Vedolizumab (Entyvio™▼) for treating moderately to severely active Crohn's disease after prior therapy [ID690]: New evidence for the consideration of the NICE Appraisal Committee

Submitted by Takeda UK Ltd.

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List of Abbreviations

ACD	Appraisal Consultation Document
CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
CDAI-70	Clinical response
CDAI-100	Enhanced clinical response
CRP	C-Reactive Protein
CT	Conventional therapy
EQ-5D VAS	EuroQol-5 Dimensions visual analogue scale
ERG	Evidence Review Group
HBI	Harvey-Bradshaw Index
HRQoL	Health-related quality of life
IBDQ	Inflammatory bowel disease questionnaire
ICER	Incremental Cost-Effectiveness Ratio
IV	Intravenous
IVRS	Interactive Voice Response System
LTS	Long-term safety
NICE	National Institute for Health and Care Excellence
NMA	Network Meta-Analysis
PAS	Patient Access Scheme
Q4wks/Q4W	Dosing every 4 Weeks
Q8wks/Q8W	Dosing every 8 Weeks
SF-36	ShortForm 36 Health Survey
RCT	Randomised controlled trial
SmPC	Summary of Product Characteristics
STA	Single Technology Appraisal
TB	Tuberculosis
TNF-α	Tumour necrosis factor-alpha
UC	Ulcerative colitis
VAS	Visual analogue scale
VDZ	Vedolizumab

1. Executive Summary

Crohn's disease (CD) is a chronic, lifelong, relapsing-remitting inflammatory disease that can affect any part of the gastrointestinal tract. It is often diagnosed at an early age (<30 years), affecting the working age population and impacting productivity.[1] The most common symptoms include diarrhoea, abdominal pain, faecal urgency and incontinence. Systemic features such as fever, weight loss, malaise and fatigue are indicators of more extensive disease. CD is becoming more common, with the incidence in children having increased dramatically over recent decades.[2]

The aims of drug treatment in CD are to reduce symptoms and maintain or improve quality of life, while minimising toxicity over both the short- and long-term.[3] Drug therapy aims to achieve this by controlling inflammation or by reducing the immune response. Standard first-line treatment involves the use of conventional therapy (CT), consisting of a combination of aminosalicylates, although their efficacy is believed to be limited,[4] glucocorticoids, and immunomodulators (e.g. azathioprine, 6-MP, methotrexate). While effective for inducing remission, corticosteroids are not useful for maintenance therapy[3] and carry significant undesirable side-effects. Immunomodulators have a role in maintaining remission in moderate to severe CD[3] but their relatively slow onset of action precludes their use during flares of disease, and they may potentially increase the risk of lymphoma.[5] The majority of CD patients need surgery at some stage of their disease to remove diseased, strictured or stenotic segments of bowel.[6] However, such surgery is not curative as CD can recur in any part of the GI tract and patients must continue with medical therapy.

Currently, if the disease does not adequately respond to CT, then antagonists of tumour necrosis factor alpha (TNF-α), such as infliximab or adalimumab, are licensed options.[7,8] The TNF-α antagonists are useful for both induction and maintenance of remission in CD, but they are associated with a number of safety concerns based on their suppression of systemic immunity (e.g. infections, malignancies). Despite their efficacy, a considerable unmet need remains as about one-third of patients do not respond to initial treatment with a TNF-α antagonist, while about two-thirds fail to maintain remission at 1 year.[9] Clinical trial evidence shows that after failure of one TNF-α antagonist, a patient's response to a second TNF-α antagonist is substantially lower.[6,10] Clinicians say they would also expect to need to dose escalate the second TNF-α antagonist in a significant proportion of patients in an effort to maintain efficacy. There is limited clinical trial evidence to support switching to a different TNF-α antagonist and neither infliximab nor adalimumab are specifically licensed[7,8] for use after failure of a prior TNF-α antagonist.

Vedolizumab (Entyvio™) is a new, gut-selective immunosuppressive biologic agent with a novel mechanism of action which was developed to address the unmet medical need in CD and ulcerative colitis (UC). Rather than blocking the cytokine TNF-α, vedolizumab selectively inhibits the trafficking of pro-inflammatory lymphocytes to the gut, thus reducing inflammation. This selective mechanism of action provides a targeted approach that avoids systemic immunosuppression and may help to avoid some of the side-effects seen with the TNF-α antagonists. Vedolizumab is licensed for the treatment of adults with moderately to severely active CD who have had an inadequate response with, lost response to, or were

intolerant to either CT or a TNF-α antagonist.[11] Hence, vedolizumab is currently the only treatment specifically licensed for use in patients with CD after failure of a TNF-α antagonist.

In this submission of new evidence we have focussed on the area that has been highlighted in the ACD for vedolizumab as that of greatest unmet clinical need in the management of CD, namely the need for new agents after failure of prior treatment including TNF-α antagonists. For these patients there are few other pharmacological options, and vedolizumab offers the potential to provide an alternative option to use of a further TNF-α antagonist, or further conventional non-biological therapy. Therefore, there have been three main changes in this updated submission of evidence to NICE:

- Focus on the evidence of the clinical effectiveness and cost-effectiveness of vedolizumab for the management of moderately to severely active CD in a sub-population of patients who have failed or are intolerant to a prior TNF-α antagonist. We believe the most appropriate positioning for vedolizumab in the treatment pathway is after the failure of a first TNF-α antagonist (either adalimumab or infliximab) as clinicians at this stage would typically prefer to try a new agent rather than another TNF-α antagonist.

- A revised patient access scheme that offers vedolizumab at the new reduced price of [redacted] per 300mg vial ([redacted] discount on the list price of £2,050 per vial).

- A modified economic model that has been updated to reflect key Appraisal Committee concerns as set out in the ACD (with a particular focus on AC concerns voiced in Sections 4.12-4.18 of the ACD, but with many other areas of ERG concern also addressed).

The key evidence for the efficacy and safety of vedolizumab, as both induction and maintenance treatment in moderate to severe CD, comes from two large randomised, double-blind trials (GEMINI II,[12] n=1,115; and GEMINI III,[13] n=416). Both trials contained a substantial proportion of patients who had either failed or were intolerant to prior TNF-α antagonist therapy (76% in GEMINI III, 50% in GEMINI II). The GEMINI II trial lasted 1 year, but recently presented evidence shows that the efficacy of vedolizumab is maintained at 2 years.[14]

In the cost-effectiveness analysis performed with the modified model the base case result showed that with the revised PAS the ICER for vedolizumab vs. conventional therapy over a lifetime horizon in the TNF-α antagonist failure population is £21,620 per QALY gained. The primary analysis has been performed against CT due to the availability of relatively robust direct evidence using the GEMINI II and III failure sub-populations, with placebo representing the CT comparator arm (patients in both arms received background CT therapy). This provides a benchmark assessment of the absolute cost-effectiveness of vedolizumab, and cost-effectiveness in patients for whom further treatment with TNF-α antagonists is not considered appropriate, or for whom they are considered unsuitable (as section 4.2 of the ACD alludes to).

Due to the extremely limited evidence for efficacy of the TNF-α antagonists, an exploratory scenario analysis was performed for vedolizumab against adalimumab or infliximab as the second TNF-α antagonist. Despite its limitations a network meta-analysis (NMA) was used

to support an assumption of at least equal efficacy between vedolizumab and adalimumab at standard and escalated doses (and with infliximab although there was no evidence available in the sub-population of interest for infliximab). The analysis focussed on a comparison of the drug and administration costs of vedolizumab and the TNF-α antagonists (setting all other components equal in the economic model). This demonstrated that even without any dose escalation for infliximab vedolizumab had at least equivalent (slightly lower) total costs. A clinical expert survey conducted by the company (see Section 4.3.3) found estimates of the proportion of patients expected to require dose escalation with infliximab in maintenance treatment (from 5mg/kg to 10mg/kg) ranging between 15%-50%. At 15% dose escalation there are estimated to be clear cost savings with vedolizumab. For adalimumab, there are lower administration costs due to sub-cutaneous administration. Hence, based on an IV infusion administration cost of £328 (based on a day case NHS reference code,[15]) dose escalation in 80% of patients receiving adalimumab as the second TNF-α antagonist was estimated for the incremental cost of vedolizumab to be offset. This reduces to 58% if 50% of the administration cost is assumed (£164 per infusion) which is more realistic reflection of the true opportunity cost of vedolizumab administration which in Maintenance treatment is estimated to involve a total infusion and observation time of 1.5 hours.[11] The clinical expert survey estimates ranged from 30% to 100% of patients in the first year of treatment would dose escalate with adalimumab if used as the second TNF-α antagonist after failure of or intolerance to the first.

In terms of budget impact there are estimated to be net cost savings if vedolizumab is used in the treatment pathway after failure of a first TNF-α antagonist, based on the likelihood that infliximab would be the most displaced biologic (see Section 5).

In sum, there is a pressing need for alternative therapy that is effective in patients who have inadequate or no response, lose response, or are intolerant to currently available treatments for CD, including the TNF-α antagonists. In addition, given the potential toxicities associated with corticosteroids, immunomodulators, and TNF-α antagonists, there is a need for a new targeted therapy, particularly one that reduces gastrointestinal inflammation without increasing the risk for toxicities commonly seen with the currently available agents. Vedolizumab is a gut-selective anti-inflammatory agent that was developed to help fulfil this important unmet medical need.

2. Introduction

2.1 Appraisal Committee's preliminary recommendations

On the 19th December 2014, the Appraisal Committee of the National Institute for Health and Care Excellence (NICE) prepared a document[16] for consultation summarising the evidence and views of using vedolizumab in the NHS in England for treating Crohn's disease. The document sets out the draft recommendations made by the committee and have currently stated that:

'Vedolizumab is not recommended, within its marketing authorisation for treating Crohn's disease, that is, for treating moderately to severely active Crohn's disease in adults whose disease has responded inadequately to, or has lost response to, either conventional therapy or a tumour necrosis factor-alpha inhibitor, or who cannot tolerate either of these treatment types.[16]

Following the release of the Appraisal Consultation Document (ACD) for vedolizumab for treating moderately to severely active Crohn's disease after prior therapy [ID690], Takeda UK Ltd requested from NICE an extension in timings to allow for a more focussed positioning, a proposed update to the Patient Access Scheme (PAS), and the submission of a revised economic model to address the issues identified in the ACD. NICE has agreed an extension in timings for the additional analyses to be reviewed. Therefore, the Committee Meeting scheduled for the 25th February 2015 has been cancelled and rescheduled to take place on the 28th May 2015.

2.2 New selective positioning for vedolizumab

Following feedback from the NICE Appraisal Committee in Sections 4.2 and 4.17 of the NICE ACD, which concludes: 'that the need for an additional treatment for Crohn's disease was greatest in people whose treatment options were limited, such as those whose disease had either failed to respond to, or lost response to TNF-α antagonists, or for whom they were unsuitable,' Takeda UK request NICE to consider vedolizumab in the TNF-α antagonist failure population of patients with moderately to severely active CD as this reflects the most likely positioning in the treatment pathway for CD for vedolizumab after patients have failed on conventional therapy (CT) and then subsequently have failed to respond to, or lost response to TNF-α antagonists (third-line indication). This positioning is in line with the licensed indication of vedolizumab according to the Summary of Product Characteristics (SmPC),[11] and due to the high unmet clinical need in patients that have exhausted all the current medical treatment options whilst wishing to avoid surgery which is non-curative in patients with moderately to severely active CD.

In Section 4.17 of the ACD, The Committee also considered the opinion of clinical experts who stated: *'that the population in whom a TNF-α inhibitor had failed, these were the people for whom access to a new agent (vedolizumab) would be of most value because of the very limited treatment options available to them.'* This opinion was also confirmed by a group of

Consultant Gastroenterologists and Specialist Clinical Pharmacists, consulted by Takeda UK, who stated that one strength of vedolizumab is due to the high unmet need in refractory IBD patients that have failed at least one anti-TNF.

2.3 Proposal of a new Patient Access Scheme

Takeda UK have previously agreed a Patient Access Scheme (PAS) for vedolizumab with the Department of Health of a simple price discount that reduces the NHS price for one 300mg vial of vedolizumab to [redacted] exclusive of VAT. To further improve the cost-effectiveness of vedolizumab in patients with moderately to severely active CD who have failed one or more TNF-α antagonists, (anti-TNF failure population), Takeda UK wish to submit a new PAS for one 300mg vial of vedolizumab of [redacted] exclusive of VAT.

2.4 Update of the economic model

In Section 4.12 of the ACD, The Committee noted the number of key concerns raised by the Evidence Review Group (ERG) regarding the structure and parameterisation of the economic model submitted by Takeda UK. Due to concerns raised by the ERG, the Committee were uncertain of the robustness of the ICERs generated. Therefore, with the consideration of a new selective positioning of vedolizumab in the TNF-α antagonist failure population (see Section 2.2), and submission of a new PAS (see Section 2.3), the economic model was updated in accordance with the above as well as addressing key concerns outlined by the NICE Appraisal Committee in Sections 4.12-4.18 of the ACD, and Section 5 of the report from the ERG (see Section 4.4).

3. Clinical evidence

3.1 Overview

Evidence for the efficacy of vedolizumab for the treatment of moderately to severely active Crohn's disease (CD) is provided from two pivotal, Phase III, randomised controlled trials (RCTs).

- **GEMINI II** (registration at Clinicaltrials.gov NCT00783692), designed to determine the effect of vedolizumab ***Induction treatment*** on clinical response and remission at 6 Weeks and to determine the effect of vedolizumab ***Maintenance treatment*** on clinical remission at 52 Weeks.[12] This trial was designed to support the registration of vedolizumab for Induction and Maintenance treatment of a broad population of patients who have failed one or more standard therapies for CD, including corticosteroids, immunomodulators (i.e. azathioprine, 6-mercaptopurine, or methotrexate) and TNF-α antagonists.

- **GEMINI III** (registration at Clinicaltrials.gov NCT01224171), designed to establish the efficacy and safety of vedolizumab for the ***Induction*** of clinical response and remission.[13] This trial was designed to focus mainly on patients for whom a TNF-α antagonist has failed (i.e. had an inadequate response to, loss of response to, or intolerance of ≥1 anti-TNF).

The populations in both studies (GEMINI II [Induction] and GEMINI III) included patients with moderately to severely active CD who had failed corticosteroids and/or immunomodulators (the second-line indication of failed conventional therapy (CT), and patients who failed TNF-α antagonist therapy (the third-line indication of failed conventional therapy and TNF-α antagonist therapy).

For the purpose of this document, based on the new, selective positioning outlined in Section 2.2, only efficacy and safety data for vedolizumab in the TNF-α antagonist failure sub-population will be presented. Study design and results from the GEMINI II and GEMINI III trials for the overall population and TNF-α antagonist naïve sub-population are reported in full in the submission presented to NICE by Takeda UK on the 22nd August 2014.

Table 1 presents the proportion of TNF-α antagonist failure patients in the GEMINI II and GEMINI III studies, including the number of anti-TNF's failed.

Table 1: Proportion of TNF-α antagonist failure patients in the GEMINI II and GEMINI III studies

	GEMINI II		GEMINI III	
	Induction cohort 1 population		Overall ITT population	
	PLA N=148	VDZ N=220	PLA N=207	VDZ N=209
Medication Use/Failure category				
Prior TNF-α antagonist use,[a] n (%)	72 (48.6)	111 (50.5)	157 (75.8)	158 (75.6)
Third-line indication				
Any prior TNF-α antagonist failure, n (%)	70 (47.3)	105 (47.7)	156 (75.4)	155 (74.2)
Inadequate response,[b] n (%)	41 (58.6)	56 (53.3)	69 (44.2)	66 (42.6)
Loss of response,[c] n (%)	22 (31.4)	40 (38.1)	69 (44.2)	71 (45.8)
Intolerance,[d] n (%)	7 (10.0)	9 (8.6)	18 (11.5)	18 (11.6)
1 prior TNF-α antagonist failure, n (%)[e]	28 (18.9)	49 (22.3)	45 (21.7)	59 (28.2)
2 prior TNF-α antagonist failures, n (%)[e]	31 (20.9)	48 (21.8)	90 (43.5)	82 (39.2)
3 prior TNF-α antagonist failures, n (%)[e]	11 (7.4)	8 (3.6)	21 (10.1)	14 (6.7)

[a] Data for prior TNF-α antagonist use at randomisation were obtained from the IVRS

[b] Inadequate response to TNF-α antagonists was defined as persistent active disease despite Induction treatment with specified medications

[c] Loss of response to TNF-α antagonists was defined as recurrence of symptoms during Maintenance dosing following prior clinical benefit

[d] Intolerance was defined as occurrence of treatment-related toxicities

[e] Multiple failures are counted once per patient

Source: Sandborn et al., 2013;[12] Sands et al., 2014.[13]

In GEMINI II, approximately half (48%) of the study population had failed TNF-α antagonist therapy, 55% of whom had failed primary TNF-α antagonist treatment.[12,17] The study showed that 19% of the total study population had failed 1 TNF-α antagonist, 21% had failed 2 TNF-α antagonists, and 7% had failed 3 TNF-α antagonists (Table 1). By design, GEMINI III included 76% who had failed at least 1 TNF-α antagonist (Table 1), of whom approximately 43% had not responded to initial treatment, demonstrating the refractory nature of the patient population enrolled in the vedolizumab program.

Given that 3 TNF-α antagonists (infliximab, adalimumab, and natalizumab) were available globally at the time GEMINI II and GEMINI III were conducted, patients in the vedolizumab studies could have failed up to 3 TNF-α antagonists. However, it should be noted that natalizumab is not currently licensed in the UK for Crohn's disease.[18]

Thus, the study populations in GEMINI II and GEMINI III represented patients with moderately to severely active CD with an extensive treatment history, having failed conventional (second-line indication) or both conventional and 1 or more TNF-α antagonist therapies (third-line indication). With up to potentially 3 failed prior agents, the latter sub-group represents the most refractory patients ever previously studied in CD.

A brief summary of the GEMINI II and GEMINI III studies are presented in Sections 3.2 and 3.3 below. For a complete description of the GEMINI II and GEMINI III study designs and methods, participants, disposition of patients, patient demographics and characteristics, outcomes, and statistical analysis, please refer to Section 6.3 (pages 76-98) of the original submission from Takeda submitted to NICE on the 22nd August 2014.

3.2 GEMINI II study overview

GEMINI II, is a pivotal, Phase 3, multicentre, multinational, randomised, double-blind, placebo-controlled trial conducted to evaluate the efficacy and safety of both Induction and Maintenance treatment with vedolizumab in 1116 patients with moderately to severely active

CD, defined as a Crohn's Disease Activity Index (CDAI) score of 220 to 450 points. This trial was designed to support the registration of vedolizumab for Induction and Maintenance treatment of a broad population of patients who have failed 1 or more standard therapies for CD.[12]

In the Induction trial (cohort 1), patients were randomly assigned, in a 3:2 ratio, to receive intravenous (IV) vedolizumab, at a dose of 300mg, or placebo at Weeks 0 and 2 and were followed through Week 6, at which time disease status was assessed. A second cohort of patients, (cohort 2), were treated with open-label vedolizumab 300mg IV at Weeks 0 and 2, with assessment at Week 6. This second cohort of patients did not contribute to the efficacy analyses performed for the Induction Study. Approximately half (48%) of the study population had failed TNF-α antagonist therapy.[12,17]

Patients who met protocol-specified criteria for clinical response during Induction were eligible for randomisation into the Maintenance efficacy study. The Maintenance phase included 3 groups of patients who were to be assigned to treatment groups based on their Induction phase treatment assignment and response to therapy. Vedolizumab-treated patients from both cohort 1 and cohort 2 who demonstrated a clinical response according to protocol-specified criteria, were to be randomized in a 1:1:1 ratio to double-blind treatment with vedolizumab administered every 8 Weeks (Q8W), vedolizumab administered every 4 Weeks (Q4W), or placebo through to Week 52. Vedolizumab-treated patients who did not demonstrate response at Week 6 of the Induction phase were to continue treatment with open-label vedolizumab, administered Q4W.[12]

After the Week 52 assessments, patients may have been eligible to enrol in Study C13008 (Long-term Safety Study) to receive open-label vedolizumab treatment. Patients who did not participate in Study C13008 were to have a final visit 16 Weeks after their final dose of study drug, and have safety information collected for up to 2 years after the study.[12]

The primary endpoints for the Induction study were the proportions of patients who achieved clinical remission at Week 6 (defined as a CDAI score of ≤150 points) and the proportions of patients who achieved enhanced clinical response at Week 6 (defined as CDAI-100 response [≥100-point decrease in the CDAI score]) in the Induction Study ITT Population. The secondary efficacy endpoint was the change from baseline in serum CRP (C-Reactive Protein) levels at Week 6.[12]

In the trial of Maintenance therapy, the primary endpoint was clinical remission at Week 52, and the secondary endpoints (in ranked order) were CDAI-100 response, glucocorticoid-free remission (defined as clinical remission at Week 52 without glucocorticoid therapy), and durable clinical remission (defined as clinical remission at ≥80% of study visits, including the final visit).[12]

The key endpoints for the Induction study ITT population (i.e. clinical remission and CDAI-100 response at Week 6, mean change in CRP levels at Week 6); and the Maintenance study ITT population (i.e. clinical remission at Week 52, CDAI-100 response at Week 52, glucocorticoid-free remission at Week 52, and durable clinical remission at Week 52) were analysed by treatment arm (vedolizumab vs. placebo) for the following two subgroups:

- Patients with prior TNF-α antagonist failure
- Patients without previous exposure to TNF-α antagonist therapy (TNF-α antagonist-naïve).

As previously mentioned above, for the purpose of presenting new evidence, based on the new selective positioning, results will be presented for patients with prior TNF-α antagonist failure only.

3.3 GEMINI III study overview

GEMINI III was a second Phase 3, multinational, randomised, double-blind, placebo-controlled study in 416 patients with moderately to severely active CD designed to establish the efficacy and safety of vedolizumab for the Induction of clinical remission in both a broad population of patients and those who had previously failed TNF-α antagonists. By design, GEMINI III included 76% who had failed at least 1 TNF-α antagonist.[13]

Patients were randomised 1:1 to receive either vedolizumab or placebo at Weeks 0, 2, and 6. Induction endpoints were assessed at both Week 6 and Week 10.[13]

As for GEMINI II, after completing the Week 10 assessments, patients were eligible to enrol into the open-label, long-term safety study (Study C13008), if study drug was well tolerated, and no major surgical intervention for CD occurred or was required. Based on analyses of un-blinded Week 0-6 data and blinded Week 10 data from GEMINI II, it was hypothesised that a third Induction dose may be needed to achieve clinical remission. Therefore, an additional dose and increased length of assessment were chosen for evaluation in GEMINI III. Thus, this study evaluated 3 doses of vedolizumab for Induction and assessed response at Week 10.[13]

The primary endpoint of the study was clinical remission at Week 6 in the sub-population of patients that had previously failed TNF-α antagonist therapy. Efficacy was also assessed for the overall population, which included both TNF-α antagonist failures and patients who were naïve to TNF-α antagonist therapy.[13]

Exploratory objectives of the GEMINI III study included the following:

- To determine the effect of vedolizumab Induction treatment on enhanced clinical response at Week 6 in the entire study population
- To determine the effect of vedolizumab Induction treatment on enhanced clinical response at Week 10 in the TNF-α antagonist failure sub-population and in the entire study population
- To determine the effect of vedolizumab Induction treatment on sustained enhanced clinical response (i.e., enhanced clinical response at both Week 6 and Week 10) in the TNF-α antagonist failure sub-population and in the entire study population.

As for the GEMINI II study, for the purpose of presenting new evidence, based on the new selective positioning, results will be presented for patients with prior TNF-α antagonist failure only.

3.4 Crohn's Disease Activity Index (CDAI) scoring system for assessment of Crohn's disease activity

In order for patients to be eligible for the GEMINI II and GEMINI III trials, a diagnosis of moderately to severely active CD (according to the Crohn's Disease Activity Index [CDAI])[19] had to be determined.

The CDAI is a research tool used to quantify the symptoms of patients with CD. This is of importance in research studies done on medications used to treat CD; most major studies on newer medications use the CDAI in order to define response or remission of disease. As CD is a disease with a variety of symptoms that affect quality of life, the quantification of symptoms may be of secondary importance to a quantitative assessment of the effect on quality of life. This has been addressed by the Inflammatory Bowel Disease Questionnaire (IBDQ) and other indices of quality of life for patients with Crohn's disease.[20]

The CDAI was developed by WR Best and colleagues from the Midwest Regional Health Centre in Illinois, in 1976.[19] The index consists of eight factors, each summed after adjustment with a weighting factor. The components of the CDAI and weighting factors are as follows:

Clinical or laboratory variable	Weighting factor
Number of liquid or soft stools each day for seven days	x 2
Abdominal pain (graded from 0-3 on severity) each day for seven days	x 5
General well-being, subjectively assessed from 0 (well) to 4 (terrible) each day for seven days	x 7
Presence of complications*	x 20
Taking Lomotil or opiates for diarrhoea	x 30
Presence of an abdominal mass (0 as none, 2 as questionable, 5 as definite)	x 10
Haematocrit of <0.47 in men and <0.42 in women	x 6
Percentage deviation from standard weight	x 1

* One point each is added for each set of complications:

- The presence of joint pains (arthralgia) or frank arthritis
- Inflammation of the iris or uveitis
- Presence of erythema nodosum, pyoderma gangrenosum, or aphthous ulcers
- Anal fissures, fistulae or abscesses
- Other fistulae
- Fever during the previous Week.

Remission of CD is defined as a CDAI score of ≤ 150. Severe disease was defined as a value of greater than 450.[19] Most major research studies on medications in CD define response as a fall in the CDAI score of ≥ 70 points, although recommendations from the Food and Drug Administration (FDA) and European Medicines Agency (EMA) now state a minimum of a 100 point decrease.[21-23] This was the case for the GEMINI II trial where a ≥70-point decrease in the CDAI score from baseline represented a clinical response, and a ≥100-point decrease in the CDAI score from baseline represented an enhanced clinical response.[12]

3.5 Results of the GEMINI II and GEMINI III Induction studies

3.5.1 Key Induction endpoints in patients by prior TNF-α antagonist failure (third-line indication)

To further understand the benefit of vedolizumab in patients with CD, the key efficacy endpoints of clinical remission, clinical response (defined as a ≥70 point decrease in the CDAI score [CDAI-70]), and enhanced clinical response (CDAI-100) were analysed in more detail in the subgroups of patients who had failed prior TNF-α antagonist therapy (third-line indication).

As stated in Section 3.3, GEMINI III was designed to analyse clinical remission at both

Week 6 and Week 10 in patients who had failed prior TNF-α antagonist therapy, the primary analysis population. In GEMINI II, patients in the population of prior TNF-α antagonist failures were a sub-population of the overall ITT population (Cohort 1) in the analysis at Week 6 and of the safety population in the exploratory analysis at Week 10.

This section presents additional analyses of efficacy in patients who had failed prior TNF-α antagonists in GEMINI II and further data from GEMINI III.

3.5.1.1 Efficacy of vedolizumab in clinical remission, clinical response, and enhanced clinical response in CD patients who previously failed TNF-α antagonist therapy (third-line indication)

Clinical remission at Week 6

In GEMINI II, clinical remission at Week 6 in the TNF-α antagonist failure sub-population of Cohort 1 was achieved by 10.5% of vedolizumab patients and 4.3% of placebo patients (95% CI for difference from placebo: -9.1, 21.3; *P* value not tested) (Table 2 and Figure 1). In the exploratory analysis of patients who had failed TNF-α antagonist treatment in the safety population, clinical remission at Week 10 was achieved by a greater percentage of patients than at Week 6 for both the vedolizumab (16.0%) and placebo (8.6%) groups (95% CI for difference from placebo: 0.2, 14.6; *P* value not tested) (Figure 1).[12]

In the TNF-α antagonist failure population of GEMINI III, no statistically significant difference was observed between the vedolizumab and placebo groups for the proportion of patients in clinical remission at Week 6. Of the 158 patients who received vedolizumab, 24 (15.2%) achieved clinical remission at Week 6 compared with 19 of 157 (12.1%) patients who received placebo. The treatment difference from placebo was 3.0% (95% CI: -4.5, 10.5; *P*=0.433) (Table 2).[13]

Clinical remission at Week 10

The proportions of patients who achieved clinical remission at Week 10 in the TNF-α antagonist failure ITT sub-population of GEMINI II and GEMINI III Induction studies are summarised by treatment group in Table 2 and Figure 1 below.

In GEMINI II, clinical remission at Week 10 in the TNF-α antagonist failure population was achieved by 14.3% of vedolizumab patients and 8.6% of placebo patients (95% CI for difference from placebo: (-3.7, 15.1; *P* value not tested) (Table 2).[17]

In the TNF-α antagonist failure sub-population of GEMINI III, 26.6% of vedolizumab-treated patients and 12.1% of placebo-treated patients achieved clinical remission at Week 10; the treatment difference from placebo was 14.4%. The proportion of TNF-α antagonist failure patients who achieved clinical remission at Week 10 increased from 15.2% at Week 6 to 26.6% at Week 10 in the vedolizumab group with the placebo group unchanged from Week 6 (12.1%; *P*=0.001) (see Table 2 and Figure 1).[13,24]

Sustained clinical remission

The proportion of patients who achieved sustained clinical remission (defined as a ≥150-point reduction in the CDAI score at both Week 6 and Week 10) in the TNF-α antagonist failure population was 12.0% of vedolizumab-treated patients and 8.3% receiving placebo; the treatment difference from placebo was 3.7% (Table 2).

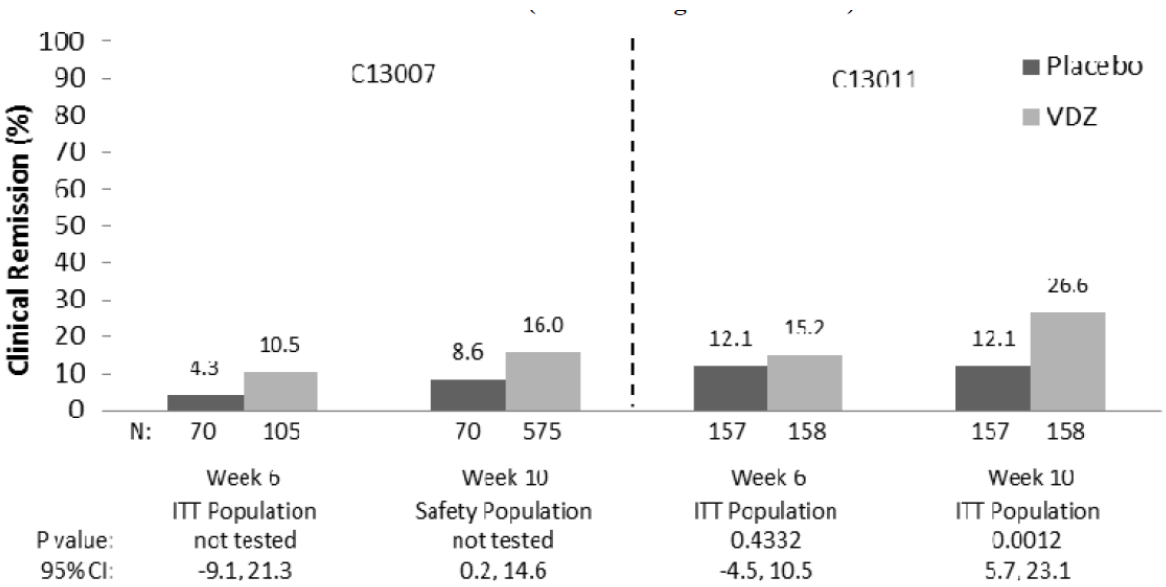
Table 2: Clinical remission at Week 6 and Week 10 in TNF-α antagonist failure patients - Induction studies GEMINI II and GEMINI III, and sustained clinical remission in TNF-α antagonist failure patients from GEMINI III

Endpoint	GEMINI II		GEMINI III	
Clinical remission at Week 6[a]				
N	PLA N=70	VDZ N=105	PLA N=157	VDZ N=158
Number (%) achieving clinical remission	3 (4.3)	11 (10.5)	19 (12.1)	24 (15.2)
95% CI	(0.9, 12.0)	(5.3, 18.0)	(7.0, 17.2)	(9.6, 20.8)
Difference from placebo[b]		6.2		3.0
95% CI for difference from placebo		(-9.1, 21.3)		(-4.5, 10.5)
P value	NT	NT		0.433
Clinical remission at Week 10[a]				
N	PLA N=70	VDZ N=105	PLA N=157	VDZ N=158
Number (%) achieving clinical remission	6 (8.6)	15 (14.3)	19 (12.1)	42 (26.6)
95% CI	(2.0, 15.1)	(7.6, 21.0)	(7.0, 17.2)	(19.7, 33.5)
Difference from placebo[b]		5.7		14.4
95% CI for difference from placebo		(-3.7, 15.1)		(5.7, 23.1)
P value	NT	NT		0.001
Sustained clinical remission[c]				
N			PLA N=157	VDZ N=158
Number (%) achieving clinical remission			13 (8.3)	19 (12.0)
95% CI			(4.0, 12.6)	(7.0, 17.1)
Difference from placebo[b]				3.7
95% CI for difference from placebo				(-2.9, 10.3)
P value				0.2755

Abbreviations: PLA = placebo; VDZ = vedolizumab; CI = confidence interval; NT = not tested
[a] Clinical remission is defined as CDAI score ≤ 150 points.
[b] Difference and 95% CI: adjusted percent vedolizumab - adjusted percent placebo and its 95% CI.
Sustained clinical remission is defined as clinical remission at both Week 6 and Week 10

Source: Sands et al., 2014;[13] CSR C13007;[17] CSR C13011.[24]

Figure 1: Clinical remission at Week 6 and 10 in the GEMINI II and GEMINI III studies (TNF-α antagonist failures)



Source: CSR C13007;[17] CSR C13011.[24]

Clinical response (CDAI-70) and enhanced clinical response (CDAI-100)

Patients who achieved a clinical response (≥70 point decrease in CDAI score from baseline [CDAI-70]) after receiving vedolizumab during Induction were considered responders and were entered into the Maintenance arm of the trial. Clinical (CDAI-70) response is a clinically meaningful endpoint that represents an improvement in symptoms of CD, and is also consistent with medical practice of continuing patients who respond to Induction treatment on to Maintenance treatment. Thus, CDAI-70 response was assessed in the TNF-α antagonist failure population in the Induction studies of GEMINI II and GEMINI III.

In the population of patients who had failed TNF-α antagonist treatment, the percentage of patients achieving CDAI-70 response was consistently greater in the vedolizumab group than the placebo group at Week 6 in GEMINI II and at Week 6 and Week 10 in GEMINI III (Figure 2 and Table 3); greater efficacy with vedolizumab over placebo was also observed for CDAI-100 response at Week 6 in GEMINI III (Figure 3). In the exploratory analysis of patients who had failed TNF-α antagonist treatment in the safety population of GEMINI II, the percentages of patients achieving CDAI-100 response and CDAI-70 response at Week 10 were greater with vedolizumab than with the placebo (Figure 2 and Figure 3).[17,24]

Table 3: Clinical response (CDAI-70) at week 10 (TNF-α antagonist failure population in GEMINI II)

Clinical response at Week 10 (Failure population)[a]		
N	PLA N=70	VDZ N=105
Number (%) achieving clinical response	16 (22.9)	34 (32.4)
95% CI	(13.0, 32.7)	(23.4, 41.3)
Difference from placebo[b]		9.5
95% CI for difference from placebo		(-3.8, 22.8)

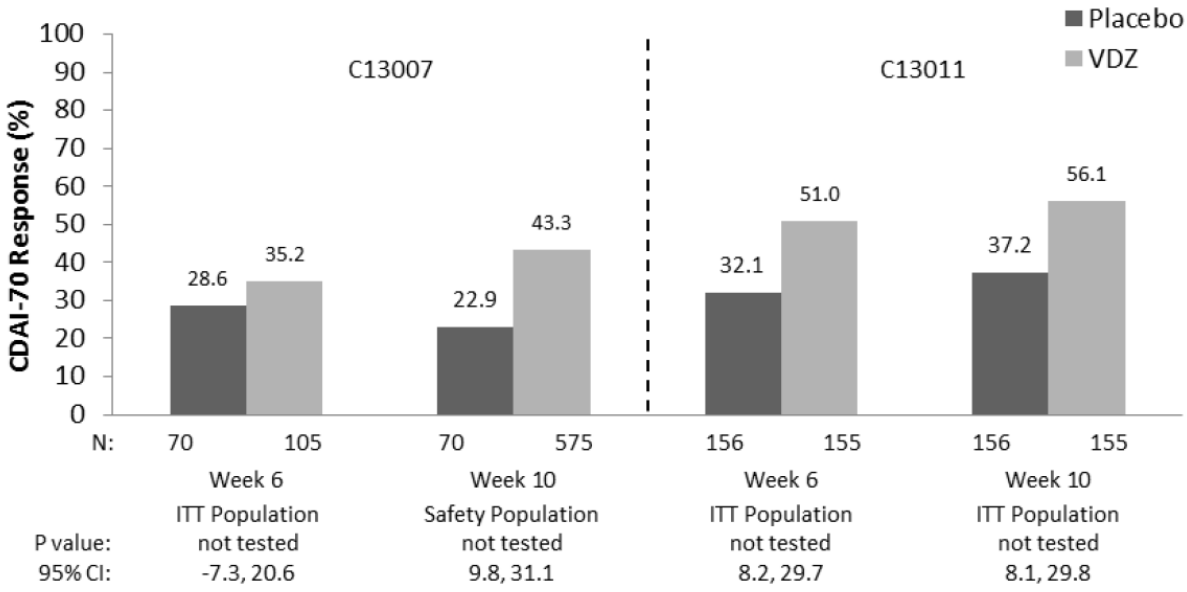
Abbreviations: PLA = placebo; VDZ = vedolizumab; CI = confidence interval

[a] Clinical response is defined as a >=70-point decrease in CDAI score from baseline

[b] Difference and 95% CI: adjusted percent vedolizumab - adjusted percent placebo and its 95% CI. Adjustment is based on the CMH chi-square test, with stratification according to: 1) concomitant use of oral corticosteroids (yes/no); 2) previous exposure to anti-TNF and/or concomitant immunomodulator use (yes/no)

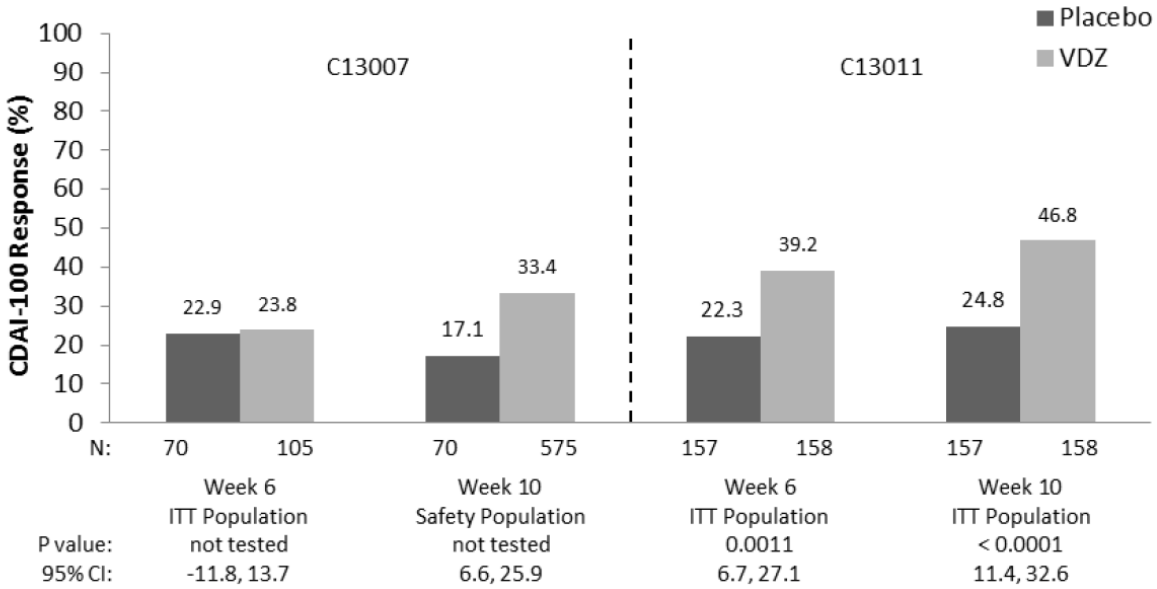
Source: CSR C13007.[17]

Figure 2: Clinical (CDAI-70) response at Weeks 6 and 10 in studies GEMINI II and GEMINI III (TNF-α failures)



Source: CSR C13007; [17] CSR C13011.[24]

Figure 3: Enhanced clinical (CDAI-100) response at Weeks 6 and 10 in studies GEMINI II and GEMINI III ((TNF-α failures)



Source: CSR C13007;[17] CSR C13011.[24]

3.5.1.2 Efficacy of vedolizumab in CD patients based on the number of previously failed TNF-α antagonist therapies

GEMINI II

The proportions of patients in the Induction study population of GEMINI II who had previously failed TNF-α antagonist therapy and achieved clinical remission at Week 6 are summarised by treatment group and number of previously failed TNF-α antagonist therapies (of a total of 3 different TNF-α antagonists currently approved for the treatment of CD) in Table 4. A trend favouring vedolizumab was observed among patients who had previously failed at least 2 TNF-α antagonist therapies, with a greater proportion of vedolizumab-treated patients achieving clinical remission at Week 6 (12.5%) compared with those who received placebo (2.4%). The treatment difference from placebo was 10.1% (95% CI -10.2, 29.8). Among patients who had previously failed only 1 TNF-α antagonist therapy, little difference was observed between the vedolizumab and placebo groups for the proportions of patients who achieved clinical remission at Week 6.[17]

Trends were observed for patients whose worst previous TNF-α antagonist failure type was inadequate response or loss of response. Greater proportions of vedolizumab-treated patients whose worst previous failure type was inadequate response or loss of response achieved clinical remission at Week 6 (10.7% and 12.5%, respectively) compared with patients who received placebo (2.4% and 0%, respectively). The treatment differences from placebo were 8.3% (95% CI -11.9, 27.9) and 12.5% (95% CI -13.5, 37.7), respectively. There were insufficient patient numbers indicating intolerance as their worst previous TNF-α

antagonist failure type to draw any meaningful comparisons between the vedolizumab and placebo treatment groups (Table 4).[17]

GEMINI III

Further analyses of clinical remission at Week 6 and at Week 10 in GEMINI III in patients with CD who failed prior TNF-α antagonist treatment by the number of TNF-α antagonists therapies and reason for failure show that, in general, a greater percentage of patients receiving vedolizumab compared to placebo achieved clinical remission and support the clinical relevance of vedolizumab induction treatment (Table 4).

Patients who had failed prior TNF-α antagonist treatment represented 76% of the study population in GEMINI III. The subgroups by number of TNF-α antagonists failed and reason for failure have an adequate number of patients to assess clinical remission. Across the two sub-groups by number of TNF-α antagonists failed and 3 sub-groups by reason for failure in GEMINI III, the percentage of patients in clinical remission at Week 6 was generally greater in the vedolizumab treatment group than in the placebo group, and the treatment effect favouring vedolizumab increased from Week 6 to Week 10 in all sub-groups, regardless of the number of agents failed or the reason for failure (Table 4). The increased frequency of clinical remission with vedolizumab treatment at Week 10 supports the need for additional dosing in patients who have not initially responded.[24]

Table 4: Clinical remission at Week 6 in GEMINI II and GEMINI III, and at Week 10 in GEMINI III, and enhanced clinical response at Week 6 in GEMINI III by number of TNF-α antagonist therapies previously failed and reason for failure (TNF-α antagonist failure sub-population)

	GEMINI II (Induction, Cohort 1)		GEMINI III			
	Week 6		Week 6		Week 10	
Sub-population	**PLA N=148**	**VDZ N=220**	**PLA N=157**	**VDZ N=158**	**PLA N=157**	**VDZ N=158**
Clinical remission[a]						
1 TNF-α antagonist failure, n	28	49	43	59	43	59
Number (%) achieving clinical remission	2 (7.1)	4 (8.2)	6 (14.0)	6 (10.2)	7 (16.3)	20 (33.9)
95% CI	(0.9, 23.5)	(2.3, 19.6)	(3.6, 24.3)	(2.5, 17.9)	(5.2, 27.3)	(21.8, 46.0)
Difference from placebo		1.0		-3.8		17.6
95% CI for difference from placebo[b]		(-22.1, 24.1)		(-16.7, 9.1)		(1.3, 34.0)
≥2 TNF-α antagonist failures, n	42	56	111	96	111	96
Number (%) achieving clinical remission	1 (2.4)	7 (12.5)	13 (11.7)	17 (17.7)	12 (10.8)	21 (21.9)
95% CI	(0.1, 12.6)	(5.2, 24.1)	(5.7, 17.7)	(10.1, 25.3)	(5.0, 16.6)	(13.6, 30.1)
Difference from placebo		10.1		6.0		11.1
95% CI for difference from placebo[b]		(-10.2, 29.8)		(-3.7, 15.7)		(1.0, 21.2)
Enhanced clinical response at Week 6[c]						
1 TNF-α antagonist failure, n	NR	NR	43	59	NR	NR
Number (%) achieving clinical response	NR	NR	8 (18.6)	27 (45.8)	NR	NR
95% CI	NR	NR	(7.0, 30.2)	(33.1, 58.5)	NR	NR
Difference from placebo	NR	NR		27.2	NR	NR
95% CI for difference from placebo[b]	NR	NR		(9.9, 44.4)	NR	NR
≥2 TNF-α antagonist failures, n	NR	NR	111	96	NR	NR
Number (%) achieving clinical response	NR	NR	26 (23.4)	33 (34.4)	NR	NR
95% CI	NR	NR	(15.5, 31.3)	(24.9, 43.9)	NR	NR
Difference from placebo	NR	NR		11.0	NR	NR
95% CI for difference from placebo[b]	NR	NR		(-1.4, 23.3)	NR	NR
Reason for failure						

Sub-population	GEMINI II (Induction, Cohort 1)		GEMINI III			
	Week 6		Week 6		Week 10	
	PLA N=148	VDZ N=220	PLA N=157	VDZ N=158	PLA N=157	VDZ N=158
Inadequate response	41	56	67	66	67	66
Number (%) achieving clinical remission[a]	1 (2.4)	6 (10.7)	7 (10.4)	14 (21.2)	7 (10.4)	19 (28.8)
95% CI	(0.1, 12.9)	(4.0, 21.9)	NR	NR	NR	NR
Difference from placebo[b]		8.3		10.8		18.3
95% CI for difference from placebo		(-11.9, 27.9)	NR	NR	NR	NR
Loss of response	22	40	103	100	103	100
Number (%) achieving clinical remission[a]	0 (0.0)	5 (12.5)	13 (12.6)	15 (15.0)	14 (13.6)	
95% CI	(0.0, 15.4)	(4.2, 26.8)	NR	NR	NR	NR
Difference from placebo[b]		12.5		2.4		11.4
95% CI for difference from placebo		(-13.5, 37.7)	NR	NR	NR	NR
Intolerance	7	9	69	63	69	63
Number (%) achieving clinical remission[a]	2 (28.6)	0 (0.0)	8 (11.6)	8 (12.7)	6 (8.7)	16 (25.4)
95% CI	(3.7, 71.0)	(0.0, 33.6)	NR	NR	NR	NR
Difference from placebo[b]		-28.6		1.0		16.7
95% CI for difference from placebo		(-70.9, 19.8)	NR	NR	NR	NR

Abbreviations: PLA = placebo; VDZ = vedolizumab; CI = confidence interval; NR = not reported

[a] Clinical remission is defined as CDAI score ≤150 points

[b] Difference and 95% CI: adjusted percent vedolizumab - adjusted percent placebo and its 95% CI

[c] Enhanced clinical response is defined as a≥100-point reduction in CDAI score from baseline

Source: CSR C13007;[17] CSR C13011.[24]

3.5.1.3 Efficacy of Induction treatment with vedolizumab on clinical remission and CDAI-100 response at Week 6 and Week 10 - a pooled analysis of the GEMINI II and GEMINI III trials

A *post hoc* analysis of data from the GEMINI II and III studies was carried out in patients with CD and previous TNF-α antagonist failure and in those who were TNF-α antagonist naïve. Data were pooled from the two trials of patients who received IV Induction therapy with vedolizumab 300mg or placebo at Weeks 0, 2, and 6. For the TNF-α antagonist failure subgroup, proportions of patients in clinical remission (CDAI ≤150) and those with a CDAI-100 response (≥100 point decrease in CDAI score) were evaluated at Weeks 6 and 10. Week 6 responders in GEMINI II who were re-randomised to placebo were included in the Week 10 analyses.[25]

The proportion of patients in clinical remission was significantly higher with vedolizumab than with placebo at Week 10, but not at Week 6, for the TNF-α antagonist failure sub-group (Table 5).[25]

In conclusion, in patients with CD for whom TNF-α antagonists had failed, remission and CDAI-100 response rates were higher with vedolizumab Induction therapy than with placebo. In patients with previous TNF-α antagonist failure, the Week 10 (but not Week 6) remission rate was significantly higher with vedolizumab than with placebo.[25]

Table 5: Clinical remission and CDAI-100 response at Week 6 and 10 in TNF-α antagonist failure and TNF-α antagonist naïve patients – a pooled analysis of GEMINI II and GEMINI III

	Number (%) of patients [P-value[a]]	
	TNF-α antagonist failure	
Endpoint	**PLA N=227**	**VDZ N=263**
Week 6 clinical remission	22 (9.7) [-]	35 (13.3) [0.157]
Week 10 clinical remission	25 (11.0) [-]	57 (21.7) [0.0008]
Week 6 CDAI-100 response	51 (22.5) [-]	87 (33.1) [0.005]
Week 10 CDAI-100 response	51 (22.5) [-]	103 (39.2) [<0.0001]

Abbreviations: PLA = placebo; VDZ = vedolizumab; CDAI = Crohn's Disease Activity Index; TNF = tumour necrosis factor
[a] P-value versus placebo and based on the CMH chi-square test

Source: Sandborn et al., 2014a.[25]

3.5.2 Clinical response in vedolizumab-treated patients who did not achieve response at Week 6 (TNF-α antagonist failure population from GEMINI II) - a *post hoc* analysis

In GEMINI II, patients who received vedolizumab during the Induction Phase and did not respond at Week 6 ("Delayed Response" Population) were assigned to receive vedolizumab Q4W during the Maintenance Phase; this assignment was not randomised. Of those patients

who had not responded to vedolizumab during Induction (n = 86 from Cohort 1; n = 265 from Cohort 2; total = 351), 6.8% (24 patients) achieved clinical remission at Week 10 (an additional 4 weeks of treatment/1 additional infusion), and 10.5% (37 patients) achieved clinical remission at Week 14 (an additional 8 weeks of treatment/2 additional infusions) (Table 6). [17,26]

Table 6: Clinical remission and enhanced clinical response at Week 10 and Week 14 in patients who did not achieve clinical response at Week 6 – delayed response population

	Week 6 Non-responders[a]			
	Induction Cohort 1 ITT population		Induction Cohort 2 open-label	
Endpoint	**PLA N=69**	**VDZ N=86**	**VDZ N=265**	**VDZ (Combined) N=351**
Clinical remission[b]				
Number (%) achieving endpoint at Week 10	3 (4.3)	4 (4.7)	20 (7.5)	24 (6.8)
95% CI	(0.0, 9.2)	(0.2, 9.1)	(4.4, 10.7)	(4.2, 9.5)
Number (%) achieving endpoint at Week 14	7 (10.1)	9 (10.5)	28 (10.6)	37 (10.5)
95% CI	(3.0, 17.3)	(4.0, 16.9)	(6.9, 14.3)	(7.3, 13.8)
Enhanced clinical response[c]				
Number (%) achieving endpoint at Week 10	5 (7.2)	12 (14.0)	44 (16.6)	56 (16.0)
95% CI	(1.1, 13.4)	(6.6, 21.3)	(12.1, 21.1)	(12.1, 19.8)
Number (%) achieving endpoint at Week 14	8 (11.6)	16 (18.6)	60 (22.6)	76 (21.7)
95% CI	(4.0, 19.1)	(10.4, 26.8)	(17.6, 27.7)	(17.3, 26.0)

Abbreviations: CI = confidence interval; ITT = intent-to-treat; PLA = placebo; VDZ = vedolizumab
[a] Patients who did not achieve clinical response at Week 6 and were designated as non-responders in the IVRS.
[b] Clinical remission is defined as CDAI score ≤ 150 points.
[c] Enhanced clinical response is defined as a ≥100-point reduction in CDAI score from baseline.

Source: Sandborn et al., 2014b ;[26] CSR C13007.[17]

In a *post hoc* subgroup analysis of these endpoints by prior TNF-α antagonist failure status indicated more patients who had not previously failed this type of therapy achieved clinical remission and enhanced clinical response at Week 52 compared with those who had previously failed TNF-α antagonist therapy (Table 7).[17]

Table 7: Clinical remission and enhanced clinical response at Week 52 – evaluation in subgroups based on prior TNF-α antagonist failure (Delayed response population)

Endpoint	PLA N=69	VDZ Q4W (Cohort 1) N=86	VDZ Q4W (Cohort 2) N=265
Clinical remission[a]			
N	31	50	184
Number (%) achieving clinical remission	2 (6.5)	6 (12.0)	22 (12.0)
95% CI	(0.8, 21.4)	(4.5, 24.3)	(7.6, 17.5)
Difference from placebo		5.5	5.5
95% CI for difference from placebo		(-16.9, 27.4)	(-13.4, 24.4)
Number (%) achieving enhanced clinical response[b]			
N	31	50	184
Number (%) achieving enhanced clinical response	1 (3.2)	9 (18.0)	36 (19.6)
95% CI	(0.1, 16.7)	(8.6, 31.4)	(14.1, 26.0)
Difference from placebo		14.8	16.3
95% CI for difference from placebo		(-7.8, 36.1)	(-2.6, 34.9)

Abbreviations: PLA = placebo; VDZ = vedolizumab; Q4W = dosing every 4 weeks; CI = confidence interval
[a] Clinical remission is defined as CDAI score ≤150
b Enhanced clinical response is defined as a ≥100-point decrease in CDAI score from baseline

Source: CSR C13007.[17]

3.5.3 Patient reported outcomes (Induction Phase GEMINI II and GEMINI III)

3.5.3.1 HRQoL outcomes in the TNF-α antagonist failure population

HRQoL scores in the Induction Phase from baseline for patients who were TNF-α antagonist failures in GEMINI II and GEMINI III is shown in Table 8.

IBDQ

Patients receiving Induction therapy with vedolizumab in GEMINI III in the TNF-α antagonist failure population achieved greater improvements in the IBDQ total score and on all the IBDQ domain scales at Week 6 and Week 10 compared to patients receiving placebo (Table 8). The improvements in HRQoL in the vedolizumab groups were considered to be clinically meaningful improvements defined as:

- **IBDQ:** An increase of ≥16 points in the IBDQ total score, ≥5 in IBDQ Bowel Function scores, ≥6 in IBDQ Emotional Function Scores, or ≥2.5 in IBDQ systemic and Social Function scores represents a clinically meaningful improvement in quality of life for patients.

- **SF-36:** An increase of ≥5 points in the Physical Component Scale, the Mental Component Scale, and SF-36 subscales represents a clinically meaningful improvement in quality of life for patients.

- **EQ-5D:** A decrease of ≥ 0.3 points in the EQ-5D score represents a clinically meaningful improvement in HRQOL for patients.

- **EQ-5D VAS:** An increase of ≥7 points in the EQ-5D VAS score represents a clinically meaningful improvement in quality of life for patients.[17,24]

SF-36

For the TNF-α antagonist failure population, although the vedolizumab treatment group achieved a greater increase in the Week 6 and Week 10 SF-36 physical and mental component summary scores compared to the placebo group, the 95% CI for the treatment difference included zero, with the exception of the Week 10 SF-36 mental component summary score (Table 8).[17,24]

EQ-5D

For the TNF-α antagonist failure patients receiving vedolizumab in GEMINI II, the decrease in EQ-5D score at Week 6 from baseline was not considered clinically meaningful (see Table 8).

EQ-5D VAS

For TNF-α antagonist failure patients receiving vedolizumab in GEMINI III, the increases in the EQ-5D VAS scores were considered clinically meaningful improvements in HRQoL at both Week 6 and Week 10 (Table 8). Compared to patients receiving placebo, patients receiving vedolizumab demonstrated significant improvements on the EQ-5D VAS scores at both Week 6 and Week 10.[24]

Table 8: Changes in HRQoL in TNF-α antagonist failure population from baseline to Week 6 in GEMINI II and from baseline to Week 6 and Week 10 in GEMINI III

	GEMINI II		GEMINI III	
HRQoL component	**Placebo**	**Vedolizumab**	**Placebo**	**Vedolizumab**
IBDQ Total Score[a] Week 6	n=69	n=104	n=150	n=154
Adjusted Mean change from baseline (95% CI)[b]	13.0 (5.8, 20.2)	15.3 (9.4, 21.2)	14.6 (9.7 to 19.4)	24.0 (19.2 to 28.7)
Difference in adjusted change from baseline vs placebo, Mean (95% CI)[c]		2.3 (-7.0, 11.6)		9.4 (2.6 to 16.2)
IBDQ Total Score[a] Week 10			n=144	n=152
Adjusted Mean change from baseline (95% CI)[b]			15.4 (10.2 to 20.6)	28.3 (23.3 to 33.3)
Difference in adjusted change from baseline vs placebo, Mean (95% CI)[c]				12.9 (5.7 to 20.1)

HRQoL component	GEMINI II		GEMINI III	
	Placebo	Vedolizumab	Placebo	Vedolizumab
SF-36 Physical Component Summary Score[a] Week 6	n= 67	n= 103	n=150	n=154
Adjusted Mean change from baseline (95% CI)[b]	1.6 (-0.1, 3.2)	3.0 (1.7, 4.3)	2.2 (1.2 to 3.3)	3.3 (2.3 to 4.3)
Difference in adjusted change from baseline vs placebo, Mean (95% CI)[c]		1.4 (-0.7, 3.5)		1.1 (–0.4 to 2.5)
SF-36 Mental Component Summary Score[a] Week 6	n= 67	n= 103	n=150	n=154
Adjusted Mean change from baseline (95% CI)[b]	1.2 (-1.2, 3.6)	2.4 (0.4, 4.3)	3.0 (1.5 to 4.6)	4.1 (2.6 to 5.7)
Difference in adjusted change from baseline vs placebo, Mean (95% CI)[c]		1.2 (-1.9, 4.3)		1.1 (–1.1 to 3.3)
SF-36 Physical Component Summary Score[a] Week 10			n=144	n=152
Adjusted Mean change from baseline (95% CI)[b]			3.4 (2.2 to 4.5)	4.6 (3.5 to 5.7)
Difference in adjusted change from baseline vs placebo, Mean (95% CI)[c]				1.2 (–0.4 to 2.8)
SF-36 Mental Component Summary Score [a] Week 10			n=144	n=152
Adjusted Mean change from baseline (95% CI)[b]			1.7 (0.1 to 3.4)	5.3 (3.7 to 6.9)
Difference in adjusted change from baseline vs placebo, Mean (95% CI)[c]				3.5 (1.2 to 5.8)
EQ-5D Score[a] Week 6	n= 69	n= 103		
Adjusted Mean change from baseline (95% CI)[b]	-0.2 (-0.6, 0.1)	-0.2 (-0.5, 0.1)		
Difference in adjusted change from baseline vs placebo, Mean (95% CI)[c]		0.0 (-0.4, 0.5)		
EQ-5D VAS Score[a] Week 6	n= 69	n= 100	n=148	n=152
Adjusted Mean change from baseline (95% CI)[b]	1.7 (-3.2, 6.6)	2.7 (-1.3, 6.8)	3.9 (0.8 to 7.0)	9.7 (6.7 to 12.8)
Difference in adjusted change from baseline vs placebo, Mean (95% CI)[c]		1.0 (-5.3, 7.4)		5.8 (1.4 to 10.2)
EQ-5D VAS Score[a] Week 10			n=141	n=148
Adjusted Mean change from baseline (95% CI)[b]			2.6 (–0.6 to 5.8)	12.7 (9.6 to 15.8)
Difference in adjusted change from baseline vs placebo, Mean (95% CI)[c]				10.1 (5.6 to 14.5)

Abbreviations: SE = Standard Error; CI=confidence interval; EQ=EuroQol; HRQoL=health-related quality of life; IBDQ=Inflammatory Bowel Disease Questionnaire; SF-36=Short Form-36; VAS=visual analogue scale.

[a] Higher IBDQ, SF-36, EQ-5D, and EQ-5D VAS scores indicate improvements in HRQoL

[b] Mean changes were adjusted for individual baseline measurements.

[c] Difference = adjusted mean change for vedolizumab – adjusted mean change for placebo.

Source: CSR C13007;[17] CSR C13011.[24]

3.6 Summary of Induction treatment (GEMINI II and GEMINI III) with vedolizumab in TNF-α antagonist failures

Clinical remission at Week 6 and Week 10

In the GEMINI II Induction study, a trend was observed in patients who had previously failed TNF-α antagonist therapy, with a greater proportion of vedolizumab-treated patients achieving clinical remission at Week 6 (10.5%) compared with patients who received placebo (4.3%). The treatment difference from placebo was 6.2% (95% CI -9.1, 21.3).[12] For patients who were TNF-α antagonist failures in GEMINI III, vedolizumab was not statistically significantly better than placebo for the primary efficacy endpoint of clinical remission at Week 6. The treatment difference from placebo was 3.0% (*P*=0.433) and the relative risk of achieving clinical remission at Week 6 was 1.2 (95% CI 0.7, 2.2).[13] However, vedolizumab was better than placebo in the Induction of clinical remission at Week 10 in the TNF-α antagonist failure population of GEMINI III. The treatment difference from placebo was 14.4% (*P*=0.001).[13]

Clinical response (CDAI-70) and Enhanced clinical response (CDAI-100)

In the population of patients who had failed TNF-α antagonist treatment, the percentage of patients achieving CDAI-70 response was consistently greater in the vedolizumab group than the placebo group at Week 6 in GEMINI II and at Week 6 and Week 10 in GEMINI III; greater efficacy with vedolizumab over placebo was also observed for CDAI-100 response at Week 6 in GEMINI III in the TNF-α antagonist failure population. The treatment difference from placebo was 16.9%. Although a trend in favour of vedolizumab was observed for enhanced clinical response at Week 6 in GEMINI II, the difference between the vedolizumab and placebo groups was not statistically significant (23.8% vs. 22.9%; 95% CI: -11.8, 13.7). However, the use of CDAI-100 response as an endpoint was requested by the FDA, and it represents a relatively strict definition of response.[17,24]

Patient-reported outcomes

As rated by IBDQ, SF-36 (physical and mental components), and EQ-5D VAS instruments, improvements in HRQoL at Week 6 were numerically greater for patients who received vedolizumab compared to patients who received placebo. The magnitude of improvement in total score as well as in the IBDQ subscales in vedolizumab-treated patients was clinically meaningful according to minimally important difference cut-offs.

In conclusion, the Induction data from GEMINIII and GEMINI III shows that TNF-α antagonist failure patients with experience with 1 to 3 prior agents, the clinical effect takes longer to be realised (Week 6), but is significant by Week 10. This is reflected in the SmPC where its states that *"Induction of remission in Crohn's disease may take up to 14 weeks in some patients."*[11] In all patients studied, the early benefit of vedolizumab treatment is further seen after 1 year of therapy.

3.7 Results of the GEMINI II Maintenance study

3.7.1 Exploratory subgroup analyses

Among patients who had previously failed TNF-α antagonist therapy, a greater proportion of vedolizumab-treated patients in the Q8W and Q4W treatment groups achieved the primary endpoint of clinical remission at Week 52 and the secondary endpoints of enhanced clinical response and corticosteroid-free remission at Week 52 compared with patients who received placebo (see Table 9).

Among patients who had previously failed TNF-α antagonist therapy, greater proportions of vedolizumab-treated patients in the Q8W and Q4W treatment groups achieved the primary endpoint of clinical remission at Week 52 and the secondary endpoints of enhanced clinical response and corticosteroid-free remission at Week 52 compared with patients who received placebo. The results observed in this subgroup of patients for clinical remission in both vedolizumab groups, for enhanced clinical response in the vedolizumab Q4W group, and for corticosteroid-free clinical remission in the vedolizumab Q8W group were consistent with the statistically significant treatment differences observed in the overall Maintenance Study ITT Population. The other treatment differences favoured the vedolizumab groups, but the 95% CIs included 0.

Treatment differences from placebo for the endpoints of clinical remission and corticosteroid-free clinical remission at Week 52 were higher for the vedolizumab Q8W treatment group than for the Q4W treatment group, whereas for the endpoint of enhance clinical response, the treatment difference from placebo was greater in the Q4W group (Table 9).

Among patients who had failed TNF-α antagonists and who responded to vedolizumab Induction treatment in GEMINI II, clinical remission at Week 52 was achieved by 28% of vedolizumab Q8W treatment group (95% CI for difference from placebo: 3.0, 27.5). 27.3% of the vedolizumab Q4W treatment group (95% CI for difference from placebo: 2.0, 26.9), and 12.8% of the placebo treatment group (Table 9).[17]

The results observed in this subgroup of patients for clinical remission in both vedolizumab groups, and for corticosteroid-free clinical remission in the vedolizumab Q8W group, were consistent with the statistically significant treatment differences observed in the overall Maintenance Study ITT Population.

The results at Week 52 in GEMINI II support the efficacy with continued vedolizumab treatment beyond Week 6 seen in GEMINI III.

Table 9: Key Maintenance efficacy endpoints in TNF-α antagonist failure patients – Maintenance study ITT population (GEMINI II)

Response at Week 52	Patients with prior TNF-α antagonist failure		
	PLA N=78	VDZ Q8W N=82	VDZ Q4W N=77
Number (%) achieving clinical remission[a]	10 (12.8)	23 (28.0)	21 (27.3)
95% CI	(5.4, 20.2)	(18.3, 37.8)	(17.3, 37.2)
Difference from placebo[b]		15.2	14.5
95% CI for difference from placebo		(3.0, 27.5)	(2.0, 26.9)
Number (%) achieving enhanced clinical response[c]	16 (20.5)	24 (29.3)	29 (37.7)
95% CI	(11.6, 29.5)	(19.4, 39.1)	(26.8, 48.5)
Difference from placebo[b]		8.8	17.1
95% CI for difference from placebo		(-4.6, 22.1)	(3.1, 31.2)
	N=38	N=41	N=43
Number (%) achieving corticosteroid-free clinical remission[d]	0	10 (24.4)	7 (16.3)
95% CI	(0.0, 9.3)	(12.4, 40.3)	(6.8, 30.7)
Difference from placebo[b]		24.4	16.3
95% CI for difference from placebo		(2.4, 45.1)	(-5.7, 37.0)

Abbreviations: PLA = placebo; VDZ = vedolizumab; Q8W = dosing every 8 weeks; Q4W = dosing every 4 weeks; CI = confidence interval

[a] Clinical remission is defined as CDAI score ≤ 150 points.

[b] Difference and 95% CI: adjusted percent vedolizumab - adjusted percent placebo and its 95% CI.

[c] Enhanced clinical response is defined as a ≥ 100-point reduction in CDAI score from baseline.

[d] Corticosteroid-free clinical remission is defined as patients using oral corticosteroids at baseline who had discontinued corticosteroids and were in clinical remission at Week 52.

Source: CSR C13007.[17]

The proportions of TNF-α antagonist failure patients in the Maintenance Study population who achieved clinical remission, enhanced clinical response, and corticosteroid-free clinical remission at Week 52 are summarised by treatment group and worst failure type in Table 10.

Among patients whose worst failure type to TNF-α antagonist therapy was inadequate response (primary failures), greater proportions of vedolizumab-treated patients in the Q8W and Q4W treatment groups achieved the primary endpoint of clinical remission at Week 52, and the secondary endpoints of enhanced clinical response and corticosteroid-free remission at Week 52 compared with patients who received placebo. The result observed in this subgroup of patients for clinical remission in the vedolizumab Q8W group was consistent with the statistically significant treatment difference observed in the overall Maintenance Study ITT Population. The other treatment differences from placebo favoured vedolizumab, but the 95% CIs included 0.

Among patients whose worst failure type to TNF-α antagonist therapy was loss of response, treatment differences from placebo favoured the vedolizumab Q4W group for the primary endpoint of clinical remission at Week 52, and the secondary endpoint of enhanced clinical response at Week 52; however, the 95% CIs included 0. For the secondary endpoint of corticosteroid-free remission at Week 52, treatment differences from placebo favoured both vedolizumab groups; however, the 95% CIs included 0.

Among patients whose worst failure type to TNFα antagonist therapy was intolerance, treatment differences from placebo favoured the vedolizumab groups for the primary endpoint of clinical remission at Week 52, and the secondary endpoint of enhanced clinical response at Week 52; however, the 95% CIs included 0. For the endpoint of corticosteroid-free remission, the small number of patients precludes interpretation of results.[17]

Table 10: Key Maintenance efficacy endpoints by worst failure type – TNF-α antagonist failure patients in the Maintenance Study (GEMINI II)

Response at Week 52 worst failure type	PLA N=78	VDZ Q8W N=82	VDZ Q4W N=77
Clinical remission[a]			
Inadequate response	N=35	N=37	N=31
Number (%) achieving endpoint	3 (8.6)	13 (35.1)	7 (22.6)
95% CI	(1.8, 23.1)	(20.2, 52.5)	(9.6, 41.1)
Difference from placebo[b]		26.6	14.0
95% CI for difference from placebo		(3.3, 47.4)	(-10.5, 36.9)
Loss of response	N=29	N=35	N=33
Number (%) achieving endpoint	6 (20.7)	7 (20.0)	9 (27.3)
95% CI	(5.9, 35.4)	(6.7, 33.3)	(12.1, 42.5)
Difference from placebo[b]		-0.7	6.6
95% CI for difference from placebo		(-20.5, 19.1)	(-14.6, 27.8)
Intolerance	N=14	N=10	N=13
Number (%) achieving endpoint	1 (7.1)	3 (30.0)	5 (38.5)
95% CI	(0.2, 33.9)	(6.7, 65.2)	(13.9, 68.4)
Difference from placebo[b]		22.9	31.3
95% CI for difference from placebo		(-18.4, 58.5)	(-8.1, 62.1)
Enhanced clinical response[c]			
Inadequate response	N=35	N=37	N=31
Number (%) achieving endpoint	7 (20.0)	13 (35.1)	11 (35.5)
95% CI	)6.7, 33.3)	(19.8, 50.5)	(18.6, 52.3)
Difference from placebo[b]		15.1	15.5
95% CI for difference from placebo		(-5.2, 35.4)	(-5.9, 36.9)
Loss of response	N=29	N=35	N=33
Number (%) achieving endpoint	7 (24.1)	8 (22.9)	13 (39.4)
95% CI	(8.6, 39.7)	(8.9, 36.8)	(22.7, 56.1)
Difference from placebo[b]		-1.3	15.3
95% CI for difference from placebo		(-22.2, 19.6)	(-7.6, 38.1)

Response at Week 52 worst failure type	PLA N=78	VDZ Q8W N=82	VDZ Q4W N=77
Intolerance	N=14	N=10	N=13
Number (%) achieving endpoint	2 (14.3)	3 (30.0)	5 (38.5)
95% CI	(1.8, 42.8)	(6.7, 65.2)	(13.9, 68.4)
Difference from placebo[b]		15.7	24.2
95% CI for difference from placebo		(-25.1, 52.8)	(-15.4, 56.4)
Corticosteroid-free clinical remission[d]			
Inadequate response	N=19	N=20	N=17
Number (%) achieving endpoint	0 (0.0)	6 (30.0)	3 (17.6)
95% CI	(0.0, 17.6)	(11.9, 54.3)	(3.8, 43.4)
Difference from placebo[b]		30.0	17.6
95% CI for difference from placebo		(-0.5, 57.7)	(-14.8, 48.5)
Loss of response	N=13	N=17	N=23
Number (%) achieving endpoint	0 (0.0)	4 (23.5)	4 (17.4)
95% CI	(0.0, 24.7)	(6.8, 49.9)	(5.0, 38.8)
Difference from placebo[b]		23.5	17.4
95% CI for difference from placebo		(-12.8, 55.2)	(-16.7, 48.9)
Intolerance	N=6	N=4	N=3
Number (%) achieving endpoint	0 (0.0)	0 (0.0)	0 (0.0)
95% CI	NA	NA	NA
Difference from placebo[b]		NA	NA
95% CI for difference from placebo		NA	NA

Abbreviations: PLA = placebo; VDZ = vedolizumab; Q8W = dosing every 8 weeks; Q4W = dosing every 4 weeks; CI = confidence interval; NA = Not applicable

[a] Clinical remission is defined as CDAI score ≤ 150 points.

[b] Difference and 95% CI: adjusted percent vedolizumab - adjusted percent placebo and its 95% CI.

[c] Enhanced clinical response is defined as a ≥ 100-point reduction in CDAI score from baseline.

[d] Corticosteroid-free clinical remission is defined as patients using oral corticosteroids at baseline who had discontinued corticosteroids and were in clinical remission at Week 52.

Source: CSR C13007.[17]

The proportions of TNF-α antagonist failure patients in the Maintenance Study of GEMINI II who achieved clinical remission, enhanced clinical response, and corticosteroid-free clinical remission at Week 52 are summarised by treatment group and number of previously failed TNF-α antagonist therapies in Table 11.

Among patients who had previously failed at least 2 TNF-α antagonist therapies, greater proportions of vedolizumab-treated patients in the Q8W and Q4W treatment groups achieved the primary endpoint of clinical remission at Week 52, and the secondary endpoints of enhanced clinical response and corticosteroid-free remission at Week 52 compared with patients who received placebo. The results observed in this subgroup of patients for clinical remission at Week 52 and enhanced clinical response at Week 52 in the vedolizumab Q4W group were consistent with the statistically significant treatment differences observed in the overall Maintenance Study ITT Population. The other treatment differences from placebo favoured vedolizumab, but the 95% CIs included 0. Among patients

who had previously failed only 1 TNF-α antagonist therapy, treatment differences from placebo favoured both vedolizumab groups for the primary endpoint of clinical remission at Week 52, and the secondary endpoint of corticosteroid-free remission at Week 52; however, the 95% CIs included 0. For the secondary endpoint of enhanced clinical response at Week 52, the treatment difference from placebo favoured the vedolizumab Q8W group; however, the 95% CI included 0.

Table 11: Key Maintenance efficacy endpoints by number of previously failed TNF-α antagonist therapies - TNF-α antagonist failure population (GEMINI II)

Response at Week 52 worst failure type Number of previously failed TNF-α antagonist therapies	PLA N=78	VDZ Q8W N=82	VDZ Q4W N=77
Clinical remission[a]			
Number of previously failed therapies: 1	N=25	N=33	N=31
Number (%) achieving endpoint	4 (16.0)	13 (39.4)	7 (22.6)
95% CI	(4.5, 36.1)	(22.9, 57.9)	(9.6, 41.1)
Difference from placebo[b]		23.4	6.6
95% CI for difference from placebo		(-2.9, 46.9)	(-19.7, 31.9)
Number of previously failed therapies: ≥2	N=53	N=49	N=46
Number (%) achieving endpoint	6 (11.3)	10 (20.4)	14 (30.4)
95% CI	(2.8, 19.9)	(9.1, 31.7)	(17.1, 43.7)
Difference from placebo[b]		9.1	19.1
95% CI for difference from placebo		(-5.1, 23.2)	(3.3, 34.9)
Enhanced clinical response[c]			
Number of previously failed therapies: 1	N=25	N=33	N=31
Number (%) achieving endpoint	8 (32.0)	13 (39.4)	9 (29.0)
95% CI	(13.7, 50.3)	(22.7, 56.1)	(13.1, 45.0)
Difference from placebo[b]		7.4	-3.0
95% CI for difference from placebo		(-17.4, 32.1)	(-27.3, 21.3)
Number of previously failed therapies: ≥2	N=53	N=49	N=46
Number (%) achieving endpoint	8 (15.1)	11 (22.4)	20 (43.5)
95% CI	(5.5, 24.7)	(10.8, 34.1)	(29.2, 57.8)
Difference from placebo[b]		7.4	28.4
95% CI for difference from placebo		(-7.8, 22.5)	(11.1, 45.6)
Corticosteroid-free clinical remission[d]			
Number of previously failed therapies: 1	N=8	N=17	N=17
Number (%) achieving endpoint	0 (0.0)	5 (29.4)	1 (5.9)
95% CI	(0.0, 36.9)	(10.3, 56.0)	(0.1, 28.7)
Difference from placebo[b]		29.4	5.9
95% CI for difference from placebo		(-11.5, 65.1)	(-34.3, 45.0)
Number of previously failed therapies: ≥2	N=30	N=24	N=26
Number (%) achieving endpoint	0 (0.0)	5 (20.8)	6 (23.1)
95% CI	(0.0, 11.6)	(7.1, 42.2)	(9.0, 43.6)
Difference from placebo[b]		20.8	23.1
95% CI for difference from placebo		(-6.4, 45.9)	(-3.3, 47.2)

Response at Week 52 worst failure type Number of previously failed TNF-α antagonist therapies	PLA N=78	VDZ Q8W N=82	VDZ Q4W N=77
Abbreviations: PLA = placebo; VDZ = vedolizumab; Q8W = dosing every 8 weeks; Q4W = dosing every 4 weeks; CI = confidence interval [a] Clinical remission is defined as CDAI score ≤ 150 points. [b] Difference and 95% CI: adjusted percent vedolizumab - adjusted percent placebo and its 95% CI. [c] Enhanced clinical response is defined as a ≥ 100-point reduction in CDAI score from baseline. [d] Corticosteroid-free clinical remission is defined as patients using oral corticosteroids at baseline who had discontinued corticosteroids and were in clinical remission at Week 52.			

Source: CSR C13007.[17]

3.8 Summary of Maintenance treatment (GEMINI II) with vedolizumab in TNF-α antagonist failures

For patients who previously failed prior TNF-α antagonist therapy, a clinical benefit for vedolizumab dosed Q8W and Q4W was seen for the endpoints of clinical remission, enhanced clinical response and corticosteroid-free remission at Week 52. The results observed in this subgroup of patients for clinical remission in both vedolizumab groups, for enhanced clinical response in the vedolizumab Q4W group, and for corticosteroid-free clinical remission in the vedolizumab Q8W group were consistent with the results observed in the overall Maintenance Study ITT Population.

3.9 Long-term efficacy of vedolizumab (up to 2 years)

The purpose of this analysis was to demonstrate the long-term efficacy (up to 2 years) of vedolizumab in patients with moderate to severely active CD, including patients that had failed on ≥1 anti-TNF. Eligible patients from GEMINI II (i.e. those that completed Induction (0-6 weeks) and Maintenance phases (weeks 6-62) could enrol in the long-term, open-label extension study (GEMINI LTS), see Section 3.2.

For pre-specified analyses for the efficacy population of GEMINI II, the Harvey-Bradshaw Index (HBI) was used to assess the proportion of patients in clinical remission (i.e. HBI score ≤4 points) and clinical response (i.e. decrease in HBI score of ≥3 points from baseline) at Weeks 52, 80, and 104.[27]

Of 814 patients treated with vedolizumab in GEMINI II, 295 completed Week 52 assessments and entered into the open-label GEMINI LTS. Clinical remission outcomes at Weeks 52, 80, and 104 are shown in Table 12.

Table 12: Clinical remission up to 2 years in GEMINI II completers - TNF-α failure population

Endpoint	TNF-α antagonist failure (n=136)
Clinical remission (HBI score ≤4 points)	
Week 52	70 (52)
Week 80	76 (56)
Week 104	69 (51)
Clinical response (decrease in HBI score of ≥3 points from baseline)	
Week 52	NR
Week 104	95 (70)

Source: Hanauer et al., 2014.[27]

Among completers with previous TNF-α antagonist failure, clinical remission was seen in 51% of patients and clinical response in 70% of patients at Week 104.[27]

3.10 Conclusion of the efficacy of vedolizumab in the TNF-α antagonist failure population

In conclusion, the results of GEMINI II demonstrate that vedolizumab is an effective treatment for patients with moderately to severely active CD, in patients who had experienced failure of TNF-α antagonist therapy (including primary failures).

Full analyses of Week 6 and Week 10 Induction data have been provided in the above sections for GEMINI II and GEMINI III (see Sections 3.5.1, 3.5.2, 3.5.3, and 3.7.1). When evaluating across both clinical remission and CDAI-100 response, what can be seen is that the clinical benefit in the TNFα antagonist failure population relative to placebo increases noticeably over this 4-week period. This is likely attributable to the refractory nature of the TNF-α antagonist failure patients enrolled in the studies (more than half of the patients in the TNF- α antagonist failure population of GEMINI II had failed more than 2 agents), who require this slightly longer treatment period to realize the full effect of vedolizumab. What is important to note is that, as evident in GEMINI II and GEMINI LTS, a statistically and clinically meaningful treatment effect is seen in all patients when treatment is continued out to 2 years.

The GEMINI III trial suggests that vedolizumab provides benefit for the population of patients who have moderately to severely active CD and have failed 1 or more TNF-α antagonists and have limited remaining treatment options. The efficacy data suggest that in patients who have previously failed TNF-α antagonist treatment the effects of vedolizumab on clinical remission may not become evident until between weeks 6 and 10. This is reflected in the SmPC where its states that *"Induction of remission in Crohn's disease may take up to 14 weeks in some patients."*[11]

As a result of the GEMINI II and GEMINI III studies, these findings support the proposed dosing recommendation at Weeks 0, 2, and 6 in the Summary of Product Characteristics (SmPC).[11]

3.11 Safety of vedolizumab in the TNF-α antagonist failure population

The safety of vedolizumab in patients with moderately to severely active CD was presented in the original submission to NICE, by Takeda UK, on the 22nd August 2014. There is no new safety data to present specifically for the TNF-α antagonist failure population.

In summary, vedolizumab is a safe and tolerable option for patients with CD and has no identified systemic immunosuppressive activity. Integrated analysis of safety in the database of 3,326 patients with CD and UC, some of whom have received vedolizumab for up to 4 years, shows that chronic treatment with vedolizumab has an acceptable risk profile. A higher frequency of upper respiratory tract infections including nasopharyngitis was observed in patients receiving vedolizumab compared to placebo in the controlled study. Given the treatment benefit with vedolizumab, this potential risk is acceptable as such infections were mild to moderate and managed medically. Given vedolizumab's mechanism of action, the occurrence of serious infections and malignancies of the gastrointestinal tract could represent a theoretical risk associated with long-term treatment. The safety data to date show that the risk for serious infections with vedolizumab treatment is low and, importantly, did not increase with chronic vedolizumab treatment up to 4 years. The types of serious infections that occurred in the studies were those frequently experienced in patients with CD and can be managed successfully.

Notably, there was no increased risk for infections with concomitant immunosuppressant and/or corticosteroid therapy, and there was no signal of increased risk for serious opportunistic infections, including PML, that are typically reported in immunosuppressed patients and those receiving TNF-α antagonist treatment or natalizumab (Tysabri®), another type of integrin receptor antagonist. Overall, results from the clinical program to date suggest no increased risk for malignancy with vedolizumab treatment; however, the number of malignancies was small and long-term exposure was limited. Continued observation of patients receiving long-term vedolizumab treatment will clarify the risk profile for serious infections and malignancy.

3.12 Conclusion

In conclusion, the results of GEMINI II demonstrate that vedolizumab is an effective treatment for patients with moderately to severely active CD, including patients who had experienced failure of TNF-α antagonist therapy (including primary failures) as well as in those naïve to TNF-α antagonists.

The GEMINI III trial suggests that vedolizumab provides benefit for the overall population of patients who have moderately to severely active CD and have failed conventional therapy, as well as for those who have failed 1 or more TNF-α antagonists and have limited remaining treatment options. The efficacy data suggest that in patients who have previously

failed TNF-α antagonist treatment the effects of vedolizumab on clinical remission may not become evident until between weeks 6 and 10. This is reflected in the SmPC where its states that *“Induction of remission in Crohn's disease may take up to 14 weeks in some patients.”*

4. Updated cost-effectiveness evidence

The following table provides an overview of the main modifications made to the economic evaluation and to the model originally submitted to NICE 6 October 2014.

MODIFICATIONS TO THE MODEL:
• Inclusion of response assessment time-points after induction therapy reflective of the SmPCs recommendations for each biologic agent • Health states cost update, including new clinical experts' survey on quantities of resource and use of most up to date English costs (2013-14) • Drug costs and doses update using the November 2014 BNF issue no. 68 • Inclusion of costs for initial adalimumab administration • Revision of cost of surgery based on HES data • Inclusion of surgery probability derived from HES data • Revision of AES list, probabilities, impact on quality of life and costs • CD excess mortality applied to the moderately to severely active CD state only • Adjustment of AEs (dis)utilities using population norm (0.91) • Improved transparency on use of GEMINI II and III efficacy and discontinuation probabilities • PAS update to [redacted]
MODIFICATIONS TO THE BASE CASE SETTINGS:
• Target population: TNF-α antagonists failure population • Comparator: Conventional Treatment (CT) • Assessment timepoint: 10 weeks for vedolizumab, 6 weeks for infliximab, 4 weeks for adalimumab (efficacy data, dosage costs, and transition probabilities have been adjusted accordingly) • Vedolizumab price: updated PAS price [redacted] • Time horizon: lifetime
NEW EXPLORATORY ANALYSES FOR COMPARISONS OF COST VS. TNF-α ANTAGONISTS:
• For adalimumab, use of accelerated induction dose and exploration of the impact of the escalated maintenance dose for both adalimumab and infliximab.

4.1 Revised treatment pathway positioning for vedolizumab

The economic model for vedolizumab has been updated to address key concerns highlighted in the Appraisal Consultation Document (ACD) of December 2014,[16] in particular those mentioned under sections 4.12 - 4.18: "Consideration of the evidence: Cost effectiveness". In addition, the other key changes have been to focus on the TNF-α antagonist failure sub-population, and an improved PAS of [redacted] per 300mg vedolizumab vial. The re-focussing on the TNF-α antagonist failure sub-population reflects feedback from the NICE Appraisal Committee (Section 4.2 and 4.17 in the ACD) that this

reflects the area of greatest unmet clinical need and the most likely positioning in the treatment pathway for CD for vedolizumab after patients have failed on conventional therapy and then subsequently have failed to respond to, or lost response to TNF-α antagonists, or for whom these therapies are considered unsuitable (e.g. which may be due to intolerance issues). The two licensed TNF-α antagonists are infliximab and adalimumab. In Section 4.17 of the ACD it has been recognised that the population in whom a TNF-α antagonist has failed are those clinical experts think are "the people for whom access to a new agent [vedolizumab] would be of most value because of the very limited treatment options available to them" (page 52 ACD). This has also been confirmed by clinical expert opinion obtained by Takeda through a questionnaire survey conducted recently (February 2015) with 8 clinicians based in England (see Section 4.4.3). The clinicians were asked the following question:

"Where do you see vedolizumab ideally fitting into the treatment pathway for moderately to severely active CD?"

The responses are reported in Table 13, which indicates support for the use of vedolizumab in a TNF-α antagonist failure population, in particular after failure of a first TNF-α antagonist, or in patients who are intolerant or contraindicated to a TNF-α antagonist. In sum, in this patient population vedolizumab offers an effective therapy with a novel mechanism of action which is different from the TNF-α antagonists, with a potentially better adverse event (AE) profile.

Table 13: Responses of clinicians to a question on ideal positioning of vedolizumab in the CD treatment pathway

Clinician respondent	**Response to question:** "Where do you see vedolizumab ideally fitting into the treatment pathway for moderately to severely active CD?"
1	Anti-TNF failure population
2	Anti-TNF failure population
3	Anti-TNF failure population, or patients with intolerance or contraindications to anti-TNFs
4	Anti-TNF failure population of where the use of anti-TNFs is not suitable, e.g. in cases of previous malignancies or TB exposure
5	First anti-TNF failure population. A trial vs 2nd TNF would be useful
6	The Anti-TNF naive population is more important – lack of systemic immunosuppression
7	Anti-TNF failure population until real world evidence emerges
8	Anti-TNF failure – whenever the use of anti-TNFs is a less safe option (e.g. in the elderly, patients with co-morbidities or previous malignancy), and patients in whom systemic immunosuppression is problematic

4.2 Patient populations considered

The aim of this revised economic evaluation was to evaluate the cost effectiveness of vedolizumab in adult patients with moderately to severely active CD who had an inadequate response with, lost response to, or were intolerant to a TNF-α antagonist. Patients who fail on a TNF-α antagonist do so either because of inadequate or no response (defined as primary failure) or because of loss of response over time (defined as secondary failure).

These patients represented a sub-group of those included in the GEMINI II clinical trial (CSR C13007)[17] and GEMINI III clinical trial (CSR 13011).[24] In this sub-population, patients had moderately to severely active CD, defined as a CDAI score greater than of 220 - 450, and documented unsuccessful previous treatment (i.e. inadequate response, loss of response or intolerance) with one or more conventional therapies (e.g. glucocorticoids or immunosuppressants such as azathioprine and 6-mercaptopurine) and one or more TNF-α antagonists. This is in line with clinical practice in England in that all moderately to severely active CD patients would be expected to be treated with CT first, prior to use of a biologic agent.

The TNF-α antagonist failure sub-group represented 50% of the ITT GEMINI II trial population, and 76% of the ITT GEMINI III trial population. In CD patients a distinction between moderate and severe disease is not particularly relevant for clinical practice as, for the purposes of drug treatment choices, patients presenting with moderate or relatively more severe CD (as defined by a CDAI score) will tend to be treated in the same way, and CDAI score measurement and endoscopic investigations to strictly define the level of severity are not typically performed in routine clinical practice. Patients with acute severe CD that represents a medical emergency and requires prompt inpatient treatment (including in many cases emergency surgery) have been excluded from the economic analysis as these are outside the vedolizumab target patient population and licensed indication.

4.3 Comparators considered

The following comparators and approach to analysis has been performed in the revised economic evaluation:

- A base case comparison with continued non-biological conventional therapy (CT), comprising a mix of 5-ASAs, corticosteroids and immunomodulators.

- Exploratory analyses comparing vedolizumab against the use of a second TNF-α antagonist after failure or intolerance to the first (either infliximab or adalimumab used as second TNF-α antagonist).

The rationale for the comparison with CT is that relatively robust evidence exists from the GEMINI II and GEMINI III trials for this comparison - all patients received background CT therapy so the placebo arms were used as representative of the CT comparator. The continued use of CT remains an option in the cases of intolerance to a TNF-α antagonist, or when further TNF-α antagonist use is unlikely to be effective or appropriate. A further rationale for performing a relatively robust comparison with CT in this patient population is that it provides a benchmark for assessing the absolute cost-effectiveness of vedolizumab. In the original submission a base case ICER of £98,500 per QALY gained was estimated for vedolizumab vs. CT in a TNF-α antagonist failure population, which was considered by the Committee to be substantially outside the range normally considered to be a cost-effective use of NHS resources. Hence, despite recognising this was an area of unmet clinical need, it could not recommend vedolizumab for treating moderately to severely active CD in people for whom a TNF-α antagonist had failed (page 52 of the ACD). In the revised analysis presented below, we demonstrate that the original ICER estimate was inaccurate and through the improvements made to the model and the closer attention given to the failure

sub-population analysis, more robust and improved cost-effectiveness results for vedolizumab vs. CT have been estimated. The main changes to the model relating to the primary analysis of vedolizumab vs. CT is presented below in Section 4.4.

The TNF-α antagonists are accepted for use in England by NICE in only a restricted patient population with severe active CD,[28] and are not specifically licensed for use in TNF-α antagonist failure patients. However, currently in clinical practice, typically if a patient has failed on a first TNF-α antagonist then (assuming the patient is not intolerant) they would try switching to a different TNF-α antagonist, and would expect to need to dose escalate above the standard maintenance dose in order to maintain efficacy (see Section 4.5). Hence, in failure patients who have failed or are intolerant to a first TNF-α antagonist, an alternative TNF-α antagonist represents a potentially relevant comparator based on current clinical practice, even though it is not 'ideal practice' to use the same class of drug that patients have previously failed with. In terms of evidence our systematic review (SR) reported in the original submission identified no RCTs for either infliximab or adalimumab covering patients who had an inadequate response to a prior TNF-α antagonist (i.e. primary failures). The SR identified the sub-populations of the GEMINI II and III studies for vedolizumab covering primary and secondary failures,[17,24] and two studies for adalimumab (one for the induction phase, and one for the maintenance phase of treatment) that contained a sub-group of patients who had experienced secondary failure on a prior TNF-α antagonist (i.e. prior infliximab). However, primary failure patients were excluded from this study.[10,29] Hence, these patients did not match the patients defined as failures in the vedolizumab trials (which included both primary and secondary failures), making a comparison problematic in the NMA (see Section 4.5). For infliximab, there was no relevant RCT evidence in a TNF-α antagonist failure population, hence an indirect comparison vs. infliximab was not possible.

Due to the limited data for the a TNF-α antagonist comparators, a robust assessment of the cost-effectiveness of vedolizumab vs. use of a second TNF-α antagonist was not possible. The ERG also noted that the NMA for TNF-α antagonist failures originally submitted may have overestimated efficacy for adalimumab due to the exclusion of patients with a primary non-response to a TNF-α antagonist (Section 3.36 of the ACD), and the committee accepted the studies included were non-comparable (Section 4.10 of the ACD). For these reasons only, exploratory analyses against adalimumab and infliximab have been performed, focussing on a comparison of the relative costs of the biologic agents. The NMA in failure patients has nonetheless been updated to include the additional study identified for adalimumab in Maintenance treatment[29] (only Induction studies were included in the original submission). However, this study also has the same limitation as the adalimumab Induction studies in that it includes only secondary failures. The NMA is included in this submission to provide support for an assumption that vedolizumab is likely to have at least equal efficacy as adalimumab for the purposes of the exploratory analysis. The additional model modifications made for comparisons with TNF-α antagonist comparators, and results are reported separately in Section 4.5 below.

4.4 Main changes in the model and economic evaluation

4.4.1 Overview of changes in response to Appraisal Committee concerns

Within the context of an updated submission in TNF-α antagonist failure patients and with improved PAS, the following sub-sections present in detail the changes that have been made to the economic model, primarily to address the main concerns outlined by the NICE Appraisal Committee in Sections 4.12-4.18 of the ACD. In addition, a number of other modifications have been made that have not been specifically highlighted in the ACD but were mentioned by the ERG or were thought anyway to be improvements in the robustness of the economic evaluation. We have made modifications to improve the model addressing as many of the criticisms that have been possible to cover in the timeframe for the response. The model enables comparisons with conventional therapy, and with other biologic agents and our modifications have covered criticisms that are relevant to both or either comparison. However, for reasons summarised in Section 4.3 above, we have focussed on a comparison with CT as this can be performed relatively robustly in the TNF-α antagonist failure patient population, and due to major limitations in the ability to perform a robust NMA for the comparison with TNF-α antagonists. However, we still detail the main model changes we have made relating to parameters for the TNF-α antagonists in summary below, and also in Section 4.5.

Table 14 below provides a summary of the main modifications to the model structure, input data and/or assumptions that have been made in the time available in order to address the criticisms outlined in the ACD relating to the cost-effectiveness analysis. The modifications are based on the Appraisal Committee (AC) consideration of the evidence with a focus on Sections 4.12 – 4.18. The Sections below do not cover all details of the modelling methods used, and in general those aspects of the model that have not changed from the original submission are not covered in this updated evidence submission. The focus is on those aspects that have been updated.

Table 14: Model modifications relating to concerns expressed in the ACD consideration of the cost-effectiveness evidence for vedolizumab in CD

AC/ERG concern	ACD Section(s)	Company comment	Revisions to the model
Target population: The results from the mixed population do not provide useful information, as treatment decisions would be influenced by whether a patient had previously had TNF-α antagonist treatment. There is high unmet need in the TNF-α antagonist failure population. There is also a high clinical need in the sub-group of patients who cannot take anti-TNF because they are contraindicated or not tolerated.	4.17, 4.2 (and 3.25)	The revised model is now focused only on the TNF-α antagonist failure subgroup. The primary analysis consists of a comparison with conventional therapy using the direct GEMINI II and III trial evidence in the TNF-α antagonist failure subgroup. There is however a lack of robust comparator evidence to inform the comparisons vs. TNF-α antagonists in this sub-group, as recognised by in the ACD (3.36 and 4.10). Because the data are not available for infliximab and are not comparable for adalimumab, we have limited our analysis vs. a second TNF-α antagonist to an exploratory analysis assuming equal efficacy between TNF-α antagonists and vedolizumab. We currently do not have access to trial data on the specific sub-group of patients who cannot take a second TNF-α antagonist due to not tolerating the first TNF-α antagonist.	We have adapted the model functionality and data inputs to allow for such exploratory analysis to be conducted (see Section 4.5).
Dosing assumption: Same induction phase duration assumed for all therapies (6 weeks) – this was considered a weakness because the dosing assumptions did not give an accurate estimate of costs and clinical outcomes in clinical practice.	4.13 (and 4.5, 3.58)	The model has been amended to reflect the marketing authorisations for vedolizumab and the TNF α antagonists, and to reflect clinical practice rather than clinical trial alignment. Therefore, vedolizumab assessment is now modelled at week 10 as per SmPC recommendation as this provides a sufficient duration over which to assess vedolizumab response. Week 6 assessment as in the original model is not expected to detect all patients who respond to treatment (vedolizumab mechanism of action leads to slower response than other biologic therapies but clinical feedback was that week 10 is an appropriate time point to decide whether to stop treatment due to non-response) . In addition, the SmPC states that non-responders can be offered a further dose at week 10 with assessment at week 14. However, this possibility	The model has been amended so that patients now receive: • Three induction doses with vedolizumab 300mg (at 0, 2 and 6 weeks) and assessment of response at 10 weeks, with responders commencing 8 weekly 300mg maintenance regimen from week 14. • Two induction doses with infliximab 100mg (5mg/kg at 0 and 2 weeks) with assessment at week 6, and with responders commencing 8 weekly 5mg/kg maintenance regimen from week 6. • Two induction doses with adalimumab 40mg (accelerated induction regimen of 160mg at week 0 and 80mg at week 2) with assessment at week, and responders starting the maintenance dose at week 4.

AC/ERG concern	ACD Section(s)	Company comment	Revisions to the model
		has not been included as data on outcomes associated with a further dose in non-responders defined by change in CDAI less than 70 is not readily available from the trial data in a failure population. Hence, the model is based on applying in the NHS a treatment continuation rule beyond the third induction dose at 6 weeks of a response (CDAI ≥70 reduction) at week 10, with vedolizumab treatment ceased in all non-responders by the 10 week time point.	(See Section 3.4.5.9). In the exploratory analysis (Section 4.5) we have explored the impact on results of a proportion of patients being prescribed adalimumab escalated dose (40mg weekly) or infliximab escalated dose (10mg/kg).
Treatment continuation assumption: The ERG considered that a discontinuation rule (of one year) maybe appropriate for patients in remission, but not for patients whose disease is not in stable clinical remission. However, the AC Committee heard from clinical experts that they would not wish people to continue treatment if it was not needed, and concluded that the company's approach to discontinuing biological treatment after 1 year of maintenance therapy was reasonable, but acknowledged that treatment would be continued in patients with high risk of surgery.	4.14 (and 3.57)	We have retained 1 year of maintenance biological therapy followed by discontinuation in the base case. The model has the functionality to explore different, longer durations of treatment in scenario analysis.	No model modification was made as the original model already allowed options for investigating 2 and 3 years duration of treatment on biologics. (Within the available timescale, we could not specifically explore modelling longer duration for patients at high risk of surgery)
Modelling of surgery: The AC considered the probability (33.75%) of repeated surgery was an unreasonably high proportion, and so it is likely the model overestimates the proportion of patients having repeated surgery. In addition, the ERG highlighted that assuming the constant risk of surgery is not supported by the evidence used (Frolkis), and that Frolkis' 16.3% annual probability of surgery used in the model overestimates the number of surgeries.	4.15 (3.62)	The model has been revised to provide a common average risk of initial surgery and repeat surgery that is lower than originally used. We did not have suitable data to model subsequent surgery conditional on the type of initial surgery (as the ERG highlighted this as a possibility). However, given the revised lower probability, we believe this revised modelling approach also satisfies the ERG concerns.	We have derived a per-cycle surgery probability from a new analysis we have performed of Hospital Episode Statistics (HES) data. This was equal to 1.11% (equivalent to 7% annual surgery). This probability has been applied to the initial surgeries from the moderate-severe state, and also to follow-up surgeries (see also Section 4.4.4.7).
Surgery type and costs: The ACD noted comments from clinical experts that there was considerable variation in the number and type of surgical procedures.	4.15	In the original model and submission due to limited availability of data a simplifying assumption was used to model surgery as a single health state with a single estimated cost of £10,581 (which was	We have now derived an average surgery costs using HES data on costs and number of surgeries for the population with a primary diagnosis of CD, based on the OPCS list of surgeries (see also

AC/ERG concern	ACD Section(s)	Company comment	Revisions to the model
		inflated from Bodger et al.,[30] estimate)	Section 4.4.9).
Risk of excess mortality due to CD: The AC considered that in the absence of data suggesting otherwise, it should be assumed that the mortality rate is the same for all treatments and that the same risk should be applied to all CD health states.	4.16 (3.63)	The model originally assumed relative mortality risks of 1.3 for mild disease, 2.3 for moderate to severe, and 3.2 for surgery but we recognise the lack of data to estimate excess mortality risks for each health state.	The base case has been revised to include the general population all-cause mortality applied to all health states Because of recently identified evidence from a published meta-analysis (Duricova et al., 2010),[31] we have included in the model the option for a scenario analysis where it is assumed that patients in the moderate-severe state only have a relative mortality risk of 1.39.
Adverse events: The AC acknowledged that vedolizumab gut-selective mechanism of action could result in a more favourable side-effect profile with less systemic effects than other treatments. The AC highlighted that the company had not presented in the submission NMA adverse-event data. The AC therefore remained unaware that any substantial benefit had not been captured in the QALY calculations. In addition, the ERG criticised the inappropriate inclusion of adverse events (and impact on costs and HRQoL), because of the incorrect calculation of the cyclic probabilities, and because of GEMINI II being of insufficient size or duration to estimate the risk of uncommon AEs. The ERG also highlighted the limited details provided on the AEs utility adjustment, and that the utility adjustment because of AE disutility may overestimate the disutility as it assumes that those patients who were not experiencing the event have perfect quality of life.	4.19	The NMA "serious AE" data represented a composite endpoint. Because of no data on specific serious AEs, it was not possible to assess the impact on costs or QoL, a specific adverse events could differ greatly across treatments. Thus, we have considered a list of single AEs identified from a new survey we have conducted with eight clinical experts. This approach – rather than using the NMA trials – has provided a AE picture more consistent with real clinical practice. Although the ERG anticipated that any impact of AEs revision on the ICER would be minimal, we have nonetheless substantially revised the analysis of AEs, to better capture the impact on QoL and use of resources.	Based on our survey of clinical experts, we have revised the list of AEs included in the model. We derived the corresponding probabilities by making use of the larger sample of controlled studies reported in the biologics SPCs and have calculated the AEs cyclic probabilities taking into account the duration of the follow-ups (see Section 4.4.4.4). The AEs treatment costs and impact on QoL have also been updated. An adjustment of disutilities taking into account the population norm for baseline utility has been applied. (see Section 4.4.4.6).
Discontinuation due to adverse events: The AC noted the ERG concern about the lack of information about the estimated rates of discontinuation because of AEs. The ERG pointed out that the discontinuation rates due to AE from the	4.16	In the comparison vedolizumab vs CT, the induction and maintenance discontinuation rates for vedolizumab were based on GEMINI II and GEMINI III trial data and details have been provided in Section 4.4.4.5.	Improved transparency in the model, with the inclusion of more detailed descriptive notes.

AC/ERG concern	ACD Section(s)	Company comment	Revisions to the model
NMA were not used.			
Pooling of trial data transparency: The AC concluded that for the TNF-α antagonist population it was appropriate to derive the clinical parameters from Gemini II and Gemini III clinical trial results for the comparison with conventional non-biologic therapy (CT). However, there was a concern over a lack of information of how GEMINI II and III had been pooled for the economic analysis, and so related to this the AC concluded these parameters were subject to considerable uncertainty.	4.16	To address transparency concerns in this submission document we have provided tables showing the link between the model efficacy data and the pooled results data from the GEMINI studies (see Section 4.4.4.1).	The transparency of the model has also now been improved by removing redundant data so it is easier now to detect the link between the efficacy data and the data included in the Clinical Data worksheet via the Data Store worksheet.
Modelling the progressive nature of CD: The ERG highlighted the model pessimistic assumption that non-responders remain in the moderate-severe state until death or surgery. However, the AC seemed satisfied that for patients in whom multiple lines of therapies failed, the assumption of long-term continuation in the moderate-severe state as in the company's model is not unreasonable.	4.12	According to NICE CD Clinical Guidance 152,[3] recurrence is almost inevitable (p. 127), and spontaneous healing is uncommon (p. 15). Therefore we believe the current model sufficiently represents the progressive nature of the condition in the longer-term and we understand the AC is broadly accepting of this.	No model revision made.
Further model structural concerns: A number of further structural concerns were raised by the ERG which meant the AC was uncertain if the model was structurally sound	4.12 and 4.17 (and 3.57)	Please see Table 15 below	Please see Table 15 below

4.4.2 Model modifications relating to ERG concerns over the model structural assumptions and parameter inputs

The ACD noted the ERG concerns regarding several structural assumptions regarding the original economic model, with these concerns discussed also in the ERG report.[32] A general concern expressed by the AC was that it was uncertain whether the model was structurally sound, making the robustness of the ICER uncertain (Section 4.12 of the ACD). Appendix 1.

Table 15 summarises company responses and model improvements that were possible to perform in the available time and where data availability allows to address ERG structural assumption concerns, and also several parameterisation issues highlighted by the ERG. In addition, as several discrepancies between the results generated using the model and those from the clinical trials have been noted by the ERG for the failure population, the ERG criticisms of the predictive validity of the model and further ERG concerns are addressed in Appendix 1.

Table 15: Model modifications relating to ERG concerns over model structure and parameter inputs

ERG issue	ERG Report section(s)	Company comments	Revisions to the model or base case
Time horizon A 10-years horizon was used in the base case, which is not so appropriate for a chronic condition.	5.2.2	A lifetime horizon is the standard timeframe underpinning economic assessment models for chronic conditions such as CD, where treatments have impact on costs and outcomes over a patient's lifetime.	The model and analysis has been updated to use a lifetime horizon in the base case to better capture lifelong costs and benefits (data input). A ten-year horizon is explored in scenario analysis (this is a compromise between the short duration of the trials and the acknowledgement that the disease is a chronic disease (and as such a shorter time horizon would omit some of the long-term benefit of treatment).
Health states costs It is unclear from the Bodger et al., study [30] whether the costs associated with complications due to surgery were already included in the health states costs.	5.2.8	Resource use/cost data available from the literature are dated and are unlikely to be relevant to CD management in current clinical practice (see Section 4.4.9). Hence, an updated survey of clinical expert opinion on resource use estimates related to remission, mild and moderate—severe CD health states has been performed by the company. This involved a questionnaire based survey of eight England-based clinical experts (consultant Gastroenterologists) to estimate resource use for each health state for CD patients. The data on the use of resources associated to post-surgery complications have been provided by a previous expert survey (included in the original submission). It should be noted that double counting is avoided as the treatment for post-surgery complications does not include surgical costs, and the responses provided by clinicians concerns the medical management of CD per se, and not post-surgical complications.	We have populated the model with the newly estimated use of resources and updated costs. The most recent NHS Reference unit costs have also been applied to resources use (i.e. 2013-14),[15] and an updated cost estimate for the surgery state in the model using up to date HES data has been estimated (see Section 4.4.9).
Induction efficacy data Lack of clarity on how the percentages of responders with moderate to severe disease were derived.	5.2.6	The computation in the model has been modified to address the issue of correlation in the induction vector (see next row below). The percentage of responders with moderate-severe disease are derived from a patient-level analysis of the data from the GEMINI trials. Using the criteria for response (CDAI reduction of >= 70 points)	Patients in remission are excluded from the computation of responders who remain in the moderate-

ERG issue	ERG Report section(s)	Company comments	Revisions to the model or base case
		and moderate-severe disease 220-600, it is possible to obtain the percentage of non-remitting responders who remain in moderate-severe disease at the end of the induction phase.	severe state at the end of the induction period.
For the derivation of the initial induction vectors, the correlation between input parameters has been ignored. The company has access to patient-level GEMINI trial data on the observed initial induction vectors for patients treated with vedolizumab and conventional non-biologic therapy; these could have been used to directly calculate the initial induction vectors and preserve the correlation between inputs (for at least the mixed-ITT and anti-TNF-α failure subgroup). The ERG recognises that assumptions may however be necessary for other biologics as the company would not have access to the data.	5.2.6	We believe the ERG concerns referred to the fact that certain induction vector inputs are derived as a difference of other data (e.g. the probability of being in the mild state at the end of 6 weeks is equal to: induction response minus remission minus moderate-severe responders). The ERG provided the example that if the probability of remission is high and similar to the probability of induction response probability, then the probability of patients being in the mild state will be negative. This is a fair criticism. To address this problem they suggested to use the proportion of responders with moderate-severe disease amongst responders not in remission.	The model has been updated so that the calculations for the mild group to be based on the percentage of responders not in remission. If the percentage of responders not in remission is 0%, then all of the probabilities for responders will be 0% for mild and moderate-severe disease.
Maintenance transition probabilities For the derivation of the transition matrices, there are difficulties with parameterising the model structure, including how the transition probabilities were derived and how the model predictions were calibrated. Patient-level data from the GEMINI II could have been used to estimate the transitions between remission /mild/moderate-to-severe in patients treated with conventional therapy and vedolizumab. The ERG recognises that observed data are not available for anti-TNFs and therefore assumptions or calibration may be necessary. An	5.2.6	The main reason for the calibration approach was to estimate transition probabilities to be used in the case of continuing treatment beyond 1 year (trial period). So it was decided to utilise the trial data points at the end of induction and the end of maintenance to estimate these transition probabilities. The modelled resulting distribution of patients by the end of the maintenance phase is consistent with what we would have expected to be seen based on the trial estimates of the percentage of patients with induction response and the percentage of responding patients showing maintenance response/remission; i.e. the model 'fit' is good at generating the expected patient distribution (please see the results in the Calibration worksheet when the 6-week assessment point is set). As such, simply using the data directly from the trial should not lead to significantly different results than what we have derived using the calibration approach. For the exploratory analysis (Section 4.5), comparable efficacy for all biologics in the maintenance phase has been assumed, but there is still a need to derive estimates of the transition probabilities to model the patient flow (even if it is just one set of transition probabilities). In the exploratory comparison, the transition probabilities	No model revision has been undertaken for the comparison of vedolizumab vs. CT. In the exploratory comparison vs. TNF-α antagonists, equal efficacy has been assumed so both infliximab and adalimumab induction and maintenance efficacy data and transition probabilities are all set equal to the NMA vedolizumab rates.

ERG issue	ERG Report section(s)	Company comments	Revisions to the model or base case
assumption may be to assume the same effectiveness in the maintenance phase for all biologic treatments.		(and induction efficacy data) has been set to be equal between vedolizumab and comparators.	
The target data-points used in the fitting process relate to (a) the probability of achieving remission and (b) response (defined as a drop in CDAI score of 70 points or more) but not remission at 1-year. The company attempts to fit the proportion of patients in remission and mild health states to these target data-points. This is not correct for the second target data-point. The ERG believes that the fitting process ignores those patients who achieved response but had moderate to severe disease and therefore the target data points does not match the data point the model is fitted to, as responders to the maintenance and not in remission may be in the mild or the moderate to severe CD state.	5.2.6	The proportion of patients who are responding at 1 year but still have moderate-severe disease for all treatments is not known. Furthermore, it is assumed that any patients who are in the moderate-severe disease at 1 year o treatment will discontinue treatment at 1 year (regardless of the assumed maximum duration on biologic treatment). Thus, to allow patients to continue treatment up to the maximum set duration, these patients need to be in the mild disease or better. Thus, for all treatments and assuming 1 year maximum duration on biologics, it was assumed that all responders at 1 year are in mild disease. This is also applied for comparator treatments. If anything, this would favour the less efficacious treatment (i.e., placebo/CT), as a greater percentage of responders are likely to be in the moderate-severe disease state for the less effective treatment.	No revision made
Responders and non-responders in the moderate-severe state The non-responder group is a mix of patients with mild and moderate to severe CD (i.e. patients with a drop in CDAI score of less than 70 but with a CDAI score 150 to 220); these patients are assumed to have moderate to severe CD in the company's model. This is inappropriate.	5.2.6	This was a simplifying assumption. Patients entered the induction phase with a CDAI score between 220 and 600. The definition of response is a 70-point reduction in CDAI score. As such, it is possible that a patient may move from moderate-severe disease to mild disease but fail to achieve response. (e.g., going from 225 to 175 would be only a 50-point decrease in CDAI but would result in mild disease). However, (a) we would anticipate these numbers representing only a small percentage of the trial population, (b) we would not anticipate these numbers differing greatly across treatments, (c) we do not have these data for the other treatments, and (d) the criteria for continuing on treatment in the trials was response. So we make a simplifying assumption that non-responders remain in moderate-severe disease. Whilst we accept the limitations of this, we do not feel that this biases results in the comparisons with conventional therapy or other biologics.	No revision made
Lack of distinction between responders and non-responders with moderate to severe CD (e.g. MS responders are	5.2.2	There is a differentiation in how these patients are followed through in the model. Non-responders discontinue treatment and thus incur less favourable outcomes downstream in the model. Responders in moderate-severe disease continue on	No revision made

ERG issue	ERG Report section(s)	Company comments	Revisions to the model or base case
likely to enjoy better health than MS non-responders.)		treatment and may subsequently improve into mild disease or even eventually remission. Also, note that the input parameter estimates for health state costs and health state utilities are an average of those for the entire health state (CDAI 220-600). There is no evidence to suggest that the average utility is higher and resource use lower for responders in moderate-severe disease as compared to non-responders in moderate-severe disease. Thus, due to lack of evidence, we do not differentiate the costs and utilities between these patients within the same CDAI-based health state.	
Prognostic features of CD Potential omission of key aspects of the condition (relapsing remitting nature of CD, importance of maintaining CFR (corticosteroid-free remission)).	5.2.2	We agree that CD is a relapsing – remitting disease, such that patients experience spikes of disease activity (flares) that do spontaneously remit (or require episodic treatment with steroids). This has not been captured in the model. However, these flares have been captured as adverse events (AEs) in the GEMINI trials (e.g. in GEMINI II they are listed as Crohn's disease exacerbation), but the trial showed that the difference between vedolizumab and placebo (conventional therapy) was not significant (20.1% vs. 21.6% respectively). We therefore concluded that the ICERs would not be affected and the inclusion of the flares would just further complicate an already complex model. Moreover, to our knowledge there are no data showing a difference in flares against any of the anti-TNFs comparators. We agree that CFR is relevant. Indeed, the GEMINI trials showed that vedolizumab improves CFR. However, due to limited comparability of data for all comparators we have chosen an overall measure of remission rather than CFR. This approach is consistent with previous models in CD.	No revision made.
According to clinical expert opinion received by the ERG, following biologic discontinuation/withdrawal, the disease is likely to deteriorate, go back to baseline or worsen. However, the model assumed that there was no increase in relapse after biologics withdrawal in patients in the remission or mild health states, as patients previously in the remission or mild health states receive conventional therapy and follow the transition matrix for the maintenance phase of patients treated with conventional therapy	5.2.2	We concur that the disease is likely to deteriorate, which is why patients are allowed to go back to moderate-severe disease (or mild disease and then to moderate-severe disease) after discontinuation.	No revision made

ERG issue	ERG Report section(s)	Company comments	Revisions to the model or base case
according to their previous health state (before discontinuation from biologic treatment). The efficacy of CT was assumed to be independent of previous biological treatment. The ERG considered that this would be unlikely.			
Discontinuation of biologics The discontinuation due to lack of efficacy should have been included, based on the interpretation of the GEMINI trials. *ERG Additional analysis 5: Inclusion of lack of efficacy.* In GEMINI II, the probability of treatment failure (defined as disease worsening, need for rescue medications or surgical intervention for treatment of CD, or study drug-related AE leading to discontinuation from the study) at 1 year was 39% in the vedolizumab Q8W arm. An analysis was undertaken whereby the annual discontinuation rate was increased from 8.54% to 39% to include discontinuation due to lack of efficacy. In this analysis, the same discontinuation rate was assumed for all biologics. It should be noted that this analysis is subject to uncertainty as the transition matrices should be recalibrated but could not be done by the ERG.	5.2.2. and 5.3	We consider treatment discontinuation due to lack of efficacy at 2 stages: (1) non-responders in the induction phase discontinue their treatment at the end of induction; and (2) those responders who have lost response by year 1 will discontinue at 1 year (even if the maximum duration on therapy is set to be beyond 1 year) We chose to exclude early discontinuation in the maintenance phase due to lack of efficacy for two reasons: (1) to allow patients the possibility of transitioning back from moderate-severe disease to mild disease and (2) due to limited data on the timing of discontinuation. However, given the short duration of time during which early discontinuation due to lack of efficacy might occur, we feel that this does not bias results in comparisons between biologics. We feel that allowing patients who have lost response to continue on vedolizumab for the full year is a conservative assumption in the primary comparison with conventional therapy as these non-responders are incurring the cost of biologic therapy bit with QoL outcome associated with moderate-severe disease.	No revision made
Patients discontinue biologic following surgery in the first cycle (induction phase); but not after primary response	5.2.2	This assumption has been made because of the chronic nature of the disease and as surgery is not considered curative in CD. Therefore, if a patient had responded to treatment but required surgery, it was assumed they would resume treatment thereafter.	No revision made

4.4.3 Clinician survey

A questionnaire was administered during February 2015 via telephone interview to a total of eight clinical experts consisting of 7 consultant gastroenterologists and 1 nurse involved in CD patient management. The hospital locations of these experts were as follows: Manchester Royal Infirmary (1 consultant and 1 nurse), Royal Liverpool (1 consultant), St Marks (1 consultant), John Radcliffe, Oxford (1 consultant), Royal Devon and Exeter (1 consultant), Guys and St Thomas', London (1 consultant) and Southampton General (1 consultant).

A primary aim of the clinician survey was to obtain estimates of the current use of hospital resources in relation to each health CDAI-defined health state included in the economic model. The clinical experts were asked the following question (see Appendix 2 for the table referred to):

"*In the table below please provide estimates of the frequency in the use of any of the following resources in the medical management of patients with CD symptoms in the following health states:*

a. *Remission (defined in clinical trials as CDAI ≤ 150)*
b. *Mild CD (defined as CDAI 151-219)*
c. *Moderate to severe CD (defined in clinical trials as CDAI 220-600)*

As some patients may experience spikes of disease activity (e.g. brief period of relapse/remission), please take this into account when thinking about an average frequency of use of each resource in each health state."

The resulting estimates of resource use derived from this source and used in the economic model are presented in Section 4.4.9 below.

In addition; the survey covered the adverse events associated with biologic and non-biological treatment that are of most clinical/patient significance, for possible inclusion in the economic model. The clinical experts were asked the following question:

"Please indicate the adverse reactions which you discuss with the patient at the time of prescription, taking into account whether they will have a significant impact on health, quality of life or costs."

The responses are presented in Table 16 and was used as a source for determining which AEs to include in the updated model (see Section 4.4.8).

Table 16: List of AEs mentioned by the clinical experts and included in the revised model

Adverse event reported by clinicians	Number of clinical experts
Nasopharyngitis	All 8 clinicians mentioned it, but there was no real concern/impact
Sepsis	8 mentions
Respiratory tract infection	8 mentions
Serious infection (mainly infliximab) and other infections	8 mentions
Tuberculosis	8 mentions
Lymphoma	8 mentions
Infusion related reaction (more common with infliximab)	8 mentions
Skin problems	8 mentions
Melanoma	3 mentions
Demyelination	3 mentions
Cardiac (congestive heart failure)	1 mention
Carcinoma for lung (for smokers)	1 mention
Systemic serum sickness	1 mention
Palmer planter syndrome	1 mention
Depression (with infliximab)	1 mention

A question was also asked relating to the use of concomitant CT alongside biologic treatment;

"In practice biologic treatment with vedolizumab or an anti-TNF is expected to be provided alongside conventional therapy with aminosalicylates, corticosteroids and immunomodulators. Please could you provide an estimate of the relative intensity of such conventional therapy compared to patients who only received conventional therapy (e.g. same intensity, 50%, 75% or other?)."

The response was that in general clinicians reported that CT treatment is optimised before introducing a TNF-α antagonist. One clinician stated that the CT regimen would be reduced to 50%, and the other clinicians had varying views on how the mix of CT medicine would change. According to two clinicians, the steroids doses would remain the same or increase, whilst the remaining CT would be reduced by 25%. According to another clinician, the intensity of CT would remain unchanged, but different treatments would be used, such as methotrexate, tacrolimus, mycophenolate. One clinical expert remarked that after the introduction of a TNF-α antagonist, it may happen that some drugs are reduced in intensity but at the same time unlicensed medications are introduced (e.g. tacrolimus) which are very expensive.

A further question was posed relating to the types of non-emergency surgical procedures performed on typical patients with moderate-severe severe symptoms and requested estimates of the frequency of procedures performed as first surgeries, those performed after the first surgery (excluding surgeries for post-surgery complications), and corrective procedures to address any surgery complications. This question proved to be difficult to

answer, as the gastroenterologists pointed out that surgeons would produce more accurate estimates. Four gastroenterologists attempted to answer the question, but there was high uncertainty and variability across the responses. However, the estimates provided for the procedure of panproctolectomy with ileostomy were consistent, and we report these because useful for the modelling of the stoma nurse costs. One clinician reported that the procedure is undertaken on 2% of the total of first surgical procedures, whilst two clinicians each estimated 5%. The fourth clinician estimated that the procedure is undertaken on 10% of the total follow-up surgeries.

The survey also covered the collection of information on the amount of dose escalation of the TNF-α antagonists when used in a patients who have already failed on a TNF-α antagonist; and the frequency of use of the first TNF-α antagonist, and the appropriate vedolizumab target population (see Section 4.1 above for the last topic). The questions and outcomes relating to the TNF-α antagonists are covered in Section 4.5.

4.4.4 Main model modifications for the comparison with conventional therapy

4.4.4.1 Clinical efficacy input data

For the base case comparison of vedolizumab vs. CT, the clinical efficacy data for the TNF-α antagonist failure subgroups was derived from pooled results data from the 1 year CSR C13007 GEMINI II RCT[17] and the 10-weeks CSR C13011 GEMINI III RCT for Induction.[24] Patients in both the vedolizumab and placebo arms continued to receive CT in GEMINI II and GEMINI III; hence, the placebo arm therefore represented a suitable proxy for the comparator arm.

In terms of assessment for induction response, the model has been amended to reflect the marketing authorisation for vedolizumab,[11] and to reflect clinical practice rather than clinical trial alignment (i.e. Induction consisting of 3 doses and assessment for response at week 10, whereas the primary analysis in The GEMINI II and III trials was at week 6).

Gastroenterologist clinical opinion supported that assessment at week 10 is more in line with clinical practice expectations. Therefore, vedolizumab assessment is now modelled at week 10 as per SmPC recommendation, rather than at 6 weeks, as week 6 assessment is not expected to detect all patients who respond to vedolizumab treatment and therefore would benefit from maintenance treatment. Based on assessment at week 10 for response, the probability in the TNF-α antagonist failure sub-population of clinical response or remission during the induction and the maintenance phases for vedolizumab or CT (placebo) from the pooled GEMINI II and GEMINI III induction phase data, and GEMINI II maintenance data for the key outcomes used in the economic model are presented in Table 17 below. Previously, *post hoc* analysis of pooled GEMINI II and GEMINI III induction results in the failure population has been performed for one of the outcomes used in the economic model base case (clinical remission at week 10) and has been presented at ECCO,[25] (see Section 3.5.1.3).

Table 17: Proportion of the TNF-α antagonist failure subgroup meeting efficacy endpoints (pooled analysis of GEMINI II and III results data)

Treatment	Vedolizumab	CT
Induction phase (6 weeks of treatment)		
	N=260	**N=226**
Clinical response at week 10	121 (46.54%)	74 (32.74%)
	N=263	**N=227**
Remission at week 10	57 (21.67%)	25 (11.01%)
Maintenance phase (treatment up to week 52)		
	N=82	**N=78**
Durable response[§]	24 (29.27%)	21 (26.92%)
Remission	23 (28.05%)	10 (12.82%)
[§]Defined as response at both weeks 10 and 52		

Source: CSR C13007;[17] CSR 13011.[24] Pooled results for Induction Phase, and GEMINI II for Maintenance Phase.

As can be seen from the data in Table 17 the Induction Phase probabilities for Induction Phase response and remission in both the vedolizumab and placebo/CT arms were higher in GEMINI III than in GEMINI II, hence a scenario using only GEMINI III for induction outcomes was investigated, on the grounds that this trial was specifically designed to assess efficacy in a TNF-α antagonist failure population in the induction phase. For this scenario, GEMINI II data was still used for maintenance outcomes. In addition, as GEMINI II covered both induction and maintenance phases and was associated with lower vedolizumab and CT probabilities of response and remission, a scenario which explored the impact on the cost-effectiveness of vedolizumab vs. CT using GEMINI II failure sub-population trial data alone was performed. Table 18 presents the separate response and remission percentages for the induction phases of GEMINI II and III used in these scenarios.

Table 18: Proportion of the TNF-α antagonist failure subgroup meeting efficacy endpoints in the induction phase of GEMINI III and GEMINI II

Treatment	Vedolizumab	CT
Induction Phase – GEMINI III		
	N=155	**N=156**
Clinical response at Week 10	87 (56.1%)	58 (37.2%)
	N=158	**N=157**
Remission at Week 10	42 (26.6%)	19 (12.1%)
Induction Phase – GEMINI II		
	N=105	**N=70**
Clinical response at week 10	34 (32.4%)	16 (22.9%)
Remission at week 10	15 (14.3%)	6 (8.6%)

Source: CSR C13007; [17] CSR C13011.[24]

4.4.4.2 Proportions of patients moderately to severely active vs mild in the maintenance phase

Because of the issue of correlation in data inputs used to calculate the distribution of patients at the end of the induction period, the model has been revised to exclude patients in remission from the computation of responders who remain in the moderate-severe state at the end of the induction period.

Hence, the proportion of non-remitting responders estimated to remain in the moderately to severely active state is now 38.37% and was 24.3% in the original model (i.e. the pooled number of GEMINI II and GEMINI III responders remaining in moderately to severely active state was 33 patients out of 136, and now is 33 patients out of 86 (N=21 for vedolizumab, 12 for CT). We have not changed the assumption that these probabilities would apply regardless of treatment arm.

4.4.4.3 Transition probabilities

For the Markov model component covering the maintenance phase of treatment, transition probabilities between the remission, mild and moderately to severely active health states were calculated based on probabilities of response and remission at the end of the induction phase and at the end of the maintenance phase (i.e. the proportion of patients in each health state at the end of induction and at the end of year 1 based on the 52 week GEMINI II trial data). Because of the issue of correlation between data inputs highlighted by the ERG (see Section 3.4.5.2) and because of the new surgery probability rate included in the model (see Section 3.4.5.7) the calculation of the induction vectors have been revised. Consequently, the transition probabilities matrices have undergone a re-calibration process. The re-calibrated matrices based on the trial data are reported in Table 19.

Table 19: Re-calibrated transition probabilities for the vedolizumab and CT arms in each 8-week cycle

From/To health state	Remission	Mild	Moderately to severely active	Surgery	Sum
Vedolizumab					
Remission	0.989	0.011	0.000	0.000	1.000
Mild	0.000	0.500	0.500	0.000	1.000
Moderately to severely active	0.000	0.000	0.989	0.011	1.000
Surgery	0.787	0.115	0.087	0.011	1.000
CT					
Remission	0.831	0.169	0.000	0.000	1.000
Mild	0.000	0.601	0.399	0.000	1.000
Moderately to severely active	0.000	0.030	0.959	0.011	1.000
Surgery	0.787	0.115	0.087	0.011	1.000

Source: CCR C13007;[17] CSR C13011;[24] HES dataset.[33]

4.4.4.4 Adverse events probabilities

The AEs included in the model were selected from the clinical expert survey as those associated with current biologic treatments and most likely to have an impact on health, treatment costs or HRQoL (see Table 16). After excluding nasopharyngitis (as the clinicians acknowledged no significant impact on costs or QoL) and the AEs which only had one mention in the survey, we have revised the AEs categories included in the model as follows: serious infection (including now tuberculosis (TB) but excluding urinary tract infection as this is not likely to have as significant an impact as other serious infections), lymphoma, acute hypersensitivity reaction, non-melanoma skin cancer and other malignancies. The category of serious infection encompasses sepsis, pneumonia, tuberculosis, respiratory tract infection and bronchitis. TB is now included as part of the category of serious infection, as in the source for AE probabilities used (i.e. the SmPCs), the TB occurrence rates were not reported separately from the general serious infection rates**.**

To ensure consistency among data sources and to capture uncommon AEs reported in studies with larger samples, the probabilities of each AE in relation to the use of vedolizumab and CT were obtained from the controlled clinical studies results reported in the respective SmPCs. The probabilities of AEs for the CT arm were derived from the pooled placebo arms results from the following SmPCs: vedolizumab SmPC 17 June 2014;[11] infliximab SmPC (29 August 2014);[34] adalimumab SmPC (10 September 2014).[7]

Based on this approach, Table 20 presents the derived 8 weekly probability of each AE for vedolizumab vs. CT that have been used in the modified economic model.

Table 20: 8-weekly probabilities of AEs for vedolizumab and conventional therapy (including the induction phase)

Adverse Event	Vedolizumab*	CT**
Serious infections	1.11%	1.83%
Lymphoma	0.00%	0.01%
Acute hypersensitivity reactions	0.63%¥	0.41%
Non-melanoma skin cancer	0.00%	0.03%

*Source: vedolizumab SmPC (17 June 2014).[11]
** Pooled placebo results data obtained from vedolizumab SmPC (17 June 2014);[11] infliximab SmPC (29 August 2014);[34] adalimumab SmPC (10 September 2014).[7]
¥ Vedolizumab infusion-related reactions probability was based on the Integrated Safety Data (including C13006, C13007, C13011) reported in the SmPC (see Section 3.11).

4.4.4.5 Discontinuations due to adverse events

Discontinuation of treatment with vedolizumab in the model could be due to lack of response by the end of the induction phase or intolerable AEs. AE-induced discontinuation was assumed to occur early (i.e. during the first year of treatment only). There are some AEs that may take longer than one year to occur (such as lymphoma and tuberculosis). However, these events are very rare and it was a simplifying assumption that these AEs are unlikely to impact to any extent on discontinuation rates over the 1-3 year duration of biologic treatment periods included in the model.

To enhance transparency of the derivation of the discontinuation rates, the vedolizumab arm probabilities of discontinuation due to AEs for the TNF-α antagonist failure subgroup are summarised in Table 21 below.

Table 21: **Annual probability of vedolizumab discontinuation due to adverse events**

Treatment	% patients in the TNF-α antagonist failure subgroup	Probability of discontinuation per cycle in TNF-α antagonist failure subgroup
Induction phase		
Vedolizumab	2.69%	0.0269
Maintenance phase		
Vedolizumab	8.54%	0.0136

Source: Combined discontinuation data reported in GEMINI II and GEMINI III trials.[12,13]

4.4.4.6 Disutilities associated with treatment-related adverse events

In the original model, the estimates of disutilities for the selected AEs associated with vedolizumab and TNF-α antagonists were obtained or derived from published studies, but were not adjusted for a population norm. In the revised model, the estimates were applied to an assumed population norm of 0.91 for the UK population aged 35-44 years.[35] The probability of serious infection has been updated, as the revised category includes now more severe pathologies than in the original submission (i.e. TB was added and urinary tract infection was removed), which all require hospitalisation. Therefore, the application of the utility weight elicited for patients affected by severe febrile neutropenia is more appropriate than the utility for non-hospitalised patients infection previously applied.[36]

Table 22 summarises the disutilities that are applied in the modified model, and the published sources used. As in the original model, each disutility was applied to the probabilities of AEs estimated from the SmPCs, converted to a per cycle probability. The disutilities are applied as long as patients are on a particular treatment.

Table 22: Mean disutility estimates for medicines-related AEs

AE	Dis-utility estimates in the original model	Adjusted disutility estimates included in the revised model	Source
Serious infection	-0.76	0.691*	Brown et al., 2001.[36]
Lymphoma	- 0.195	0.177	Hornberger et al., 2010.[37]
Acute hypersensitivity reaction	-0.11[¥]	0.10	Beusterien et al., (2010).[38]
Non-melanoma skin cancer	- 0.03	0.027	Beusterien et al., (2009)*.[39]

[¥] Utility based on pyrexia.

* In the original model the disutility for serious infection (0.52) was derived in relation to the health state of 'Infection without hospitalisation'. In the revised model the disutility of 0.76 was derived from the health state of 'Febrile neutropenia with hospitalisation'.

4.4.4.7 Probability of surgery

In the economic model, surgery was defined as a combination of procedures including panproctocolectomy with ileostomy or anal pouch formation, extended right hemicolectomy, drainage procedures, sigmoid colectomy, and ileal resection, which is consistent with clinical practice. Surgery is typically considered when other available treatment options are felt to be insufficient,[3] Hence, in the base case patients can transition to the surgery state from the moderately to severely active state if they have inadequately responded or lost response to vedolizumab or are in moderately to severely active state after continuing with CT.

As a model modification use has been made of the comprehensive list of procedures included in the HES dataset (see the appropriate worksheet in the model for the list). Based on this data all probabilities of surgery were set to be equal to 1.11% during each 8-week cycle. This updated probability was derived from the 1,584 annual average number of surgical spells for CD calculated from the HES moving average total covering the period January 2012 to November 2014 (HES dataset).[33] This was divided by 22,779 patients affected by moderately to severely active CD in England (Table 2.2.1, p44 of the original NICE submission dossier), to obtain an annual probability of surgery equal to 7%. By applying the formula 1-(1-0.07)^(8/52) an 8-week cyclic probability of 1.11% was obtained.

4.4.5 Mortality

In the base case, the relative risk of mortality has been set to 1.00 across all health states. However, a published meta-analysis has been identified showing an increased risk of mortality associated with CD compared to the general population.[31] This study was performed for CD as a whole and does not make a distinction between severity in order to inform the separate health states of the model. However, it could be used to justify the use of a higher relative mortality risk (RMR) in patients in the moderate to severe health state. Hence, in scenario analysis a health-state specific mortality risk multiplier for the moderately to severely active state was applied in each cycle, with account taken of the time spent in this health state (Table 23).

Table 23: Relative risk of mortality by health state used in scenario analysis

Health state	Relative mortality risk (RMR)	Source
Remission	1.00	Assumption
Mild	1.00	Assumption
Moderately to severely active	1.39	Duricova et al., 2010 [31]
Surgery	1.00	Assumption

4.4.6 Regimens considered in the economic analysis

The base case comparator of conventional therapy (CT) was assumed to consist of a combination of azathioprine, 6-mercaptopurine, methotrexate, aminosalicylates (ASAs), and corticosteroids (see Section 4.4.7.3 for further details).

In the modified model the regimens and assessment time point for induction and maintenance treatment for vedolizumab was consistent with the regimen and assessment times recommended in the SmPC and adopted in clinical practice (Table 24). Hence, patients received 3 induction doses of vedolizumab 300mg (at 0, 2 and 6 weeks). Following an assessment at week 10 responders started an 8-weekly 300mg maintenance regimen (Q8W) which was modelled to begin at week 14.

Table 24: Vedolizumab and the TNF-α antagonist regimens considered in the economic analysis

Technologies	Standard induction and maintenance regimens[$]	Assessment timepoint for response
Vedolizumab	300 mg intravenous infusions at 0, 2 and 6 weeks (induction); followed by 300mg intravenous infusion at week 14 for responders, and every 8 weeks thereafter (Q8W for maintenance).	10 weeks

[$]The induction period terminated with the last dose given, and the maintenance period began when the next dose was received, i.e. week 14 for vedolizumab, week 6 for infliximab and week 4 for adalimumab.

4.4.7 Medicines acquisition and administration costs

4.4.7.1 Vedolizumab drug acquisition costs

The list price for vedolizumab 300mg is £2,050 per vial. However, an updated Patient Access Scheme (PAS) has been applied, consisting of a discounted vedolizumab price of

[redacted] per 300mg vial (Table 25). In scenario analysis the full vedolizumab NHS list price has been applied to illustrate the impact of the PAS. No vial sharing has been assumed (i.e. unused medicine in opened vial is discarded) in the analysis of drug costs.

Table 25: Drug acquisition costs for vedolizumab

	Price per vial	Induction Phase (6 weeks)*		Maintenance Phase (per 8-week cycle)		Annual cost per patient[¥]	
		No. of vials	Cost per patient	No. of vials	Cost per patient	Year 1 (base case duration)	Year 2 (scenario analysis duration)
Vedolizumab (Entyvio™) 300mg powder in vial	£2,050 (list price) [redacted] (PAS price)	3	£6,150 (list price) [redacted] (PAS price)	1	£2,050 (full price) [redacted] (PAS price)	£16,400 (full price) [redacted] (PAS price)	£12,300 (full price) [redacted] (PAS price)

* For vedolizumab assessment at 10 weeks, the induction period ended with the administration of the dose at week 6 and the maintenance phase began with the administration at week 14.

[¥] The calculation of annual costs in this table is based on 5 maintenance cycles (and therefore 5 doses) in year 1 (i.e. up to the cycle ending at week 54) and 6 maintenance cycles (and therefore 6 doses) in year 2 (i.e. up to the cycle ending at week 102 which is assumed to represent 2 years treatment duration in scenario analysis)

4.4.7.2 Vedolizumab administration costs

Vedolizumab IV infusion is estimated to take 30 minutes, under continuous observation. The first two infusions of vedolizumab require an expected two additional hours of observation to identify signs of acute hypersensitivity reactions. All subsequent infusions of vedolizumab are expected to require approximately one hour observation following completion of the infusion. However, for simplicity in the base case a single cost of £328 per administration of vedolizumab was applied (NHS Reference cost)[15] for the Inflammatory Bowel Disease with Single Intervention, with CC Score 0-3 (HRG code FZ37N, 2013-14) (Table 26). As this cost is reflective of a day case cost, and hence may overestimate the actual opportunity cost of drug administration with vedolizumab based on a 1 hour 30 minute administration expected in maintenance treatment, a unit cost 50% of this was applied in scenario analysis (i.e. £164 per administration).

Table 26: Cost of vedolizumab administration

Biologic	Cost per IV infusion or injection**	Induction Phase		8-week maintenance cycle		Total annual cost per patient[¥]	
		No. of administrations per patient	Cost per pt.	No. of administrations per patient	Cost per pt.	Year 1	Year 2
Vedolizumab Vial	£328*	3	£984	1	£328	£2,624	£1,968

Abbreviations: IV = intravenous; pt = patient

[¥] For vedolizumab, the calculation of the annual administration cost was based on 5 maintenance cycles in year 1 (i.e. up to the cycle ending at week 54), and 6 maintenance cycles in year 2 (i.e. up to the cycle ending at week 102, assumed to represent 2 years treatment duration).

4.4.7.3 Conventional therapy (CT)

Based on updated information in the British National Formulary 68 (November 2014), the dose regimen for azathioprine and mercaptopurine, and the price per pack for prednisolone, azathioprine and methotrexate has changed since the original submission, with a consequent revision of the daily dose and cost in the model (see the bold highlighted updates in Table 27).

Table 27: **CT doses and acquisition costs per patient – updates in bold**

	Price per pack*	Pack size*	Strength*	Dose regimen*	Dose per day	Daily cost	Proportion of patients receiving each drug[¥]
Aminosalicylates							
Balsalazide	£30.42	130 cap	750mg	1.5g twice daily	4	£ 0.94	5%
Mesalazine	£39.21	120 tab	400mg	1.2-2.4g daily	4.5	£ 1.47	5%
Olsalazine	£19.77	112 cap	250mg	500mg twice daily	4	£ 0.71	5%
Sulfasalazine	£8.07	112 cap	500mg	500mg 4 times daily	4	£ 0.29	5%
Corticosteroids							
Budesonide	£75.05	100 cap	3mg	3mg 3 times daily	3	£ 2.25	6%
Prednisolone	**£1.33**	28 tab	5mg	4, 5 mg tablets daily	4	£ 0.19	19%
Immunomodulators							
Azathioprine	**£3.56**	56 tab	50mg	**2-2.5mg/kg daily**	**3.10**	**£ 0.20**	57%

	Price per pack*	Pack size*	Strength*	Dose regimen*	Dose per day	Daily cost	Proportion of patients receiving each drug[¥]
Mercaptopurine	£50.47	25 tab	50mg	**1-1.5mg/kg (maintenance dose)**	**1.72**	**£ 3.48**	10%
Methotrexate	**£2.77**	28 tab	2.5mg	10-25mg once weekly	7	**£ 0.69**	11%

*Source: British National Formulary 68 (September 2014).[40] The cheapest non-proprietary prices have been used in the model, with the exception of mesalazine, for which the price of Asacol was used, as Asacol is the most used proprietary medicine.
[¥]Source: UK IBD Audit Steering Group (Royal College of Physicians, 2013).[41]

The updates produced a CT weighted average cost per cycle equal to £49.10 for the CT comparator. The cost of CT used alongside vedolizumab (and any other biologic) was estimated to be 75% of the regimen prescribed to patients in the CT arm (£36.82 per cycle), as a compromise of the different views expressed in the clinical expert survey regarding the intensity of the CT regimen expected to be used as concomitant therapy alongside biologic therapy in the treatment of moderately to severely active CD (see Section 4.4.3). In scenario analysis the impact of alternative assumptions of 50% and 100% of the CT comparator arm cost applied to the vedolizumab arm were investigated.

4.4.8 Healthcare costs associated with adverse events (AEs)

The unit costs used for estimating the costs of AE management have used the latest NHS reference costs in the updated model. With the exception of lymphoma, each AE cost was estimated as the average of relevant HRG codes covered by the Department of Health NHS reference costs 2013-14.[15] The cost of lymphoma was calculated as the average of the unit costs provided in three NICE TA reports,[42-44] inflated to 2013 values. Full details of the codes used and corresponding estimated AE costs can be found in Appendix 3. Table 28 summarises the average costs by AE applied in the model.

Table 28: **Estimated average costs of AE episodes applied in the model**

Adverse event	Average cost per episode
Serious infections	£1,742
Lymphoma	£ 16,509 (average of £18,082 from TA226; £12,545 from TA243; £18,900 from TA65, where the original value of £14,297 was inflated using the 2012/13 HCHS Pay and Prices Index (Curtis, 2013)[45]
Acute hypersensitivity reaction	£442
Non-melanoma skin cancer	£1,860
Source: Department of Health. NHS reference costs 2013-14.[15]	

Each updated AE cost was multiplied by the respective revised probability of occurrence and then summed to yield the expected AE cost per cycle for each treatment arm. As the AE costs for vedolizumab consisted of the biologic AE cost and the CT AE cost, the total expected AE per cycle cost was calculated to reflect respectively the proportions of patients responding to the initial vedolizumab treatment and the proportion of patients who switched to CT if they discontinued the initial biologic. Costs for biologic-related AEs were therefore applied occurring anytime during the model time horizon as long as patients are on a particular treatment. The costs of concomitant CT AEs costs were applied from week 14 until the end of year 1, which is the base case timepoint at which it is assumed all remaining patients treated with vedolizumab (or other biologic) switch to CT. AEs costs related to CT were then applied until either the end of the simulated time horizon or death**.** In the CT comparator arm, AE CT costs were applied from Week 6, until either the end of the simulated time horizon or death

In the base case of the revised model it was also assumed that patients treated with vedolizumab (or other biologics) received 75% intensity of the standard CT regimen, the simplifying assumption was made that these patients experienced 100% of the CT-related AEs. This was a conservative assumption for the comparison of vedolizumab versus CT, but it did not affect the comparison of vedolizumab versus the TNF-α antagonists. It was also assumed that the escalated maintenance dose of adalimumab 40mg every week was not associated with a higher incidence of AEs than the standard dosing (40mg every other week), which may also be conservative.

4.4.9 Use and costs of healthcare services for CD management

From the literature reviews performed a retrospective single centre study was identified which represented an investigation of the determinants of healthcare costs for UK patients affected by CD. Bassi et al., (2004).[46] However, it was not possible to adopt resource quantities from this source, because the breakdown provided was by hospitalised and ambulatory groups, and therefore did not match the vedolizumab model health states. Bodger et al., (2009)[30] derived health states costs from Bassi's estimates by integrating health states information provided in a study modelling the lifetime clinical course and costs of Crohn's disease in a 24-year population based inception cohort of patients in Minnesota Silverstein et al., (1999).[47] However, Bodger's article did not report the quantities of resources obtained, and only provided estimates of total health state costs, which were estimated through the NHS Reference Costs inflated to 2006/07, so are likely to be out of date.

Due to the limitations of the existing resource use evidence the model was updated using resource use estimates for medical (non-surgical) CD symptom management from the clinical expert survey conducted in February 2015 (see Section 4.4.3). The resources and frequency estimated by the clinical experts included: outpatient visits, laboratory tests, radiology investigations, endoscopies, hospital admissions and other resources. The full list of resources, quantities and the unit costs (NHS Reference Costs 2013-14)[15] applied in the vedolizumab model for each health state based on the survey is provided in Table 29.

For some diagnostic procedures use was made of average unit costs across NHS reference codes as there are a range of possible procedures performed. The unit cost selection was informed by the fact that biopsy is performed in nearly (if not all) endoscopic investigations, and that all CT and MRI scan makes us of contrast or involve a comparison of pre- and post-contrast. In a few cases, a straightforward mapping of the resource described by the clinicians and the NHS reference cost codes was not possible, and therefore use was made of the code describing a compatible procedure (e.g. this was the case for costing the *fistulogram*, the *barium follow through* and the *double balloon enteroscopy*). One of the clinicians surveyed identified the use of the SeHCAT scan to be performed after surgery to detect bile acid malabsorption. The scan itself cost £195, plus £204 administration costs (NHS Ref Costs RA362 Nuclear Medicine category 2).[48] However, it is uncertain whether this test is routinely used in clinical practice, and therefore use of this investigation was not included.

The survey has identified Home Parenteral Nutrition as a lifetime requirement for those patients suffering from short bowel syndrome following surgery. From responses in the survey it appears that the proportion of patients requiring HPN is likely to be less than 1% of the overall moderately to severely active CD population. We therefore decided to apply HPN costs to 0.5% of the TNF-α antagonists failure cohort of the model. We derived the annual cost of HPN by inflating to 2013-14 values[45] the daily cost of HPN (£60, 2005 value) reported in Table 8 of the NICE costing report[49] on nutritional support in adults.

The survey also identified X-rays and a substantial list of laboratory investigations. However, we understand that diagnostic (including physiological and clinical measurement tests and plain x-rays) and pathology services that are undertaken in admitted patient care, critical care, outpatients or emergency medicine are included as part of the composite costs of these types of care (NHS Ref Cost 2013-14),[15] and therefore these costs have been excluded to avoid the possibility of double counting.

Finally, a cost was applied for the continual use of a stoma nurse to the proportion of patients who underwent panproctolectomy with ileostomy; although due to a lack of data the costs of stoma consumables were not included. Based on the clinical expert survey responses, it was assumed this cost would apply to 5.5% of the 1.1% of patients in the surgery state only (Table 29). This represents a conservative approach, as stoma nurse visits (and also stoma consumables costs, not currently included) would in reality apply to the above proportion of patients in any state, and not only whilst in the surgery state.

Table 29: **Health States resource use per patient (excluding surgery)**

Resources	Annual average units per patient			Unit costs[¥]
	Remission	Mild	Moderate-to-Severe	
Outpatient visits				
IBD consultant	1.28	2.81	8.75	£130
Dietician	0.00	0.38	2.69	£80
Surgeon	0.00	0.00	1.50	£116

Resources	Annual average units per patient			Unit costs[¥]
	Remission	Mild	Moderate-to-Severe	
Stoma nurse	0.13	0.13	0.92	£47
Other IBD nurse	1.04	2.13	6.21	£51
(Clinical) psychologist	0.00	0.10	2.40	£139
Helpline	1.17	2.54	8.17	£29
Pharmacist	0.00	0.33	1.00	£85
Radiology				
Plain x-ray	0.00	0.00	0.94	£0
Barium enema	0.00	0.00	0.00	N/A
Barium follow through	0.00	0.00	0.28	£153
Ultrasound of the abdomen	0.00	0.00	0.75	£52
CT scan of abdomen/pelvis	0.00	0.00	1.16	£131
MRI scan of abdomen/pelvis	0.06	0.41	1.28	£221
WBC scan	0.00	0.00	0.00	N/A
DEXA scan	0.31	0.31	0.31	£70
Fistulogram	0.00	0.00	0.10	£130
MRI small bowel	0.00	0.00	0.50	£212
Endoscopies				
Oesphagogastroduodenoscopy	0.00	0.03	0.69	£443
Sigmoidoscopy	0.00	0.21	0.56	£487
Colonoscopy	0.38	0.56	1.23	£583
Double balloon enteroscopy	0.00	0.00	0.40	£832
Wireless capsule endoscopy	0.00	0.03	0.43	£671
Hospitalisations				
No of admissions	0.00	0.00	0.89	£3,128
Length of admission (days)	0.00	0.00	8.21	N/A
Other				
Nutritional support	0.00	0.00	0.50	£62
Home parenteral nutrition	Applicable lifelong to <1% of total CD population			£26,409/year

[¥]See Table 32 for the list of the NHS reference cost codes used for estimating unit costs.

The costs of surgery included the surgical procedure itself and post-surgery complications. The average cost of the surgical procedure in the updated model was estimated as £6,704, which we derived from analysis of the HES dataset (HES dataset).[33] The data from the HES sums all surgical procedures completed over the past 3 years for a primary diagnosis of Crohn's Disease. The calculation of cost involved, for the age 15+ population, dividing the total costs of a hospital spell due to a surgical procedure from December 2013 to November 2014 (£10,196,655) by the number of spells during the same period (1,521). The source of

cost is the ICD-10 code mapped to the appropriate HRG from the grouper (i.e. how costs are calculated when hospitals charge CCGs for services provided). Information on the codes used and the HES data are provided within the modified economic model.

The most common post-surgery complications in CD expected to be seen were assessed by two English-based Gastroenterologists (this has not changed from the original submission). In order to update the costs of treating these complications (i.e. wound infection, prolonged ileus/small bowel obstruction, abdominal abscess and anastomic leak), the NHS Reference Costs 2013-14 [15] were applied in relation to the average use of resources estimated by the two Gastroenterologists. Resource use estimates and unit costs of healthcare resource utilisation for post-surgery complications are provided in Table 30.

Table 30: **Estimated use of resources and costs of post-surgery complications**

Resources	Type of complications				Unit costs[¥]
	Wound infection	**Prolonged ileus/small bowel obstruction**	**Abdominal abscess**	**Anastomic leak**	
Additional hospital days	4	4.5	7	9.5	£274
Outpatient visits	1	1	2.5	2.5	£130
Endoscopy	0	0	0	0	N/A
Total cost of each complications	£1,226	£1,363	£2,243	£2,928	N/A
Probability of surgery-related complications	8.13%	4.52%	1.61%	4.27%	N/A
Average cost of complications	**£322,42**				
[¥] For the source of unit costs see Table 32.					

A summary of the estimated annual quantities of resources used, the unit costs and the annual and per-cycle cost by health state are presented in Table 31.

Table 31: **Summary of healthcare costs by health state per 8-week cycle**

Health state	8 week cycle cost applied in the modified model
Remission	£100
Mild	£205
Moderately to severely active CD	£1,239
Surgery (including post-surgery complications)	£7,293

4.4.10 Summary of data sources for resource use and unit costs

The following table provides a summary of data sources for unit costs used in the economic model for the comparison of vedolizumab and conventional therapy (Table 32). For completeness this also includes a summary of unit cost sources for adalimumab and infliximab that are used in the exploratory comparison with the TNF-α antagonists.

Table 32: **Summary of data sources for NHS resources and unit costs**

Resources	**Source for quantities**	**Source for unit costs**
Medicines		
Vedolizumab	GEMINI II study	NHS list price and PAS price (Takeda UK)
Infliximab	SmPC	BNF 68 November 2014
Adalimumab	SmPC	BNF 68 November 2014
Conventional Therapy	UK IBD Audit Steering Group (Royal College of Physicians, 2013).	BNF 68 November 2014
Biologics administration		
IV infusion (vedolizumab and infliximab)	SmPC	NHS Ref. Costs 2013-14. Currency code FZ37N Day Case, Inflammatory Bowel Disease with Single Intervention, with CC Score 0-3
Initial sub-cutaneous injections (adalimumab)	Experts' opinion	NHS Ref. Costs 2013-14. Currency Code: N27AF Specialist Nursing, Treatment Room Nursing Services, Adult, Face to face
Health States service use		
IBD consultant	Experts' opinion	NHS Ref. Costs 2013-14. Outpatient attendances; Service Code 301 Gastroenterology
Dietician	Experts' opinion	NHS Ref. Costs 2013-14. Community Health Services; Currency Code A03 Dietician
Surgeon	Experts' opinion	NHS Ref. Costs 2013-14. Outpatient attendances; Service Code 104 Colorectal Surgery
Stoma nurse (after surgery)	Experts' opinion	NHS Ref. Costs 2013-14. Community Health Services Currency Code N24AF Specialist Nursing, Stoma Care Services, Adult, Face to face
Other IBD nurse	Experts' opinion	NHS Ref. Costs 2013-14. Community Health Services Currency Code N29AF Other Specialist Nursing, Adult, Face to face
(Clinical) psychologist	Experts' opinion	NHS Ref. Costs 2013-14. Outpatient attendances; Average of: Service Code 656 Clinical psychology and Service Code 713 Psychotherapy
Helpline	Experts' opinion	NHS Ref. Costs 2013-14. Community Health Services Currency Code N29AN Other Specialist Nursing, Adult, Non face to face
Pharmacist	Experts' opinion	NHS Ref. Costs 2013-14. Community Health Services Currency Code A01A1 Other Therapist, Adult, One to One
Nutritional support	Experts' opinion	NHS Ref. Costs 2013-14. Outpatient attendances; Service Code 654 Dietetics
Barium follow through	Experts' opinion	NHS Ref. Costs 2013-14. Radiology (outpatient). Average of: Currency Codes RA16Z, RA17Z, RA18Z Contrast fluoroscopy procedures
Ultrasound of the abdomen	Experts' opinion	NHS Ref. Costs 2013-14. Radiology (outpatient). Average of Currency Codes RA23Z, RA24Z Ultrasound scan
CT scan of abdomen/pelvis	Experts' opinion	NHS Ref. Costs 2013-14. Radiology (outpatient). Average

Resources	**Source for quantities**	**Source for unit costs**
		of Currency Codes RA10Z, RA12Z, RA13Z, RA14Z Computerised tomography scan
MRI scan of abdomen/pelvis	Experts' opinion	NHS Ref. Costs 2013-14. Radiology (outpatient). Average of Currency Codes RA05Z, RA07Z Magnetic Resonance Imaging Scan
DEXA scan	Experts' opinion	NHS Ref. Costs 2013-14. Radiology (outpatient). Currency Code RA15Z Dexa scan
Fistulogram	Experts' opinion	NHS Ref. Costs 2013-14. Radiology (outpatient). Currency Code RA16Z Contrast Fluoroscopy Procedures, less than 20 minutes
MRI small bowel	Experts' opinion	NHS Ref. Costs 2013-14. Radiology (outpatient). Currency Code RA03Z Magnetic Resonance Imaging Scan, one area, pre and post contrast
Oesphagogastroduodenoscopy	Experts' opinion	NHS Ref. Costs 2013-14. Endoscopies. Currency Code FZ61Z Diagnostic Endoscopic Upper Gastrointestinal Tract Procedures with Biopsy, 19 years and over
Sigmoidoscopy	Experts' opinion	NHS Ref. Costs 2013-14. Endoscopies. Currency Code FZ55Z Diagnostic Flexible Sigmoidoscopy with Biopsy, 19 years and over
Colonoscopy	Experts' opinion	NHS Ref. Costs 2013-14. Endoscopies. Currency Code FZ52Z Diagnostic Colonoscopy with Biopsy, 19 years and over
Double balloon enteroscopy	Experts' opinion	NHS Ref. Costs 2013-14. Endoscopies. Currency Code FZ13C Minor Therapeutic or Diagnostic, General Abdominal Procedures, 19 years and over
Wireless capsule endoscopy	Experts' opinion	NHS Ref. Costs 2013-14. Endoscopies. Currency Code FZ42A Wireless Capsule Endoscopy, 19 years and over
Home parenteral nutrition	Experts' opinion	NICE CG no. 32, 2006
Hospitalisation for medical and non-surgical treatment	Experts' opinion	NHS Ref. Costs 2013-14. Elective inpatients. Currency Code FZ37P Inflammatory Bowel Disease without Interventions, with CC Score 5+[§]
Surgical procedure	HES Data	HES Data (based on the ICD-10 code)
Post-surgical complications additional hospital days	Experts' opinion	NHS Ref. Costs 2013-14. Elective inpatients, additional hospital stay. Currency Code FZ37P Inflammatory Bowel Disease without Interventions, with CC Score 5+[§]
Post-surgical outpatient visits	Experts' opinion	NHS Ref. Costs 2013-14. Outpatient attendances; Service Code 301 Gastroenterology
Adverse events		
Serious infections, lymphoma, tuberculosis, hypersensitivity reaction, injection site reaction	Pooled estimates from clinical controlled studies reported in the SmPCs	2013-14 NHS Reference Costs[¥]

[§] The choice of code FZ37P was guided by the survey average length of stay equal to 8.21 days.

¥See Appendix 3 for the list of the codes for costing the AEs

4.4.11 Base case and scenario/sensitivity analyses

4.4.11.1 Deterministic sensitivity analyses for the comparison vs. CT

Univariate sensitivity analysis was performed on all data inputs, except drug costs. The list of parameters varied and the respective range of variation is reported in Appendix 4.

4.4.11.2 Scenario analyses for the comparison vs. CT

Using the modified economic model a number of scenario analyses were performed for the comparison vs. CT in patients who had failed on an TNF-α antagonist (Table 33)

Table 33: Scenario analyses: vedolizumab 300mg vs. CT

Scenario analysis	Change from base case and rationale
A. Time horizon = 10 years	The appropriate time horizon is lifetime and was used in the base case. However, 10 years was considered a key 'pragmatic' scenario analysis due to precedence in previous HTAs and the greater uncertainty associated with a lifetime extrapolation
B. Induction/assessment duration = 6 weeks*	The ten-week assessment was used in the base case, consistent with clinical practice. In this scenario we assessed 6 weeks as the clinical endpoints measurement time, including adverse events.
C. Type of response: enhanced (100-CDAI point reduction from baseline)	In the base case we used 70-CDAI point drop as this has been acknowledged by experts as a clinically meaningful response. In this scenario we explore 100-CDAI drop, primary endpoint in the GEMINI trials.
D1. Source of efficacy data: GEMINI II C13007	Whilst in the base case the comparison vs. CT was based on GEMINI trial pooled results data, in this scenario we used the results from GEMINI II trial only as an alternative data source
D2. Source of efficacy data: GEMINI III C13011 (induction) and GEMINI II C13007 (maintenance)	Whilst in the base case the comparison vs. CT was based on GEMINI trial pooled results data, in this scenario we used the results from GEMINI III for induction, and GEMINI II for maintenance as an alternative data source.
E. Mortality RR=1.39 for the moderately to severely active state	In the base case, previous cost-effectiveness studies in CD have not included this excess risk so the impact of assuming no excess mortality risk has been used in the base case
F. Buxton et al., utilities • remission =0.827 • mild = 0.695 • mod-severe = 0.425 • S= 0.425 (assumed=MS)	This scenario analysis makes use of published utilities (used in previous HTA): the model by Bodger et al.,: namely made use of the study by Buxton et al., 2007 using EQ-5D to estimate CDAI utilities.
G. IV infusion cost = £ 164	The base case applied the full day cost. This cost is 50% of base case estimate to reflect expected lower opportunity cost associated with a 1.5 hour maintenance phase IV infusion with vedolizumab.
H1. Biologics treatment duration = 2 year	The base case adopted that 1 year duration consistently with GEMINI II efficacy data. However, the 2-years duration is supported by new data from GEMINI LTS[14] showing patients still taking and benefitting from vedolizumab.
H2. Biologics treatment duration = 3 years	This scenario is designed to test the impact of a longer time duration for vedolizumab than in the base case.
L1. Discounting = 0%	Variation around 3.5% represents standard practice.
L2. Discounting = 6%	Variation around 3.5% represents standard practice.
M1. Use of CT by patients taking biologics: 50% of the CT arm regimen	Given the lack of evidence, this scenario supports the case of a CT regimen for patients taking biologics of lower intensity than in the base case (75%). Expert clinical opinion from England was that an intensity of 50% for CT alongside a biologic therapy was plausible.
M2. Use of CT by patients taking biologics: 100% of the CT arm regimen	Given the lack of evidence, this scenario supports the case of a CT regimen for patients taking biologics of equal intensity between the biologics and CT arms.
N. Vedolizumab price = £2,050 (without the PAS)	Impact of applying NHS list price on the ICER
*When the 6-week assessment time was implemented, vedolizumab responders and non-responders patients received in cycle 1 two doses (at 0 and 2 week); whilst in cycle 2 (week 6) only responders to vedolizumab or conventional therapy received one dose of vedolizumab.	

4.4.11.3 Probabilistic sensitivity analysis of Vedolizumab vs. CT

Probabilistic sensitivity analysis (PSA) was performed to examine the combined effect of the uncertainty in all the variable parameters. Values were sampled from the uncertainty distributions associated with each parameter (see Appendix 4). Cost-effectiveness acceptability curves were derived using bootstrapping sampling techniques (3,000 simulations).

4.4.12 Revised results

4.4.12.1 Base case results

The base case result in patients who have previously failed on a TNF-α antagonist demonstrated an ICER of £21,620 per QALY gained for vedolizumab compared to CT, based on an incremental lifetime cost of [redacted] and incremental QALYs of [redacted] (Table 34).

Whilst vedolizumab drug and administration costs with CT exceeded the drug costs associated with CT alone, this was offset by the lower health state costs for vedolizumab due to a greater proportion of patients achieving clinical response and remission, and hence a lower proportion of patients in the moderately to severely active CD state over the model time horizon. There was an estimated difference in the number of lifetime surgeries between the two arms (vedolizumab: 1.49; CT: 1.55). Further disaggregated results are provided in Appendix 5.

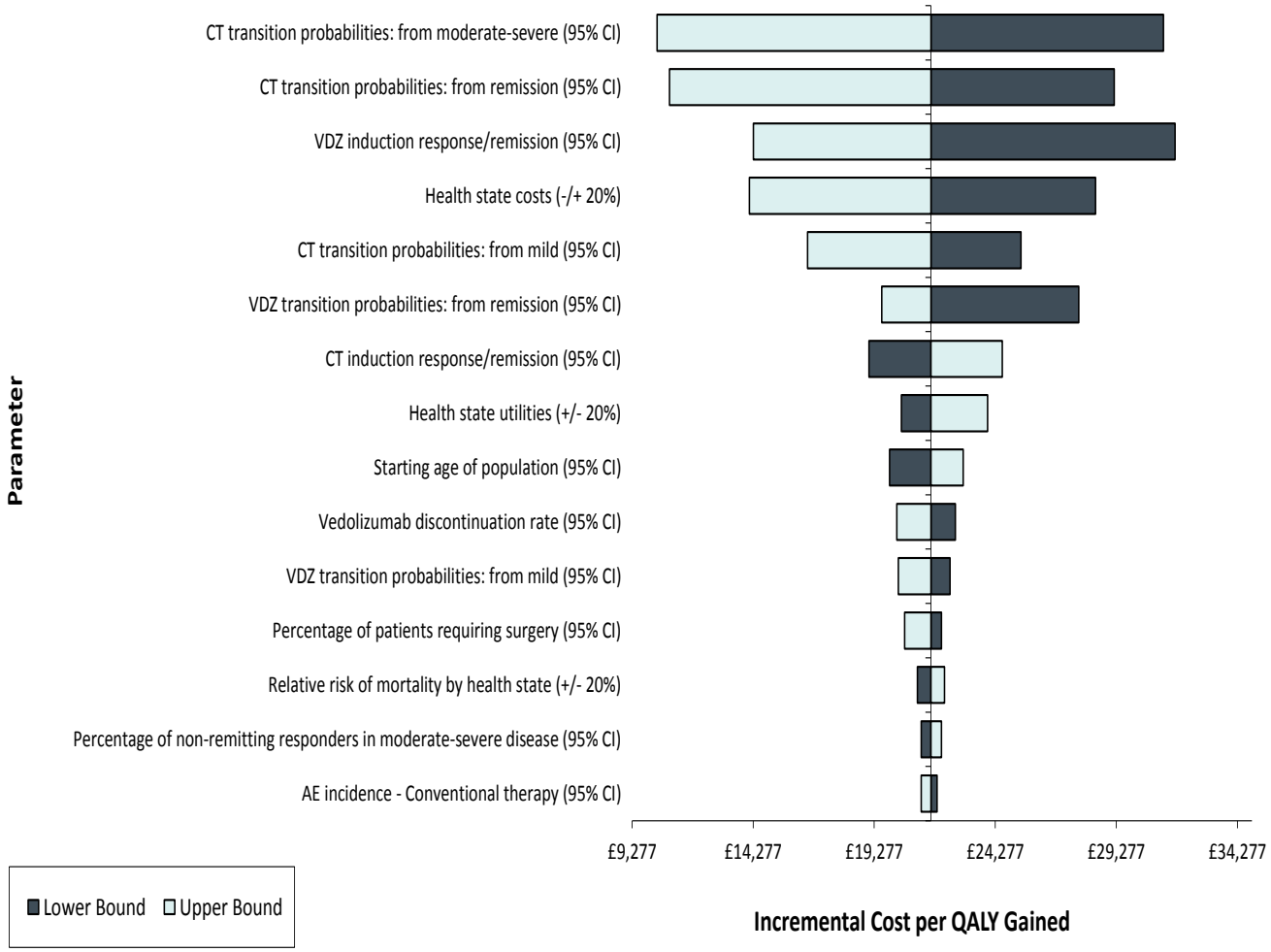
Table 34: Base case - vedolizumab vs. CT in the TNF-α antagonist failure population (with updated PAS)

	Vedolizumab	CT	Increment
Costs			
Biologic therapy (acquisition)	[redacted]	£0.00	[redacted]
Biologic therapy (administration)	£1,830	£0.00	£1,830
Conventional therapy	£7,175	£7,225	-£50
Health-state costs	£178,363	£184,657	-£6,293
Adverse event costs	£5,277	£5,329	-£52.46
Total discounted costs	[redacted]	**£197,211**	[redacted]
Outcomes			
Discounted Life years gained (LYG)	**22.664**	**22.664**	**0.000**
Discounted QALYs gained	[redacted]	**13.064**	[redacted]
Incremental cost per QALY	**£21,620**		

4.4.12.2 Deterministic sensitivity analysis results

The one-way sensitivity analysis showed that the ICER was most sensitive to the CT arm transition probability from the moderately to severely active state (ICER: £10,307 to £31,226), and to variation in the transition probability from the remission state (ICER: £10,820 to £29,191), which were varied according to the 95% confidence limits generated through the Dirichlet distribution (Figure 4), There was relative sensitivity to varying the both response and remission outcomes at 10-week assessment (£14,284 to £31,704), which were varied according to the 95% confidence limits generated through the Beta distribution. The 15 most sensitive variables tested in univariate sensitivity analysis are presented in the Tornado diagram below (Figure 4).

Figure 4: **Tornado diagram for 15 most sensitive variables in deterministic sensitivity analysis**



4.4.12.3 Scenario analyses

The scenarios that generated the highest ICERs in the TNF-α antagonist failure population for vedolizumab vs. CT (Table 35) were:

- A: Time horizon = 10 years (£49,405/QALY), which was the base case in the original submission but is insufficiently long to capture all potential costs and benefits of the treatment of CD.
- C. Type of response: enhanced (100-CDAI point reduction from baseline) (£44,349/QALY), which represents a strict definition of response and continuation into maintenance treatment for clinical practice.
- B. Assessment at week 6 (£37,598/QALY), which due to the vedolizumab mechanism of action represents too short a duration with which to determine response to vedolizumab treatment (see section 4.2 of the SmPC).[11]
- D1: Efficacy based on GEMINI II induction and maintenance outcomes only (£31,502/QALY)

Scenarios producing lower ICERs than in the base case included:

- F: Applying Buxton et al. utilities (£13,251/QALY)
- D: Efficacy based on GEMINI III induction but GEMINI II maintenance phase outcomes (£17,981/QALY).
- G: Reducing the vedolizumab infusion administration cost by 50% (£21,318/QALY).

The results were also moderately sensitive to the choice of discount rate over a lifetime horizon, varying from £205/QALY at 0% discount rate to £33,517/QALY at 6% (Table 35).

Table 35: Scenario analysis results: vedolizumab vs. CT in the TNF-α antagonist failure population

	Vedolizumab vs. CT		
	Incremental Cost £	**Incremental QALY**	**Incremental cost/QALY £**
Base case	[redacted]	[redacted]	**£21,620**
Scenario Analysis			
A. Time horizon = 10 years	[redacted]	[redacted]	**£49,405**
B. Induction/assessment duration = 6 weeks*	[redacted]	[redacted]	**£37,598**
C. Type of response: enhanced (100-CDAI point reduction from baseline)	[redacted]	[redacted]	**£44,349**
D1. Source of efficacy data: GEMINI II C13007	[redacted]	[redacted]	**£31,502**
D2. Source of efficacy data: GEMINI III C13011 (induction) and GEMINI II C13007 (maintenance)	[redacted]	[redacted]	**£17,981**
E. Mortality RR=1.39 for the moderately to severely active state	[redacted]	[redacted]	**£22,107**
F. Buxton et al., utilities • remission =0.827 • mild = 0.695 • mod-severe = 0.425 • S= 0.425 (assumed=MS)	[redacted]	[redacted]	**£13,251**
G. IV infusion cost = £ 164	[redacted]	[redacted]	**£16,418**
H1. Biologics treatment duration = 2 year	[redacted]	[redacted]	**£24,695**
H2. Biologics treatment duration = 3 years	[redacted]	[redacted]	**£26,207**
L1. Discounting = 0%	[redacted]	[redacted]	**£205**
L2. Discounting = 6%	[redacted]	[redacted]	**£33,517**
M1. Use of CT by patients taking biologics: 50% of the CT arm regimen	[redacted]	[redacted]	**£21,318**
M2. Use of CT by patients taking biologics: 100% of the CT arm regimen	[redacted]	[redacted]	**£21,922**
N. Vedolizumab price = £2,050 (without the PAS)	[redacted]	[redacted]	**£39,066**

4.4.12.4 Probabilistic sensitivity analysis results

The scatterplot and cost-effectiveness acceptability curves from the PSA are presented in Figure 5 and Figure 6. At a willingness to pay threshold of £30,000 the probability that

vedolizumab is cost-effective compared to CT is 61% (Figure 6). The probabilistic ICER is £27,428/QALY (95%CI: -£7,883, £82,947).

Figure 5: Scatterplot for incremental costs and QALYs for vedolizumab vs. CT in the TNF-α antagonist failure population

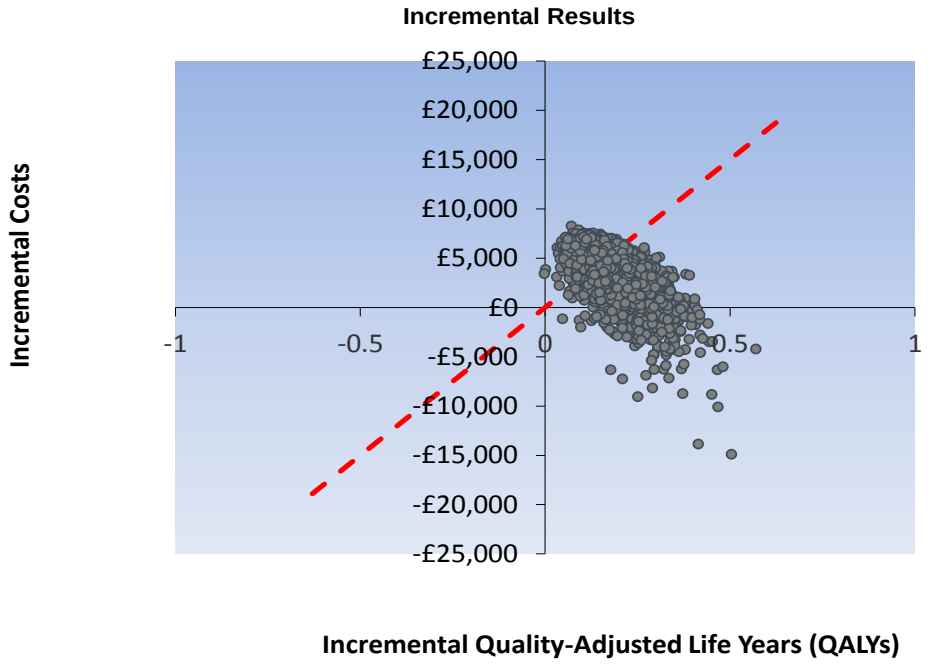
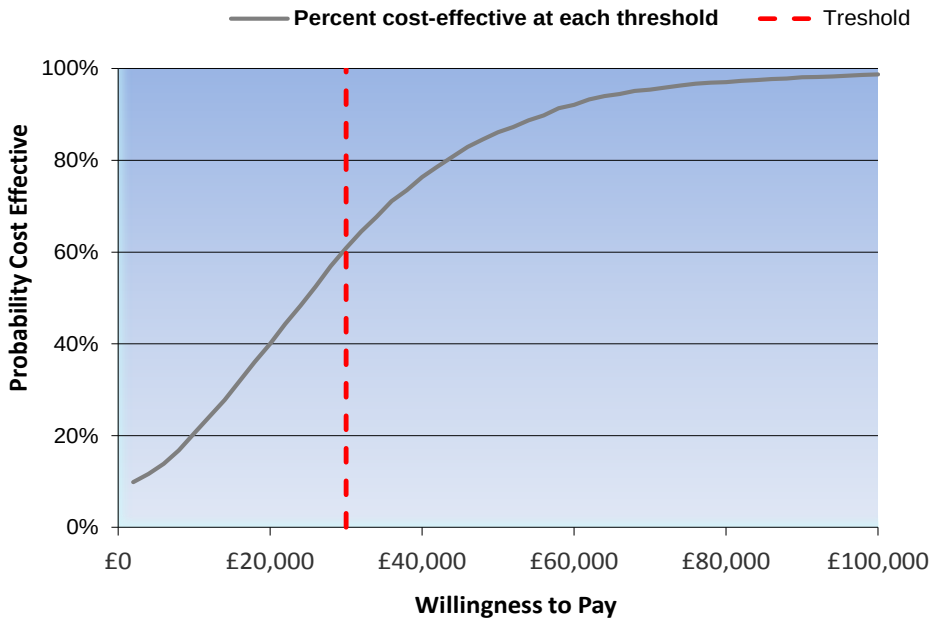


Figure 6: Cost-effectiveness acceptability curve for vedolizumab vs. CT in the TNF-α antagonist failure population



4.5 Exploratory analysis vs. TNF-α antagonists

4.5.1 Introduction

Due to limitations in the data available for the comparators for a robust assessment of the relative efficacy and safety of vedolizumab vs. the TNF-α antagonists in a TNF-α antagonist failure population, only exploratory analysis has been performed focussing on cost comparisons and the degree to which dose escalation is expected to be necessary in clinical practice for adalimumab and infliximab. It should also be noted that unlike vedolizumab, neither TNF-α antagonist has a specific indication for the treatment of patients who have had an inadequate response, lost response or are intolerant to prior TNF-α antagonist treatment.[7,34]

The following sub-sections address the main methods (including specific model adaptations) for the exploratory comparisons with the TNF-α antagonists.

4.5.2 Clinical evidence

The NMA comparison of vedolizumab and TNF-α antagonists was limited by the lack of comparable TNF-α antagonist evidence in a failure population. No evidence was identified from the systematic review performed for the original submission for infliximab, and whilst there is some data for adalimumab, there is none in the same comparable 'failure' patient population as that for vedolizumab. The adalimumab trials[10,29] are in secondary failure patients only, and exclude those who never had an initial response to treatment (i.e. primary failures), whereas the vedolizumab data is for both primary and secondary failure patients and hence includes those who had an inadequate or no response as well as those who lost response. As the primary failure patients would be expected to have a relatively poorer prognosis, it is likely the results from the TNF-α antagonist population NMA are conservative, and the relative effectiveness of vedolizumab has been underestimated. This has also been recognised by the ERG in the ACD (see Section 3.36 of the ACD).

The NMA performed for the TNF-α antagonist failure population also demonstrated no significant differences in the induction treatment phase between vedolizumab and adalimumab. In the original submission a comparison of response and remission outcomes in the maintenance phase was not performed – there was data for this phase from one adalimumab trial in a secondary failure population only (the CHARM study),[29] but this study was not included in the original submission NMA (due partly to only providing data on clinical remission as an outcome and not on durable response, and also a lack of information on patient characteristics by treatment arm for adalimumab 40mg or placebo/CT). However, despite its limitations we have updated the TNF-α antagonist failure NMA to include this study in order to provide an indication of the relative efficacy of vedolizumab and adalimumab in maintenance treatment. As with the induction phase comparison due to the CHARM study excluding primary failure patients the relative efficacy of adalimumab is likely to be overestimated. In addition, patients in both the Induction and Maintenance phases of the GEMINI II study were more heavily pre-treated than in the adalimumab trials. Despite this the results from the NMA has demonstrated no significant difference in clinical response or remission in the induction phase, or in clinical remission over 52 weeks in the

maintenance phase between vedolizumab and adalimumab, although both are superior to placebo/CT (see Table 36, Table 37 and Table 38). In this NMA the relatively robust data is that for vedolizumab, supporting the efficacy of vedolizumab in the broader TNF-α antagonist failure population, whereas efficacy has not been established in this patient population for adalimumab, or infliximab (hence, the non-inclusion of this sub-population in the licensed indications for the TNF-α antagonists in moderately to severely active CD). The use of these agents in current clinical practice is due to the lack of alternative biologic agents prior to vedolizumab being licensed, and illustrates the high unmet clinical need for a new agent. Further details on the methods and networks for the TNF-α antagonist failure NMA are provided in Appendix 6.

Table 36: Pairwise comparisons for clinical response in induction phase (TNF-α antagonist failure sub-population)*

Treatment regimen (induction)	**Clinical Response:** Each biologic vs. placebo/conventional therapy Odds Ratio (95% CrI)	**Clinical Response:** Vedolizumab vs. each TNF-α antagonist Odds Ratio (95% CrI)
Vedolizumab 300mg	1.9 (1.3, 2.8)	-
Adalimumab160mg/80mg	2.1 (1.4, 3.3)	0.9 (0.3, 1.7)

*Based on a fixed effects model. There was a lack of contrasts in the network in order to perform random effects modelling

Table 37: Pairwise comparisons for clinical remission in induction phase (TNF-α antagonist failure sub-population)*

Treatment regimen (induction)	**Clinical Remission:** Each biologic vs. placebo/conventional therapy Odds Ratio (95% CrI)	**Clinical Remission:** Vedolizumab vs. each TNF-α antagonist Odds Ratio (95% CrI)
Vedolizumab 300mg	2.5 (1.5, 4.3)	-
Adalimumab160mg/80mg	3.5 (1.8, 7.4)	0.7 (0.3, 1.6)

*Based on a fixed effects model. There was a lack of contrasts in the network in order to perform random effects modelling

Table 38: Pairwise comparisons for clinical remission in Maintenance Phase (TNF-α antagonist failure sub-population)*

Treatment regimen (Maintenance)	**Clinical Remission:** Each biologic vs. placebo/conventional therapy Odds Ratio (95% CrI)	**Clinical Remission:** Vedolizumab vs. each TNF-α antagonist Odds Ratio (95% CrI)
Vedolizumab 300mg Q8W	2.7 (1.1, 6.5)	-
Vedolizumab 300mg Q4W	2.6 (1.2, 6.3)	1.1 (0.5, 2.1)

Treatment regimen (Maintenance)	Clinical Remission: Each biologic vs. placebo/conventional therapy Odds Ratio (95% CrI)	Clinical Remission: Vedolizumab vs. each TNF-α antagonist Odds Ratio (95% CrI)
Adalimumab 40mg eow	4.1 (1.8, 10.4)	0.7 (0.2, 2.1)
Adalimumab 40mg ew	4.8 (2.0, 12.1)	0.56 (0.2, 2.0)

*Fixed effects model. There was a lack of contrasts in the network in order to perform random effects modelling.
Q8W = every 8 weeks, Q4W=every 4 weeks, eow = every other week, ew = every week

There was a lack of comparable data from the NMA to perform a robust assessment of safety outcomes. Table 39 shows the comparison of vedolizumab and adalimumab 160/80mg discontinuations due to AEs in the induction phase that was possible to derive from the relative failure population induction phase trials for these agents. This did not demonstrate any significant difference in this outcome between drugs, although the induction phase represents too short a duration with which to assess relative safety outcomes.

Table 39: Pairwise comparisons for treatment discontinuations due to AEs in the induction phase (TNF-α antagonist failure sub-population)*

Treatment regimen (induction)	Discontinuations: Each biologic vs. placebo/conventional therapy Odds Ratio (95% CrI)	Discontinuations: Vedolizumab vs. each TNF-α antagonist Odds Ratio (95% CrI)
Vedolizumab 300mg	0.4 (0.1, 0.9)**	-
Adalimumab160mg/80mg	0.5 (0.1, 2.4)**	0.6 (0.1, 7.9)

***Fixed effects model. There was a lack of contrasts in the network in order to perform random effects modelling.

Due to limitations in the NMA and in the time available we have not been able to quantify the relative AE profiles for the comparator products in an TNF-α antagonist failure population, and further research is needed to enable a robust comparison of the probabilities of the key AEs identified in the clinical expert survey as important for the biologic agents (see Table 16). An advantage of vedolizumab recognised by the NICE AC in the ACD is the fewer systematic adverse effects relative to existing biological treatments (see Section 4.9 of the ACD). This is supported by a qualitative comparison we have performed of the respective SmPCs with regards to the AEs in Table 40 below, which demonstrates a generally better AE profile for vedolizumab over either adalimumab or vedolizumab.

Table 40; Comparison of the adverse event profiles for each biologic from the SmPCs for the AEs mentioned as important in the clinical expert survey

Adverse event	Infliximab	Adalimumab	Vedolizumab
Nasopharyngitis		Nasopharyngitis was very common (≥1/10)	Nasopharyngitis was very common (≥1/10)
Sepsis	• Sepsis was a common (≥1/100 to <1/10) AE	Sepsis (fatal or life threatening) was a common (≥1/100 to <1/10) AE	Reported
Respiratory tract infection	• URTI and sinusitis were very common (≥1/10) AEs • Lower respiratory tract infection (e.g. bronchitis, pneumonia) was a common (≥1/100 to <1/10) AE	URTI and LRTI, sinusitis, pharyngitis, were very common (≥1/10) AEs	Bronchitis, gastroenteritis, URTI, influenza, sinusitis and pharyngitis were common. Other RTI and localised candidiasis were uncommon (≥1/1000 to <1/100). .
Serious infection	• TB, bacterial infections, including sepsis and pneumonia, invasive fungal, viral, and other opportunistic infections observed in patients. Some of these infections have been fatal; the most frequently reported opportunistic infection with a mortality rate of >5% include pneumocystosis, candidiasis, listeriosis and aspergillosis • Viral infection (e.g. influenza, herpes) was a very common (≥1/10) AE • Bacterial infections (e.g. sepsis, cellulitis) were common (≥1/100 to <1/10) • Opportunistic infections (such as invasive fungal infections, pneumocystosis etc.) were rare (≥1/10,000 to <1/1000)	Pneumonia was very common (≥1/10) Other systemic infections (fatal or life threatening) including sepsis, opportunistic infections and TB have been reported. Common infections (≥1/100 to <1/10) included systemic infections, intestinal infections , skin and soft tissue infections, ear and oral infections, urinary and reproductive tract infections, fungal infections and joint infections. Neurological infections (including viral meningitis) and opportunistic infections were uncommon (≥1/1000 to <1/100).	Salmonella sepsis, listeria meningitis, cytomegaloviral colitis.
Tuberculosis (TB)	• Reports of active TB in patients receiving infliximab. The majority of these TB cases were extrapulmonary,	TB (fatal or life threatening) has been reported as an uncommon (≥1/1000 to <1/100) AE.	Reported

Adverse event	Infliximab	Adalimumab	Vedolizumab
	presenting as local or disseminated disease. • TB was an uncommon (≥1/10,00 to <1/100) AE in clinical studies with infliximab • Patients must be evaluated for both active and inactive (latent) TB before commencing treatment with infliximab.		
Lymphoma	• 5 cases of lymphoma and 26 cases of non-lymphoma malignancies with infliximab vs. 0 cases of lymphoma and 1 cases of non-lymphoma malignancy with placebo • Cases of lymphoma, NHL, and Hodgkin's disease were rare (≥1/10,000 to <1/1000) AEs in clinical trials.	Lymphoma fatal or life threatening) has been reported as uncommon (≥1/1000 to <1/100).	None reported
Infusion related reaction	Injection site reaction were common Infusion-related reaction was very common	Injection site reactions were very common (≥1/10).	Infusion site reaction, including site pain and irritation, chills and feeling cold were uncommon (≥1/1000 to <1/100).
Skin problems	Psoriasis, urticarial, rash, pruritus, hyperhidrosis, dry skin, fungal dermatitis, eczema and alopecia were common	Non-melanoma skin cancer was common Rash (including exfoliative rash) was very common (≥1/10). Psoriasis, urticarial, bruising dermatitis, onychoclasis, hyperhidrosis alopecia and pruritus were common (≥1/100 to <1/10).	Rash, pruritis, eczema, erythema, acne were common Folliculitis was uncommon (≥1/1000 to <1/100).
Melanoma	• Melanoma was a rare (≥1/10,000 to <1/1000) AE	Uncommon (≥1/1000 to <1/100)	None reported
Demyelination	CNS and peripheral demyelinating disorders have been reported as rare.	CNS and peripheral demyelinating events have been reported as rare (≥1/10,000 to <1/1000)	None reported

Adverse event	Infliximab	Adalimumab	Vedolizumab
Cardiac (congestive heart failure)	Cardiac failure, arrhythmia, syncope, bradycardia were uncommon.	Congestive heart failure, arrhythmia and myocardial infarction were uncommon (≥1/1000 to <1/100)	None reported
Carcinoma for lung (for smokers)		Lung neoplasm was uncommon (≥1/1000 to <1/100). Other solid organ neoplasms (e.g. breast cancer and thyroid neoplasm) were uncommon.	None reported
Systemic serum sickness	Uncommon		None reported
Palmer planter syndrome	Palm and soles pustular psoriasis was common (≥1/100 to <1/10).	Palmoplantar pustular psoriasis was common (≥1/100 to <1/10)	None reported
Depression	• Common (≥1/100 to <1/10) AE	Common (≥1/100 to <1/10)	None reported

Source: SmPC for infliximab;[34] SmPC for adalimumab;[7] SmPC for vedolizumab.[11]

For the purposes of the exploratory analyses ERG advice was followed and due to comparator data limitations comparable efficacy between the biologics was assumed, and also we have not quantified the impact of a difference in AE profiles on QALY outcomes for vedolizumab relative to adalimumab or infliximab due to lack of comparable AE probability data. In the model discontinuation rates due to AEs have been set the same between vedolizumab, adalimumab and infliximab. Hence, the exploratory analyses focus on a comparison of the relative costs of vedolizumab and adalimumab or infliximab. For modelling purposes the NMA derived vedolizumab transition probabilities were applied to both adalimumab and infliximab (as per Table 41 below).

Table 41: Re-calibrated transition probabilities in each 8-week cycle for the comparison of vedolizumab vs. TNF-α antagonists

From/To health state	Remission	Mild	Moderately to severely active	Surgery	Sum
Vedolizumab					
Remission	0.933	0.067	0.000	0.000	1.000
Mild	0.000	0.500	0.500	0.000	1.000
Moderately to severely active	0.000	0.000	0.989	0.011	1.000
Surgery	0.787	0.115	0.087	0.011	1.000
CT					
Remission	0.836	0.164	0.000	0.000	1.000
Mild	0.000	0.602	0.398	0.000	1.000
Moderately to severely active	0.000	0.031	0.957	0.011	1.000
Surgery	0.787	0.115	0.087	0.011	1.000

Source: NMA, CSR C13007 [17]and HES dataset.[33] It should be noted that matrices are based on NMA induction data and Gemini II maintenance data because of lack of availability of all the necessary maintenance data to calibrate the matrices suing NMA data.

4.5.3 Regimens, drug costs and dosing of the TNF-α antagonist in a TNF-α antagonist failure population

The dosing regimen and response assessment time point (10 weeks) for vedolizumab applied in the model has been presented in Section.4.4.6, and was in line with marketing authorisation recommendations. The same approach has been used for the selection of regimens and assessment time points for the TNF-α antagonists patients, which were as follows:

- Two induction doses of adalimumab (based on an induction regimen of 160mg at week 0 and 80mg at week 2, which was identified as standard clinical practice in

England). The adalimumab maintenance dose of 40 mg was given every other week (standard dose) or every week (escalated dose) to responders at week 4, starting from week 4.

- Two induction doses of infliximab 5mg/kg at 0 and 2 weeks. The standard maintenance dose for infliximab 5mg/kg was administered at week 6 to the patients showing a response at the week 6 assessment, and every 8 weeks thereafter. Infliximab escalated dose consisted of escalation to 10mg/kg infusion from the first maintenance dose.

The regimens and assessment timepoints for response following induction treatment for vedolizumab, and the TNF-α antagonists were consistent with the regimens and assessment times recommended in the SmPC's and adopted in clinical practice, and were also those recommended as clinically appropriate by the Evidence Review Group (ERG).

Feedback from clinical experts in England was that in patients who have failed on a first TNF-α antagonist, dose escalation is likely to be considered necessary in a significant proportion of patients in order to maintain clinical benefit with a second TNF-α antagonist. This is consistent with reports from the literature, both from England[50,51] and from other parts of Europe.[52,53] The clinical expert survey (reported in Section 4.4.3) reported the following responses to questions regarding use of TNF-α antagonists in CD (Table 42). This showed a broad spread in which TNF-α antagonist is used first after failure on CT, and which second, but broadly there appears to be an even distribution between the two. In terms of dose escalation it is clear that this occurs with both adalimumab and infliximab, with a greater proportion likely to dose escalate with adalimumab. There is uncertainty in terms of the proportion of patients expected to be dose escalated, with a wide range between 30% and 100% with adalimumab mentioned, although there were three mentions of 50% (Table 42). In the exploratory analysis reported in this submission, we have explored the impact of dose escalation of 30%, and 100% with adalimumab, and 15% and 50% with infliximab, although the model can be set to explore any specific assumption regarding proportion of patients who dose escalate. It is assumed dose escalation will commence from the start of Maintenance treatment. Vedolizumab represents a biologic agent with a different mechanism of action from the TNF-α antagonists, hence it is not expected that dose escalation to every 4 weeks administration will be necessary in clinical practice when used after failure on a TNF-α antagonist, as it is the first time this type of agent will have been used. Hence, the response according to its first use will be expected to be maintained without the need for dose escalation, whereas as patients have tried and failed on a TNF-α antagonist, switching to another TNF-α antagonist typically requires dose escalation in a proportion of patients in order to maintain long term benefit (in particular remission) – see also the discussion in Section 1 Executive summary.

Table 42: Clinical expert responses to questions on the use and dose escalation of TNF-α antagonists

Clinician respondents*	*Question:* "Of the moderate – severe CD patients who have failed to respond to (either inadequate response or loss of response) to a first anti-TNF and then proceed to receive a different second anti-TNF, what proportion would you expect to require dose escalation on the second anti-TNF in order to maintain long run benefit…….		*Question:* For patients who receive infliximab or adalimumab as a first anti-TNF, in what proportion would you expect that anti-TNF to be infliximab?"
	If the second anti-TNF is adalimumab?"	"If the second anti-TNF is infliximab?"	
1	30%	15%	30%
2	50%	30%	33%
3	50%	30%	40%
4	50%	40%	40%
5	>50%	50%	40%
6	80%	50%	50%
7	100% within 1 year	50%	50%
8	-	50%	60%

*Not an ID number - ordered according to size of escalation or choice of infliximab as first TNF-α antagonist.

The acquisition costs per cycle during the Induction and maintenance phases for infliximab and adalimumab are shown in Table 43 (vedolizumab costs are reported in Table 25. This shows the cost of the standard dose of adalimumab and infliximab, and the escalated doses (based on clinical practice consisting of escalation to weekly adalimumab administration, and 10mg/kg infliximab administration every 8 weeks during maintenance treatment).

Table 43: Drug acquisition costs for TNF-α antagonists at standard and escalated doses

Biologic	Preparation	Price per vial or pens /syringe	Induction Phase [α] (2 weeks)		Maintenance Phase (per 8-week cycle) [α]		Annual cost per patient[¥]	
			Vials or pens/ syr.	cost per patient	Vials or pens/ syr.	Cost per patient	Year 1	Year 2
Infliximab (Remicade®) standard dose (5mg/kg)	100mg powder in vial*	£419.62*	8	£3,357	4[§]	£1,678	£13,425	£10,068
Infliximab (Remicade®) escalated dose (10mg/kg)	100mg powder in vial*	£419.62*	8	£3,357	7[§]	£2.937	£23,493	£20,136
Adalimumab (Humira®) –	40mg powder in vial or	£352.14*	6	£2,113	4	£1,409	£10,567	£8,454

Biologic	Preparation	Price per vial or pens /syringe	Induction Phase [α] (2 weeks)		Maintenance Phase (per 8-week cycle) [α]		Annual cost per patient[¥]	
			Vials or pens/ syr.	cost per patient	Vials or pens/ syr.	Cost per patient	Year 1	Year 2
standard dose every other week	prefilled pen/syringe*							
Adalimumab (Humira®) – escalated dose every week	40mg powder in vial or prefilled pen/syringe*	£352.14*	6	£2,113	8	£2,817	£19,015	£16,902

[α] For infliximab and adalimumab, the induction phase ended with the dose given at week 2, and the Maintenance Phase began at Week 6 for infliximab and week 4 for adalimumab.

[¥] The annual costs were based on 6 maintenance cycles in year 1 (i.e. up to the cycle ending at Week 54) and 6 maintenance cycles in year 2 (i.e. up to the cycle ending at week 102).

[§] Given the patients' average body weight of 68.89kg from GEMINI II and III, 4 x 100mg vials were needed to make the single dose of 344mg, or 7 x 400mg vials for the escalated dose of 10mg/kg

Source: British National Formulary 68, September 2014.[40]

For administration costs Infliximab is hospital-administered intravenously over 2 hours using a pump, followed by 1–2 hours observation period. This is longer than is expected for vedolizumab, however to be conservative the same unit cost of £328 is applied in the economic model (see also Table 26 for vedolizumab administration costs).

For adalimumab, based clinical expert opinion received, the first three sub-cutaneous injections are assumed to occur in a hospital outpatient setting where the patient is also kept under observation and trained to self-inject for subsequent administrations. Therefore, for adalimumab administration the model included a cost of £51 per outpatient attendance to Other Specialist Nursing, Adult, Face to face based on NHS Reference Costs 2013-14 (Service Code N29AF).[15]

The administration costs applied for adalimumab and infliximab are shown in Table 44.

Table 44: Administration costs for the TNF-α antagonists

Biologics	Cost per IV infusion or injection*	Induction Phase		8-week maintenance cycle		Total annual cost per patient[¥]	
		No. of administrations per patient	Cost per pt.	No. of administrations per patient	Cost per pt.	Year 1	Year 2
Infliximab (Remicade®) Vial	£328	2	£656	1	£328	£2,624	£1,968
Adalimumab (Humira®) pen/syringe	£22 (first 3 hospital injections)	2	£44	1	£22	£66	£0

Abbreviations: IV = intravenous; pt = patient

For infliximab and adalimumab, the calculation of the annual administration cost was based on 6 maintenance cycles in year 1 (i.e. up to the cycle ending at week 54), and 6 maintenance cycles in year 2 (i.e. up to the cycle ending at week 102).

*No vial sharing assumed (i.e. unused medicine in opened vial is discarded). Therefore, the drug costs calculation was based on whole unit costs.

4.5.4 Exploratory analyses results

4.5.4.1 Vedolizumab vs. adalimumab

The results of the following scenarios regarding dose escalation for adalimumab are presented below based on the ranges reported in the clinical expert survey (Table 42). All cost comparisons are made using the PAS price for vedolizumab. For 30% dose escalation with adalimumab as the second TNF-α antagonist, there is a net cost associated with vedolizumab over the lifetime horizon [redacted] per patient). This is primarily driven by the incremental administration cost estimated for vedolizumab (Table 45). At the other end of the range, 100% dose escalation results in a net saving for vedolizumab, with drug cost savings offsetting additional drug acquisition costs. The break-even cost proportion of patients who would need to dose escalate is approximately 80%. This reduces to 58% if 50% of the administration cost is assumed (£164 per infusion) which is more realistic reflection of the true opportunity cost of vedolizumab administration which in Maintenance treatment is estimated to involve a total infusion and observation time of 1.5 hours – see scenario analysis in Section 4.4.12.3.

Table 45: Vedolizumab versus adalimumab with alternative assumptions regarding dose escalation of the maintenance dose of 40mg to every week (lifetime horizon)

	Vedolizumab (PAS price applied)	Adalimumab	Incremental cost
Scenario with 30% dose escalation for adalimumab (to 40mg every week)			
Biologics acquisition cost	[redacted]	£8,097	[redacted]
Biologics administration cost	£1,860	£55	£1,805
Total discounted costs*	£201,847	£199,635	£2,214
Scenario with 100% dose escalation for adalimumab (to 40mg every week)			
Biologics acquisition cost	[redacted]	£11,227	[redacted]
Biologics administration cost	£1,860	£55	£1,805
Total discounted costs*	[redacted]	£202,766	[redacted]

NB: There is rounding of costs in the table.

*The total costs includes costs of conventional therapy, health state costs and AE costs which are (virtually) the same across the biologics in the model for the exploratory analysis. There are minor computational differences in these other costs between the biologics; hence the increment is the sum of the drug acquisition and administration increments in the rows above the total increment.

Based on a base case maximum one year duration of treatment assumed for treatment responders

4.5.4.2 Vedolizumab vs. Infliximab

The results of the following scenarios regarding dose escalation for infliximab are presented below based on the ranges reported in the clinical expert survey (Table 42). All cost comparisons are made using the PAS price for vedolizumab. For both 15% and 50% dose escalation with infliximab as the second TNF-α antagonist, there is a net saving associated with vedolizumab over the lifetime horizon [redacted] per patient and [redacted] per patient respectively). This is driven lower drug acquisition costs estimated for vedolizumab (

Table 46). Even at 0% drug escalation of infliximab there is virtually cost neutrality between the two drugs (£18 drug related cost saving for vedolizumab).

Table 46: Vedolizumab versus infliximab with alternative assumptions regarding dose escalation of the maintenance dose of 5mg/kg to 10mg/kg every 8 weeks (lifetime horizon)

	Vedolizumab (PAS price applied)	Infliximab	Incremental cost
Scenario with 15% dose escalation for infliximab (to 10mg/kg)			
Biologics acquisition cost	[redacted]	£9,286	[redacted]
Biologics administration cost	£1,860	£1,697	£163
Total discounted costs*	[redacted]	£202,467	[redacted]
Scenario with 50% dose escalation for infliximab (to 10mg/kg)			
Biologics acquisition cost	[redacted]	£10,685	[redacted]
Biologics administration cost	£1,860	£1,697.40	£163
Total discounted costs*	[redacted]	£203,866	[redacted]

NB: There is rounding of costs in the table.

*The total costs includes costs of conventional therapy, health state costs and AE costs which are (virtually) the same across the biologics in the model for the exploratory analysis. There are minor computational differences in these other costs between the biologics; hence the increment is the sum of the drug acquisition and administration increments in the rows above the total increment.

Based on a base case maximum one year duration of treatment assumed for treatment responders

4.6 Discussion and conclusion

Crohn's Disease is a highly debilitating IBD condition in relatively young people, that can result in a significant impairment to patient HRQoL, and ability to contribute to society. In this updated submission of new evidence the focus has been on the use of vedolizumab in patients with moderately to severely active CD, who have failed, or are intolerant to, a TNF-α antagonist. In this subgroup of patients there is a high unmet need for the effective and cost-effective management of CD. The treatment options for this subgroup are currently limited to the standard practice of switching to a second TNF-α antagonist, unless intolerance to the first TNF-α antagonist prevents this, and forces a return to treatment with conventional therapy (CT). We believe the most appropriate positioning for vedolizumab in the treatment pathway is after the failure of a first TNF-α antagonist (either adalimumab or infliximab) as clinicians at this stage would typically prefer to try a new agent rather than another TNF-α antagonist.

Due to limitations in comparator data with which to perform a robust assessment of the comparative efficacy of vedolizumab and the use of a second TNF-α antagonist in a failure population, the focus of attention in the updated economic analysis has been on a comparison with conventional therapy (proxied by placebo arm in the GEMINI trials), which provides both a benchmark for assessing the absolute cost-effectiveness of vedolizumab, and also provides an estimate of vedolizumab cost-effectiveness in patients for whom further TNF-α antagonist treatment is considered unsuitable. Using the modified economic model as described in the previous sections, a base case ICER of £21,620 per QALY gained has been estimated in the TNF-α antagonist failure sub-population. Whilst a number of modifications have been made to the model the two primary changes that account for the vast majority of

the differences between the new estimated ICER and the ICER of £98,310/QALY gained in the original submission. We have changed the model time horizon to be a lifetime horizon, whereas the original submission presented a 10 year time horizon. The difference in time horizon illustrates that the anticipated benefits of treatment will extend well beyond 10 years. As CD is a chronic condition affecting relatively young people, the benefits of response and remission can extend over a longer time period and a lifetime horizon is appropriate for the base case. We have explored a short 10 year time horizon in scenario analysis, and this increases the ICER (as can be seen in Table 35). As a further model modification, we have revised the health state-specific resource use to be based on the survey reported in Section 4.3.3 rather than the dated literature cost estimates in the original model, and results have changed as a consequence of this. The reduction in updated PAS price has also contributed to the improved ICER.

Further sensitive variables were identified in the scenario analysis. Using a 6 week assessment time for vedolizumab increases the ICER (£37,598), but does not reflect how vedolizumab works so leads to an underestimate of responders, and does not reflect the marketing authorisation recommendation and hence expected clinical practice of assessment at 10 weeks. One interesting one was the variation in cost-effectiveness associated with scenarios D1 and D2 which relates to the differing response and remission results that for the TNF-α antagonist failure population were seen between the GEMINI II and GEMINI III induction phases, with higher probabilities of response/remission in the latter (Table 18). The primary aim of GEMINI III trial was to assess efficacy in the TNF-α antagonist failure population and has a larger sub-group sample size than GEMINI II. In addition, in GEMINI II there were a large proportion of patients who had failed two (55%) or three (11%) prior TNF-α antagonists, representing 66% of the overall TNF-α antagonist failure population. In GEMINI II, there were 30-35% of patients who had failed prior treatment with 2 or more TNF-α antagonists, hence less heavily pre-treated than in GEMINI III. This difference may account for the lower response and remission rates in GEMINI II compared to GEMINI III in the TNF-α antagonist failure sub-population. Patients in GEMINI II are likely to be more heavily pre-treated than is the case in clinical practice. The scenario using GEMINI III induction data instead of the pooled trial efficacy data resulted in an ICER of £17,981/QALY.

Using CT as a benchmark, the results appear favourable relative to the results of economic evaluations for TNF-α antagonists conducted in the wider CD population. The lifetime cost-effectiveness against CT was estimated at £21,300/QALY gained for infliximab, and £10,310/QALY for adalimumab (Bodger et al., 2009),[30] while over a 10-year time horizon ICERs of £545,000/QALY and £416,000/QALY respectively were reported (Dretzke, 2011).[54] These results are not directly comparable to those in this submission for vedolizumab, and may be conservative, as we have focused on a sub-population who failed a previous TNF-α antagonist and are therefore relatively difficult to treat and likely to be less responsive to further biologic treatment.

In contrast to the robust evidence supporting the efficacy of vedolizumab in patients who have failed a TNF-α antagonist, there is very limited clinical trial evidence to support the use of the TNF-α antagonists in this sub-population. The only evidence that was identified from our systematic review is for adalimumab,[10,29] and that was only in a secondary failure population with a health status likely to be less severe than the mixed failures (i.e. primary

and secondary) that were included in the vedolizumab trials. Nevertheless, it was clear from discussions with English clinical experts that despite infliximab and adalimumab not being specifically licensed (or NICE accepted) for use in patients who have failed a prior TNF-α antagonist, these agents are being used in practice due to a lack of alternative options. In addition, the dose of the second TNF-α antagonist is often escalated in clinical practice in an effort to maintain benefit.

Due to the lack of robust evidence for the TNF-α antagonists in this setting, exploratory analyses were performed. This is based on an assumption of comparable efficacy, although it is recognised that the NMA performed is likely to have underestimated the efficacy of vedolizumab relative to adalimumab. Hence, focusing on cost comparisons vedolizumab is at least cost neutral against infliximab even without dose escalation for the latter. Against adalimumab, cost neutrality is attained with 80% dose escalation of adalimumab, an estimate that is within the bounds of the estimated proportion of patients requiring adalimumab dose escalation from the expert clinical survey conducted. This reduces to 58% when applying a unit cost that is more representative of the opportunity cost of the infusion time for vedolizumab. Hence, a key driver of the cost differences at lower rates of dose escalation are the administration costs rather than drug costs (with updated vedolizumab PAS applied). The exploratory analysis also does not take into account the more favourable AE profile for vedolizumab relative to adalimumab or infliximab.

5. Budget Impact

The following estimates and assumptions have been used to derive an estimate of the gross and net drug budget impact of the introduction of vedolizumab in a TNF-α antagonist failure population. In the interests of time the focus has been on the drug acquisition and administration costs, and estimates of net resource use related to avoided surgery and adverse events have not been made. The net estimates are based on an expectation of some displacement of adalimumab and infliximab use in the TNF-α antagonist failure population.

The key estimates, assumptions and sources for the budget impact calculations are as follows:

Drug acquisition costs:

- It has been estimated that 0.2% of the population of England are adults diagnosed with CD (113,896), and of this number 20% of CD patients are assumed to have moderately to severely active disease, which equates to a net number of 22,779 cases in England.[55]

- Of these patients it is estimated that 50% will be resistant / intolerant to conventional therapy[55] so the net number estimated to be potentially eligible for vedolizumab under the licence 22,779 x 0.50 = Net number 11,389.

- Based on clinical expert opinion (Consultant Gastroenterologist) it is estimated that 80% of the patients failing on conventional therapy will be prescribed a TNF-α antagonist, and that 50% of these patients will fail or be intolerant to a TNF-α antagonist, giving a total net number of patients of 4,556 eligible patients for the sub-population of TNF-α antagonist failures.

- An annual CD incidence of 6% has been estimated in the UK (Steed et al.,[56] and TA187),[55] hence of the eligible vedolizumab patients 6% are assumed to be new patients each year and would receive induction therapy receiving 3 doses and assessment of response at week 10, with responders getting a further 5 doses in a year. Based on pooled GEMINI II and III trial data (GEMINI II and III),[12,13] 46.5% of the TNF antagonist failure population are assumed to respond at week 10 and receive another 5 doses in the year (full cost of [redacted] based on PAS price), whilst 53.5% are non-responders and only receive the 3 induction doses [redacted] This data is reported in Section 3.5.1.1 of this submission. Hence, the weighted cost for the incident population is calculated as follow = 0.06 x [redacted]

- Based on annual prevalence data, 94% (TA187)[55] of eligible patients assumed not to be new patients in each year and hence eligible for maintenance therapy, and so receive 6 doses (one every 8 weeks) during the year [redacted]

A proportion of the prevalent patients will not respond after previous induction therapy (I.e. 46.5%) and hence not receive maintenance therapy (9.6/157 per 100,000), estimated to be 46.5% who respond (GEMINI II data). Hence, of the 94% prevalent CD population, in any one year it is assumed that 46.5% receive a full year of vedolizumab treatment. Therefore, the weighted cost for the prevalent population is calculated as follows: [redacted] for vedolizumab.

- For calculation of net costs, the annual weighted costs of adalimumab and infliximab have been estimated in the same way.

- Adalimumab: for new incident patients the cost of the 160/80mg Induction regimen is £2,113, and the Maintenance cost for 40mg every other week for patients who respond to treatment is £8,454 (total year cost of £10,567). The proportion of patients estimated to respond to treatment at week 6 is 50.9% (estimate for adalimumab secondary failure patients from the NMA). For new patients who are non-responders (49.1%) the cost of Induction therapy alone is applied (£2,113). For prevalent patients the annual cost is estimated to be £12,678 for Maintenance therapy. This is based on an assumption that 50% of prevalent patients receiving Maintenance treatment with adalimumab as a second anti-TNF after failure of the first will need to be dose escalated to receive adalimumab 40mg once weekly to maintain benefit (based on consultant gastroenterologist opinion). Hence, the weighted cost of adalimumab used in Maintenance is (0.5 x £8,454 [annual Maintenance cost of standard dose]) + (0.5 x £16,902 [annual Maintenance cost of escalated dose]). Therefore the weighted average cost is estimated by summing the results of the following equations: For new patients receiving induction: 0.06 x (£8,454 x 0.501) + (£2,113 x 0.491) = £316; For prevalent patients receiving only Maintenance therapy: 0.94 x (£12,678 x 0.509) = £6,066 Total weighted cost is £316 + £6,066 = **£6,382**

- For infliximab it is assumed that 25% of patients who respond at week 6 will receive an increased dose of 10mg/kg, and 75% continue to receive the standard dose. For new incident patients the cost of induction is £3,357 for 5mg/kg dose (assuming 100mg vials used and body weight of 68kg), and the Maintenance cost for patients who respond to treatment is £9,964 (total year cost of £13,321 made up of 0.75 x £8,390.40 and 0.25 x £14,683 + Induction costs of £3,357). The proportion of patients estimated to respond to treatment at week 6 is 50.9% (no estimates exist for infliximab in anti-TNF failure patients; hence this estimate is for adalimumab secondary failure patients from the NMA which is assumed to apply to infliximab failure patients). For new patients who are non-responders (49.1%) the cost of induction therapy alone is applied (£3,357). For prevalent patients the annual cost is estimated to be £11,956 for Maintenance therapy. It is assumed that 50% of prevalent patients receiving Maintenance treatment with infliximab as a second anti-TNF after failure of the first will be dose escalated to receive infliximab 10mg/kg in order to maintain benefit (based on consultant gastroenterologist opinion). Therefore the weighted average cost is estimated by summing the results of the following equations: For new patients receiving induction: 0.06 x (£13,321 x 0.509) + (£3,357x 0.491) = £506; For prevalent patients receiving only Maintenance therapy: 0.94 x (£11,956 x 0.509) = £5,720. Total weighted cost is £506 + £5,720 = **£6,226**.

Drug administration costs:

- Drug administration costs for vedolizumab and infliximab IV infusion have also been calculated using a weighted calculation as above. Both vedolizumab and infliximab have an initial yearly estimated cost for administration of £2,624 for a new patient and an annual cost of £1,968 for a prevalent patient receiving a full year of maintenance therapy. These costs are based on a unit cost of £328 per infusion.[15] For the incident CD population the weighted cost estimate is 0.06 x (£2,624 x 0.465) + (£1,968 x 0.535) = £136. For prevalent patients receiving only maintenance therapy based on prevalence data 0.94 x (£1,968 x 0.465) = £860, which gives a total weighted average drug administration cost of **£996.**

- For adalimumab the proportion of patients estimated to respond to treatment at week 6 is 50.9% based on the NMA in failure patients. As no estimates exist for infliximab TNF-α antagonist patients, the same percentage responders as for adalimumab is assumed to apply to infliximab failure patients (50.9%). These percentages have been used to calculate the drug administration costs for infliximab for incident patients: 0.06 x (£2,624 x 0.509) + (£1,968 x 0.491) = £130.15, and for prevalent patients receiving only maintenance therapy based on prevalence data 0.94 x (£1,968 x 0.509) = £942. Total weighted cost of £942 + £130 = **£1,072**.

- No drug administration costs for adalimumab have been included in the calculation of budget impact which is conservative as in the economic analysis (Section 4.5.3 Table 44) it has been assumed there is a cost for the first 3 initial administered injections.

Drug budget impact estimates

Based on the estimates and calculations above the estimated gross costs from the introduction of vedolizumab is provided below, assuming an uptake of 15% of eligible moderately to severely active CD patients who have failed a prior TNF-α antagonist in 2015, rising to 55% by 2019, based on company forecasts (Table 47).

Table 47: Estimated gross budget impact of vedolizumab (with PAS)

Type of cost	2015 15%	2016 40%	2017 45%	2018 50%	2019 55%
Drug acquisition	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug administration	£680,666	£1,815,110	£2,041,999	£2,268,888	£2,495,776
Total annual gross costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on responses from our clinical expert survey the prescription of adalimumab and infliximab as a first or second line anti-TNF is about even, (Section 4.5.3 see Table 42) assumptions have been made that the uptake of vedolizumab, consists of 60% displacement for infliximab (due to the same method of delivery) and 20% displacement for adalimumab

and the remaining 20% of patients would have otherwise received CT alone. This has enabled a net drug budget impact estimate to be made. This shows a net saving of £168k in 2015 and £616k in 2019 (**Error! Reference source not found.**).

Table 48: Estimated net budget impact of vedolizumab (with PAS)

Type of cost	2015 15% (683.4)	2016 40% (1822.4)	2017 45% (2050.2)	2018 50% (2278)	2019 55% (2505.8)
Drug acquisition costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug administration	£680,666	£1,815,110	£2,041,999	£2,268,888	£2,495,774
Infliximab displaced costs	-£2,552,909	-£6,807,757	-£7,658,727	-£8,509,697	-£9,360,666
Infliximab drug administration costs	-£439,563	-£1,172,168	-£1,318,689	-£1,465,210	-£1,611,731
Adalimumab displaced costs	-£872,292	-£2,326,111	-£2,616,875	-£2,907,639	-£3,198,403
Total net cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative net costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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8. Appendices

Appendix 1: Responses to additional ERG concerns

Table 49 below provides company responses to the concerns of the ERG regarding the predictive validity of the model and how results were presented. In addition, responses to other issues raised by the ERG are provided in Table 50.

Table 49: Response to concerns on the model predictive validity and presentation of results

ERG issue	Company response	Revisions to the model or base case
The model seems to under-predict the proportion of patients receiving CT and being in remission.	It is important to highlight that for GEMINI II trial CT arm, the maintenance data were taken from the trial patients who were randomized to the CT arm after responding to vedolizumab during the induction. The model uses the GEMINI induction and maintenance data for CT. But the maintenance data for CT in GEMINI are not from patients who received CT in induction. So it is only loosely based on the GEMINI data, because the GEMINI trial did not follow those CT induction patients after the induction phase. Therefore, these patients started off in better condition than those who had received CT in the modelled CT arm. As such, we would expect the modelled population receiving CT induction and continuing CT in maintenance to experience lower outcomes than those who were in the actual trial.	Regarding point 2, We have compared the percentage of patients discontinuing due to adverse events against the trial data. The results show that in the failure population, we estimate that 6% of patients discontinue VDZ in the first year due to adverse events in the model. The predicted value from the trial data is 6.67% (2.69% in induction plus 8.54% of those continuing in maintenance (response in induction phase was only 46.54%). Considering that we have some death, I'd say we are doing pretty well in predicting treatment discontinuation due to AEs.
For patients taking vedolizumab, it under-predicted the proportion discontinuing treatment and overpredicted the proportion that remained on treatment.	As for the discontinuation from VDZ, as noted in previous responses, we have specifically kept patients who have lost response on treatment for one year. Therefore we are not overestimating the percentage of patients in response/remission at one year for VDZ. So, if anything, we are being conservative by forcing patients no longer in response to stay on the more expensive treatment.	
The model predicted greater survival for biological compared with CT (not observed in the study used to inform he model)	As for mortality, due to the small risk of death overall relative to the number of patients in the trial, the percentage of deaths observed in the trial might be substantially different than the model (which is based on UK population data) predicts. When in the original submission we applied health state specific mortality risk, there was a non-zero difference in mortality in the base case in favour of the more efficacious treatment. This non-zero difference was not statistically different from the zero mortality risk over the duration of the trial (one year). The modelled difference in mortality over time reflects the chronic nature of the risk over time. We nonetheless modelled no excess risk of mortality by health state.	
A pairwise comparison instead of full incremental analysis was presented. Probabilistic ICERs were not presented.	Presentation of full incremental analysis is not possible/appropriate in the anti-TNF failure population, given the nature of the exploratory analyses vs anti-TNFs.	We have presented in the dossier mean and 95%CI for the ICERs generated by the PSA.

Table 50: **Further responses to ERG comments**

ERG issue	Company response
The utility values for patients undergoing surgery were assumed equal to patients in the moderate-severe state. It was unsure whether the assumption is appropriate because the aim of surgery is to improve QoL.	We understand this concern and it is a limitation of the available data in patients undergoing surgery. We therefore have to maintain current assumption that surgery state utility is equal to the moderate-severe state utility (0.57). We assume that the improvement in QoL after surgery is captured when patients transition from surgery to better health states in the subsequent cycles (i.e., a short-term reduction in quality of life followed by an improvement in quality of life).
The assumption that non-responders have moderate to severe CD is inappropriate, as patients could have a drop in CDAI score of less than 70 and nonetheless been able to achieve the mild threshold.	This was a simplifying assumption. Patients entered the induction phase with a CDAI score between 220 and 600. The definition of response is a 70-point reduction in CDAI score. As such, it is possible that a patient may move from moderate-severe disease to mild disease but fail to achieve response. (e.g., going from 225 to 175 would be only a 50-point decrease in CDAI but would result in mild disease). However, (a) we would anticipate these numbers representing only a small percentage of the trial population, (b) we would not anticipate these numbers differing greatly across treatments, (c) we do not have these data for the other treatments, and (d) the criteria for continuing on treatment in the trials was response. So we make a simplifying assumption that non-responders remain in moderate-severe disease. We do not feel that this biases results in the comparisons with conventional therapy or other biologics.
Relevance to clinical practice of drop of 70 or more in CDAI score to identify patients going onto receive maintenance treatment .	A CDAI reduction of ≥70 was not a primary endpoint in the induction phases of the GEMINI II and GEMINI III trials, but was considered by some clinical expert opinion to reflect a clinically meaningful improvement in patient symptoms that would lead to a decision to continue further treatment with a biologic agent. CDAI-70 was also the outcome used to determine continuation to maintenance treatment in the GEMINI II trial. Furthermore, this measure is consistent with that observed in the trials for adalimumab and infliximab. As such, in order to provide a comparison of response between vedolizumab and infliximab, this criteria was necessary.
The induction phase for patients on vedolizumab is assumed to be 6 week and patients are assumed to receive 2 doses before response assessment (instead of 3 doses as per SmPC).	The induction period ends when the last induction dose is given and the maintenance phase begin when the first maintenance dose is given. Therefore, the 6 weeks assessment implies an induction period of 2 weeks. This is consistent with the trial design and is now explored in scenario analysis. In the base case analysis with 10-weeks assessment, the cost of the third induction dose given at week 6 is included in the model in the second cycle, as this cycle begins at the onset of week 6. We have not modelled a dose at week 10. The first maintenance dose is given at week 14 (cycle 3).
Arbitrary distributions used in the PSA and SA. The transition probabilities are varied using a Dirichlet distribution based on the predicted probability and the number of patients entering maintenance. This is arbitrary. An alternative option would have been to sample the probabilities of response and remission and calibrate the model for each sample. The correlation between health state utility values is also not included.	Confidence intervals could be generated using variance data when available from each of the parameters sources, but we could not addressed this and the other points given the time constraints.
It should also be noted that the drug acquisition cost for infliximab is conditional on the patient weight. Table 54 summarises the number of vials needed per infusion according to the weight of patients. The ERG believes that using the mean weight is not appropriate and that the distribution of patients within weight band should be used instead; it is unclear whether the drug acquisition for infliximab would be affected.	We would not expect this to result in a substantially different result due to the assumption of drug wastage. Given that the mean weight is 68.89kg, we would expect that only an incrementally larger percentage of these patients would fall below 60kg (receiving less than 4 vials per infusion) than would be above 80kg (receiving 5 vials per infusion). We do not have these data stratified by weight bands for all of the studies included.

Appendix 2: The resource use table from the clinical expert survey

The table below reproduces the template which was used by the interviewer to record the estimates on hospital resources use provided by clinicians to respond Q1 during the telephone interview.

Service/Resource Item	***Frequency of use (please specify per week, month or other time period, e.g.: 2 visits every 3 months; 1 MRI scan per year)***		
	Remission	**Mild**	**Moderate-to-Severe**
Outpatient visits:			
IBD related (consultant)			
Dietician			
Stoma Nurse			
Other_____			
Other_____			
Other_____			
Laboratory:			
Please specify lab test:_____			
Please specify lab test:_____			
Please specify lab test:_____			
Radiology:			
Plain x-ray			
Barium enema			
Barium follow through			
Ultrasound of the abdomen			
CT scan of abdomen/pelvis			
MRI scan of abdomen/pelvis			
WBC scan			
DEXA scan			
Fistulogram			
Other_____			
Other_____			
Endoscopies:			
Oesphagogastroduodenoscopy			
Sigmoidoscopy			
Colonoscopy			
Other_____			
Other_____			

Service/Resource Item	*Frequency of use (please specify per week, month or other time period, e.g.: 2 visits every 3 months; 1 MRI scan per year)*		
	Remission	**Mild**	**Moderate-to-Severe**
Hospital Admission:			
No of admissions			
Length of each admission (days)			
Other:			
Please specify:_____			

Appendix 3: English tariff codes used in the model for estimating adverse events treatment costs

The costs for treating AEs were based on the following NHS Reference Costs 2013-14 in Table 51.

Table 51: **NHS Reference Costs 2013-14 used to estimate costs of treating AEs**

Adverse Event	Description	Stay Type	Average Cost	Activity
Serious infection	***Average of following 5 types***		**£1,742.14**	
Sepsis	**Weighted average of following 6 codes**		**£1,932.33**	
	WA03A Septicemia with Major CC	Short stay	£648	599
	WA03B Septicaemia with Intermediate CC	Short stay	£551	4,443
	WA03C Septicemia without CC	Short stay	£513	18,032
	WA03A Septicemia with Major CC	Long Stay	£4,722	2,504
	WA03B Septicaemia with Intermediate CC	Long Stay	£3,316	11,604
	WA03C Septicemia without CC	Long Stay	£2,240	30,743
Pneumonia	**Weighted average of following 12 codes**		**£1,577.89**	
	DZ11D Lobar, Atypical or Viral Pneumonia, with Major CC	Short stay	£782	938
	DZ 11G Lobar, Atypical or Viral Pneumonia, with Intermediate CC	Short stay	£493	34,351
	DZ11J Lobar, Atypical or Viral Pneumonia, without CC	Short stay	£438	26,167
	DZ23D Bronchopneumonia with Major CC	Short stay	£591	207
	DZ23F Bronchopneumonia with Intermediate CC	Short stay	£481	2,359
	DZ23G Bronchopneumonia without CC	Short stay	£438	1,812
	DZ11D Lobar, Atypical or Viral Pneumonia, with Major CC	Long stay	£5,413	4,439
	DZ11G Lobar, Atypical or Viral Pneumonia, with Intermediate CC	Long stay	£2,432	62,317
	DZ11J Lobar, Atypical or Viral Pneumonia, without CC	Long stay	£1,433	22,740
	DZ23D Bronchopneumonia with Major CC	Long stay	£4,608	963
	DZ23F Bronchopneumonia with Intermediate CC	Long stay	£2,239	3,918
	DZ23G Bronchopneumonia without CC	Long stay	£1,690	2,098
Tuberculosis	**Average of the following 4 estimates**		**£2,915.04**	
	DZ14C Pulmonary, Pleural or Other Tuberculosis, with CC	Short stay	£692	224
	DZ14E Pulmonary, Pleural or Other Tuberculosis, without CC	Short stay	£512	469
	DZ14C Pulmonary, Pleural or Other Tuberculosis, with CC	Long stay	£4,720	987
	DZ14E Pulmonary, Pleural or Other Tuberculosis, without CC	Long stay	£2,748	937
Respiratory infection	**Weighted average of following 3 codes**		**£1,094.96**	
	DZ22D Unspecified Acute Lower Respiratory Infection with Major CC	Short stay	£619	234
	DZ22G Unspecified Acute Lower Respiratory Infection with Intermediate CC	Short stay	£451	13,906
	DZ22J Unspecified Acute Lower Respiratory Infection without CC	Short stay	£386	13,447
	DZ22D Unspecified Acute Lower Respiratory Infection with Major CC	Long stay	£4,749	866
	DZ22G Unspecified Acute Lower Respiratory Infection with Intermediate CC	Long stay	£1,940	17,550
	DZ22J Unspecified Acute Lower Respiratory Infection without CC	Long stay	£1,243	4,086
Bronchitis	**Weighted average of following 10 codes**		**£1,190.47**	
	DZ21A Chronic Obstructive Pulmonary Disease or Bronchitis, with length of stay 1 day or less, discharged home	Short stay	£437	85,314
	DZ21L Chronic Obstructive Pulmonary Disease or Bronchitis, with Intubation	Short stay	£1,128	84
	DZ21M Chronic Obstructive Pulmonary Disease or Bronchitis, with NIV, without Intubation, with CC Score 8+	Short stay	£723	166
	DZ21N Chronic Obstructive Pulmonary Disease or Bronchitis, with NIV, without Intubation, with CC Score 4-7	Short stay	£664	388
	DZ21P Chronic Obstructive Pulmonary Disease or Bronchitis, with NIV, without Intubation, with CC Score 0-3	Short stay	£617	263
	DZ21Q Chronic Obstructive Pulmonary Disease or Bronchitis, without NIV, without Intubation, with CC Score 13+	Short stay	£512	180
	DZ21R Chronic Obstructive Pulmonary Disease or Bronchitis, without NIV, without Intubation, with CC Score 10-12	Short stay	£515	818
	DZ21S Chronic Obstructive Pulmonary Disease or Bronchitis, without NIV, without Intubation, with CC Score 7-9	Short stay	£492	2,274
	DZ21Y Chronic Obstructive Pulmonary Disease or Bronchitis, without NIV, without Intubation, with CC Score 4-6	Short stay	£476	4,934
	DZ21U Chronic Obstructive Pulmonary Disease or Bronchitis, without NIV, without Intubation, with CC Score 0-3	Short stay	£512	5,491
	DZ21A Chronic Obstructive Pulmonary Disease or Bronchitis, with length of stay 1 day or less, discharged home	Long stay	£1,226	1,897
	DZ21L Chronic Obstructive Pulmonary Disease or Bronchitis, with Intubation	Long stay	£3,560	178
	DZ21M Chronic Obstructive Pulmonary Disease or Bronchitis, with NIV, without Intubation, with CC Score 8+	Long stay	£3,440	1,302
	DZ21N Chronic Obstructive Pulmonary Disease or Bronchitis, with NIV, without Intubation, with CC Score 4-7	Long stay	£2,396	2,908
	DZ21P Chronic Obstructive Pulmonary Disease or Bronchitis, with NIV, without Intubation, with CC Score 0-3	Long stay	£2,087	2,060
	DZ21Q Chronic Obstructive Pulmonary Disease or Bronchitis, without NIV, without Intubation, with CC Score 13+	Long stay	£4,041	1,498
	DZ21R Chronic Obstructive Pulmonary Disease or Bronchitis, without NIV, without Intubation, with CC Score 10-12	Long stay	£3,002	6,179
	DZ21S Chronic Obstructive Pulmonary Disease or Bronchitis, without NIV, without Intubation, with CC Score 7-9	Long stay	£2,267	15,777
	DZ21Y Chronic Obstructive Pulmonary Disease or Bronchitis, without NIV, without Intubation, with CC Score 4-6	Long stay	£1,811	33,533
	DZ21U Chronic Obstructive Pulmonary Disease or Bronchitis, without NIV, without Intubation, with CC Score 0-3	Long stay	£1,509	38,240
Lymphoma	***Average of following 3 estimates***		**£16,509.00**	
	TA65: Non-Hodgkin's lymphoma (R-CHOP), NICE 2003		£18,082	
	TA243: Follicular lymphoma (R-CVP), NICE 2012		£12,545	
	TA226: Follicular non-Hodgkin's lymphoma, NICE 2011		£18,900	
Acute hypersensitivity reactions	**Average of the following 4 estimates**		**£442.11**	
	WA16W Shock or Anaphylaxis, with CC	Short stay	£381	461
	WA16Y Shock or Anaphylaxis, without CC	Short stay	368	3,229
	WA16W Shock or Anaphylaxis, with C	Long stay	£1,254	131
	WA16W Shock or Anaphylaxis, without CC	Long stay	£992	293
Skin cancer	**Average of the following 18 estimates**		**£1,859.76**	
	JD07A Skin Disorders with Interventions, with CC Score 12+	Short stay	£ 857	45
	JD07B Skin Disorders with Interventions, with CC Score 8-11	Short stay	£ 854	60
	JD07C Skin Disorders with Interventions, with CC Score 4-7	Short stay	£ 995	171
	JD07D Skin Disorders with Interventions, with CC Score 0-3	Short stay	£ 1,085	784
	JD07E Skin Disorders without Interventions, with CC Score 19+	Short stay	£ 573	197
	JD07F Skin Disorders without Interventions, with CC Score 14-18	Short stay	£ 555	1617
	JD07G Skin Disorders without Interventions, with CC Score 10-13	Short stay	£ 496	4791
	JD07H Skin Disorders without Interventions, with CC Score 6-9	Short stay	£ 479	12167
	JD07J Skin Disorders without Interventions, with CC Score 2-5	Short stay	£ 448	28246
	JD07A Skin Disorders with Interventions, with CC Score 12+	Long stay	£ 7,726	2,120
	JD07B Skin Disorders with Interventions, with CC Score 8-11	Long stay	£ 5,292	2,195
	JD07C Skin Disorders with Interventions, with CC Score 4-7	Long stay	£ 3,865	3,893
	JD07D Skin Disorders with Interventions, with CC Score 0-3	Long stay	£ 2,285	8,753
	JD07E Skin Disorders without Interventions, with CC Score 19+	Long stay	£ 4,752	625
	JD07F Skin Disorders without Interventions, with CC Score 14-18	Long stay	£ 4,013	4,669
	JD07G Skin Disorders without Interventions, with CC Score 10-13	Long stay	£ 3,087	10,164
	JD07H Skin Disorders without Interventions, with CC Score 6-9	Long stay	£ 2,426	17,876
	JD07J Skin Disorders without Interventions, with CC Score 2-5	Long stay	£ 1,880	23,697

Appendix 4: Parameters varied in univariate and probabilistic sensitivity analysis

The following table provides all the variables and ranges in the univariate and probabilistic sensitivity analysis.

Table 52: Bounds for deterministic and probabilistic sensitivity analysis

	Base Case	Univariate Sensitivity Analysis		Probabilistic Sensitivity Analysis			
Parameter	**Value**	**Lower Bound**	**Upper Bound**	**Distribution**	**N / Calc.**	**Alpha**	**Beta**
Population Inputs							
Starting age		Starting age of population (+/- 5%)			% in tails		
Starting age (years)	36.57	29.62	44.23	Gamma	20%	96.04	0.40
Percent male		Percent male (95% CI)			N		
Percent male	43.92%	42.85%	44.99%	Beta	8238	3618	4620
Weight (in kg)		Average weight (+/- 5%)			% in tails		
Weight	68.89	55.81	83.34	Gamma	20%	96.04	0.72
Efficacy - Induction Period							
Conventional therapy		Conventional therapy efficacy - induction period (95% CI)			N		
Remission	9.69%	6.97%	12.80%	Beta	393	38	355
Response	30.97%	26.50%	35.63%	Beta	393	122	271
Vedolizumab		Vedolizumab efficacy - induction period (95% CI)			N		
Remission	13.31%	9.48%	17.66%	Beta	263	35	228
Response	45.25%	39.28%	51.28%	Beta	263	119	144
Transition probabilities (post-induction)							
Vedolizumab		VDZ transition probabilities (95%CI)			N		
Remission to:							
Remission	98.87%	95.73%	99.98%	Dirichlet	82	81	74
Mild	1.13%	4.27%	0.02%	Dirichlet	82	1	0
Moderate-to-severe	0.00%	0.00%	0.00%	Dirichlet	82	0	0
Surgery	0.00%	0.00%	0.00%	Dirichlet	82	0	0

Parameter	Base Case	Univariate Sensitivity Analysis		Probabilistic Sensitivity Analysis			
	Value	Lower Bound	Upper Bound	Distribution	N / Calc.	Alpha	Beta
Mild to:							
Remission	0.00%	0.00%	0.00%	Dirichlet	82	0	0
Mild	50.00%	39.27%	60.73%	Dirichlet	82	41	33
Moderate-to-severe	50.00%	60.73%	39.27%	Dirichlet	82	41	51
Surgery	0.00%	0.00%	0.00%	Dirichlet	82	0	0
Moderate-to-severe to:							
Remission	0.00%	0.00%	0.00%	Dirichlet	82	0	0
Mild	0.00%	0.00%	0.00%	Dirichlet	82	0	0
Moderate-to-severe	98.89%	98.89%	98.89%	Dirichlet	82	81	87
Surgery	1.11%	1.11%	1.11%	Dirichlet	82	1	3
Conventional therapy		CT transition probabilities (95%CI)					
Remission to:					N		
Remission	83.07%	74.05%	90.49%	Dirichlet	78	65	65
Mild	16.93%	25.95%	9.51%	Dirichlet	78	13	11
Moderate-to-severe	0.00%	0.00%	0.00%	Dirichlet	78	0	0
Surgery	0.00%	0.00%	0.00%	Dirichlet	78	0	0
Mild to:							
Remission	0.02%	0.00%	0.00%	Dirichlet	78	0	0
Mild	60.14%	49.13%	70.66%	Dirichlet	78	47	43
Moderate-to-severe	39.86%	50.87%	29.34%	Dirichlet	78	31	33
Surgery	0.00%	0.00%	0.00%	Dirichlet	78	0	0
Moderate-to-severe to:							
Remission	0.00%	0.00%	0.00%	Dirichlet	78	0	0
Mild	2.97%	0.45%	7.69%	Dirichlet	78	2	5
Moderate-to-severe	95.92%	96.41%	91.25%	Dirichlet	78	75	77
Surgery	1.11%	1.14%	1.06%	Dirichlet	78	1	1

Parameter	Base Case Value	Univariate Sensitivity Analysis Lower Bound	Univariate Sensitivity Analysis Upper Bound	Probabilistic Sensitivity Analysis Distribution	N / Calc.	Alpha	Beta
Surgery		Surgery transition probabilities (95%CI)					
Remission	78.69%	69.01%	86.98%	Dirichlet	78	61	60
Mild	11.51%	16.74%	7.03%	Dirichlet	78	9	12
Moderate-to-Severe	8.69%	12.63%	5.31%	Dirichlet	78	7	5
Surgery	1.11%	1.61%	0.68%	Dirichlet	78	1	2
Other Efficacy Parameters							
Probability of surgery		Probability of surgery (95% CI)			N		
Induction	0.83%	0.01%	3.30%	Beta	100	1	99
Maintenance	1.11%	0.04%	3.88%	Beta	100	1	99
Percentage of non-remitting responders in moderate-severe state		Percentage of responders in moderate-severe (95% CI)			N		
Percentage	38.37%	28.44%	48.82%	Beta	86	33	53
Mortality relative risks		Relative risk of all-cause mortality (+/- 20%)			% in tails		
Remission	1.0	0.81	1.21	Gamma	20%	96.04	0.01
Mild	1.0	0.81	1.21	Gamma	20%	96.04	0.01
Moderate-Severe	1.0	0.81	1.21	Gamma	20%	96.04	0.01
Surgery	1.0	0.81	1.21	Gamma	20%	96.04	0.01
Health State Costs		Health state costs (-/+ 20%)			% in tails		
Remission	£99.91	£80.93	£120.86	Gamma	20%	96.04	1.04
Mild	£204.97	£166.04	£247.95	Gamma	20%	96.04	2.13
Moderate-to-Severe	£1,239.11	£1,003.73	£1,498.91	Gamma	20%	96.04	12.90
Surgery	£7,292.88	£5,907.53	£8,821.97	Gamma	20%	96.04	75.94
Health state utilities		Health state utilities (+/- 20%)			N		
Remission	0.82	0.74	0.89	Beta	100	82	18
Mild	0.73	0.64	0.81	Beta	100	73	27
Moderate-to-Severe	0.57	0.47	0.67	Beta	100	57	43
Surgery	0.57	0.47	0.67	Beta	100	57	43

Parameter	Base Case	Univariate Sensitivity Analysis		Probabilistic Sensitivity Analysis			
	Value	Lower Bound	Upper Bound	Distribution	N / Calc.	Alpha	Beta
Adverse events incidence							
Vedolizumab		AE incidence - Vedolizumab (95% CI)			N		
Serious Infection	0.011	0.64%	1.71%	Beta	1,434	16	1,418
Lymphoma	0.000	0.00%	0.00%	Beta	1,434	0	1,434
Acute hypersensitivity reaction	0.006	0.29%	1.09%	Beta	1,434	9	1,425
Non-melanoma skin cancer	0.000	0.00%	0.000%	Beta	1,434	0	1,434
Conventional therapy		AE incidence - CT (95% CI)					
Serious Infection	0.018	1.48%	2.22%	Beta	5,004	92	4,912
Lymphoma	0.000	0.00%	0.06%	Beta	5,004	1	5,003
Acute hypersensitivity reaction	0.004	0.26%	0.61%	Beta	5,004	21	4,983
Non-melanoma skin cancer	0.000	0.00%	0.09%	Beta	5,004	1	5,003
Cost per adverse event		Cost per adverse event (+/- 20%)			% in tails		
Serious Infection	£1,742.14	£1,411.20	£2,107.41	Gamma	20%	96.04	18.14
Lymphoma	£16,509	£13,372.96	£19,970.42	Gamma	20%	96.04	171.90
Acute hypersensitivity reaction	£442.11	£358.13	£534.81	Gamma	20%	96.04	4.60
Non-melanoma skin cancer	£1,859.76	£1,506.48	£2,249.70	Gamma	20%	96.04	19.36
Adverse event disutilities		Adverse event disutilities (+/- 20%)			N		
Serious Infection	0.760	0.67	0.84	Beta	100	76	24
Lymphoma	0.195	0.12	0.28	Beta	100	20	81
Acute hypersensitivity reaction	0.110	0.06	0.18	Beta	100	11	89
Non-melanoma skin cancer	0.030	0.01	0.07	Beta	100	3	97
Proportion Discontinuing due to AEs							
Vedolizumab		Vedolizumab discontinuation rate (95% CI)			N		
Induction	2.69%	1.10%	4.96%	Beta	263	7	256
Maintenance	8.54%	3.55%	15.43%	Beta	82	7	75

Appendix 4: Disaggregated presentation of base case results

TNF-α antagonist failure population: vedolizumab vs. CT

The disaggregated results for costs and QALY gains are provided in Table 53 and Table 54 respectively below

Table 53: Direct non-drug medical costs, by health state

Health states	Vedolizumab	CT	Increment
Remission (CDAI<150)	£580	£273	£308
Mild (CDAI = 150-220)	£1,430	£952	£478
Moderate-to-Severe (CDAI = 220 -600)	£187,914	£195,440	-£7,526
Surgery	£11,124	£11,587	-£462

There is rounding of the values in the table

Table 54: QALY gain by health state

Health states	Vedolizumab	CT	Increment
Remission (CDAI<150)	0.730	0.343	0.387
Mild (CDAI = 150-220)	0.781	0.520	0.261
Moderate-to-Severe (CDAI = 220 -600)	11.671	12.138	-0.467
Surgery	0.130	0.136	-0.005

Appendix 5: Methods for the NMA in TNF-α antagonist failure population

8.1 Studies included in the NMA and the networks created

8.1.1 Overview of studies included

The systematic review performed for the NMAs has been provided in the original submission to NICE. In this appendix we provide an overview of the methods used for the updated NMA in the TNF-α antagonist failure sub-population, GEMINI II and GEMINI III contained data on induction and maintenance treatment with vedolizumab for patients who had inadequate response, loss of response, or intolerance to a prior TNF-α antagonist (primary and secondary failures). There were two studies with data on outcomes for patients treated with adalimumab after loss of response or intolerance to infliximab, one covering the induction phase of treatment including only patients who had previously failed or were intolerant to infliximab,[10] the other covering the Maintenance Phase of treatment with a sub-group of patients who had failed or were intolerant to infliximab.[29] These studies excluded primary failures to infliximab. Hence, the patient populations across the trials are not directly comparable. As those patients in the adalimumab studies who never experienced a response to prior infliximab treatment were excluded it is likely that the failure population in the vedolizumab trials which included both primary and secondary failures are harder to treat, and so outcomes may not be as good as for the patients in the adalimumab trial. Nonetheless, with these limitations in mind, a comparison of outcomes between vedolizumab and adalimumab for the TNF-α antagonist treatment failure population has been performed.

8.1.2 The networks

8.1.2.1 Networks for induction and maintenance therapy in TNF-α antagonist failure patients

For the outcomes of response and remission the network in TNF-α antagonist failure patients for induction therapy and for maintenance therapy each consisted of evidence from 3 RCTs covering vedolizumab and TNF-α antagonists (adalimumab only), and is presented in Figure 7 and Figure 8.

Figure 7: Network diagram of the interventions compared for the outcomes of clinical response (drop in CDAI ≥ 70), enhanced clinical response (drop in CDAI ≥ 100), clinical remission (CDAI ≤150) and discontinuation due to AEs in the TNF-α antagonist failure sub-population in induction treatment.

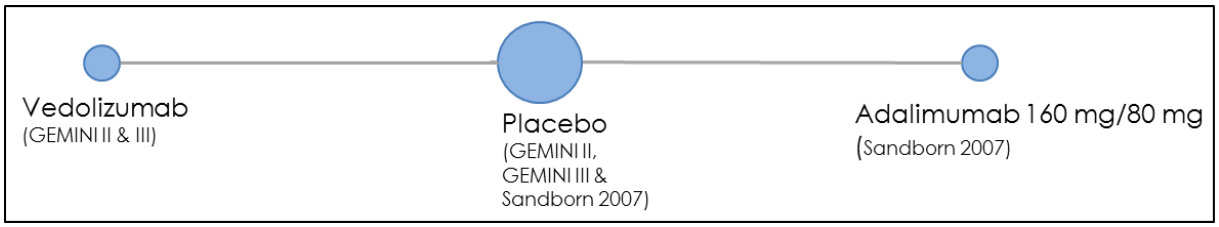
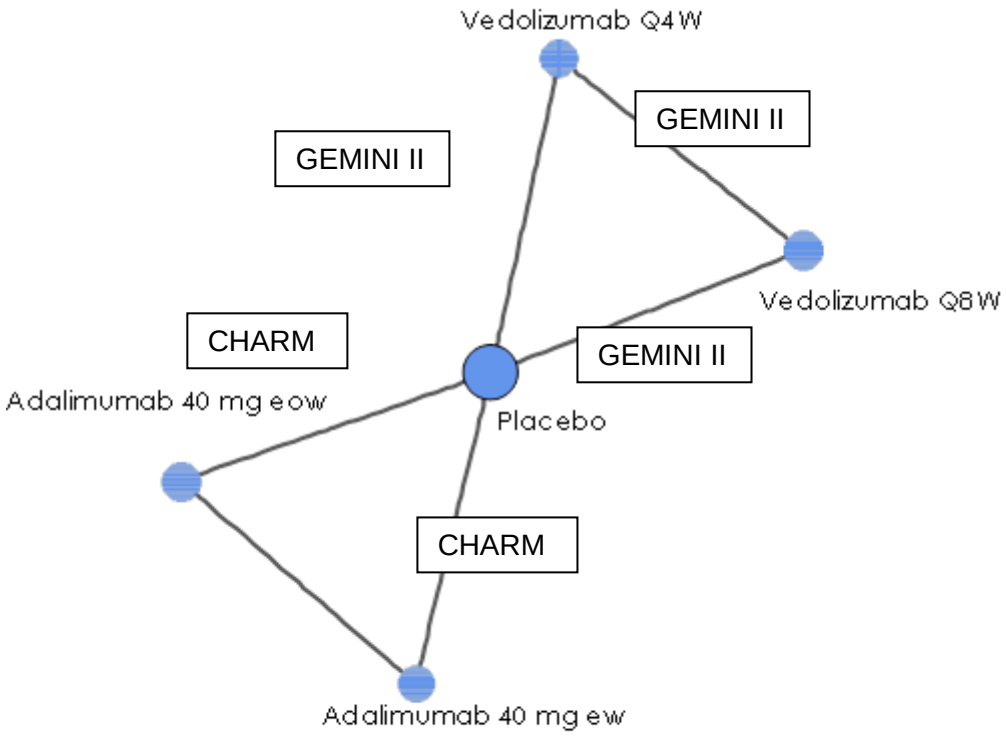


Figure 8: Network diagram of the interventions compared for the outcomes of clinical response (drop in CDAI≥70), enhanced clinical response (drop in CDAI≥100), clinical remission (CDAI≤150) and discontinuation due to AEs in the TNF-α antagonist failure sub-population in maintenance treatment



8.2 Study characteristics

Table 57 shows the key study design features and patient characteristics of the studies included in the NMA. The information was not specifically available for the TNF-α antagonist failure patient sub-population, hence characteristics are for the overall study populations. The study design for each trial included was similar and there were similarities in patient characteristics (e.g. age, % male, baseline CDAI score). For the Maintenance Phase the CHARM study contains patients of a similar age and baseline CDAI as in GEMINI II, but the percentage male is lower (Table 34). In addition, the information is not available in the CHARM publication to determine patient characteristics by treatment arm.

Table 55: Study design and patient characteristics of RCTs included in the TNF-α antagonist failure NMA

Study	Study design					Patient baseline characteristics					
	Study design	Patient population	TNF-α antagonist treatment failure sub-group	Duration wks	Interventions	Patient No.s (randomised)	Mean age (yrs)	% Male	% failure	Baseline CDAI score	Mean CD duration
Induction phase											
GEMINI II Sandborn 2013 Vedolizumab	DB Pb-RCT Central randomization; stratified by 1) concomitant CS use and 2) prior anti-TNF or IM exposure	Adults with moderately to severely active CD (diagnosed ≥ 3 months before enrolment) who, during the last 5 years, had failed ≥ 1 standard CD therapies	Primary and secondary failures	6	Placebo/CT	148	38.6	47	49	324.6	8.2
					Vedolizumab 300 mg	220	36.3	48	51	327.3	9.2
GEMINI III Sands 2014 Vedolizumab	DB Pb-RCT Central randomization; stratified by 1) prior anti-TNF failure vs. anti-TNF–naïve	Adults with moderately to severely active CD (diagnosed ≥ 3 months before enrolment); during the last 5 years, with an inadequate response to, loss of response to, or intolerance of ≥ 1 of IM, anti-TNF	Primary and secondary failures	10	Placebo/CT	207	37.1	43	76	297.4	NR
					Vedolizumab 300mg	209	38.6	44	76	311.4	NR
Sandborn 2007 Adalimumab	DB Pb-RCT Central randomization; stratified by investigation site with block sizes of 4	Adults with moderately to severely active CD ≥ 4 months and intolerant of or lost response to infliximab (excluding primary failures)	Secondary failures	4	Placebo/CT	166	37	39	100	313	NR
					Adalimumab 160 mg/80 mg	159	39	31	100	313	NR

Study	Study design					Patient baseline characteristics					
	Study design	Patient population	TNF-α antagonist treatment failure sub-group	Duration wks	Interventions	Patient No.s (randomised)	Mean age (yrs)	% Male	% failure	Baseline CDAI score	Mean CD duration
Maintenance phase											
GEMINI II Sandborn 2013 Vedolizumab	DB Pb-RCT Central randomization; stratified by 1) concomitant CS use and 2) prior anti-TNF or IM exposure. Responders (CDAI 70) to 6 weeks vedolizumab randomised to maintenance therapy	Adults with moderately to severely active CD (diagnosed ≥ 3 months before enrolment) who, during the last 5 years, had failed ≥ 1 standard CD therapies	Primary and secondary failures	52	Placebo/CT	153	37.2	47	54	325	9.6
					Vedolizumab Q8W	154	35.1	44	57	325	7.7
					Vedolizumab Q4W	154	34.9	53	54	317	8.4
CHARM Colombel 2007 Adalimumab	DB Pb-RCT Central randomization; stratified by induction response at week 4 (CDAI 70) and prior TNF-α antagonist exposure	Adults with moderately to severely active CD (diagnosed ≥ 4 months before enrolment) excluding primary failures	Secondary failures	56	Placebo/CT	170	36.7	37.7	50	317	NR
					Adalimumab 40mg eow	172					
					Adalimumab 40mg ew	157					
Abbreviations: DB Pb-RCT: Double blind placebo controlled RCT; CD=Crohn's disease; ew=every week, eow=every other week; Q8W=every 8 weeks, Q4W=every 4 weeks NR=not reported											

8.3 NMA methods and analyses

8.3.1 Modelling methods

The NMAs were performed in the base case using a Bayesian fixed effects modelling approach. Fairly informative priors were needed for the models to run, although model runs with different priors showed that the choice of prior had little effect on the results. It was not possible to run random effects models due to the small networks in the TNF-α antagonist failure patient sub-population meaning there were no duplicate comparisons and hence heterogeneity is not possible to estimate.

The NMAs were performed based on the Lu and Ades (2004) method for combining direct and indirect evidence,[57] with repeated measurements handled using a technique described by Dakin et al.[58] The models used the R package R2WinBUGS to run the models in OpenBUGS .[59] A binomial distribution was assumed and a logistic link function used. Three chains, starting from different initial values, were run in each analysis. Burn-in was 20,000 iterations for each chain, followed by 20,000 iterations used for analysis, and a Thin rate of 50. Thus results are based on 60,000 iterations. The code used to run the base case fixed effects models are presented below.

Bayesian Fixed Effects model code

```
model {

for(i in 1:total.n) # number of comparisons
 {
 logit(p[sw[i],t[i]]) <- mu[sw[i]] + d[t[i]] - d[b[i]] # model
 r[i] ~ dbin(p[s[i], t[i]], n[i]) # binomial likelihood
 }

for(j in 1:s.n) { mu[j]~dnorm(0,.01) } # priors for x trial baselines

d[1] <- 0
for (k in 2:t.n) {d[k] ~ dnorm(0,.01) } # priors for basic parameters

# pairwise differences
 for (c in 1:(t.n-1))
 { for (k in (c+1):t.n)
 { lor[c,k] <- d[k] - d[c] # odds ratios
 log(or[c,k]) <- lor[c,k]
 }
 }
}
```

Total.n = number of records in the network; s.n = number of studies; b = the reference treatment for each study; t.n = number of treatments

8.3.2 Outcomes of interest

The NMA was performed separately for the Induction and Maintenance Phases of treatment with a focus on key efficacy endpoints of most interest for populating the economic model:

- **Clinical response in induction treatment** – Two definitions of clinical response where applied in the NMAs: a reduction in CDAI score of ≥ 70, or enhanced clinical response defined as a reduction in CDAI score of ≥ 100 (used in scenario analysis). This was assessed at Week 6 and Week 10 for vedolizumab, and the primary time point for induction for each of the TNF-α antagonists (i.e. Week 4 for adalimumab). The base case analysis consisted of induction response assessed at Week 10 for vedolizumab, with response defined as reduction in CDAI ≥70. Although response assessment at 6 weeks represented the primary end point in the GEMINI trials, feedback from a consultant Gastroenterologist was that in clinical practice 10 weeks represents a more realistic time at which to assess clinical response, and is also consistent with the recommendation in the vedolizumab SmPC. In addition, clinical expert opinion was that a change of ≥ 70 from baseline in CDAI represented a clinically meaningful response (at 10 weeks), indicating that patients outcomes are improving. A limitation of the 10 weeks assessment time with response defined as CDAI-70 is that these represent additional post-hoc analysis of the trial data, rather than primary analyses.
- **Clinical remission in induction treatment** - Clinical remission is defined as a CDAI score of ≤ 150. This was assessed at the10 week assessment time points for vedolizumab, and week 4 for adalimumab.
- **Durable clinical response in maintenance treatment** – Durable clinical response is defined as response at both the start and end of the maintenance phase (measured at Week 52 or 56 in each study included in the NMA).
- **Clinical remission in maintenance treatment** – This outcome (measured at Week 52 or 56 in each study included in the NMA) was defined in the same way as remission in induction.
- **Discontinuations due to adverse events** - the proportion of patients who discontinued treatment due to AEs were assessed in the NMA for the induction and maintenance phases of treatment.

8.3.3 Analysis of comparative treatment effect

The proportion of patients who achieved each efficacy outcome and the proportion of patients who discontinued treatment due to AEs were analysed as dichotomous endpoints. In each study the data used was the ITT or FAS dataset.

The NMA results for each outcome were presented as Odds Ratios with 95% credible intervals. In each trial patients in the placebo arm also received conventional therapy (CT) hence placebo provides a proxy for treatment with CT. The placebo/CT outcomes were based on pooled placebo data from the trials included in the NMA. Placebo/CT represented the baseline reference comparator for each biologic in the NMA.

8.3.4 Limitations

Whilst there is direct trial evidence from large sub-groups within GEMINI II and GEMINI III for a comparison with conventional therapy (as proxied by placebo), there is no direct evidence for vedolizumab versus the use of a second TNF-α antagonist, hence the need for an indirect comparison. The characteristics of the patients in the trials were reasonably reflective of CD patients in England and Wales, hence it is not expected that there are major generalisability concerns over the data used in the NMA.

A systematic review and NMA has been performed that covers a TNF-α antagonist failure sub-population. Whilst a strength is the size of the sub-populations who are TNF-α antagonist failures in the vedolizumab trials (representing about 50% of GEMINI II, and 76% of GEMINI III populations), the main limitation is clearly a lack of RCT data for the comparators. The lack of data is reflected in the marketing authorisations for the TNF-α antagonists, with neither specifically licensed for use after prior failure of a TNF-α antagonist. No relevant studies were found for infliximab, and only limited data was available for adalimumab. Whilst there is some data for adalimumab, there is none in the same comparable 'failure' patient population as that for vedolizumab. The adalimumab trials are in secondary failure patients only, so they exclude those who never had an initial response to a TNF-α antagonist, whereas the vedolizumab data is for both primary and secondary failure patients. As the primary failure patients could be expected to have relatively poorer outcomes it is likely the results are conservative, and the relative effectiveness of vedolizumab has been underestimated. However, despite this caveat, the results show no statistically significant differences in response and remission outcomes between vedolizumab and adalimumab in this sub-population of patients. Nor, based on the limited data available is there any evidence of a difference in longer run efficacy (i.e. clinical remission) between standard maintenance dose frequency of vedolizumab administered every 8 weeks, and the 4 weekly dose or with the escalated dose for adalimumab of 40mg every week.

Other limitations with the NMA data for adalimumab are as follows:

- It was not possible to include an assessment of discontinuations due to AEs in the maintenance phase. As the maintenance phase typically lasts for one year in CD trials this is the more clinically meaningful phase in which to assess this outcome

- Due to the gut selectivity of vedolizumab it is not associated with systemic immunosuppression and so is expected to have a lower risk of serious infection than the TNF-α antagonists.

- A general methodological limitation of having a small network for the NMA is that we were limited to using fixed effects models, and it is not therefore possible to fully account for and explore heterogeneity by using random effects models as well.

Related to the above limitations in the NMA in the TNF-α antagonist failure sub-population, in the economic analysis a comparison of vedolizumab against adalimumab and infliximab is included only as an exploratory analysis.