG reported that the probability of vedolizumab being cost effective was less than 1% at a maximum acceptable ICER of £20,000 per QALY gained for the mixed, TNF-naive and TNF-failure patient groups. The probability of cost effectiveness increased to 2% at a maximum acceptable ICER of £30,000 per QALY gained.

Innovation

5.41 Justifications for considering vedolizumab to be innovative:

- The company stated that vedolizumab has a gut-selective mechanism of action that is independent of TNF.

- It added that vedolizumab can provide a ‘step change’ to current treatment by offering a novel and effective treatment to increase the rate and duration of remission and consequently the time to surgery.
- The company indicated that successfully managing Crohn’s disease symptoms and prolonging remission may have societal benefits that are unlikely to be included in the QALY calculation. These include effects on carers and on employment (for example, absenteeism, workplace disability and loss of earnings).

6 Equality issues

6.1 No potential equality issues were identified during the scoping process or in the consultees’ submissions. The ERG heard from a clinical expert that ethnic minority patients’ access to biological treatment is lower than white British patients’ and that the reasons for this are unclear. However, the ERG could not find any empirical evidence to support this view. Another clinical expert told the ERG that having surgery or creating a stoma may be problematic for some people from some cultures and backgrounds and that a treatment that could delay or reduce the risk of such procedures could be important in terms of equity.

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Appendix A: Clinical efficacy section of the European public assessment report

The European public assessment report can be found here (the conclusions on clinical efficacy and safety are given on pages 127–128 and page 147 respectively).