NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Vedolizumab for the for the treatment of adult patients with moderately to severely active Crohn's disease

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Abbreviations

Abbreviation	Term
5-ASAs	5-aminosalicylates
6-MP	6-mercaptopurine
ADA	Adalimumab
AE(s)	Adverse event(s)
Anti-TNF	Tumour Necrosis Factor Antagonist
ATC	Anatomical therapeutic chemical
AZA	Azathioprine
BIM	Budget impact model
BMI	Body mass index
BNF	British National Formulary
BSG	British Society of Gastroenterology
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CE	Conformité Européenne
CEAC	Cost effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CMH	Cochran–Mantel–Haenszel
CmT	Computed tomography
CONSORT	Consolidated standards of reporting trials
CrI	Credible interval
CRP	C-reactive protein
CSF	Corticosteroid-free
CT	Conventional therapy
DEXA	Dual-energy X-ray
ECG	Electrocardiogram
EED	Economic evaluation database
EMA	European Medicines Agency
EOW	Every other week
EPAR	European public assessment report
EQ-5D	EuroQol -5 dimension
ERG	Evidence review group

ET	Early termination
EW	Every week
FDA	Food and drug administration
GC	Glucocorticoid
GPRD	General Practice Research Database
HAHA	Human anti-human antibodies
HRG	Healthcare resource groups
HRQL	Health-related quality of life
i.v.	Intravenous(ly)
IBD	Inflammatory bowel disease
IBDQ	Inflammatory bowel disease questionnaire
ICER	Incremental cost-effectiveness ratio
IFU	Indications for use
IND	Induction
INF	Infliximab
IRR	Infusion-related reactions
ITT	Intention to treat
IVRS	Interactive voice response system
IWRS	Interactive web response system
JC virus	John Cunningham virus
LOCF	Last observation carried forward
LOR	Loss of response
LTS	Long-term safety
LYG	Life years gained
MAdCAM-1	Mucosal addressin cell adhesion molecule-1
MedDRA	Medical dictionary for regulatory activities
MeSH	Medical subject heading
MLN0002	Vedolizumab, formerly LDP-02 and MLN02
MNT	Maintenance
MRI	Magnetic resonance imaging
MTC	Mixed treatment comparison
MTX	Methotrexate
N/A	Not available
NHS	National Health Service
NICE	National Institute for Health and Care Excellence

NR	Not reported
PbR	Payment by results
PF	Primary failure
PML	Progressive multifocal leukoencephalopathy
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PRO	Patient Reported Outcomes
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
PT	Preferred term
Pts	Patients
P-Y	Person-years
Q4W	Every 4 week dosing
Q8W	Every 8 week dosing
QALY	Quality-adjusted life-year
RCT	Randomised controlled trial
RR	Relative risk
SAE(s)	Serious adverse event(s)
SCAI	Simple Colitis Activity Index
SCCAI	Simple Clinical Colitis Activity Index
SD	Standard deviation
SE	Standard error
SF	Secondary failure
SF-36	Medical Outcomes Study 36-item Short Form
SmPC	Summary of product characteristics
SMR	Standardised mortality ratio
TA	Technology appraisal
TB	Tuberculosis
TGA	Therapeutic goods administration
TNF	Tumour necrosis factor
TPY	Total person years
TTO	Time trade off
UC	Ulcerative colitis
UCDAI	Ulcerative Colitis Disease Activity Index
UEG	United European Gastroenterology

UK	United Kingdom
US	United States
VAS	Visual analogue scale
VAT	Value added tax
VCAM-1	Vascular cell adhesion molecule-1
VDZ	Vedolizumab
WBC	White blood cell
Wk(s)	Week(s)

Glossary

Term	Definition	Source
CDAI	The Crohn's Disease Activity Index or CDAI is frequently used to assess disease severity. It gives a score ranging from 0 to over 600, based on a diary of symptoms kept by the patient for 7 days, and other measurements such as the patient's weight and haematocrit (see Appendix **Error! Reference source not found.**). A CDAI score of less than 150 is considered to be remission, a score greater than 220 is considered to define moderate to severe disease, and a score greater than 300 is considered to be severe disease.	(Takeda Data on File, 2012a, 2012b)
Clinical remission	CDAI score ≤150 points	(Takeda Data on File, 2012a, 2012b)
Clinical response	A ≥ 70-point decrease in CDAI score from baseline (Week 0).	(Takeda Data on File, 2012a, 2012b)
Corticosteroid-free remission	Clinical remission in patients using oral corticosteroids at baseline (Week 0) who have discontinued corticosteroids and are in clinical remission at Week 52.	(Takeda Data on File, 2012a)
Durable clinical remission	Clinical remission at ≥80% of study visits, including final visit (Week 52)	(Takeda Data on File, 2012a)
Durable clinical response	Clinical response at ≥80% of study visits, including final visit (Week 52).	(Takeda Data on File, 2012a)
Enhanced clinical response	A ≥ 100-point decrease in CDAI score from baseline (Week 0).	(Takeda Data on File, 2012a, 2012b)
Inadequate Response	Signs and symptoms of persistently active disease, despite a history of: • *Corticosteroids:* at least one 4-week induction regimen of the dose equivalent of prednisone 30 mg daily orally for 2 weeks or IV for 1 week or 2 failed attempts to taper corticosteroids below the dose equivalent of 10 mg daily on 2 separate occasions. • *Immunomodulators*: at least one 8-week regimen of azathioprine (≥ 1.5 mg/kg), 6-mercaptopurine (≥ 0.75 mg/kg), or methotrexate (≥ 12.5 mg/week). • *TNF-alpha antagonists*: at least one 4-week induction regimen of a TNF-alpha antagonist (Infliximab 5 mg/kg IV, 2 doses at least 2 weeks apart; Adalimumab one 80 mg subcutaneous dose followed by a 40 mg dose at least 2 weeks apart; certolizumab pegol 400 mg subcutaneous, 2 doses at least 2 weeks apart).	(Takeda Data on File, 2012a, 2012b)
Intolerance	• *Intolerance to corticosteroids:* including, but not limited to Cushing's syndrome, osteopenia/osteoporosis, hyperglycaemia, insomnia, infection. • *Intolerance to immunomodulators*: including,	(Takeda Data on File, 2012a, 2012b)

Term	Definition	Source
	but not limited to nausea/vomiting, abdominal pain, pancreatitis, liver function test abnormalities, lymphopenia, thiopurine methyltransferase genetic mutation, infection. • *Intolerance to TNF-alpha antagonists:* including, but not limited to infusion-related reaction, demyelination, congestive heart failure, infection.	
Loss of Response	Recurrence of symptoms during maintenance dosing following prior clinical benefit (discontinuation despite clinical benefit did not qualify).	(Takeda Data on File, 2012a, 2012b)
Nonresponder	Patients who did not achieve a clinical response (a ≥ 70 point decrease in CDAI score from baseline) at Week 6.	(Takeda Data on File, 2012a, 2012b)
Overall safety population (GEMINI II)	The safety population in the GEMINI II trial included all enrolled patients, including both Cohort 1 and Cohort 2. • Placebo safety group includes patients who received placebo in Cohort 1 and patients who responded to Vedolizumab in the induction phase (up to week 6) and were randomized to placebo in the maintenance phase (up to week 52). • The Vedolizumab safety group includes patients from Cohort 1 and Cohort 2 who responded to Vedolizumab in the induction phase (up to week 6) and were randomized to Vedolizumab (Q4W or Q8W) in the maintenance phase (up to week 52) and patients from Cohort 1 and Cohort 2 who received but did not respond to Vedolizumab in the induction phase (up to week 6) and received Vedolizumab (Q4W) in the maintenance phase (up to week 52).	(Takeda Data on File, 2012a)
Overall safety population (GEMINI III)	All patients who received any amount of study drug.	(Takeda Data on File, 2012b)
Rescue medication(s)	Any new medication or any increase in dose of a baseline medication required to treat new or unresolved Crohn's disease symptoms (other than antidiarrheals for control of chronic diarrhoea)	(Takeda Data on File, 2012a, 2012b)
Serious infection	Serious adverse event of infection according to the classification for adverse event reporting in MedDRA.	(Takeda Data on File, 2012a, 2012b)
Sustained clinical remission	CDAI score ≤150 points at both Week 6 and Week 10.	(Takeda Data on File, 2012a, 2012b)
Sustained enhance clinical response	A ≥ 100-point decrease in CDAI score from baseline (Week 0) at both Week 6 and Week 10.	(Takeda Data on File, 2012a, 2012b)
TNF-alpha antagonist experienced sub-population	Subgroup of patients who have been intolerant to Infliximab or must have previously responded to Infliximab and then lost response. Patients who had a primary non response to Infliximab as defined by the investigator, received Infliximab or another TNF antagonist within the past	(Sandborn et al., 2007b)

Term	Definition	Source
	8 weeks, previously received Adalimumab or participated in an Adalimumab clinical trial were excluded.	
TNF-alpha antagonist failure sub-population	Subgroup of patients defined as having previously failed TNF-alpha antagonist therapy.	(Takeda Data on File, 2012a, 2012b)
TNF-alpha antagonist mixed population	Anti-TNF–naive and anti-TNF–failure patients, representing the intention to treat [ITT] population of the Vedolizumab trials.	(Sandborn et al., 2007b; Takeda Data on File, 2012a, 2012b)
TNF-alpha antagonist naïve sub-population	Subgroup of patients defined as naive to TNF-alpha antagonist therapy.	(Takeda Data on File, 2012a, 2012b)
Treatment Failure	Need for rescue medications or major surgical intervention for treatment of Crohn's disease, or study drug-related adverse events leading to discontinuation of study drug.	(Takeda Data on File, 2012a, 2012b)

Executive summary

Crohn's disease

Crohn's disease is a chronic, lifelong relapsing inflammatory disease affecting any part of the gastrointestinal tract. All aspects of an individual's life—physical, emotional, cognitive, social—are affected as a result of Crohn's disease (Wolfe & Sirois, 2008). The disease is often diagnosed at an early age (< 30 years), affecting the working age population and impacting work productivity (Burisch & Munkholm, 2013). Crohn's disease results in a total economic burden of between €2.1-16.7 billion in Europe (Yu, Cabanilla, Wu, Mulani, & Chao, 2008). As such Crohn's disease has a high clinical, humanistic, and economic burden.

Current treatments for Crohn's disease, including conventional therapies (corticosteroids and immunomodulators) and TNF-alpha antagonists (Infliximab and Adalimumab), are associated with a significant failure rate; approximately 10-40% of patients treated with Infliximab have a sustained response after 1 year and 20% of adult patients required dose intensification and experienced a loss of response after initiation of Adalimumab therapy (Molnár et al., 2012). Many patients experience a loss of response and subsequently relapse. In addition, Crohn's disease patients who lose response to one anti-TNF agent have a lower chance of responding to a second one. Current treatments are associated with serious side effects:

- Long-term exposure to corticosteroids results in an increased risk of numerous adverse events including infection, psychological disturbances, diabetes, hypertension, and osteoporosis.
- Potential adverse events generally associated with the use of immunomodulators, include bone marrow suppression, leukopenia, nausea, vomiting, and hepatic brosis.
- The major risks associated with TNF-alpha antagonists are risks of infection and malignancy.

Surgery is not a curative treatment in Crohn's disease after TNF-alpha antagonist failure and can result in multiple complications and a large humanistic burden. Up to 70% of Crohn's disease patients may require surgery at least once over the course of the disease (Kopylov, Ben-Horin, Zmora, Eliakim, & Katz, 2012; Lichtenstein, Hanauer, & Sandborn, 2009).

Development of Vedolizumab

Vedolizumab targets the site of inflammation in the gut and is the first gut-selective biologic for the treatment of Crohn's disease (Soler et al., 2009). It has an anti-inflammatory profile that differs from currently available systemic biologics. Vedolizumab is a selective antagonist that binds exclusively to the α4β7 integrin heterodimer, engineered to target lymphocyte trafficking localised in the gut.

Efficacy of Vedolizumab based on pivotal clinical trial data

GEMINI II

GEMINI II is a Phase 3, randomized, placebo-controlled trial of the induction and maintenance of clinical response and remission by Vedolizumab in patients with moderate to severe Crohn's disease (William J Sandborn et al., 2013a; Takeda Data on File, 2012a).

Vedolizumab is effective when directly compared to placebo at achieving clinical remission (39.0% versus 21.6%) and enhanced clinical response (43.5% versus 30.1%), at 52 weeks, in Crohn's disease. Similar findings were observed for enhanced clinical response at Week 52. A statistically significantly greater proportion of Vedolizumab-treated patients achieved the primary efficacy endpoint of clinical remission at Week 6, with a treatment difference from placebo of 7.8%. Although a trend in favour of Vedolizumab was observed for the other primary endpoint of enhanced clinical response at Week 6, differences between the Vedolizumab and placebo groups did not reach statistical significance.

In addition, Vedolizumab improves corticosteroid-free remission at 52 weeks in Crohn's disease patients. In GEMINI II, among patients receiving corticosteroids at the start of the maintenance phase, statistically significantly greater proportions of Vedolizumab-treated patients achieved corticosteroid-free clinical remission at week 52 compared with patients who received placebo.

GEMINI III

GEMINI III is a Phase 3, randomized, placebo-controlled trial of the induction of clinical response and remission by Vedolizumab in patients with moderate to severe Crohn's disease (Sands et al., 2014; Takeda Data on File, 2012b). The efficacy of Vedolizumab in TNF-alpha antagonist failure and the overall population in GEMINI III

is summarized in the below table. The primary endpoint of clinical remission at Week 6 in the TNF-alpha antagonist failure population was not met. However, a potential treatment benefit of Vedolizumab versus placebo was reflected in the induction of clinical remission at Week 10 in this sub-population and at week 6 and 10 in the overall population.

Vedolizumab is the only biologic treatment indicated for CD patients who have failed anti-TNF therapy. Following failure on one anti-TNF therapy, it is rational to switch patients to Vedolizumab given its gut-targeting mechanism of action and demonstrated efficacy in TNF-Failure patients.

	Clinical remission		**Enhance clinical response**		**Sustained Remission**
	Week 6	**Week 10**	**Week 6**	**Week 10**	
TNF-alpha antagonist failure population					
% Difference from placebo	3.0	14.4	16.9	22	3.7
95% CI	(-4.5, 10.5)	(5.7, 23.1)	(6.7, 27.1)	(11.4, 32.6)	(-2.9, 10.3)
P-value[e]	0.433	0.0012	n/a	n/a	0.2755
Overall population					
% Difference from placebo	6.9	15.5	16.4	23.7	7.0
95% CI	(0.1, 13.8)	(7.8, 23.3)	(7.7, 25.2)	(14.5, 32.9)	(0.9, 13.1)
P-value[e]	0.0478	< 0.0001	n/a	n/a	0.0249
Abbreviations: CI = confidence interval; n/a, not available; TNF=tumour necrosis factor; VDZ, Vedolizumab					

Effectiveness of Vedolizumab compared to TNF-alpha antagonists

Based on an indirect analysis, Vedolizumab is at least similar to Infliximab and Adalimumab at achieving sustained efficacy (clinical remission and durable clinical response) at 52 weeks in Crohn’s disease patients.

In the treatment of anti-TNF–naïve patients with Crohn’s disease, Vedolizumab did not show significant differences in the efficacy endpoints studied, when compared with other biologics in the induction setting. Results were consistent regardless of whether the week 6 or week 10 data for Vedolizumab were used in analyses. In the maintenance setting, data for anti-TNF–naïve patients were available only for Vedolizumab and Infliximab. Vedolizumab did not show significant differences in

efficacy results when compared with Infliximab, and rates of discontinuation due to adverse events were significantly better for Vedolizumab.

Data for the anti-TNF–failure population were available only for Vedolizumab. Data were available for Adalimumab in the anti-TNF–experienced population. In induction therapy, Vedolizumab did not show significant differences in most efficacy endpoints when compared with Adalimumab. However, Adalimumab had significantly higher rates of clinical remission when week 6 data for Vedolizumab were analysed but not when the 10-week data for Vedolizumab were analysed.

HRQL outcomes of Vedolizumab

In GEMINI II, as rated by IBDQ, SF-36 (physical and mental components), and EQ-5D instruments, improvements in HRQL at Week 6 and 52 were consistently greater for patients who received Vedolizumab compared to patients who received placebo (Takeda Data on File, 2012a).

In GEMINI III, improvement in IBDQ was consistently greater for patients who received Vedolizumab compared with 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 (Takeda Data on File, 2012b).

Safety profile of Vedolizumab

Safety and tolerability of Vedolizumab have been evaluated in a robust clinical development program, spanning over more than 2,800 patients (J Colombel, Sands, Rutgeerts, et al., 2013). In Crohn's disease, Vedolizumab has shown a similar rate of adverse events compared to placebo. Overall median exposure to Vedolizumab was approximately one year (range, 1 day to 5 years) with more than 900 people treated with Vedolizumab for ≥2 years. Across the integrated safety population, Vedolizumab demonstrated a tolerable safety profile for the treatment of adults with moderately to severely active Crohn's disease and ulcerative colitis. The incidence rate of serious infections of interest was low with Vedolizumab and consistent with the mechanism of action, there were no cases of PML reported. In contrast to currently available biologics, Vedolizumab has no identified systemic immunosuppressive activity.

Economic evaluation of Vedolizumab

The cost-effectiveness of vedolizumab was assessed in comparison with conventional therapy, infliximab and adalimumab using a decision tree for the induction period and a Markov model for the maintenance period. Data to inform the clinical inputs to the model were taken from the GEMINI 2 and GEMINI 3 clinical trials as well as an MTC for comparisons with infliximab and adalimumab. Comparisons with infliximab and adalimumab were limited to patients that were TNF-naïve. Costs were taken from standard NHS sources and utilities were taken from EQ-5D data collected in the GEMINI 2 and GEMINI 3 clinical trials.

Compared with conventional therapy, vedolizumab is found to provide 0.126 additional QALYs over a 10-year time horizon and to cost £7,639 more. Most of these costs relate to the cost of vedolizumab, with cost offsets due to avoiding poorer health states. QALY benefits are largely due to avoiding poorer health states with the use of vedolizumab. The ICER for vedolizumab, compared with conventional therapy is £60,600.

Vedolizumab is found to be more cost-effective in patients that have previously failed on TNF therapy and in those patients with moderate disease. In patients that have failed on TNF therapy, the ICER for vedolizumab compared with conventional therapy is £20,532 pounds. And compared with adalimumab in this population it is £2,602. Vedolizumab dominates infliximab in this population. In patients with moderate disease (both TNF-naïve and TNF-failures), the ICER for vedolizumab is £18,531 compared with conventional therapy.

The model is most sensitive to transition probabilities, health state costs and utilities, along with the time horizon for the assessment.

Section A – Decision problem

1 Description of technology under assessment

1.1	Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

Brand name	Entyvio®
Approved name	Vedolizumab
Therapeutic class	Immunosuppressants, selective immunosuppressants, ATC code: L04AA33

1.2	What is the principal mechanism of action of the technology?

Vedolizumab is a gut-selective immunosuppressive biologic which reduces gastrointestinal inflammation. (Soler et al., 2009). Vedolizumab is a humanized monoclonal antibody that binds exclusively to the α4β7 integrin on gut-homing T helper lymphocytes and selectively inhibits adhesion of these cells to mucosal addressin cell adhesion molecule-1 (MAdCAM-1) and fibronectin, but not vascular cell adhesion molecule-1 (VCAM-1) (Soler et al., 2009). Vedolizumab does not bind to, nor inhibit function of, the α4β1 and αEβ7 integrins and has no identified systemic immunosuppressive effects.

The inhibition of α4β7 integrin is a shared mechanism of action of both Vedolizumab and Natalizumab and has thus raised a question of whether or not Vedolizumab may also increase the risk of progressive multifocal leukoencephalopathy (PML) which is a usually fatal viral disease characterized by progressive damage or inflammation of the white matter of the brain.. Published evidence supports the concept that PML associated with Natalizumab results from antagonising the α4β1 integrin and not the α4β7 integrin (Allen, 2012a; Danese, De la Rue, & Gasbarrini, 2005; Milch et al., 2013). As of 20 August 2014, there have been no reported cases of PML in patients receiving Vedolizumab for inflammatory bowel disease (IBD, (Gledhill & Bodger, 2013)).

Figure 1.2.1: Vedolizumab mechanism of action: blocks capture of pathogenic gut-homing lymphocytes

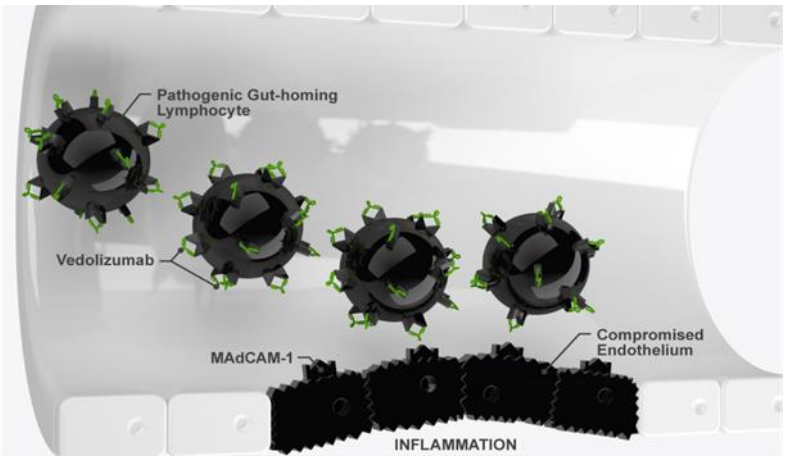
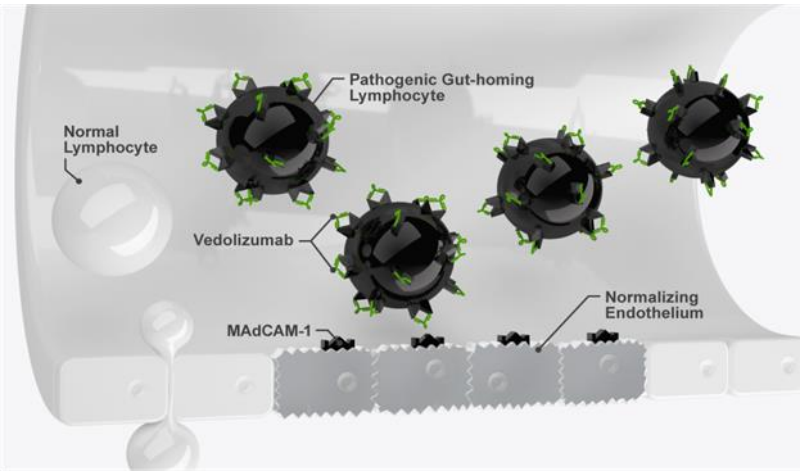


Figure 1.2.2: Vedolizumab mechanism of action: reduces inflammation by preventing selective migration of pathogenic gut-homing lymphocytes



1.3	**Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).**

On 22 May 2014, the European Medicines Agency (EMA) granted marketing authorisation for the medicinal product Entyvio (EMA, 2014b), 300 mg powder for concentrate for solution for infusion

> *'for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha antagonist.*

Marketing authorisation was also received at the same time for

> *'the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha antagonist. '*

1.4	**Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the marketing authorisation).**

Based on the Committee for Medicinal Products for Human Use (CHMP) review of data on quality, safety and efficacy, the CHMP considered by consensus, that the risk-benefit balance of Vedolizumab is favourable and therefore recommended the granting of the Marketing Authorisation (EMA, 2014a). Key discussions from the European public assessment report (EPAR) on Vedolizumab are summarized in the below table.

Table 1.4.1: EPAR discussion points on Vedolizumab in Crohn's disease

Theme	Objection	Response/ conclusion
Duration of maintenance	The CHMP commented on the duration of the maintenance phase of the study, which was from week 6 to 52, whereas EMA guideline recommends duration of at least 1 year.	The use of disease activity data from the first study visit of the long-term safety study (C13008, GEMINI LTS) can supply the missing data on remission at week 52, and so this can be accepted.
Clinical trial design: placebo controlled	The study was designed against placebo, however conventional therapies (5-ASAs, corticosteroids, immunomodulators, antibiotics, probiotics and antidiarrheal) were concomitantly administered to patients. The lack of an anti-TNF-alpha compound comparator arm was considered by EMA to represent a limit of the study in consideration of today's standard of care.	Takeda will present a mixed treatment comparison to TNF-alpha antagonists in this submission.
Magnitude of effect in GEMINI II	The magnitude of the effect was seen as limited in the second line indication in Crohn's disease (GEMINI II results), with regard to the time required for induction of remission and the effect size compared to anti-TNF-alpha agents	The effect size compared to placebo, especially when administered with concomitant corticosteroids, is considered of clinical relevance for an agent with a different mechanism of action to existing therapies, and with a safety profile that would appear to be beneficial to that of the anti-TNF agents.
Safety profile	According to EMA, the safety profile of Vedolizumab did not raise major objections and can be considered reassuring in Crohn's disease, however long term data is not available	Adverse events of special interest, in particular infections, PML and malignancy will be carefully monitored in the post-approval safety studies as part of a risk management plan.

1.5	**What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.**

Entyvio® (Vedolizumab) is indicated for the treatment adult patients with moderately to severely active Crohn's Disease (CD) who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNF-alpha antagonist (EMA, 2014a).

1.6	**Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.**

We do not anticipate clinical evidence relevant to this appraisal to become available during the course of this appraisal.

1.7	**If the technology has not been launched, please supply the anticipated date of availability in the UK.**

Product will be available to purchase in the UK from July 2014. The launch date for Vedolizumab for Crohn's disease in the UK is July 2014

1.8	**Does the technology have regulatory approval outside the UK? If so, please provide details.**

Table 1.8.1: Regulatory approval for Vedolizumab

Regulatory agency	Indications	Date
EMA (Europe)	Entyvio is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha antagonist. Entyvio is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha antagonist.	22 May 2014
FDA (USA)	Entyvio (Vedolizumab) in adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to a tumour necrosis factor (TNF) blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids. Entyvio (Vedolizumab) is indicated in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to a tumour necrosis factor (TNF) blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids.	20 May 2014
TGA (Australia)	Treatment of adult patients with moderate to severe Crohn's disease who have had an inadequate response with, lost response to, or are intolerant to either conventional therapy or a tumour necrosis factor-alpha antagonist. Treatment of adult patients with moderate to severe ulcerative colitis who have had an inadequate response with, lost response to, or are intolerant to either conventional therapy or a tumour necrosis factor-alpha antagonist.	27 June 2014

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

Vedolizumab is currently undergoing a Single Technology appraisal for ulcerative colitis. The appraisal has been initiated with the manufacturer submission. SMC dossiers will be submitted in September 2014 and expected public availability of outcome in February 2015.

1.10	**For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.**

Table 1.10.1: Unit costs of technology being appraised

Pharmaceutical formulation	Powder for concentrate for solution for infusion. White to off white lyophilised cake or powder. Each pack contains 1 vial which contains 300 mg of Vedolizumab
Acquisition cost (excluding VAT)	Basic NHS List Price = £2,050 per vial [redacted]
Method of administration	Vedolizumab is administered as an intravenous infusion over 30 minutes.
Doses and dosing frequency	The recommended dose regimen of Vedolizumab is 300 mg administered by intravenous infusion at 0, 2 and 6 weeks and then every 8 weeks thereafter. Patients with Crohn's disease, who have not shown a response may benefit from a dose of Vedolizumab at Week 10. Continue therapy every 8 weeks from Week 14 in responding patients. Therapy for patients with Crohn's disease should not be continued if no evidence of therapeutic benefit is observed by Week 14.
Average length of a course of treatment	Patient will usually be treated until relapse, intolerance or discontinuation due to side effects.
Average cost of a course of treatment	The annual cost of treatment with Vedolizumab per patient is estimated to be [redacted]

Anticipated average interval between courses of treatments	If therapy is interrupted and there is a need to restart treatment with Vedolizumab, dosing at every 4 weeks may be considered. The treatment interruption period in clinical trials extended up to one year. Efficacy was regained with no evident increase in adverse events or infusion-related reactions during re-treatment with Vedolizumab
Anticipated number of repeat courses of treatments	Not applicable
Dose adjustments	Some patients who have experienced a decrease in their response may benefit from an increase in dosing frequency to Vedolizumab 300 mg every 4 weeks.

1.11	**For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.**

Not applicable

1.12	**Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?**

Selection

Vedolizumab is contraindicated in patients with active tuberculosis (TB). Before starting treatment with Vedolizumab, patients must be screened for TB according to the local practice. TB diagnosis following NICE guidance requires health providers to offer Mantoux testing, in the case of a positive Mantoux test interferon-gamma testing is to be considered. In the case of an inconclusive Mantoux test a patient should be referred to a TB specialist (NICE, 2011).

Vedolizumab treatment should not be initiated in patients with active, severe infections until the infections are controlled, and physicians should consider withholding treatment in patients who develop a severe infection while on chronic treatment with Vedolizumab.

Current biologic therapies available for Crohn's disease also require TB tests (EMA, 2009a, 2009b).

Administration

No investigations or additional test are required for administration

1.13	**Is there a need for monitoring of patients over and above usual clinical practice for this technology?**

As a result of the lack of data, the Vedolizumab product information contains details on infections, neurological symptoms and infusion-related reactions.

Infections

Caution should be exercised when considering the use of Vedolizumab in patients with a controlled chronic severe infection or a history of recurring severe infections.

Patients should be monitored closely for infections before, during and after treatment.

There is also patient alert card which provides information on the risk of infections and the early signs and symptoms of PML and the need to provide this card to other health care professionals so that health care professionals are informed of the potential risks of serious infections, opportunistic infections, including PML (EMA, 2014a).

Neurological symptoms

A regulatory requirement for Vedolizumab includes the provision of a short pamphlet providing information to physicians on the identified and potential risks of treatment with Vedolizumab and the need to monitor patients for emerging neurological signs/symptoms.

Infusion-related reactions

With respect to administration, which is in itself a 30 minute infusion, all patients should be observed continuously during each infusion. For the first 2 infusions, they should also be observed for approximately 2 hours following completion of the infusion for signs and symptoms of acute hypersensitivity reactions. For all subsequent infusions, patients should be observed for approximately 1 hour following completion of the infusion.

1.14	**What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?**

It is expected that Vedolizumab will be added-on to existing therapies in clinical practice. In the pivotal trials, patients were maintained on baseline medications including 5-acetylsalicylcic acids (ASAs), corticosteroids and immunomodulators (azathioprine or 6-mercaptopurine). Corticosteroid use was gradually reduced from Week 6 for patients who achieved a clinical response, and treatment with Vedolizumab was associated with significantly higher rates of corticosteroid free remission at Week 52 compared to placebo (William J Sandborn et al., 2013b; Sands et al., 2014).

2 Context

2.1	**Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.**

Clinical burden

Inflammatory bowel diseases (IBDs) are chronic diseases with a relapsing-remitting course that requires lifelong treatment (Lakatos, 2009). Crohn's disease and ulcerative colitis are the two major illnesses comprising IBD. Crohn's disease is characterized by chronic relapsing inflammation that mainly affects the gastrointestinal tract and is often accompanied by abdominal pain, fever, malaise, anorexia, diarrhoea, weight loss, and clinical signs of bowel obstruction or diarrhoea with passage of blood or mucus, or both (Baumgart & Sandborn, 2012; Mowat et al., 2011a). Crohn's disease may lead to intestinal obstruction due to strictures, fistulae (often perianal), or abscesses (Mowat et al., 2011b).

Crohn's disease is a multisystem disorder that can affect any age group, but initial diagnosis is most commonly made in the second and third decades (Lichtenstein et al., 2009) of life (i.e., teenagers and young adults).

Crohn's disease may be defined by age of onset, location, or behaviour (Mowat et al., 2011b). Diagnosis of Crohn's disease is complex and must integrate patient history, physical symptoms, and evidence from imaging and laboratory studies (Baumgart & Sandborn, 2012). Once diagnosis is established, it is important to determine disease activity, which, in combination with phenotypic and endoscopic features, allows stratification of patients and selection of appropriate therapeutic strategies (Baumgart & Sandborn, 2012). The Harvey Bradshaw Index is used to assess disease activity in daily clinical practice and the Crohn's Disease Activity Index (CDAI, see Appendix **Error! Reference source not found.**) is the gold standard for classifying disease activity in clinical trials. A Crohn's Disease Activity Index score < 150 indicates clinical remission and a Crohn's Disease Activity Index score > 450 indicates severe disease (Yoshida, 1999). Most clinical trials in Crohn's disease define response as a ≥ 70-point reduction in the Crohn's Disease Activity Index score. The Crohn's Disease Activity Index can be used to categorize the disease as mild to moderate, moderate to severe, severe fulminant, or remission.

Crohn's disease typically has a chronic, relapsing course with approximately 50% of patients being in clinical remission at any particular time (Lichtenstein et al., 2009). If an individual patient remains in remission for 1 year, there is an 80% chance that this individual will remain in remission over the course of the subsequent year. For a patient with active disease in the past year, there is a 70% chance that this patient will have active disease in the subsequent year and a 50% chance that this patient will be in remission within the following 3 years" (Lichtenstein et al., 2009). Overall, 20% of patients have disease relapse every year, and 67% have a combination of years in relapse and years in remission within the first 8 years after initial diagnosis (Lichtenstein et al., 2009). Less than 5% of patients are expected to have a continuous course of active disease (Lichtenstein et al., 2009).

Table 2.1.1: Crohn's disease status

Crohn's disease status	Percentage of patients
Within 8 years of diagnosis	67% combination of years in relapse and years in remission
Active disease in the last year	70% active disease in subsequent year
	50% in remission within following 3 years
Continuous course of active disease	~5%
Relapse	20% every year

Source: Lichtenstein et al., 2009

Humanistic and societal burden

Results from qualitative research studies indicate that all aspects of an individual's life—physical, emotional, cognitive, social—are affected as a result of IBD (Wolfe & Sirois, 2008).

Aspects of physical wellbeing affected by IBD include systemic functioning related to bowel and other bodily functions; daily functioning (ability to physically participate in daily tasks such as school, work, travel, physical activity, housework); energy/vitality (e.g., fatigue, inability to perform normal activities due to lack of energy, increased need for sleep); and pain (cramping, joint pain, pain during sex) (Wolfe and Sirois, 2008).

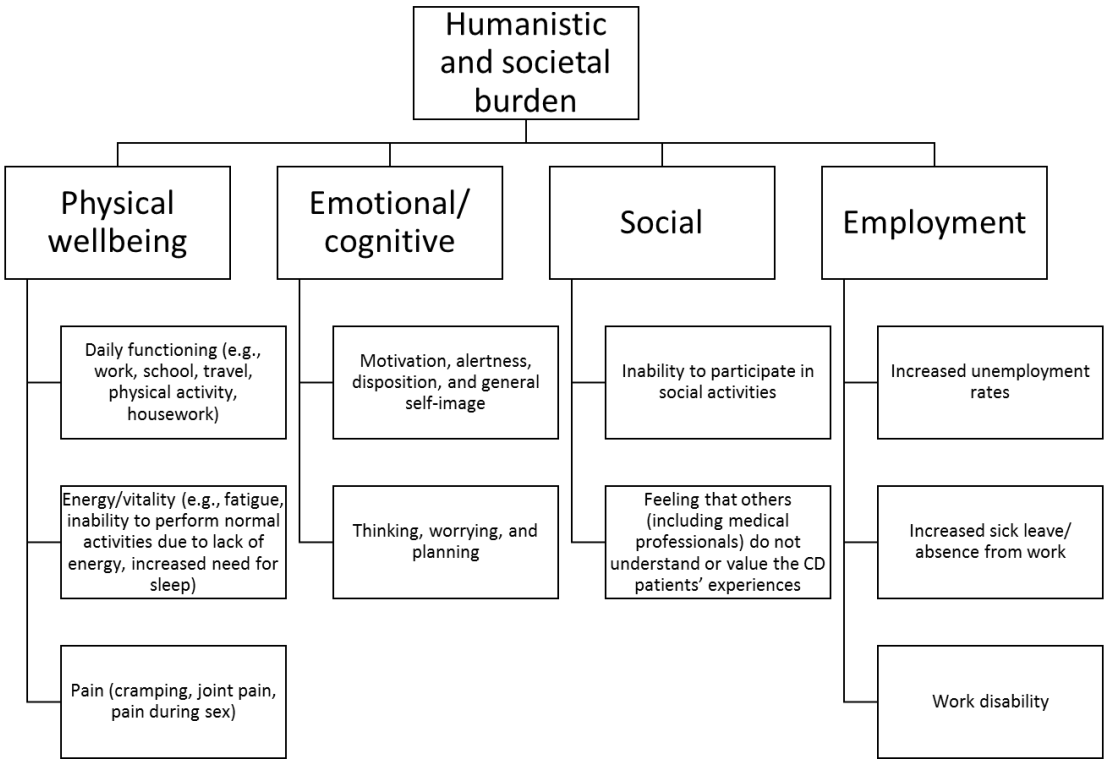
Social aspects affected by IBD include inability to participate in social activities and the feeling that others (including medical professionals) do not understand or value the IBD patients' experiences (Wolfe and Sirois, 2008).

Patients also feel that the disease itself, as well as the required medications, compromises their cognitive abilities, including motivation, alertness, disposition, and general self-image. Cognitive concerns also centre on patients spending a great deal of time thinking, worrying, and planning as a result of IBD (Wolfe and Sirois, 2008).

Both unemployment and disability reduce Norwegian Inflammatory Bowel Disease Questionnaire (IBDQ) and Medical Outcomes Study 36-item Short Form (SF-36) scores, but the most pronounced (clinically significant) effect on HRQL is in patients reporting IBD-related sick leave (Bernklev et al., 2006). Since Crohn's disease is a chronic disorder in which the onset of symptoms usually occurs in young-to-middle-aged adults, the impact on sick leave, unemployment, and work disability can be substantial (Bernklev et al. 2006).

Patients with chronic Crohn's disease have reduced HRQL compared with the general population, particularly in general health and vitality (Høivik et al., 2012). Treatment with biologics has been shown to lead to significant improvements in HRQL (Vogelaar, Spijker, & van der Woude, 2009).

Figure 2.1.1: Humanistic and societal burden of Crohn's disease



2.2	**Please provide the number of patients covered by this particular therapeutic indication in the marketing authorisation and also including all therapeutic indications for the technology, or for which the technology is otherwise indicated, in England and Wales and provide the source of the data.**

According to NICE TA 187, the prevalence of Crohn's disease in the UK is estimated to be approximately 50-100 per 100,000 people. In total, it affects approximately 60,000 people in the UK. Using estimates derived from the NICE adalimumab and Infliximab appraisal (TA187, (NICE, 2010b)) the table below estimates the number of patients eligible for treatment with Vedolizumab in Crohn's disease. Estimates for anti-TNF use in inflammatory bowel disease is derived from the IBD audit (CEEU of Royal College of Physicians, 2013) which provides information on clinical practice with regards to Infliximab and Adalimumab between September 2011 and February 2013. Information on eligible patients following failure on biologic therapy is more difficult to ascertain. In this case we have used data for patients who initiated treatment with Infliximab but then did not continue treatment in the follow-up period for reasons of loss of response, no response or intolerance.

Table 2.2.1: Estimated eligible patient population for Vedolizumab based on licenced indication in Crohn's disease and ulcerative colitis

	Crohn's Disease		Ulcerative colitis		Total
	Estimate	**Number**	**Estimate**	**Number**	**Number**
Number of adult in England and Wales		56,948,200		56,948,200	
Number of adults with diagnosis	0.20%	113,896	0.24%	136,676	250,572
Number with moderate severe disease	20.00%	22,779	52.33%	71,523	94,302
Number eligible for biologic therapy	51.11%	11,642	6.30%	4,506	16,123
Sources	ONS, 2014; NICE, 2010b; Royal College of Physicians, 2013		ONS, 2014; NICE, 2013b; Royal College of Physicians, 2013; Informa UK, 2013		

In ulcerative colitis, the NICE Clinical Guidelines (CG166) estimate the incidence in the UK to be approximately 10 per 100,000 people annually, and a prevalence of approximately 240 per 100,000 (NICE, 2013b). As with Crohn's disease, estimates for anti-TNF use in IBD are derived from the IBD audit. Data for patients who initiated treatment with Infliximab, but then did not continue treatment in the follow-up period for reasons of loss of response, no response or intolerance, were used to estimate eligible patients following failure on biologic therapy. No specific data were available for Adalimumab or golimumab.

2.3 Please provide information about the life expectancy of people with the disease in England and Wales and provide the source of the data.

Overall, the mortality rate in patients with Crohn's disease is slightly increased compared to the general adult population, with a pooled standardized mortality rate (SMR) of 1.4 based on population-based studies (Duricova et al., 2010; Hovde & Moum, 2012). A large study examining mortality in Crohn's disease among a cohort of approximately 6,000 patients identified through the General Practice Research Database (GPRD) in the UK reported a SMR of 1.7 (Card, Hubbard, & Logan, 2003). Importantly, the currently available mortality rate estimates were conducted prior to

the introduction of immunomodulatory agents; therefore, the applicability of these data may be of limited use given the current treatment landscape (Hovde & Moum, 2012).

Table 2.3.1 summarises several specific causes of death that contributed to the excess mortality observed among Crohn's disease patients based on a recent meta-analysis (Duricova et al., 2010). In addition, corticosteroid treatment in patients with Crohn's disease has also been shown to be associated with increased risk of death (Lewis et al., 2008).

Table 2.3.1: Cause-specific mortality in patients with Crohn's disease

Cause	SMR	CI
Lung cancer	2.72	1.35-5.45
Chronic obstructive pulmonary disease	2.55	1.19-5.47
Other gastrointestinal diseases	2.49	1.68-3.71
Genitourinary diseases	3.28	1.69-6.35

2.4 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific sub-groups were addressed.

NICE Guidance

A Technology Appraisal for Infliximab and Adalimumab in Crohn's disease was published in 2010 (TA187), and the guidance from this technology appraisal was subsequently incorporated into the Crohn's disease clinical guidelines (CG152) on diagnosis and treatment in 2012 (NICE, 2012). Currently, treatment generally follows a standard step-up approach. Initial treatment often begins with anti-inflammatory agents, progressing to more potent agents for patients who fail to demonstrate a response. A summary of the NICE clinical guidelines is described below.

Inducing remission in Crohn's disease

- Monotherapy with a conventional glucocorticosteroid (prednisolone, methylprednisolone, or intravenous hydrocortisone) should be used to induce

remission in people with a first presentation or a single inflammatory exacerbation of Crohn's disease in a 12-month period.

- If people with a first presentation or a single inflammatory exacerbation of Crohn's disease in a 12-month period decline, cannot tolerate, or in whom a conventional glucocorticosteroid is contraindicated budesonide and 5-ASA can be considered. Budesonide can also be considered for people with one or more of distal ileal, ileocecal, or right-sided colonic disease.
- Add azathioprine or mercaptopurine to a conventional glucocorticosteroid or budesonide to induce remission of Crohn's disease if:
    - There are 2 or more inflammatory exacerbations in a 12-month period, or
      The glucocorticosteroid dose cannot be tapered.

- Consider adding methotrexate to a conventional glucocorticosteroid or budesonide to induce remission in people who cannot tolerate azathioprine or mercaptopurine, or in whom thiopurine methyltransferase activity is deficient, if:
    - There are 2 or more inflammatory exacerbations in a 12-month period, or
      The glucocorticosteroid dose cannot be tapered.

- Infliximab and Adalimumab are recommended as treatment options for adults with severe active Crohn's disease whose disease has not responded to conventional therapy, or who are intolerant of or have contraindications to conventional therapy. Infliximab or Adalimumab should be given as a planned course of treatment until treatment failure (including the need for surgery), or until 12 months after the start of treatment, whichever is shorter.

Maintaining remission in Crohn's disease

- Offer azathioprine or mercaptopurine as monotherapy to maintain remission when previously used with a conventional glucocorticosteroid or budesonide to induce remission.
- Consider methotrexate to maintain remission only in people who need methotrexate to induce remission, or have tried but did not tolerate azathioprine or mercaptopurine for maintenance or these drugs are contraindicated.

- Treatment with Infliximab or Adalimumab should only be continued if there is clear evidence of ongoing active disease as determined by clinical symptoms, biological markers, and investigation, including endoscopy if necessary. People whose disease relapses after treatment is stopped should have the option to start treatment again.
- After surgery: consider azathioprine or mercaptopurine to maintain remission after surgery in people with adverse prognostic factors otherwise consider 5-ASA treatment to maintain remission after surgery.

Surgery

- If Crohn's disease is limited to the distal ileum consider surgery as an alternative to medical treatment early in the course of the disease taking into account the benefits and risks of medical treatment and surgery, risk of recurrence after surgery, and individual preferences and any personal or cultural considerations or if patients has refractory disease
- Consider balloon dilation particularly in people with a single stricture that is short, straight and accessible by colonoscopy. Take into account the following factors when assessing options for managing a stricture:
    - whether medical treatment has been optimised
    - the number and extent of previous resections
    - the rapidity of past recurrence (if appropriate)
    - the potential for further resections
    - the consequence of short bowel syndrome
    - the person's preference, and how their lifestyle and cultural background might affect management.
- Ensure that abdominal surgery is available for managing complications or failure of balloon dilation.

Sub-groups

No sub-groups were addressed within these guidelines

British Society for Gastroenterology guidelines

The British Society for Gastroenterology (BSG) has also produced guidelines on the treatment of Crohn's disease (Mowat et al., 2011b). To summarise, the BSG guideline suggest that treatment should be tailored to the severity of disease and that

treatment decisions should carefully take benefit and risks into account. Corticosteroids or budesonide should be used to induce remission. In patients with severe active Crohn's disease, or disease refractory to corticosteroids, anti-TNF therapy may be used in induction. In maintaining remission azathioprine or mercaptopurine should be considered as first-line treatment, followed by methotrexate and possibly anti-TNF agents.

Sub-groups

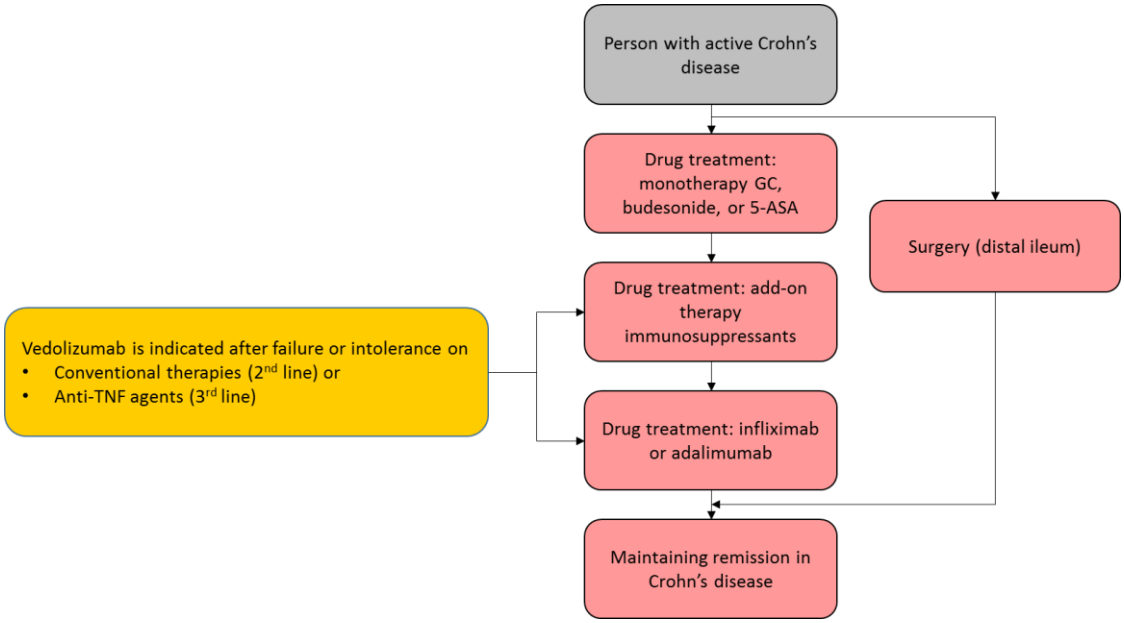
No sub-groups were addressed within these guidelines.

2.5	**Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.**

The aim of drug treatment is to induce and maintain remission, with the optimal outcome of maintaining corticosteroid free remission, reducing Crohn's disease complications and the need for hospitalisations and surgery. Treatment generally follows a standard step-up approach. Initial treatment often begins with anti-inflammatory agents, progressing to more potent agents for patients who fail to demonstrate a response.

In line with its licence, Vedolizumab is expected to fit in the clinical pathway as an option following failure/intolerance on conventional therapies (second-line) or anti-TNFs (third-line). The lack of systemic immunosuppression, no cases of extra-pulmonary or systemic TB with Vedolizumab in contrast to anti-TNFs, and the long-lasting efficacy in those who respond, combine to make Vedolizumab a useful option for second-line Crohn's disease patients (following failure on conventional therapies). (EMA, 2014a). In the third-line setting (after both conventional therapy and anti-TNF-alpha), there is a recognised unmet need for therapeutic alternatives in this anti-TNF-alpha failed population (EMA, 2014a).

Figure 3.5.1: Proposed positioning of Vedolizumab in current NICE clinical guidelines treatment path for adults with Crohn's disease



2.6	**Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.**

Treatment limitations of conventional therapies and TNF-alpha antagonists

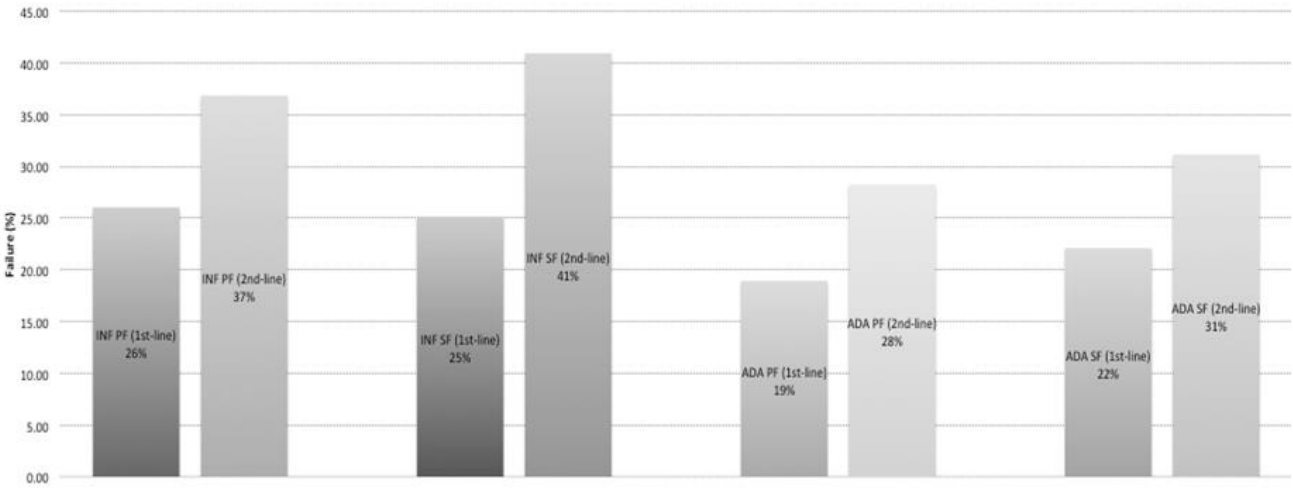
Conventional therapies are the mainstay of drug therapy in the UK for mild-moderate disease and TNF-alpha antagonists have been shown to be effective for both induction and remission of moderate to severe Crohn's disease. However, conventional therapy and TNF-alpha antagonists have efficacy and safety limitations (Bosani, Ardizzone, & Porro, 2009; McLean, Shea-Donohue, & Cross, 2012).

Despite their efficacy compared with conventional treatments, a considerable portion of patients with IBD (between 20% and 40%) will not respond to induction therapy with TNF antagonists (i.e., primary non-response) or will lose response to TNF antagonists over time (i.e., secondary non-response) (Allen, 2012b; Allez et al., 2010; McLean et al., 2012; Yanai & Hanauer, 2011). The reported rate of secondary non-response has varied from around 10% per year in smaller studies to 50% per year in placebo-controlled trials (Allez et al., 2010). One review of the literature evaluating 6284 patient years of follow-up calculated that the annual risk for loss of response to Infliximab therapy specifically in patients with Crohn's disease is 13% per patient

year (Gisbert & Panés, 2009). Recent real-world analyses have revealed that a large proportion of patients may be experiencing suboptimal medical therapy for Crohn's disease, indicated by an increased frequency of surgery and hospitalization, and prolonged corticosteroid use (Davis, Mody, Rubin, & Wang, 2013; Rubin, Uluscu, & Sederman, 2012). This, coupled with the potential for serious systemic adverse events and serious infections with TNF antagonists (Bongartz, Sutton, Sweeting, Buchan, & Matteson, 2006; Clark et al., 2007; Curtis et al., 2007; Lichtenstein et al., 2009; McLean et al., 2012), leaves a need for additional treatment modalities for moderate to severe IBD.

Secondary non-response is frequently managed through dose intensification of the TNF antagonist either by increasing the dose or decreasing the dosing interval, resulting in increased treatment costs (Gisbert & Panés, 2009; Molnár et al., 2012; Pariente et al., 2012; Wu, Mulani, Yu, Tang, & Pollack, 2008; Yanai & Hanauer, 2011). In addition, in patients who are intolerant to or lose response to TNF-alpha antagonists current clinical practice suggests patients' cycle through the available TNF-alpha antagonists, trialling successive anti-TNF-alpha agents where adequate response to the prior TNF-alpha antagonists was not observed (CEEU of Royal College of Physicians, 2013). However, failure on one TNF-alpha antagonists leads to increased likelihood of failure on next line TNF-alpha antagonists in Crohn's disease; patients who previously received Infliximab were less likely to achieve a response with Certolizumab and Adalimumab (Jean-Frédéric Colombel et al., 2007; Schreiber et al., 2007)). TNF-Failure rates and management of anti-TNF-Failure was confirmed in an UK expert clinician surveys ((Takeda Data on File, 2013), Figure 2.6.1).

Figure 2.6.1: First- versus second-line treatment TNF-alpha antagonist treatment failure in Crohn's disease patients



ADA, Adalimumab; INF, Infliximab, PF, primary failure; SF, secondary failure
Source: (Takeda Data on File, 2013)

This indicates there is a need for other treatment options, especially after first-line anti-TNF-alpha failure, to improve the management and outcomes for people with Crohn's disease. The practice of TNF cycling may be a direct consequence of the limited number of treatment options currently available.

Surgery

Surgical resection, with the exception of total colectomy and ileostomy for Crohn's disease limited to the colon, rarely results in a long term remission (Lichtenstein et al., 2009); however, approximately 70% of patients with Crohn's disease may require surgery at least once over the course of their disease (Kopylov et al., 2012; Lichtenstein et al., 2009). Once patients are started on corticosteroids, up to 38% of patients will require surgery within 1 year (Lichtenstein, Hanauer, and Sandborn 2009). Repeat operations are required in 30% to 70% of patients (Shaffer & Wexner, 2013).

Crohn's disease of the colon treated with limited surgical resection is associated with a higher recurrence rate compared to a total proctocolectomy. In practice, most physicians and patients appear to prefer avoidance of a permanent stoma by performing a limited surgical resection over total proctocolectomy, however, formal data of patient preferences is lacking (Lichtenstein, Hanauer, and Sandborn 2009).

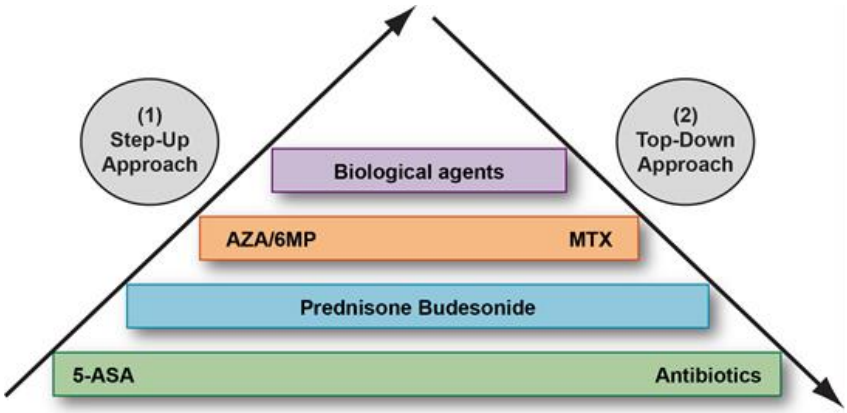
Surgery in patients with Crohn's disease is associated with substantial morbidity, with up to 22% of patients experiencing surgery-related complications (Kopylov et al., 2012). A recent audit of IBD cases in an Australian hospital revealed that 27% of Crohn's disease surgeries were potentially avoidable with proper medical management (Gapasin, Van Langenberg, Holtmann, Hetzel, & Andrews, 2012). Even minor procedures such as limited resections for ileal disease may result in impaired body image and sexuality, particularly in younger patients. Surgical patients also face a high risk of clinical relapse (up to 75%) and re-intervention (up to 45% of patients require reintervention by 10 years post-operatively) (Gapasin et al., 2012).

Top down approach

Traditional treatment strategies have focused on induction of clinical remission using a step-wise approach to medical therapy, starting with 5-ASAs, then corticosteroids, immunomodulators, and finally the biologics ("step-up" approach) (Rubin et al., 2012). However, in recent years, clinical trials of earlier use of immune-modifying or biologic therapies (or combinations of them) have shown more rapid remission and improved short- and long-term outcomes (Rubin et al., 2012). As experience of successful therapy with anti-TNF agents has accumulated, it has been suggested that an early introduction of anti-TNFs (top-down approach) may lead to more favourable outcomes versus the traditional step-up approach (Etchevers, Aceituno, & Sans, 2008; Rubin et al., 2012). Figure 2.6.2 illustrates approaches to therapy using either the "step-up" or the "top-down" approach.

The top down approach is reserved for patients with severe disease at admission. The traditional treatment strategy is the norm in the UK.

Figure 2.6.2: Approaches to treatment in Crohn's disease



5-ASA = 5 aminosalicylic acid; 6MP = 6-mercaptopurine; AZA = azathioprine; MTX = methotrexate.
Source: (Etchevers et al., 2008)

In the step-up approach, long-term treatment with agents that are not very effective leads to uncontrolled inflammation and eventual tissue damage (Panaccione et al., 2008). A top-down approach to treatment, where biologics are introduced early in treatment, may result in more favourable long-term outcomes, such as higher rates of mucosal healing, and reductions in hospitalization and surgery rates (Panaccione et al., 2008; Ricart, García-Bosch, Ordás, & Panés, 2008; Shergill & Terdiman, 2008). Concerns related to safety and cost of the earlier use of anti-TNF therapies have limited acceptance of the top-down approach (Rubin et al., 2012). Therefore, the risks and benefits of each type of approach must be carefully balanced.

A study by Rubin and colleagues (2012) that analysed administrative claims data to evaluate outcomes of the top-down approach in patients with Crohn's disease. Results showed that the top-down approach was associated with a lower risk of concomitant corticosteroid use, anti-TNF dose escalation, discontinuation/switch of anti TNF, and Crohn's disease-related surgery compared with the step-up approach (Rubin et al., 2012).

2.7 Please identify the main comparator(s) and justify their selection.

The relevant main comparator is current standard of care, comprising 5-ASAs, corticosteroids and immunomodulators. This reflects the baseline therapies in the Vedolizumab registration studies (GEMINI II and III,(William J Sandborn et al., 2013a; Sands et al., 2014)) and are supported by current NICE clinical practice guidelines (NICE, 2012). In the GEMINI II and III trials, patients received

Vedolizumab or placebo in addition to 5-ASAs, corticosteroids and immunomodulators, therefore the placebo arm of both trials represents current standard of care and is the main comparator presented in this submission.

In addition, supplementary comparisons with anti-TNF treatments (Adalimumab, Infliximab) where comparable evidence are available, will also be presented because these treatments are regulatory approved with a similar indications as Vedolizumab and are recommended by NICE in acute severe patients who have failed conventional therapy.

Table 2.7.1: Comparators

Treatment	UK Label Indication and NICE guidance
Infliximab (Remicade®) (EMA, 2009b; NICE, 2010a)	• Treatment of moderately to severely active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies. • Treatment of fistulising, active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy).
Adalimumab (Humira ®) (EMA, 2009a; NICE, 2010a)	• Adalimumab is indicated for treatment of moderately to severely active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies

2.8 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

In the combined studies of ulcerative colitis and Crohn's disease the adverse reactions that occurred in ≥5% were nausea, nasopharyngitis, upper respiratory tract infection, arthralgia, pyrexia, fatigue, headache and cough. These reactions would be treated according to local clinical practice guidelines (EMA, 2014a).

Infusion-related reactions (IRR) were reported in 4% of patients receiving Vedolizumab. Most infusion-related reactions occurred within the first 2 hours. Of those patients who had infusion-related reactions, those dosed with Vedolizumab had more infusion-related reactions with in the first two hours compared with those

who received placebo. Most infusion-related reactions were not serious and occurred during the infusion or within the first hour after infusion was completed.

If a severe IRR, anaphylactic reaction, or other severe reaction occurs, administration of Vedolizumab must be discontinued immediately and appropriate treatment initiated (e.g., epinephrine and antihistamines).

If a mild to moderate IRR occurs, the infusion rate can be slowed or interrupted and appropriate treatment initiated. Once the mild or moderate IRR subsides, the infusion may be continued. Physicians should consider pre-treatment (e.g., with antihistamine, hydrocortisone and/or paracetamol) prior to the next infusion for patients with a history of mild to moderate IRR to Vedolizumab, in order to minimise risk of recurrence (EMA, 2014a).

2.9	**Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.**

Location of care, staff usage and administration costs

Vedolizumab treatment should be initiated and supervised by specialist healthcare professionals experienced in the diagnosis and treatment of Crohn's disease. Vedolizumab is an intravenous use only drug, which needs to be reconstituted and further diluted prior to intravenous administration over 30 minutes; patients should be monitored during and after infusion. Therefore it is expected that Vedolizumab will be a secondary care delivered product (EMA, 2014b).

Monitoring requirements

- All patients should be observed continuously during each infusion. For the first two infusions, they should also be observed for approximately two hours following completion of the infusion for signs and symptoms of acute hypersensitivity reaction. For all subsequent infusions, patients should be observed for approximately one hour following completion of the infusion

- Before starting treatment with Vedolizumab, patients must be screened for tuberculosis according to local practice. Patients should be monitored closely for infection before, during and after treatment.

- Healthcare professionals should monitor patients receiving Vedolizumab for any new onset or worsening of neurological signs and symptoms for PML, and should consider neurological referral if they occur (EMA, 2014b)**.**

The resource use described here is aligned with the resource use included in the economic analysis.

2.10 Does the technology require additional infrastructure to be put in place?

Other than the routine monitoring outlined above, there is no need for additional infrastructure to be put in place for Vedolizumab as NHS currently uses biologic therapy to treat Crohn's disease.

3 Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

3.1 Identification of equality issues

3.1.1 Please let us know if you think that this appraisal:

- **could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licenced;**
- **could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology**
- **could lead to recommendations that have any adverse impact on people with a particular disability or disabilities**

Please provide us with any evidence that would enable the Committee to identify and consider such impacts.

There are no issues of equality to be considered here.

3.1.2 How has the analysis addressed these issues?

Not applicable.

4 Innovation

4.1	**Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.**

Takeda believes that Vedolizumab offers innovation because of its unique mechanism of action targeting disease control independently of TNF. No other gut-selective agents are currently approved for the treatment of Crohn's disease in the UK. Vedolizumab is an effective, well-tolerated new Crohn's disease treatment and has proven safety, gut-selectivity, and no known immunosuppressive or systemic effects in patients with Crohn's disease that is uncontrolled on conventional therapy with or without prior TNF-alpha antagonist exposure.

Crohn's disease is a chronic, remitting, relapsing disease that is currently without a medical cure. Vedolizumab can provide a 'step change' to current treatment by offering a novel and effective treatment to increase the rate and duration of remission and consequently the time to surgery. Consequently, Vedolizumab can be considered to represent an incremental change in the treatment path towards better long-term disease management for patients with Crohn's disease.

Mechanism of action

The unique mechanism of action of Vedolizumab targets disease control independently of TNF. No other gut-selective agents are currently approved for the treatment of Crohn's disease in the UK, so Vedolizumab is a unique offering. It binds specifically to the α4β7 integrin, which is preferentially expressed on gut homing T helper lymphocytes, and modulates inflammation (EMA, 2014a). This is distinctly different to anti-TNF drugs which target the pro-inflammatory cytokine TNF-alpha that is found throughout the body in tissue and the circulatory blood system and consequently anti-TNF drugs are known to have effects beyond the gut. The benefit with Vedolizumab's gut specific action lowers the chance of extra-intestinal effects.

Efficacy and safety

Further, the published efficacy and safety data for Vedolizumab indicate that it has the potential to make a clinically significant and substantial impact on health-related patient and health system benefits by addressing a range of current challenges in the management of Crohn's disease. Failure of conventional therapies is common and many patients also fail to respond to, lose response to, or cannot tolerate current systemically-acting TNF-alpha antagonists (see section 2.6). Conventional therapies such as glucocorticoids can cause unacceptable adverse events and are not long-term treatment options; TNF-alpha antagonists are associated with systemic adverse events predispose patients to serious infection and have been associated with increased risk of certain cancers (see section 2.6).

Consequently, there are unmet needs for Crohn's disease therapies demonstrating efficacy (key endpoints such as durable remission, and corticosteroid free remission) in patient with uncontrolled disease. New products must also show a favourable safety profile to overcome issues with conventional therapies and TNF-alpha antagonists.

Step change

Currently, patients who fail conventional treatments can progress to receive a TNF-alpha antagonist. Failure on a TNF-alpha antagonist can be dealt with by increasing dose or switching to another member of the same class. From both a disease management and economic perspective, neither option is optimal (see section 2.6). Ultimately, surgery becomes the only option available, itself a far from satisfactory intervention (see section 2.6).

4.2	**Discuss whether and how you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation.**

Crohn's disease has a clinically meaningful, negative impact of HRQL, which can be at least partly reversed by treatment. This featured in the QALY calculation as presented in Section 7.7. Additionally, successful management of Crohn's disease symptoms and prolongation of remission may have societal benefits that are less straightforward to calculate but that may increase the value of Vedolizumab for the treatment of moderate to severe Crohn's disease.

Although there are no data to demonstrate benefits of successful intervention, Takeda has identified a number of issues related to indirect costs, life factors and the lives of carers that might all benefit from the improved management of Crohn's disease symptoms demonstrated in the GEMINI programme.

Employment

Several studies have shown that Crohn's disease (or undifferentiated IBD) has a direct impact on employment status and opportunities in Europe (including the UK) and North America (Albert et al., 2008; Gomollon Garcia et al., 2012; Juan et al., 2003; Lichtenstein, Yan, Bala, & Hanauer, 2004). In addition, Crohn's disease has been associated with absenteeism, workplace disability, and loss of earnings (See Section 2.6, (Bassi, Dodd, Williamson, & Bodger, 2004; Dorrian, Dempster, & Adair, 2009; Jess, 2013; Reinisch et al., 2007a)). This can be expected to have a range of personal, social and business implications, from impaired HRQL to indirect economic burden (Bernklev et al., 2006).

A recent systematic review of 30 non-interventional and 17 interventional studies of IBD overall or Crohn's disease or ulcerative colitis specifically, revealed low but variable employment rates: up to half those of a non-IBD cohort (Büsch et al., 2014). Workplace disability and absenteeism was also found to be associated with IBD. On the other hand, intervention with anti-TNF drugs was associated with lower rates of absenteeism and presenteeism is clinical trials, which needs conformation using real-world evidence.

Birth outcomes and fertility

- An extensive study of published data revealed that conventional treatments as well as Crohn's disease itself were associated with an increased risk of adverse birth outcomes: low birth weight, pre-term births and/or congenital abnormalities (Nørgård, 2011)
- Female infertility may be a negative consequence of surgery, whereas male fertility appears to be largely unaffected by IBD drugs (O'Connor, Qasim, & O'Moráin, 2010).

Impact on carers

- Two studies in southern Europe (Greece and Portugal) reveal that carers of patients with IBD (Crohn's disease or ulcerative colitis) experience high levels of emotional and physical distress (Argyriou, Kapsoritakis, Tsakiridou, & Potamianos, 2014; Magro et al., 2009). Levels of distress were associated with factors that can be managed with successful treatment: disease activity, complications, disease duration (Argyriou et al., 2014). The major concern expressed by carers in the study in Portugal was the IBD-associated cancer risk (Magro et al., 2009).

4.3	**Please identify the data you have used to make these judgements, to enable the Appraisal Committee to take account of these benefits.**

Please see section 6.5.3 which summarises the efficacy and HRQL benefits associated with Vedolizumab treatment in patient with moderate to severe Crohn's disease.

5 Statement of the decision problem

Scope	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	Adults with moderately to severely active Crohn's disease in whom the disease has responded inadequately to, or is no longer responding to, either conventional therapy or a TNF-alpha antagonist, or who are intolerant to either of them.	The patient population considered within this appraisal is in line with the final scope population.	
Intervention	Vedolizumab	Vedolizumab	
Comparator(s)	1. Conventional treatment strategies without Vedolizumab (including antibiotics, drug treatment with conventional corticosteroids alone or in combination with azathioprine, mercaptopurine or methotrexate; aminosalicylates; budesonide alone or in combination with azathioprine, mercaptopurine or methotrexate) 2. TNF-alpha antagonists (Infliximab and Adalimumab)	1. The relevant main comparator is current standard of care, comprising 5-ASAs, corticosteroids and immunomodulators. 2. Supplementary comparisons with anti-TNF treatments (Adalimumab, Infliximab) where comparable evidence are available, will also be presented.	This reflects the baseline therapies in the Vedolizumab registration studies and are supported by current NICE clinical practice guidelines and UK IBD patient audit data. In the GEMINI II and III trial, patients received Vedolizumab or placebo in addition to 5-ASAs, corticosteroids and immunomodulators, therefore the placebo arm of the GEMINI II and III trials represents current standard of care and is the main comparator presented in this submission.
Outcomes	The outcome measures to be considered include: • disease activity (remission, response, relapse) • surgery • adverse effects of treatment • Health-related quality of life.	The outcomes considered within this appraisal is in line with the final scope population.	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.	The modelling approach uses a joint decision tree and Markov model (cohort health state transition) structure. The decision tree structure is used to capture the induction	

Scope	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
	The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. Biosimilars are not expected to be in established NHS practice at the time of appraisal and are not included as comparators.	phase of treatment, in which patients are given a dosage so as to induce a response to treatment. The Markov model is used to capture the maintenance phase in which responding patients are treated with less frequency and/or intensity to maintain that response.	
Sub-groups to be considered	If evidence allows, the following sub-groups should be considered: 1. People who have not previously received a TNF-alpha antagonist 2. People for whom a TNF-alpha antagonist has failed 3. People for whom TNF-alpha antagonists are not suitable because of intolerance or contraindication.	We include analyses in the following sub-groups of patient population including 1. anti-TNF naïve population 2. anti-TNF-Failure population (those who have previously tried a biologic, including those who have failed an anti-TNF therapy) 3. mixed population (includes both anti-TNF naïve and anti-TNF-Failure patients)	

Section B – Clinical and cost-effectiveness

6 Clinical evidence

6.1 Identification of studies

6.1.1	**Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.2, Appendix 2**

A full systematic review of the clinical effectiveness of Vedolizumab in moderate to severe Crohn's disease has been conducted. The aim of this review was to assess the best available evidence to evaluate the efficacy and safety of biologics and surgery in patients with moderate to severe Crohn's disease to inform a mixed treatment comparison (MTC, (Takeda Data on File, 2014)).

The review and MTC had a global remit and therefore included biologic therapies not licenced in the UK for Crohn's disease (Certolizumab (Cimzia), and Natalizumab (Tysabri, Antegren), data presented here will not include these two drugs. The evidence base for Vedolizumab is discussed in the following sections, whilst the clinical evidence retrieved for other UK-relevant comparators will be reported in section 6.7 as part of the MTC results.

The systematic review was conducted in line with Cochrane methodology and NICE recommendations and following Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) recommendations, according to the protocol developed in April 2013. As result of this NICE appraisal, the review was updated based on searches performed on February 12, 2014, and were limited to publications from April 1, 2013 onward.

Electronic databases and internet sources were searched using a predefined search strategy, without time horizons or language restrictions. Any non–English-language sources that appeared to be relevant at the inclusion and exclusion stage were marked for inclusion at the title/abstract (level 1) screening for discussion.

Electronic databases

The search strategy for the original and updated review included searches of the following electronic databases:

- MEDLINE (using PubMed platform)
- Embase (using Elsevier Platform)
- The Cochrane Library (using the Wiley platform), including the following:
    - The Cochrane Database of Systematic Reviews
    - The Cochrane Central Register of Controlled Trials
    - Database of Abstracts of Reviews of Effectiveness

Internet and other sources

For the original review, ClinicalTrials.gov was searched for ongoing studies of the drugs of interest. For the update, the following websites were searched for ongoing studies of the drugs of interest:

- ClinicalTrials.gov
- World Health Organization's International Clinical Trials Registry Platform Search Portal (http://apps.who.int/trialsearch/)

Although searching of United European Gastroenterology was included in the protocol, it was not possible due to technical difficulties with the website which were not addressed by the United European Gastroenterology within our timeline (March 2014). Bibliographic reference lists of the 5 most up-to-date and robust systematic reviews and meta-analysis, identified during screening for each review, were reviewed for relevant publications.

Identification of included studies

The literature review study-selection process occurred in the following 2 phases:

- Level 1 screening: titles and abstracts of studies identified from the electronic databases were reviewed independently by 2 researchers to determine each study's eligibility according to the inclusion and exclusion criteria for level 1.
- Level 2 screening: full texts of studies selected at level 1 were obtained and independently reviewed by 2 researchers to determine eligibility according to the inclusion and exclusion criteria for level 2.

Where consensus was not reached or if there was any uncertainty about the inclusion of studies, a third researcher was consulted. A qualitative assessment was conducted on each of the included studies, using the assessment criteria recommended in the NICE manufacturer's template.

6.2 Study selection

6.2.1	**Describe the inclusion and exclusion selection criteria, language restrictions and the study-selection process. A justification should be provided to ensure that the rationale is transparent.**

Table 6.2.1.1: Table of inclusion and exclusion criteria used for level 1 screening

Criteria	Included	Excluded
Study design	• Randomised, controlled, prospective clinical trials • Non-randomised, controlled clinical trials • Long-term follow-up studies (e.g., open-label follow-up of randomized clinical trials) • Prospective observational studies (e.g., Phase 4 studies) • Systematic reviews and meta-analyses[a]	• Single-arm clinical trials • Preclinical studies • Phase 1 studies • Pilot studies • Prognostic studies • Retrospective studies • Case reports • Commentaries and letters (publication type) • Consensus reports • Non-systematic reviews
Population	Patients with Crohn's disease (both treatment-naïve and treatment-experienced)	Patients who do not have Crohn's disease
Intervention	Biologics search: [b] • Vedolizumab • Certolizumab (Cimzia) • Natalizumab (Tysabri, Antegren) • Infliximab (Remicade) • Adalimumab (Humira) Additional search: • Surgery (of any type)	Studies that do not investigate one of the biologics of interest in at least one of the arms
Outcomes	None	None: the studies were not excluded on the basis of outcomes at the level 1 screening process

[a] Systematic reviews and meta-analyses were used for identification of primary studies.

[b] We have extracted and present information on biologics relevant for this appraisal, i.e., Vedolizumab, Infliximab, and Adalimumab only. Natalizumab and Certolizumab have not been approved for use in Crohn's disease in the UK.

Source: (Takeda Data on File, 2014)

Table 6.2.1.2: Table of inclusion and exclusion criteria used for level 2 screening

Criteria	Included	Excluded
Study design	• Randomised, double-blind clinical trials • Randomised, open-label clinical trials • Randomised, open-label follow-up studies • Prospective studies with more than 1 treatment arm	Same as the criteria for level 1 (Table 6.2.1.2), with the addition of systematic reviews and meta-analyses:
Population	Patients with Crohn's disease (both biologic treatment-naïve and biologic treatment-experienced)	Patients who do not have Crohn's disease
Intervention	Same as the criteria for level 1 (Table 6.2.1.2)	Same as the criteria for level 1 (Table 6.2.1.2)
Outcomes[a]	• Clinical response • Sustained clinical response • Durable clinical response • Durable clinical remission • Mucosal healing All of the above with timing and definition • Safety outcomes (AEs, SAEs, specific AEs of interest) Quality-of-life outcomes, including IBDQ • Surgery • Hospitalizations • Change in CDAI from baseline • Mean CDAI at baseline and each subsequent visit • Amended search for studies of surgery: ○ Any clinical outcomes as noted above ○ Any surgical outcomes, including complications	▪ None ▪ For IBD articles, exclude if IBD results not broken down into Crohn's disease and ulcerative colitis

AE = adverse event; CDAI = Crohn's Disease Activity Index; IBD = inflammatory bowel disease; IBDQ = Inflammatory Bowel Disease Questionnaire; SAE = serious adverse event

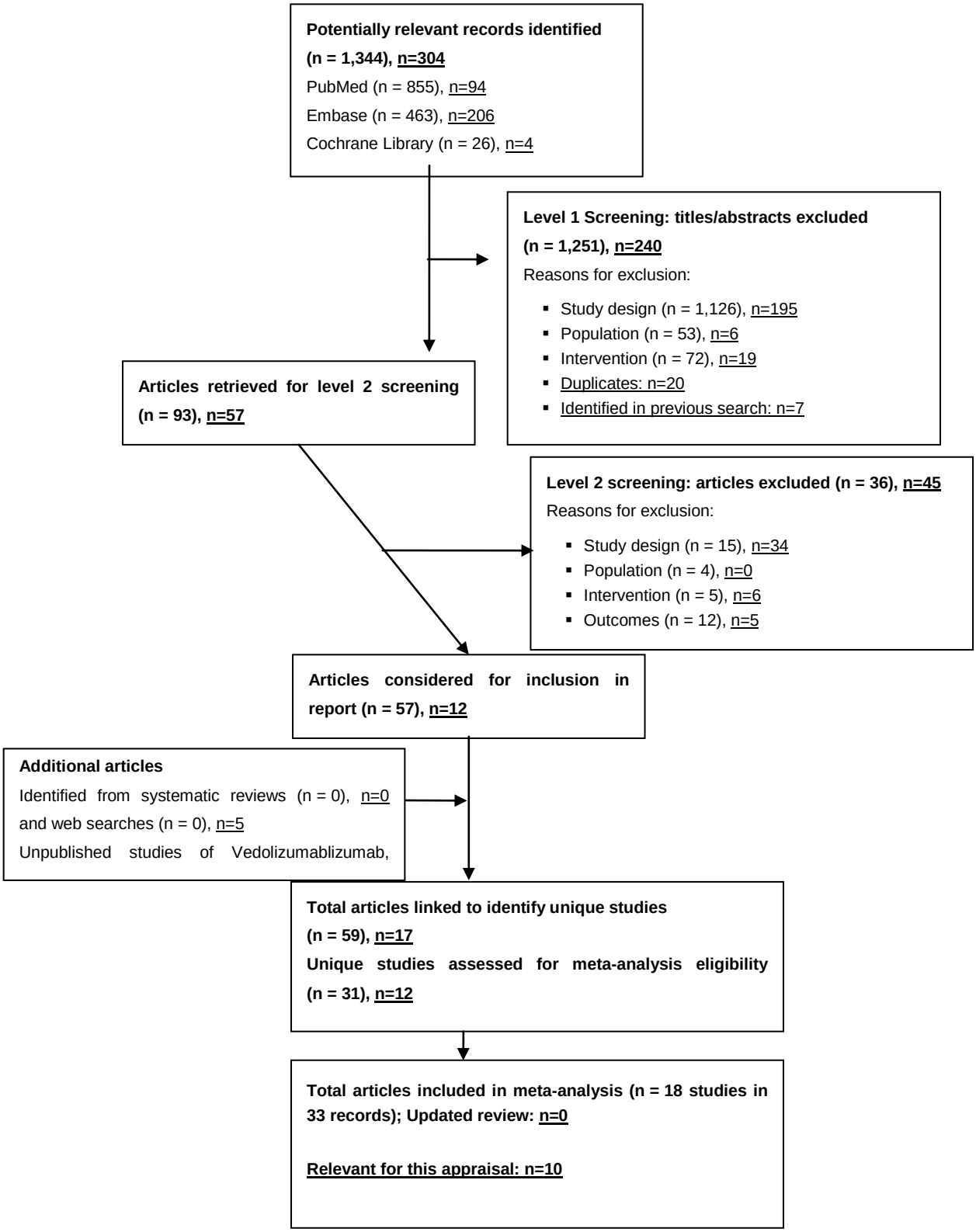
[a] Outcomes to be included were finalized following review of the clinical study reports. As definitions of response, remission, and mucosal healing, along with the timings of outcome measurement, may differ between studies, heterogeneity of reporting was considered during data extraction

Source: (Takeda Data on File, 2014)

6.2.2	**A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 6.2.4.**

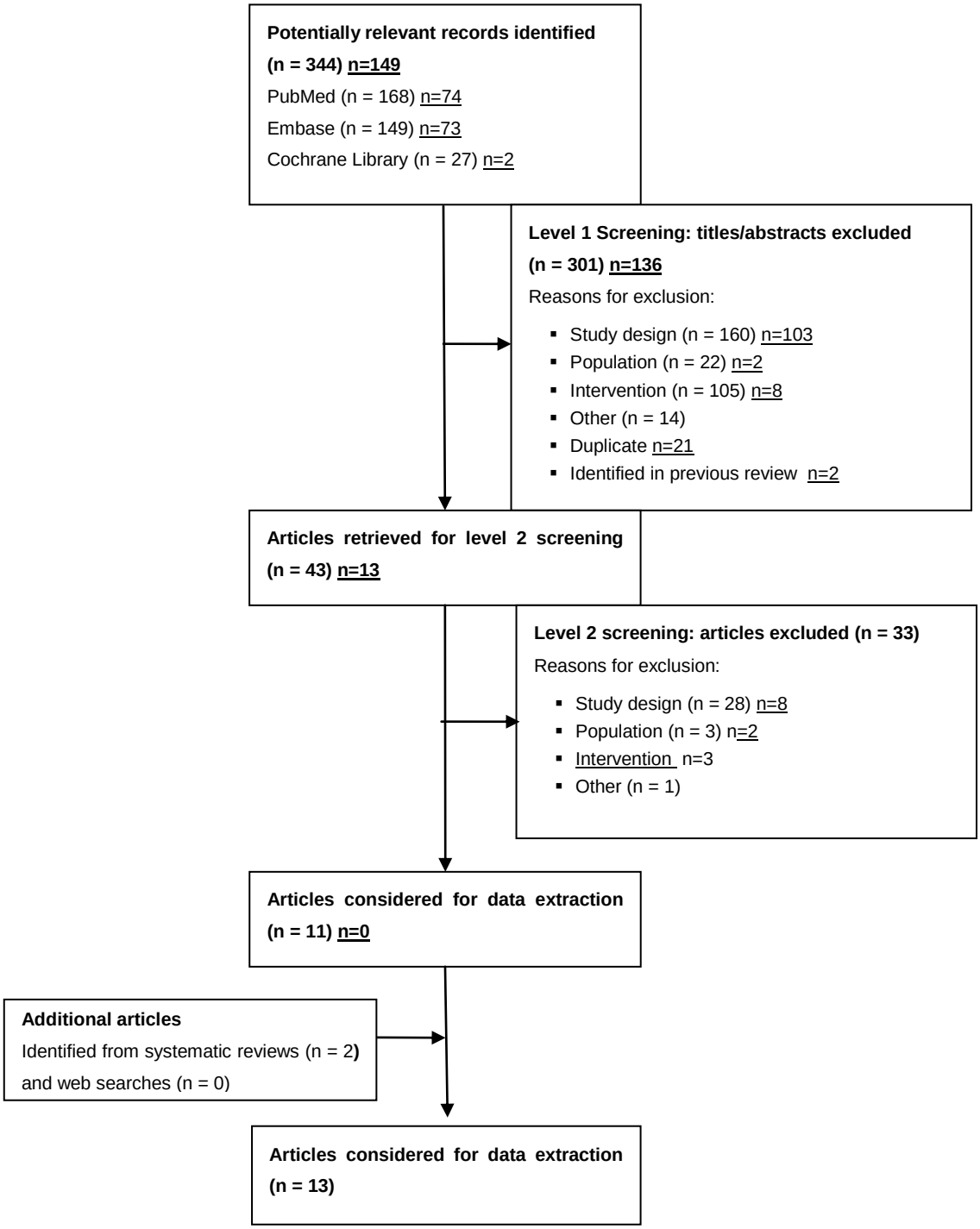
The original search and the updated search flow diagram of studies included at each stage are shown below. The new updated search results are denoted by underlined text (Takeda Data on File, 2014). As described above, this review had a global remit. 10 studies identified were relevant for this appraisal; Cetolizumab and Natalizumab trials have been excluded.

Figure 6.2.2.1: Original and Updated biologics search PRISMA diagram



PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Figure 6.2.2.2: Original and Updated surgery search PRISMA diagram



PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

6.2.3	**When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.**

There were four sources for clinical evidence on Vedolizumab which relate to 2 Phase III placebo-controlled pivotal studies that were retrieved as part of the systematic review (Takeda Data on File, 2014).

Table 6.2.3.1: Randomised clinical trials for Vedolizumab in Crohn's disease

Study	Reference Source
C13007 **(GEMINI II)**	• FINAL CLINICAL STUDY REPORT C13007: A Phase 3, Randomised, Placebo-Controlled, Blinded, Multicentre Study of the Induction and Maintenance of Clinical Response and Remission by Vedolizumab (MLN0002) in Patients With Moderate to Severe Crohn's Disease. October 2012 • Sandborn, W.J. et al., 2013. Vedolizumab as induction and maintenance therapy for Crohn's disease. The New England journal of medicine, 369(8), pp.711–21. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23964933 [Accessed April 30, 2014].
C13011 **(GEMINI III)**	• FINAL CLINICAL STUDY REPORT C13011 A Phase 3, Randomised, Placebo-Controlled, Blinded, Multicentre Study of the Induction of Clinical Response and Remission by Vedolizumab in Patients with Moderate to Severe Crohn's disease. 30 August 2012 • Sands, B.E. et al., 2014. Effects of Vedolizumab Induction Therapy for Patients With Crohn's Disease in Whom Tumor Necrosis Factor Antagonist Treatment Had Failed. Gastroenterology, (in press). Available at: http://www.ncbi.nlm.nih.gov/pubmed/24859203 [Accessed July 14, 2014].

6.2.4	**Complete list of relevant RCTs. Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form. A suggested format is presented below.**

Table 6.2.4.1: List of relevant RCTs for Vedolizumab in Crohn's disease

Trial no. (acronym)	Intervention	Comparator	Duration	Population
C13007 (GEMINI II) (William J Sandborn et al., 2013a)	**Induction study:** Vedolizumab 300 mg i.v. at Weeks 0 and 2	**Induction study:** Placebo at Weeks 0 and 2	**Induction study:** 6 weeks	Adult patients (18 to 80 years) with Crohn's disease for ≥3 months, a CDAI score of 220 to 450, the presence of one of the following: a serum CRP >2.87 mg/L, colonoscopic findings showing ≥3 large ulcers or ≥10 aphthous ulcers, or faecal calprotectin concentrations ≥250 mcg/g of stool plus evidence of ulcers on computed tomography or magnetic resonance enterography, small bowel radiography, or capsule endoscopy, and either no response to or unacceptable AEs from one or more previous treatments
	Maintenance study: Vedolizumab 300 mg i.v. every 4 or 8 weeks	**Maintenance study:** Placebo every 8 weeks	**Maintenance study:** 52 weeks	
C13011 (GEMINI III) (Sands et al., 2014)	Vedolizumab 300 mg i.v. administered at Weeks 0, 2, and 6	Placebo administered at Weeks 0, 2, and 6	10 weeks	Adult patients (aged 18 to 80 years) severely active Crohn's disease (CDAI of 220 to 400 points) and a CRP >2.87 mg/L, or colonoscopy photo of active Crohn's disease within 4 months prior to randomisation, or a faecal calprotectin >250 mcg/g stool at screening plus imaging or endoscopic evidence of Crohn's disease within 4 months prior to screening, despite treatment with immunomodulators, TNF antagonists, and/or, for patients outside the US, corticosteroids

6.2.5	**Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.**

Vedolizumab has been studied in 2 head-to-head trial Phase 3 placebo-controlled trials: GEMINI II and GEMINI III. GEMINI II (William J Sandborn et al., 2013a) was designed to compare the efficacy and safety of Vedolizumab against placebo plus conventional therapy for induction and maintenance of moderately to severely active Crohn's disease. GEMINI III was designed to evaluate efficacy at Week 6 and Week 10 in a subgroup of patients defined as having failed at least one conventional therapy and failed TNF-alpha antagonist therapy (including primary non-responders), and the overall population, which also included patients who failed at least one conventional therapy and were naïve to TNF-alpha antagonist therapy (Sands et al., 2014).

The relevant main comparator is current standard of care, comprising 5-ASAs, corticosteroids and immunomodulators. This reflects the baseline therapies in both Vedolizumab phase 3 studies in which patients received Vedolizumab or placebo in addition to 5-ASAs, corticosteroids and immunomodulators, therefore the placebo arm of both studies represents current standard of care and is the main comparator presented in this submission.

None of the biologics have head-to-head trial data with another biologic. All systematically-identified published clinical trials compared biologic therapies with conventional therapy plus a placebo biologic. As such, an indirect comparison was conducted using the placebo arm of the clinical trials (which represents conventional therapy in the model) as the common comparator. Further detail on the MTC is provided in Section 6.6.

6.2.6	**When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.**

No relevant Vedolizumab randomised clinical trial (RCT) has been excluded.

6.2.7	**Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 6.8 and key details should be presented in a table; the following is a suggested format.**

The systematic review did not identify relevant non-RCT data providing clinical efficacy information. A long-term safety study of Vedolizumab (C13008, GEMINI LTS) presented in the Section 6.8.

6.3 Summary of methodology of relevant RCTs

6.3.1	**As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, the information should be tabulated**.
6.3.2	**Methods. Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.**

A summary of the methodology of the GEMINI II and III trials is provided in Table 6.3.2.1. In addition Figure 6.3.2.1 and 6.3.2.2 provide an overview of the treatment assignment within the GEMINI II and GEMINI III trial respectively.

Figure 6.3.2.1: GEMINI II treatment phases, randomization, and treatment assignments

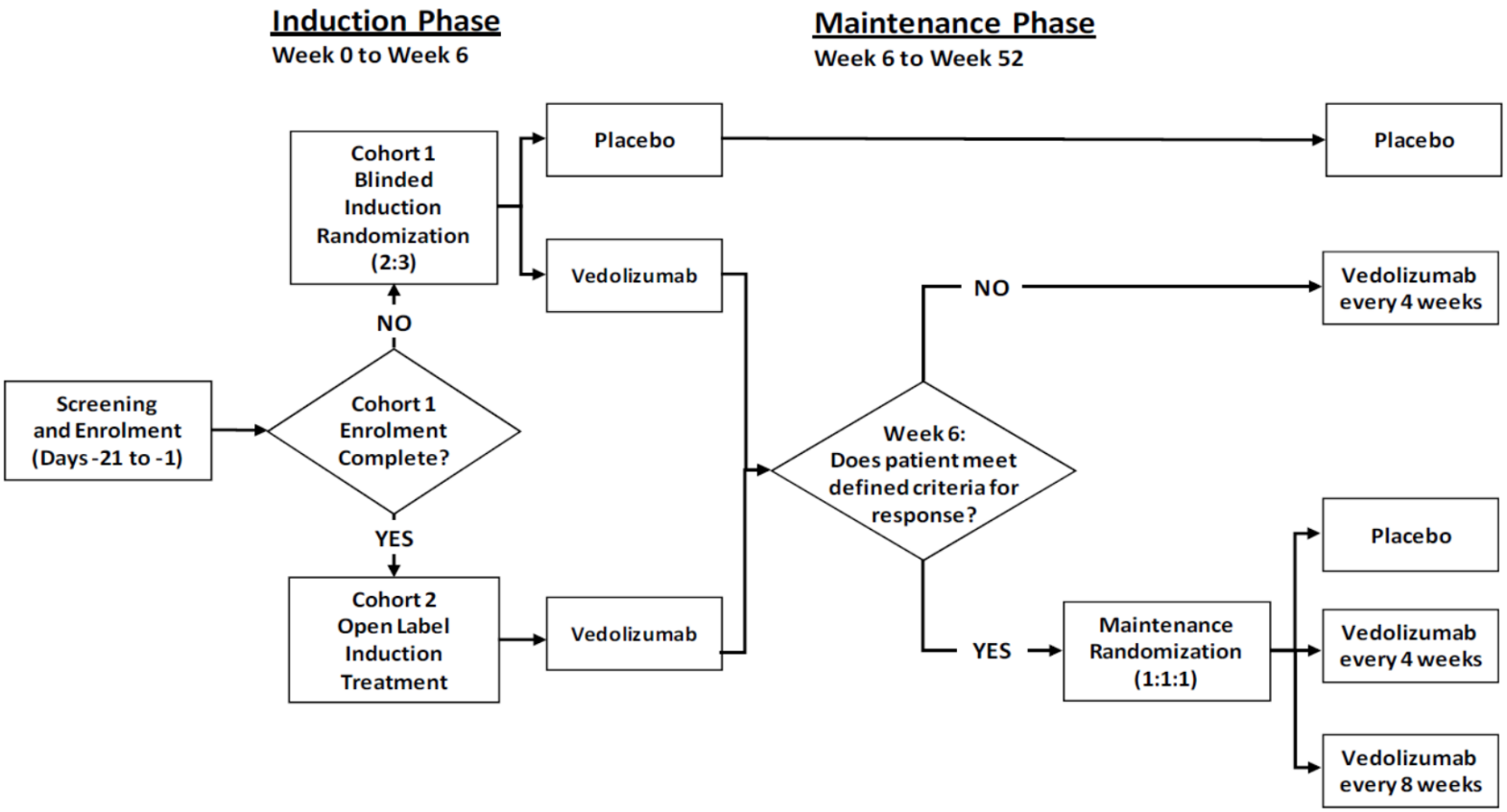
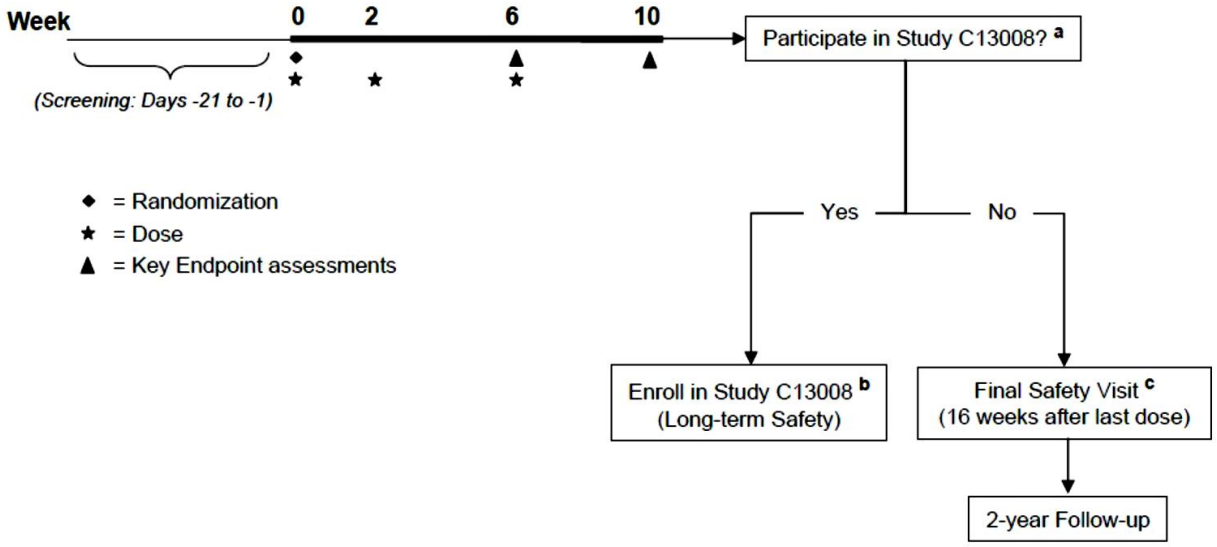


Figure 6.3.2.2: GEMINI II - patient treatment and visit schedule



a After completing the Week 10 assessments, patients were eligible to enroll in Study C13008 if study drug was well tolerated and no surgical intervention for CD occurred or was required.

b Eligible patients were to have enrolled in Study C13008 within 5 weeks after their final dose in this study.

c Patients who were not eligible for or declined enrollment in Study C13008 were to return for an on-study Final Safety visit (Week 22, or 16 weeks after last dose) and complete the 2-year follow-up.

Table 6.3.2.1: Comparative summary of methodology of GEMINI II and III trials

	GEMINI II	GEMINI III
Location	GEMINI II was conducted between December 2008 and May 2012 at 285 medical centres worldwide in 39 countries, including regions of North America, Europe (Western, Central, and Eastern), Asia, Australia, and Africa.	GEMINI I was conducted at 107 sites in 19 countries from November 2010 to April 2012. Participating countries included regions of North America, Europe (Western, Central, and Eastern), Asia, Australia, and Africa.
Design	This Phase 3, multicentre, randomised, double-blind, placebo-controlled study that consisted of separate induction and maintenance phases.	This Phase 3 multicentre, randomised, double-blind, placebo-controlled study evaluated the safety and efficacy of Vedolizumab as induction treatment in patients with moderate-to-severe Crohn's disease who had failed prior therapies.
Duration of Study	Induction Phase: Week 0 to Week 6 Maintenance Phase: Week 6 to Week 52 Total study duration: 52 weeks	10-week study
Method of Randomisation	**Induction** **Cohort 1**: patients were randomly assigned, in a 3:2 ratio, to receive i.v. Vedolizumab (300 mg) or placebo at days 1 and 15 with two stratification factors: • concomitant use or non use of glucocorticoids • concomitant use or non use of immunosuppressive agents or prior use or non use of TNF antagonists. The proportion of patients with previous exposure to TNF antagonists was limited to 50%. **Cohort 2:** To fulfil sample-size requirements for the maintenance trial, additional patients were enrolled in an open-label group (cohort 2), which received the same active induction regimen given in the blinded study. **Maintenance** Patients from both cohorts who had a clinical response to Vedolizumab at week 6 were randomly assigned, in a 1:1:1 ratio, to receive Vedolizumab every 8 weeks, Vedolizumab every 4 weeks, or placebo for up to 52 weeks. Randomization was stratified according to three factors: • cohort	Patients were randomly assigned, in a 1:1 ratio, to receive i.v. Vedolizumab (300 mg) or placebo with three stratification factors: • the presence or absence of previous TNF-alpha antagonist failure • concomitant use of oral corticosteroids • concomitant use of immunomodulators (6-MP, azathioprine, or methotrexate). Investigators performed patient enrolment, monitored by an interactive voice response system (IVRS). Stratified block randomization was computer generated centrally using 8 strata and a block size of 16.

	• concomitant use or non use of glucocorticoids • concomitant use or non use of immunosuppressive agents or prior use or non use of TNF antagonists. Eligible subjects were randomised using a centralised Interactive Web Response System (IWRS).	
Method of Blinding	Double blind: Patients received Vedolizumab or placebo by i.v. infusion according to their randomisation treatment group or treatment assignment. All patients and all study personnel except for those directly involved with study drug preparation (e.g., the site pharmacist) were blinded to study drug assignment for the entire study. Patients receiving Vedolizumab every 8 weeks were administered placebo every other visit (4 weeks) to preserve blinding For both Vedolizumab and placebo infusions, the unblinded site pharmacist or designee was to mask the i.v. bags after preparation to maintain the study blind.	Double blind: All patients and all study personnel, except for those directly involved with study drug preparation, were blinded to study drug assignment for the entire study.
Interventions	Vedolizumab: 300mg i.v.: **Induction** (Week 0 and Week 6) • Cohort 1: Vedolizumab: 300 mg i.v. at Week 0 and Week 6, n=220 • Cohort 2: Vedolizumab: 300 mg i.v. at Week 0 and Week 6, n=747 **Maintenance:** • Every 8 weeks: n=154 • Every 4 weeks: n=154 (placebo every other visit to maintain blinding)	Vedolizumab 300 mg i.v. administered at Weeks 0, 2, and 6, n=209
Comparator	Placebo **Induction** • Cohort 1: Week 0 and Week 6, n=148 **Maintenance** (ITT) • Every 4 weeks n=153	Placebo, administered at Weeks 0, 2, and 6, n=207
Primary Outcomes	**Induction** • Clinical remission (CDAI score ≤150 points) at week 6 • CDAI-100 response (enhanced clinical response, ≥100-point decrease in the CDAI score) at Week 6 **Maintenance** • Clinical remission at Week 52	• Clinical remission (a CDAI score ≤150) in patients with prior TNF-alpha antagonist failure in at Week 6.
Secondary Outcomes	**<u>Efficacy</u>** **Induction**	**<u>Efficacy</u>** • Clinical remission at Week 6 in the overall

	• Mean change in CRP levels at Week 6 **Maintenance** • CDAI-100 response at week 52 • Corticosteroid free remission at Week 52 • durable clinical remission (defined as clinical remission at ≥80% of study visits, including the final visit) **<u>Safety</u> (induction and maintenance)** • AEs, • SAEs, • vital signs • results of standard laboratory tests (i.e., clinical chemistry, haematology, coagulation, urinalysis, and HAHA), and • results of 12-lead ECGs	population • Clinical remission at Week 10 in both the TNF antagonist failure and overall populations • Sustained clinical remission (CDAI ≤150 at both week 6 and 10) in both the TNF antagonist failure and overall populations • CDAI-100 response (enhanced clinical response, ≥100-point decrease from baseline in CDAI) in the TNF antagonist failure population at week 6 **<u>Safety</u>** • AEs, • SAEs, • vital signs • results of standard laboratory tests (i.e., clinical chemistry, haematology, coagulation, urinalysis, and HAHA • results of 12-lead ECGs
Other endpoints	Key endpoints in sub-groups of patients • with previous exposure to TNF-alpha antagonist therapy • defined as having failed TNF-alpha antagonist therapy • on concomitant therapies Additional selected endpoints • The IBDQ, SF-36, and EQ-5D questionnaires were to be completed during screening and prior to dosing at Weeks 6, 30, and 52 (in patients who had not been withdrawn prior to these visits), and, if applicable, the ET visit.	Key endpoints in sub-groups of patients • on concomitant therapies for Crohn's disease • key baseline demographic and disease characteristics • baseline CRP levels ≥5 mg/l: • baseline faecal calprotectin ≥250 µg/g: Additional selected endpoints • Enhanced clinical response at Week 6 in the entire study population • Enhanced clinical response -at Week 10 in the TNF-alpha antagonist failure sub-population and in the entire study population • Sustained enhanced clinical response (i.e., enhanced clinical response at both Week 6 and Week 10) in the TNF-alpha antagonist failure sub-population and in the entire study population • Change from baseline in IBDQ, SF-36, and EQ-5D scores at Week 6 and Week 10 in the TNF antagonist failure sub-population and in the entire study population

Duration of Follow-up	52 weeks	10 weeks
Reference	(William J Sandborn et al., 2013a; Takeda Data on File, 2012a)	(Sands et al., 2014; Takeda Data on File, 2012b)

Participants

6.3.3	**Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one RCT. Highlight any differences between the trials.**

The eligibility criteria of the GEMINI II and III trials are identical (See table 6.3.3.1, (William J Sandborn et al., 2013a; Sands et al., 2014)).

Table 6.3.3.1: Patient eligibility criteria for GEMINI II and III

Inclusion criteria

• Age 18 to 80 years
• Diagnosis of Crohn's disease established ≥3 months prior to enrolment with known involvement of ileum and/or colon
• Moderately to severely active Crohn's disease (CDAI score 220-450) and 1 of the following:
  o CRP level > 2.87 mg/L
  o Colonoscopy with documentation of ≥ 3 large ulcers or 10 aphthous ulcers
  o Fecal calprotectin >250 mcg/g stool and ulcers
• Inadequate response to, loss of response to, or intolerance to at least one of the following: immunomodulators, TNF-alpha antagonists, or corticosteroids (Outside US only) within the last 5 years.
• May be receiving a therapeutic dose of oral 5-ASA, oral corticosteroid therapy, probiotics, antidiarrheals, azathioprine or 6-MP, methotrexate, antibiotics.

Exclusion criteria
• Previous treatment with Vedolizumab, Natalizumab, efalizumab, or rituximab. • Treatment with Adalimumab within 30 days and treatment with Infliximab or Certolizumab pegol within 60 days before enrolment was not permitted. • Patients with more than three small-bowel resections, the short-bowel syndrome, extensive colonic resection, intestinal stricture, abdominal abscess, active or latent TB, or cancer (exception of certain cancers for which the recurrence risk after adequate treatment is accepted to be low (eg, non metastatic basal cell and squamous cell skin cancers, cervical carcinoma in situ). • Concurrent lactation or pregnancy, • Unstable or uncontrolled medical condition, major neurological disorder, general anesthesia within 30 days, or planned major surgery during the study. • Active drug or alcohol dependence and active psychiatric disease or other complicating factor(s) that could result in non adherence to study procedures.

6.3.4	**Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.**

GEMINI II

The demographic and baseline characteristics for patients in the induction phase were similar in the placebo and Vedolizumab groups and are shown in table 6.3.4.1 (William J Sandborn et al., 2013a).

GEMINI III

Most baseline demographics were similar between the treatment groups with the exception of the Vedolizumab-treated patients had a slightly higher baseline CDAI compared to the placebo group (313.9 vs 301.3, p=0.015), and more placebo-treated patients (51%) were <35 years of age compared to Vedolizumab-treated patients (42%) (See Table 6.3.4.2, (Sands et al., 2014; Takeda Data on File, 2012b)).

Table 6.3.4.1: Demographic and baseline characteristics (GEMINI II induction phase)

Characteristic	**Placebo (N=148)**	**Vedolizumab**			Total (N=1115)
		Cohort 1 (N=220)	**Cohort 2 (N=747)**	**Combined (N=967)**	
Age, years	38.6±13.2	36.3±11.6	35.6±12.0	35.7±11.9	36.1±12.1
Male gender, n(%)	69 (46.6)	105 (47.7)	346 (46.3)	451 (46.6)	520 (46.6)
White race, n(%)†	124 (83.8)	182 (82.7)	689 (92.2)	871 (90.1)	995 (89.2)
Body weight, kg	68.7±18.9	67.1±19.1	70.8±19.6	69.9±19.5	69.8±19.4
Current smoker, n(%)	34 (23.0)	54 (24.5)	210 (28.1)	264 (27.3)	298 (26.7)
Duration of disease, years	8.2±7.8	9.2±8.2	9.2±7.6	9.2±7.8	9.0±7.8
CDAI score‡	325±78	327±71	322±67	323±68	324±69
Median C-reactive protein, mg/L§	13.7	15.3	10.2	10.6	11.5
Median faecal calprotectin,, µg/g¶	653	852	657	688	686
Site of disease, n(%)					
Ileum only	21 (14.2)	37 (16.8)	123 (16.5)	160 (16.5)	181 (16.2)
Colon only	43 (29.1)	62 (28.2)	211 (28.2)	273 (28.2)	316 (28.3)
Ileum and colon	84 (56.8)	121 (55.0)	413 (55.3)	534 (55.2)	618 (55.4)
Concomitant medications for CD, n(%)‖					
Glucocorticoids only	45 (30.4)	67 (30.5)	269 (36.0)	336 (34.7)	381 (34.2)
Immunosuppressants only	25 (16.9)	37 (16.8)	119 (15.9)	156 (16.1)	181 (16.2)

Characteristic	Placebo	Vedolizumab			Total
Glucocorticoids+ immunosuppressants	26 (17.6)	38 (17.3)	125 (16.7)	163 (16.9)	189 (17.0)
No glucocorticoids or immunosuppressants	52 (35.1)	78 (35.5)	234 (31.3)	312 (32.3)	364 (32.6)
Prednisone-equivalent dose, mg					
Median	20	20	20	20	20
Interquartile range	10-30	10-20	12.5-30	10-30	10-30
Prior anti-TNF therapy for CD, n/total (%)					
Receipt of ≥1 TNF antagonist	72/148 (48.6)	111/220 (50.5)	506/747 (67.7)	617/967 (63.8)	689/1115 (61.8)
TNF-Failure:					
≥1 TNF antagonist	70/148 (47.3)	105/220 (47.7)	470/747 (62.9)	575/967 (59.5)	645/1115(57.8)
Inadequate response**	41/70 (58.6)	56/105 (53.3)	223/470 (47.4)	279/575 (48.5)	320/645 (49.6)
LOR††	22/70 (31.4)	40/105 (38.1)	189/470 (40.2)	229/575 (39.8)	251/645 (38.9)
Unacceptable AEs	7/70 (10.0)	9/105 (8.6)	58/470 (12.3)	67/575 (11.7)	74/645 (11.5)
≥2 TNF antagonists	42/148 (28.4)	56/220 (25.5)	300/747 (40.2)	356/967 (36.8)	398/1115 (35.7)
Haemoglobin concentration, g/L	124.7±18.6	121.6±18.4	125.2±16.8	124.4±17.3	124.4±17.4
White cell count, x109/L	8.8±3.0	9.0±3.3	9.2±3.4	9.2±3.4	9.1±3.4
Prior surgery for CD, n(%)	54 (36.5)	98 (44.5)	314 (42.0)	412 (42.6)	466 (41.8)
History of fistulising disease, n(%)	56 (37.8)	90 (40.9)	264 (35.3)	354 (36.6)	410 (36.8)
Draining fistulae at baseline, n(%)	23 (15.5)	38 (17.3)	104 (13.9)	142 (14.7)	165 (14.8)

* Plus–minus values are means ±SD. Cohort 1 included patients who were randomly assigned, in a 3:2 ratio, as part of the double-blind trial of induction therapy, to receive IV Vedolizumab, at a dose of 300 mg, or placebo at weeks 0 and 2. Cohort 2 included patients who received open-label Vedolizumab at a dose of 300 mg at weeks 0 and 2. There were no significant differences (at P<0.05) between the placebo group and the Vedolizumab group in Cohort 1.
† Race was determined by the investigator.
‡ The CDAI consists of 8 components, each of which is adjusted by a weighting factor. The components were subsequently added together to yield a composite score; scores range from 0 to approximately 600, with higher scores indicating more severe disease activity.
§ Data on C-reactive protein levels were available for 147 patients in the placebo group, 220 patients in Vedolizumab Cohort 1, and 747 patients in Vedolizumab Cohort 2, for a total of 1114 patients. Among these, 127 patients in the placebo group (86.4%), 183 in Vedolizumab Cohort 1 (83.2%), and 617 in Vedolizumab Cohort 2 (82.6%) (800 patients [82.7%] in the combined Vedolizumab groups and 917 patients [83.2%] in the total population) had elevated C-reactive protein levels (>2.87 mg per litre).
¶ Data on faecal calprotectin concentrations were available for 142 patients in the placebo group, 210 in Vedolizumab Cohort 1, and 719 in Vedolizumab Cohort 2.
‖ The glucocorticoids used included prednisone, methylprednisolone, prednisolone, budesonide, hydrocortisone, and triamcinolone. The immunosuppressive agents included azathioprine, mercaptopurine, and methotrexate.
** Included in this category were patients who did not have an initial response.
†† LOR (loss of response) indicates that the patient had a response initially but subsequently did not have a response.

Table 6.3.4.2: Demographic and baseline characteristics (GEMINI III)

Characteristic	Placebo			Vedolizumab		
	Overall (n=207)	TNF-Failure (n=157)	TNF-Naïve (n=50)	Overall (n=209)	TNF-Failure (n=158)	TNF-Naïve (n=51)
Median age (range), years	34.8 (19-77)	36.6 (19-77)	30.6 (19-60)	36.9 (20-69)	37.5 (20-69)	35.7 (20-64)
Male gender, n (%)	118 (57)	95 (61)	23 (46)	118 (56)	90 (57)	28 (55)
Median body weight (range), kg	71.3 (41-147)	71.2 (41-125)	71.7 (43-147)	69.5 (40-144)	70.3 (40-144)	67.1 (40-99)
Median BMI (range), kg/m2	23.3 (15-48)	23.3 (15-480)	22.9 (17-43)	23.3 (15-43)	23.3 (15-43)	22.6 (16-33)
Median duration of disease (range), years	8.0 (0.3-42.9)	9.6 (1.0-42.9)	4.4 (0.3-24.8)	8.4 (0.3-41.8)	9.4 (0.5-41.8)	4.7 (0.3-40.8)
CDAI score (SD)	301.3 (55.0)	306.1 (55.4)	286.1 (51.1)	313.9 (53.2)	316.1 (52.6)	307.3 (54.8)
Mean C-reactive protein (SD), mg/L	18.5 (22.0)	18.8 (23.6)	17.7 (16.1)	19.0 (23.2)	20.7 (24.7)	13.9 (16.8)
Mean faecal calprotectin (SD), µg/g¶	1426.5 (2357.8)	1459.5 (2475.0)	1321.0 (1954.0)	1148.1 (1878.6)	1249.2 (2071.6)	836.9 (1043.8)
Site of disease, n(%)						
Ileum only	29 (14)	20 (13)	9 (18)	33 (16)	21 (13)	12 (24)
Colon only	52 (25)	40 (25)	12 (24)	48 (23)	40 (25)	8 (16)
Ileum and colon	126 (61)	126 (61)	97 (62)	29 (58)	128 (61)	97 (61)
History of CD surgery, n (%)	89 (43)	80 (51)	9 (18)	92 (44)	73 (46)	19 (37)
History of fistulising disease, n (%)	77 (37)	67 (43)	10 (20)	71 (34)	57 (36)	14 (27)
Corticosteroid use, n (%)	108 (52)	85 (54)	11 (22)	110 (53)	86 (54)	11 (22)
Immunosuppressive use, n(%)	69 (33)	42 (27)	15 (30)	71 (34)	43 (27)	15 (29)
5-ASA use, n (%)	61 (29)	29 (18)	32 (64)	68 (33)	37 (23)	31 (61)
Prior immunosuppressive exposure, n (%)	193 (93)	147 (94)	46 (92)	176 (84)	135 (85)	41 (80)
Prior TNF antagonist failure, n (%)	157 (76)	157 (100)	-	158 (76)	158 (100)	-
1 prior TNF antagonist failure, n (%)*	45 (22)	43 (27)	-	59 (28)	59 (37)	-
2 prior TNF antagonist failure, n (%)*	90 (43)	90 (57)	-	82 (39)	82 (52)	-
3 prior TNF antagonist failure, n (%)*	21 (10)	21 (13)	-	14 (7)	14 (9)	-

CDAI=Crohn's Disease Activity Index; SD=standard deviation; TNF, tumour necrosis factor.
* Multiple failures are counted once per patient. Data on numbers of patients with 1, 2, and 3 TNF antagonist failures were captured via electronic case report form only (not via interactive voice response system). Missing/unreported values in the TNF antagonist failure population: placebo, n=3; Vedolizumab, n=3. Missing/unreported values in the overall population: placebo, n=51; Vedolizumab, n=54

Outcomes

6.3.5	**Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life (HRQL), and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one RCT.**

The efficacy outcomes in the GEMINI II and III trials are mainly based on the CDAI which is the most commonly used tool to determine disease activity in clinical trials for Crohn's disease. In addition, CRP (Magro, et al 2014) and faecal calprotectin (NICE 2013) are useful biomarkers in assessing inflammatory activity in Crohn's disease patients. Patient reported outcomes measures used are the SF-36 and EQ-5D which are well validated and commonly used in many disease areas including Crohn's disease. In addition, the IBDQ is obtained which is a validated tool in IBD including Crohn's disease.

The outcomes used, and their reliability and validity, in the GEMINI II trial are summarized in Table 6.3.5.1 and in Table 6.5.3.2 for GEMINI III.

Table 6.3.5.1: Outcome measures for the GEMINI II trial

C13007 (GEMINI II)	Outcome(s) and measures	Reliability/ validity/ current use in clinical practice
Primary outcome	**Induction** • Clinical remission (CDAI score ≤150 points) at week 6 • CDAI-100 response (enhanced clinical response, ≥100-point decrease in the CDAI score) at Week 6 **Maintenance** • Clinical remission at Week 52	These scores are clinical trial based performance measures. The outcomes reported are based on the CDAI which is the gold standard for classifying Crohn's disease activity in clinical trials and can be used to categorize the disease as mild to moderate, moderate to severe, severe fulminant, or remission (Lichtenstein et al., 2009; Yoshida, 1999). CDAI is used within clinical practice and also feature in both national guidelines from the British Society of gastroenterology (Mowat et al., 2011a) as well as guidance from NICE (NICE, 2012). In real life clinical practice, clinicians are more likely to assess patients based on subjective symptom control. In more detail, a combination of clinical symptoms, biomarkers and longitudinal symptoms will be determined. If needed further investigations will be done such as endoscopy or MRI. In addition, Harvey Bradshaw Index is usually recorded and extra intestinal manifestations and perianal disease activity are also taken into account.
Secondary outcomes	**Efficacy** **Induction** • Mean change in CRP levels at Week 6 **Maintenance** • CDAI-100 response at week 52 • Corticosteroid free remission at Week 52 • Durable clinical remission (defined as clinical remission at ≥80% of study visits, including the final visit) **Safety (induction and maintenance)** • AEs, • SAEs, • vital signs • results of standard laboratory tests (i.e., clinical chemistry, haematology, coagulation, urinalysis, and HAHA), and • results of 12-lead ECGs	C-reactive protein (CRP) is a useful biomarker in assessing inflammatory activity (Magro, et al 2014)
Other outcomes	Key endpoints in sub-groups of patients • with previous exposure to TNF-alpha antagonist therapy • defined as having failed TNF-alpha antagonist therapy • on concomitant therapies	• IBDQ: The validity, reliability, and responsiveness of the IBDQ are well established. Studies have shown that an increase in the IBDQ score of 16 to 32 corresponds to clinically meaningful improvement (Reinisch et al., 2007a).

C13007 (GEMINI II)	Outcome(s) and measures	Reliability/ validity/ current use in clinical practice
	Additional selected endpoints • The IBDQ, SF-36, and EQ-5D questionnaires were to be completed during screening and prior to dosing at Weeks 6, 30, and 52 (in patients who had not been withdrawn prior to these visits), and, if applicable, the ET visit.	• SF-36: The SF-36 has been extensively validated and is particularly useful for comparing HRQL of a given disease population with that of the general population.

Table 6.3.5.2: Outcome measures for the GEMINI III trial

C13011 (GEMINI III)	Outcome(s) and measures	Reliability/ validity/ current use in clinical practice
Primary outcome	• Clinical remission (CDAI score ≤150) in patients with prior TNF-alpha antagonist failure at Week 6.	These scores are clinical trial based performance measures. The outcomes reported are based on the CDAI which is the gold standard for classifying Crohn's disease activity in clinical trials and can be used to categorize the disease as mild to moderate, moderate to severe, severe fulminant, or remission (Lichtenstein et al., 2009; Yoshida, 1999). CDAI is used within clinical practice and also feature in both national guidelines from the British Society of gastroenterology (Mowat et al., 2011a) as well as guidance from NICE (NICE, 2012). In real life clinical practice, clinicians are more likely to assess patients based on subjective symptom control. In more detail, a combination of clinical symptoms, biomarkers and longitudinal symptoms will be determined. If needed further investigations will be done such as endoscopy or MRI. In addition, Harvey Bradshaw Index is usually recorded and extra intestinal manifestations and perianal disease activity are also taken into account.
Secondary outcomes	**Efficacy** • Clinical remission at Week 6 in the overall population • Clinical remission at Week 10 in both the TNF antagonist failure and overall populations • Sustained clinical remission (CDAI ≤150 at both week 6 and 10) in both the TNF antagonist failure and overall populations • CDAI-100 response (enhanced clinical response, ≥100-point decrease from baseline in CDAI) in the TNF antagonist failure population at week 6 **Safety** • AEs, • SAEs, • vital signs • results of standard laboratory tests (i.e., clinical chemistry, haematology, coagulation, urinalysis, and HAHA • results of 12-lead ECGs	CDAI related outcomes see above
Other	Key endpoints in sub-groups of patients • on concomitant therapies for	• CRP (Magro et al., 2009) and faecal calprotectin (NICE, 2013a))

C13011 (GEMINI III)	Outcome(s) and measures	Reliability/ validity/ current use in clinical practice
outcomes	Crohn's disease • key baseline demographic and disease characteristics • baseline CRP levels ≥5 mg/l: • baseline faecal calprotectin ≥250 µg/g: Additional selected endpoints • Enhanced clinical response at Week 6 in the entire study population • Enhanced clinical response -at Week 10 in the TNF-alpha antagonist failure sub-population and in the entire study population • Sustained enhanced clinical response (i.e., enhanced clinical response at both Week 6 and Week 10) in the TNF-alpha antagonist failure sub-population and in the entire study population • Change from baseline in IBDQ, SF-36, and EQ-5D scores at Week 6 and Week 10 in the TNF antagonist failure sub-population and in the entire study population	are useful biomarkers in assessing inflammatory activity • CDAI related outcomes see above • IBDQ: The validity, reliability, and responsiveness of the IBDQ are well established. Studies have shown that an increase in the IBDQ score of 16 to 32 corresponds to clinically meaningful improvement (Reinisch et al., 2007b). • SF-36: The SF-36 has been extensively validated and is particularly useful for comparing HRQL of a given disease population with that of the general population.

Statistical analysis and definition of study groups

6.3.6	**State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample-size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.**

The GEMINI II and III Phase 3 trial were designed to test the hypothesis that treatment with Vedolizumab, with its new gut-selective mechanism of action, would have potential for a favourable benefit to risk profile as a new treatment for IBD. Within the GEMINI II trial the effects of induction therapy and maintenance therapy with Vedolizumab was tested. Within the GEMINI III trial the effects of induction therapy with Vedolizumab was tested. Power considerations were based on the primary and key secondary efficacy endpoints. Tables 6.3.6.1, 6.3.6.2, and 6.3.6.3 summarizes the statistical analysis to test the hypotheses for the GEMINI II (induction and maintenance) and GEMINI III trials

Table 6.3.6.1: Statistical analysis in the GEMINI II trial – induction therapy

Primary analysis	The primary analyses of induction formally evaluated the efficacy of 300 mg Vedolizumab versus placebo as an induction therapy.
Statistical analyses used for testing this hypothesis	Primary endpoints were analysed with the Cochran-Mantel-Haenszel chi-square test with adjustment for stratification factors. Sequential testing and the Hochberg method was used to maintain the overall Type 1 error rate at a 5% significance level. If the P-value for one of the 2 primary end points was greater than 0.05, then the other P-value was considered to indicate statistical significance only if it was 0.025 or lower. A total of 9 subgroup analyses were pre-specified; risk differences and 95% confidence intervals were determined for the proportions of patients in the Vedolizumab and placebo groups who were in remission and who had CDAI-100 responses at Week 6.
Sample size calculation – rationale and assumptions	It was calculated that, with 370 patients, the study would have 91% power to detect a 16% difference in clinical remission rates and 82% power to detect a 15% difference in CDAI-100 response rates between the Vedolizumab and placebo groups. This assumed clinical remission rates of 37% and 21% with Vedolizumab and placebo, respectively, and CDAI-100 response rates of 46% and 31%, respectively.
Data management, patient withdrawals	Patients who withdrew from the study early were considered treatment failures.

Table 6.3.6.2: Statistical analysis in the GEMINI II trial – maintenance therapy

Primary analysis	The primary analyses of maintenance evaluated the efficacy and safety of Vedolizumab Q4W versus placebo and Vedolizumab Q8W versus placebo as a maintenance therapy.
Statistical analyses used for testing this hypothesis	The proportions of patients who met the criteria for the endpoints were analysed in a similar manner to the induction phase Endpoints were tested for significance in a pre-specified, ranked order with the Hochberg method applied to maintain the alpha level at 5% in the comparison of the 2 Vedolizumab regimens with placebo.
Sample size calculation – rationale and assumptions	It was calculated that, with 501 patients, the study would have 89% power to detect a 16% difference in clinical remission rates. This assumed clinical remission rates of 38% and 22% with Vedolizumab and placebo, respectively.
Data management, patient withdrawals	Patients who withdrew from the study early were considered treatment failures.

Table 6.3.6.3: Statistical analysis in the GEMINI III trial

Primary analysis	The primary analyses of induction formally evaluated the efficacy of 300 mg Vedolizumab versus placebo as an induction therapy. The primary efficacy analysis was restricted to patients with prior TNF antagonist failure (i.e, TNF antagonist failure population, prespecified as ~75% of enrolled patients), among whom the proportion of patients in clinical remission at week 6 was assessed.
Statistical analyses used for testing the hypothesis	The proportion-based endpoints, such as clinical remission, sustained clinical remission, and enhanced clinical response, were tested using the Cochran–Mantel–Haenszel (CMH) chi-square test at a 5% significance level with stratification according to concomitant use of oral corticosteroids and concomitant use of immunomodulators (6-MP, azathioprine, or methotrexate) for the TNF antagonist failure ITT sub-population; or with stratification according to previous failure of TNF antagonist therapy, concomitant use of oral corticosteroids, and concomitant use of immunomodulators (6-MP, azathioprine, or methotrexate) for the overall ITT population. The CMH chi-square p-value and the risk difference, along with its 95% two-sided CI, were performed. The risk difference was the primary test. In addition, the relative risk was provided along with the 95% two-sided CI estimate.
Sample size calculation – rationale and assumptions	It was calculated that, with 396 patients (296 patients who failed on TNF-alpha antagonists), the study would have 91% power to detect a 12% difference in clinical remission rate in the TNF-alpha antagonist failure sub-population. This assumed clinical remission rates of 17% and 5% with Vedolizumab and placebo, respectively.
Data management, patient withdrawals	Patients who withdrew from the study early were considered treatment failures.

6.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

Subgroup analyses were carried out to assess risk differences (percentages) and 95% confidence intervals (CI) if treatment effects are consistent within subgroup for the primary outcomes. Results from these analyses were to be considered consistent with the primary analysis if the 95% CI for the risk difference within a subgroup included the point estimate for the primary analysis.

Predefined subgroup analysis GEMINI II and III

Subgroup analyses were planned for the primary endpoints in GEMINI II and III and efficacy secondary endpoints in GEMINI III (See Table 6.5.3.1 and 6.3.5.2) to investigate whether or not treatment effects were consistent across sub-groups. The following sub-groups were pre-specified in the statistical analysis plan (Takeda Data on File, 2012a, 2012b)

- Age: (<35 yrs, ≥35 years)
- Sex
- Duration of Crohn's disease (≥1 yr < 3yrs; ≥3 to < 7yr; ≥7 yrs)
- Baseline CDAI score (≤330; >330)
- Baseline CRP (≤5mg/L; >5 mg/L)
- Basline fecal calprotectin (≤500 mmcg/g; >500 mcg/g)
- Disease localization: ileal, colonic, and ileocolonic
- Prior treatment history: any prior anti-TNF-Failure, prior immunosuppressive failure but not prior anti-TNF-Failure, prior corticosteroid failure only

Additional post hoc analysis

Analyses not described in the final statistical analysis plan were performed in order to summarize important patient sub-groups or to clarify results of planned analyses. Most of the post hoc analyses were either requested from regulatory authorities or based on recommendations of key opinion leaders. The following analyses were added after the database was locked, the study was unblinded, and the results were reviewed:

GEMINI II:

- Clinical remission and enhanced clinical response were analysed at Week 52 in ITT patients who met the protocol definition of clinical response at Week 6.
- Clinical remission and enhanced clinical response at Week 10 until Week 52 were summarized for patients who did not achieve clinical response at Week 6.
- Median prednisone doses change from baseline as well as median prednisone dose percent change from baseline
- Clinical remission and enhanced clinical response at induction and maintenance and corticosteroid free remission at week 52 were summarized for patients with
    - baseline concomitant immunomodulator use (with and without baseline corticosteroid use).
    - baseline concomitant corticosteroid use (with and without baseline immunomodulatory use)
    - previous TNF-alpha antagonist failure type (inadequate response, loss of response, and intolerance) and by number of TNF-alpha antagonist therapies patients had previously failed.

GEMINI III:

- Efficacy endpoints of clinical remission at Week 6, clinical remission at Week 10, sustained clinical remission, and enhanced clinical response were summarized for patients with
  - baseline concomitant immunomodulator use (with and without baseline corticosteroid use).
  - baseline concomitant corticosteroid use (with and without baseline immunomodulatory use)
  - previous TNF-alpha antagonist failure type (inadequate response, loss of response, and intolerance) and by number of TNF-alpha antagonist therapies patients had previously failed.

6.3.8	**Participant flow. Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.**

Figure 6.3.8.1: GEMINI II consort diagram

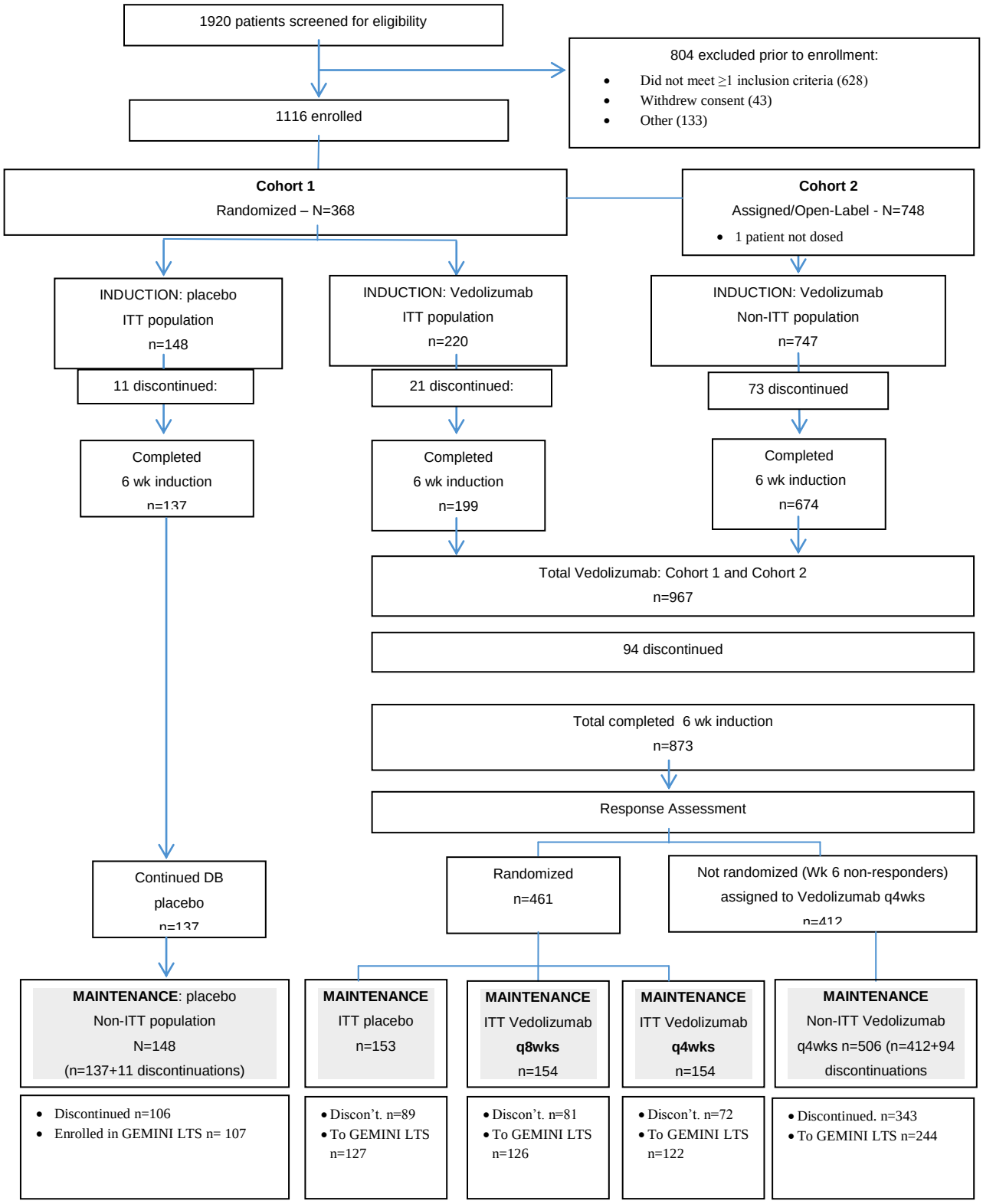
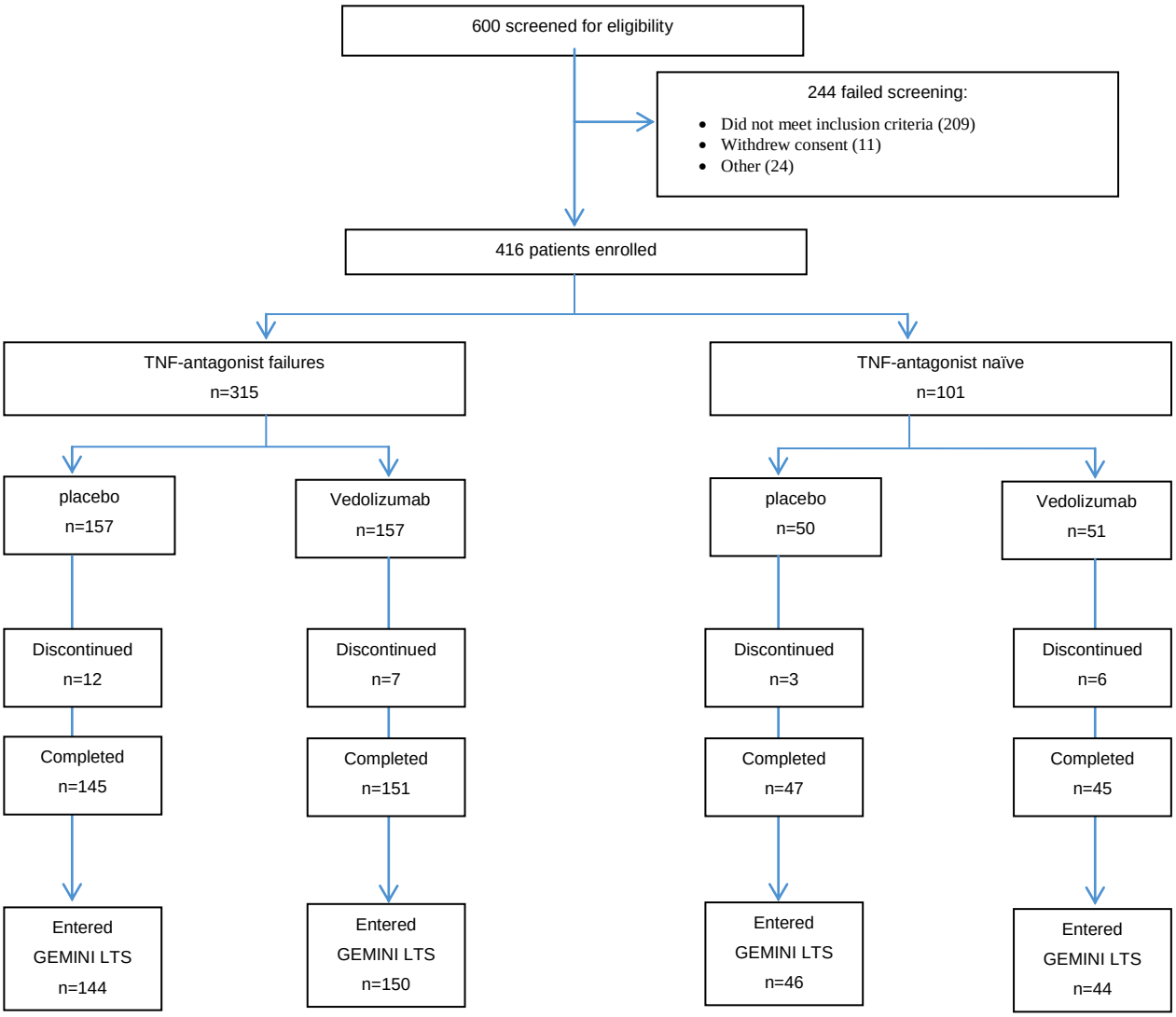


Figure 6.3.8.2: GEMINI III consort diagram



6.4 Critical appraisal of relevant RCTs

6.4.1 The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG. The following are the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.

- Was the method used to generate random allocations adequate?
- Was the allocation adequately concealed?
- Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?
- Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?
- Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?
- Is there any evidence to suggest that the authors measured more outcomes than they reported?
- Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

6.4.2 Please provide as an Appendix a complete quality assessment for each RCT. See section 10.3, Appendix 3 for a suggested format.

6.4.3 If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A suggested format for the quality assessment results is shown below.

Table 6.4.3.1: Quality assessment results for GEMINI II and GEMINI III

Trial no. (acronym)	C13007 (GEMINI II)	C13011 (GEMINI III)
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	Yes
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. All patients who prematurely discontinued for any reason were to be considered as not achieving remission for the primary efficacy analysis.	Yes. All patients who prematurely discontinued for any reason were to be considered as not achieving remission for the primary efficacy analysis.

6.5 Results of the Relevant RCTS

6.5.1 Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. If there is more than one RCT, tabulate the responses.

6.5.2 The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan–Meier plots.

6.5.3 For each outcome for each included RCT, the following information should be provided.

- The unit of measurement.
- The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.
- A 95% confidence interval.

- Number of participants in each group included in each analysis and whether the analysis was by 'intention-to-treat'. State the results in absolute numbers when feasible.
- When interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.
- Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.
- Discuss and justify definitions of any clinically important differences.
- Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.

Summary of efficacy and HRQL data for Vedolizumab from the GEMINI clinical trial programme

A Phase III, multicenter, randomized, double-blind, placebo-controlled study (GEMINI II) evaluated the safety and efficacy of Vedolizumab as induction treatment in 1115 patients and as maintenance treatment in 461 patients with moderate to severe CD (William J Sandborn et al., 2013b). At Week 6, clinical remission rates were significantly higher in the patients receiving Vedolizumab (14.5%) vs patients receiving placebo (6.8%); p=0.02 (William J Sandborn et al., 2013b). There was a positive trend favouring Vedolizumab over placebo in the number of patients achieving a CDAI-100 response at Week 6 (31.4% vs 25.7%; p=0.23) (William J Sandborn et al., 2013b). In the maintenance study, significantly more Vedolizumab-treated patients in the every-8-weeks (39.0%) and every-4-weeks (36.4%) groups achieved clinical remission at Week 52 vs placebo-treated patients (21.6%; p<0.001 and p=0.004, respectively) (William J Sandborn et al., 2013b). Patients receiving Vedolizumab every 4 or 8 weeks were significantly more likely to achieve a CDAI-100 response and have a corticosteroid free remission at Week 52 compared to patients receiving placebo, although there was no significant difference between the treatment groups in the number of patients with a durable clinical remission (William J Sandborn et al., 2013b).

In GEMINI II, as rated by IBDQ, SF-36 (physical and mental components), and EQ-5D instruments, improvements in HRQL at Week 6 were greater for patients who received Vedolizumab compared to patients who received placebo (Takeda Data on File, 2012a).

In addition, a Phase III, multicenter, randomized, double-blind, placebo-controlled study (GEMINI III) evaluated the safety and efficacy of Vedolizumab as induction treatment in 416 patients with moderate to severe CD who had failed prior anti TNF therapy (Sands et al., 2014). For the primary endpoint, no statistically significant difference was observed between the Vedolizumab (15.2%) and placebo (12.1%) groups for the number of patients in clinical

remission at Week 6 in the TNF antagonist failure group (p=0.4332) (Sands B 2012). In exploratory analyses, compared to placebo Vedolizumab was associated with a higher number of patients achieving clinical remission at Week 10 (26.6% vs 12.1%, p=0.0012) and a CDAI-100 response at Week 6 (39.2% vs 22.3%; p=0.0011) in the TNF antagonist failure population, suggesting a potential treatment benefit for Vedolizumab in this population beyond the 6-week period (Sands B 2012). In the overall population, Vedolizumab-treated patients had higher rates of clinical remission at Weeks 6 and 10, sustained remission, and CDAI-100 response at Week 6 compared to placebo-treated patients (Sands et al., 2014).

In GEMINI III, improvement in IBDQ was consistently greater for patients who received Vedolizumab compared with 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 (Takeda Data on File, 2012b).

The following sections will provide detailed efficacy and HRQL outcomes from the GEMINI II and III trials. Adverse event and safety data will be provided in Section 6.9.

GEMINI II (C13007): Induction phase

A total of 368 patients were enrolled in Cohort 1 (induction phase cohort, see Figure 6.3.2.1 and included in the analysis. All randomized patients received at least 1 dose of blinded study drug and are included in the ITT population.

Primary efficacy endpoints: Clinical remission (CDAI score ≤150 points) and CDAI-100 response (enhanced clinical response, ≥100-point decrease in the CDAI score) at Week 6.

Patients treated with Vedolizumab, compared to patients treated with placebo, had significantly higher rates of clinical remission at week 6. The treatment difference from placebo was 7.8% (95% CI 1.2, 14.3; p = 0.0206). Vedolizumab induction therapy was also associated with a higher number of patients achieving a CDAI-100 response at Week 6, although this did not reach statistical significance. Table 6.5.3.1 summarizes the outcomes for the primary endpoints (William J Sandborn et al., 2013b).

In analysis of sub-groups of patients of the according to demographic characteristics and measure of disease activity in the ITT population the risk difference from placebo favoured Vedolizumab in the majority of the sub-groups, although there was greater variability and the

95% CIs for the differences from placebo often included zero in these analyses (William J Sandborn et al., 2013b).

Table 6.5.3.1: Clinical remission and enhanced clinical response at Week 6 – ITT population

	Clinical remission[a]		**Enhance clinical response[b]**	
	Placebo n=148	**Vedolizumab n=220**	**Placebo n=148**	**Vedolizumab n=220**
Number (%) achieving endpoint 95% CI	10 (6.8) (2.7, 10.8)	32 (14.5) (9.9, 19.2)	38 (25.7) (18.6, 32.7)	69 (31.4) (25.2, 37.5)
Difference from placebo[c] 95% CI for difference from placebo P-value for difference from placebo[d]		7.8 (1.2, 14.3) 0.0206		5.7 (-3.6, 15.0) 0.2322
Relative risk[e] 95% CI for relative risk		2.1 (1.1, 4.2)		1.2 (0.9, 1.7)

Abbreviations: CI = confidence interval
a Clinical remission is defined as CDAI score ≤ 150 points.
b Enhanced clinical response is defined as a □ 100-point reduction from baseline in CDAI score.
c Difference and 95% CI: adjusted percent Vedolizumab - adjusted percent placebo and its 95% CI.
d P-value is based on the CMH chi-square test, with stratification according to: 1) concomitant use of oral corticosteroids (yes/no); 2) previous exposure to TNF□ antagonists and/or concomitant immunomodulatory use (yes/no).
e Adjusted Relative Risk and its 95% CI.

Secondary efficacy endpoints:

Changes from baseline in CRP at Week 6

- Among patients in the Induction Study ITT Population, no treatment difference was observed for changes from baseline in CRP. The median change from baseline at Week 6 in CRP was -0.5 mg/L in the placebo group and -0.9 mg/L in the Vedolizumab group (William J Sandborn et al., 2013b).

Other key efficacy endpoints:

Clinical remission and enhanced response by Week 10 and 14 in induction non responders:

- Of patients who had not achieved clinical remission to Vedolizumab by Week 6 (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) (Takeda Data on File, 2012a).

Key efficacy endpoints in sub-groups

Clinical remission at week 6 in patients who were TNF-alpha antagonist naïve and patients with prior TNF-alpha antagonist failure.

- A trend was observed in patients who are TNF naïve and TNF-Failure, with a greater proportion of Vedolizumab-treated patients achieving clinical remission at Week 6 (treatment difference 8.2% and 6.2% respectively) (S. Hanauer & Feagan, 2013).

Prior immunomodulator or corticosteroid failure:

- For the endpoint of clinical remission at Week 6, the treatment benefit of Vedolizumab over placebo was maintained in patients with prior corticosteroid failure. A trend favouring Vedolizumab was observed in patients with prior immunomodulatory failure (S. Hanauer & Feagan, 2013).

Concomitant therapy use at baseline:

- In general, analyses of clinical remission in sub-groups of patients according to baseline concomitant corticosteroid or immunomodulator use showed trends that were supportive of the primary efficacy analysis population as a whole (S. Hanauer & Feagan, 2013).

HRQL outcomes

Changes from week 6 HRQL outcomes are summarized by treatment group in Table 6.5.3.2 (Takeda Data on File, 2012a).

IBDQ

- An increase of ≥ 16 points in the IBDQ Total score, ≥ 5 in IBDQ Bowel Function domain scores, ≥ 6 in IBDQ Emotional Function domain scores, or ≥ 2.5 in IBDQ Systemic and Social Function domain scores, represents clinically meaningful improvements in HRQL for patients. At Week 6, patients treated with Vedolizumab reported higher scores on all IBDQ domain scales and the Total score compared to the placebo group. Although the 95% CIs for differences from baseline to Week 6 included zero for most scales, except for Bowel Function, the increases in all IBDQ domain scale scores and IBDQ Total score were considered to be clinically meaningful improvements.

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 HRQL for patients. At Week 6, higher scores were observed for Vedolizumab patients on SF-36 Physical and Mental Component Summary scores and all SF-36 scales except for physical functioning scale compared to the placebo group. Additionally, for the Role-physical, Bodily Pain and Social Functioning scales, the 95% CI of differences from baseline to Week 6 excluded zero.

EQ-5D and EQ-5D VAS

- A decrease of ≥ 0.3 points in the EQ-5D score represents a clinically meaningful improvement in HRQL for patients. An increase of ≥ 7 points in the EQ-5D VAS score represents a clinically meaningful improvement in HRQL for patients. At Week 6, compared to placebo, patients receiving Vedolizumab had greater improvements in HRQL as measured by EQ-5D and EQ-5D VAS scores; however, the 95% CIs in the difference of scores between the 2 groups included 0. The decrease in the EQ-5D score was clinically meaningful in both groups.

Table 6.5.3.2: Overall observed changes in HRQL from baseline to Week 6 in GEMINI II

	Placebo	Vedolizumab
IBDQ Total Score[a]	**n=146**	**n=212**
Adjusted mean (SE) change from baseline (95% CI)[b]	16.5 (2.75) (11.1 to 21.9)	23.1 (2.28) (18.6 to 27.6)
Difference in adjusted change from baseline vs placebo, mean (SE) (95% CI)[c]	---	6.5 (3.58) (–0.5 to 13.6)
SF-36 Physical Component Summary[a]	**n=144**	**n=211**
Adjusted mean (SE) change from baseline (95% CI)[b]	2.4 (0.56) (1.3 to 3.6)	3.5 (0.47) (2.6 to 4.4)
Difference in adjusted change from baseline vs placebo, mean (95% CI)[c]	---	1.0 (0.73) (–0.4 to 2.5)
SF-36 Mental Component Summary[a]	**n=144**	**n=211**
Adjusted mean change from baseline (95% CI)[b]	2.4 (0.86) (0.8 to 4.1)	4.6 (0.71) (3.2 to 6.0)
Difference in adjusted change from baseline vs placebo, mean (SE) (95% CI)[c]	---	2.2 (1.11) (0.0 to 4.4)
EQ-5D Score[a]	**n=146**	**n=211**
Adjusted mean change from baseline (95% CI)[b]	–0.3 (–0.5 to –0.0)	–0.5 (–0.7 to –0.3)
Difference in adjusted change from baseline vs placebo, mean (95% CI)[c]		–0.2 (–0.5 to 0.1)
EQ-5D VAS Score[a]	**n=146**	**n=208**
Adjusted mean (SE) change from baseline (95% CI)[b]	5.4 (1.65) (2.2 to 8.7)	6.9 (1.38) (4.2 to 9.6)
Difference in adjusted change from baseline vs placebo, mean (95% CI)[c]	---	1.5 (2.15) (–2.8 to 5.7)

Abbreviations: CI=confidence interval; EQ=EuroQol; HRQL=health-related quality of life; IBDQ=Inflammatory Bowel Disease Questionnaire; SF-36=Short Form-36; VAS=visual analog scale.
a Higher IBDQ, SF-36, and EQ-5D VAS scores indicate improvements in HRQL; lower EQ-5D scores indicate improvements in HRQL.
b Mean changes were adjusted within the ANCOVA model with factors for treatment and baseline measurement.
c Difference = adjusted mean change for Vedolizumab – adjusted mean change for placebo.

HRQL outcomes in TNF naïve and prior anti-TNF-Failure sub-groups

A comparison of the differences in adjusted mean HRQL scores in the induction phase from baseline by those patients who has a prior anti-TNF-Failure and patients had not previously failed on anti-TNF therapies is shown in Table 6.5.3.3. A significant higher improvement in IBDQ score was seen for patients who had not previously failed on anti-TNF therapies compared to patients who did previous fail on these therapies (Takeda Data on File, 2012a).

Table 6.5.3.3: Observed changes in HRQL in TNF naïve and TNF-Failure from baseline to Week 6 in GEMINI II

	PRIOR Anti-TNF-Failure		No PRIOR Failure	
	Placebo	**Vedolizumab**	**Placebo**	**Vedolizumab**
IBDQ Total Score[a]	n=69	n=104	n=77	n=108
Adjusted Mean (SE) change from baseline (95% CI)[b]	13.0 (3.65) (5.8, 20.2)	15.3 (2.97) (9.4, 21.2)	19.6 (3.94) (11.8, 27.4)	30.6 (3.33) (24.1, 37.2)
Difference in adjusted change from baseline vs placebo, Mean (SE) (95% CI)[c]		2.3 (4.72) (-7.0, 11.6)		**11.0 (5.18)* (0.8, 21.3)**
Physical Component Summary	n= 67	n= 103	n= 77	n= 108
Adjusted Mean (SE) change from baseline (95% CI)[b]	1.6 (0.83) (-0.1, 3.2)	3.0 (0.67) (1.7, 4.3)	3.1 (0.76) (1.6, 4.6)	3.9 (0.64) (2.7, 5.2)
Difference in adjusted change from baseline vs placebo, Mean (SE) (95% CI)c		1.4 (1.07) (-0.7, 3.5)		0.8 (1.00) (-1.2, 2.8)
Mental Component Summary	n= 67	n= 103	n= 77	n= 108
Adjusted Mean (SE) change from baseline (95% CI)[b]	1.2 (1.22) (-1.2, 3.6)	2.4 (0.98) (0.4, 4.3)	3.6 (1.19) (1.3, 6.0)	6.7 (1.00) (4.7, 8.7)
Difference in adjusted change from baseline vs placebo, Mean (SE) (95% CI)[c]		1.2 (1.57) (-1.9, 4.3)		3.1 (1.56) (0.0, 6.2)
EQ-5D VAS Score	n= 69	n= 100	n= 77	n= 108
Adjusted Mean (SE) change from baseline (95% CI)[b]	1.7 (2.48) (-3.2, 6.6)	2.7 (2.06) (-1.3, 6.8)	8.4 (2.06) (4.3, 12.4)	11.0 (1.74) (7.6, 14.4)
Difference in adjusted change from baseline vs placebo, Mean (SE) (95% CI)[c]		1.0 (3.22) (-5.3, 7.4)		2.6 (2.71) (-2.7, 8.0)

Abbreviations: SE = Standard Error; CI=confidence interval; EQ=EuroQol; HRQL=health-related quality of life; IBDQ=Inflammatory Bowel Disease Questionnaire; SF-36=Short Form-36; VAS=visual analog scale.
a Higher IBDQ, SF-36, and EQ-5D VAS scores indicate improvements in HRQL; lower EQ-5D scores indicate improvements in HRQL.
b Mean changes were adjusted for individual baseline measurements.
c Difference = adjusted mean change for Vedolizumab – adjusted mean change for placebo.
*** denotes statistically significant results.**

GEMINI II (C13007): Maintenance phase

The Maintenance Study ITT Population includes Vedolizumab-treated patients who had a clinical response at Week 6; at the start of the Maintenance Phase, these patients were randomized to 1 of 2 Vedolizumab IV dosing regimens (300 mg Q4W or Q8W, n=154 each) or

placebo (n=153). The data presented here is for the ITT population (William J Sandborn et al., 2013b; Takeda Data on File, 2012b).

The non-ITT population consists of patients who received placebo in the induction phase who remained on placebo for the maintenance phase and non responders to Vedolizumab by week 6. Patients were responders if they achieved a clinical response (a ≥ 70 point decrease in CDAI score from baseline). The non-ITT population has been included in the safety assessment (See Section 8.9).

Primary efficacy endpoints: Clinical remission (CDAI score ≤150 points) at Week 52

Patients treated with Vedolizumab Q8W and Q4W, compared to patients treated with placebo, had significantly higher rates of clinical remission at week 52. The treatment difference from placebo was 17.4% (95% CI 7.3, 27.5; p = 0.0007) and 14.7% (95% CI 4.6, 24.7; p = 0.0042) respectively. Table 6.5.3.4 summarizes the outcomes for the primary endpoints (William J Sandborn et al., 2013b).

In analysis of sub-groups of patients of the according to demographic characteristics and measure of disease activity in the ITT population the risk difference from placebo favoured Vedolizumab in the majority of the sub-groups, although not all of the treatment difference 95% CIs excluded zero (William J Sandborn et al., 2013b).

Table 6.5.3.4: Clinical remission at Week 52 – ITT population

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

Abbreviations: 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 P-value is based on the CMH chi-square test, with stratification according to: 1) concomitant use of oral corticosteroids (yes/no); 2) previous exposure to TNF antagonists and/or concomitant immunomodulatory use (yes/no).
d Adjusted Relative Risk and its 95% CI.

Key secondary efficacy endpoints

Patients receiving Vedolizumab every 4 or 8 weeks were significantly more likely to achieve a CDAI-100 response and have a corticosteroid free remission at Week 52 compared to patients receiving placebo (See Table 6.5.3.5). In contrast, the number of patients with a durable clinical remission did not differ significantly between the study groups due to baseline differences at re-randomization (See Table 6.5.3.5, (William J Sandborn et al., 2013b)).

Key efficacy endpoints in sub-groups

Clinical remission rates were greater for patients treated with Vedolizumab than those who treated with placebo, regardless of prior exposure to TNF antagonists (Table 6.5.3.6) Similar improvements with Vedolizumab vs placebo were found in the enhanced clinical response (CDAI-100 responses), and corticosteroid-free clinical remissions at Week 52 in all sub-groups. Although a higher number of patients achieved clinical remission with Vedolizumab in the immunomodulator and corticosteroid failure sub-groups than the TNF antagonist failure subgroup, the treatment differences between placebo and Vedolizumab were generally similar among all sub-groups (S. Hanauer & Feagan, 2013).

Table 6.5.3.5: Enhanced clinical response, corticosteroid free remission, and durable clinical remission at Week 52 – ITT population

	Enhanced clinical response[a]			Corticosteroid-free Clinical Remission[b]			Durable Clinical Remission[c]		
	Placebo	**VDZ Q8W**	**VDZ Q4W**	**Placebo**	**VDZ Q8W**	**VDZ Q4W**	**Placebo**	**VDZ Q8W**	**VDZ Q4W**
	n=153	**n=154**	**n=154**	**n=82**	**n=82**	**n=80**	**n=153**	**n=154**	**n=154**
Number (%)	46 (30.1)	67 (43.5)	70 (45.5)	13 (15.9)	26 (31.7)	23 (28.8)	22 (14.4)	33 (21.4)	25 (16.2)
95% CI	(22.8, 37.3)	(35.7, 51.3)	(37.6, 53.3)	(7.9, 23.8)	(21.6, 41.8)	(18.8, 38.7)	(8.8, 19.9)	(14.9, 27.9)	(10.4, 22.1)
Difference from placebo[d]		13.4	15.3		15.9	12.9		7.2	2.0
95% CI		(2.8, 24.0)	(4.6, 26.0)		(3.0, 28.7)	(0.3, 25.5)		(-1.5, 16.0)	(-6.3, 10.2)
P-value[e]		0.0132	0.0053		0.0154	0.0450		0.1036	0.6413
Relative risk[f]		1.4	1.5		2.0	1.8		1.5	1.1
95% CI		(1.1, 1.9)	(1.1, 2.0)		(1.1, 3.6)	(1.0, 3.3)		(0.9, 2.4)	(0.7, 1.9)

Abbreviations: CI = confidence interval VDZ, Vedolizumab
a Enhanced clinical response is defined as a ≥100-point reduction in CDAI score from baseline.
b 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.
C Durable clinical remission is defined as CDAI score ≤ 150 points at ≥ 80% of study visits including final visit (Week 52).
d Difference and 95% CI: adjusted percent Vedolizumab - adjusted percent placebo and its 95% CI.
e P-value is based on the CMH chi-square test, with stratification according to: 1) concomitant use of oral corticosteroids (yes/no); 2) previous exposure to TNF antagonists and/or concomitant immunomodulatory use (yes/no).
f Adjusted Relative Risk and its 95% CI.

Table 6.5.3.6: Results at Week 52 by prior TNF antagonist status

Study Endpoint	Patients With Prior TNF Antagonist Failure[a]				
	Vedolizumab Every 8 Wks (n=82)	Vedolizumab Every 4 Wks (n=77)	Placebo (n=78)	Between Group Difference (95% CI)	
				Every 8 Wks vs Placebo	Every 4 Wks vs Placebo
Clinical Remission (%)	28.0	27.3	12.8	15.2 (3.0 to 27.5)	14.5 (2.0 to 26.9)
CDAI-100 Response (%)	29.3	37.7	20.5	8.8 (-4.6 to 22.1)	17.1 (3.1 to 31.2)
	Patients Without TNF Antagonist Exposure[b]				
	Vedolizumab Every 8 Wks (n=66)	Vedolizumab Every 4 Wks (n=71)	Placebo (n=71)	Between Group Difference (95% CI)	
				Every 8 Wks vs Placebo	Every 4 Wks vs Placebo
Clinical Remission (%)	51.5	46.5	26.8	24.8 (8.9 to 40.6)	19.7 (4.2 to 35.2)
CDAI-100 Response (%)	60.6	53.5	38.0	22.6 (6.3 to 38.9)	15.5 (-0.7 to 31.7)

CDAI=Crohn's Disease Activity Index; CI=confidence interval; TNF=tumour necrosis factor; Wks=weeks
a Treatment failure (inadequate response, loss of response, or intolerance) defined as follows: inadequate response to TNF antagonist=persistently active disease despite induction treatment with specified agents; loss of response to TNF antagonist=recurrence of symptoms during maintenance dosing following prior clinical benefit; intolerance=occurrence of treatment-related protocol-defined toxicities.
b Patients without prior exposure to TNF antagonist therapy (ie, TNF antagonist-naïve patients)

Other key efficacy endpoints

- In the Vedolizumab-treated patients, the CDAI score decreased steadily until Week 52, whereas the CDAI score stabilized starting at Week 26 in the placebo group (P. J. Rutgeerts et al., 2013)
- By Week 52, the median corticosteroid dose decreased from Week 6 by 27.8% in the placebo group vs 66.2% in the Vedolizumab every 8 weeks group (p=0.0381 vs placebo) and 69.4% in the Vedolizumab every 4 weeks group (p=0.1114 vs placebo) (P. J. Rutgeerts et al., 2013).
- A post hoc analysis demonstrated that in patients with elevated CRP levels at baseline, the levels returned to normal (≤2.87 mg/L) by Week 52 in a greater proportion of Vedolizumab-treated patients than of placebo-treated patients (William J Sandborn et al., 2013b).

- At Weeks 6 and 52, patients receiving Vedolizumab reported higher scores on all IBDQ domain scales and the total score compared to patients receiving placebo (Takeda Data on File, 2012a).

Although only a small number of patients had a draining fistula at baseline (placebo – 18; Vedolizumab every 8 weeks – 17; Vedolizumab every 4 weeks – 22), positive trends were seen for the proportions of patients in the Vedolizumab groups (46.7% for every 8 weeks and 23.8% for every 4 weeks) who achieved fistula closure compared to the placebo group (11.1%) (Takeda Data on File, 2012a).

HRQL outcomes

IBDQ

Maintenance therapy with Vedolizumab either every 4 weeks or every 8 weeks resulted in higher scores on all IBDQ domain scales and higher IBDQ total score (Table 6.5.3.7) from baseline to week 52 compared to placebo, with the increases considered clinically meaningful (Takeda Data on File 2012a). There were no major differences between Vedolizumab and placebo in the improvements in the total IBDQ scores at Week 30.

An increase of ≥ 16 points in the IBDQ Total score, ≥ 5 in IBDQ Bowel Function domain scores, ≥ 6 in IBDQ Emotional Function domain scores, or ≥ 2.5 in IBDQ Systemic and Social Function domain scores, represents clinically meaningful improvements in HRQL for patients.

Table 6.5.3.7: IBDQ changes from baseline by study visit in GEMINI II maintenance therapy

	Placebo	**Vedolizumab Every 4 Weeks**	**Vedolizumab Every 8 Weeks**
Week 30 IBDQ[a]	n=121	n=126	n=120
Adjusted mean change from baseline (95% CI)[b]	38.6 (32.7 to 44.5)	40.3 (34.6 to 46.1)	40.4 (34.5 to 46.3)
Difference in adjusted change from baseline vs placebo, mean (95% CI)[c]	---	1.7 (–6.5 to 10.0)	1.8 (–6.6 to 10.1)
Week 52 IBDQ[a]	n=82	n=92	n=79
Adjusted mean change from baseline (95% CI)[b]	35.5 (28.0 to 43.0)	46.1 (39.1 to 53.2)	50.7 (43.0 to 58.3)
Difference in adjusted change from baseline vs placebo, mean (95% CI)[c]	---	10.6 (0.3 to 21.0)	15.1 (4.4 to 25.9)

Abbreviations: CI=confidence interval; IBDQ=Inflammatory Bowel Disease Questionnaire;
a Higher IBDQ scores indicate less severe disease.
b Mean changes were adjusted for individual baseline measurements.
c Difference = adjusted mean change for Vedolizumab – adjusted mean change for placebo.

SF-36

Although there were no major differences between Vedolizumab and placebo in the SF-36 assessments at Week 30, by Week 52, both Vedolizumab regimens resulted in higher scores on all SF-36 scales and the physical and mental component summary scores compared to the placebo group (Table 6.5.3.8). For Vedolizumab every 8 weeks, the 95% CI of the differences from baseline to Week 52 excluded zero for all scales, except the mental component summary score and the Mental Health scale. For Vedolizumab every 4 weeks, the 95% CI of the differences from baseline to Week 52 excluded zero for the Role-Emotional, General Health, Bodily pain, Physical functioning scales and the physical component summary score (Takeda Data on File, 2012a).

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

Table 6.5.3.8: SF-36 changes from baseline by study visit in GEMINI II maintenance therapy

	Placebo	Vedolizumab Every 4 Weeks	Vedolizumab Every 8 Weeks
Week 30 Physical Component Summary	n=121	n=125	n=120
Adjusted mean change from baseline (95% CI)[b]	6.6 (5.5 to 7.9)	7.6 (6.3 to 8.9)	6.4 (5.1 to 7.8)
Difference in adjusted change from baseline vs placebo, mean (95% CI)[c]	---	1.0 (–0.9 to 3.0)	–0.1 (–2.1 to 1.8)
Week 52 Physical Component Summary	n=82	n=91	n=79
Adjusted mean change from baseline (95% CI)[b]	5.9 (4.2 to 7.6)	8.7 (7.1 to 10.3)	9.4 (7.7 to 11.1)
Difference in adjusted change from baseline vs placebo, mean (95% CI)[c]	---	2.8 (0.5 to 5.2)	3.5 (1.1 to 5.9)
Week 30 Mental Component Summary	n=121	n=125	n=120
Adjusted mean change from baseline (95% CI)[b]	8.2 (6.4 to 10.0)	7.6 (5.8 to 9.3)	9.6 (7.8 to 11.5)
Difference in adjusted change from baseline vs placebo, mean (95% CI)[c]	---	–0.6 (–3.2 to 1.9)	1.5 (–1.1 to 4.0)
Week 52 Mental Component Summary	n=82	n=91	n=79
Adjusted mean change from baseline (95% CI)[b]	7.8 (5.5 to 10.0)	10.0 (7.9 to 12.2)	10.7 (8.4 to 13.0)
Difference in adjusted change from baseline vs placebo, mean (95% CI)[c]	---	2.3 (–0.8 to 5.4)	3.0 (–0.3 to 6.2)

Abbreviations: CI=confidence interval; LOCF=last observation carried forward; SF-36=Short Form-36.
a Higher SF-36 scores indicate less improvement in HRQL.
b Mean changes were adjusted for individual baseline measurements.
c Difference = adjusted mean change for Vedolizumab – adjusted mean change for placebo.

EQ-5D and EQ-5D VAS

Both Vedolizumab maintenance treatment regimens resulted in greater improvements in the EQ-5D score and EQ-5D VAS score from baseline to Week 52 compared to placebo, with the improvements in all groups considered clinically meaningful (Table 6.5.3.9). From baseline to Week 30, the 95% CIs for the differences in the EQ-5D scores and EQ-5D VAS scores between Vedolizumab and placebo included zero (Takeda Data on File, 2012a).

A decrease of ≥ 0.3 points in the EQ-5D score represents a clinically meaningful improvement in HRQL for patients. An increase of ≥ 7 points in the EQ-5D VAS score represents a clinically meaningful improvement in HRQL for patients.

Table 6.5.3.9: EQ-5D and EQ-5D VAS SF-36 changes from baseline by study visit in GEMINI II maintenance therapy

	Placebo	Vedolizumab Every 4 Weeks	Vedolizumab Every 8 Weeks
Week 30 EQ-5D Score	n=121	n=126	n=120
Adjusted mean change from baseline (95% CI)[b]	–1.1 (–1.4 to –0.9)	–1.1 (–1.3 to –0.8)	–1.0 (–1.3 to –0.8)
Difference in adjusted change from baseline vs placebo, mean (95% CI)[c]		–0.0 (–0.3 to 0.4)	0.1 (–0.3 to 0.4)
Week 52 EQ-5D Score	n=81	n=92	n=79
Adjusted mean change from baseline (95% CI)[b]	–1.0 (–1.3 to –0.7)	–1.4 (–1.7 to –1.1)	–1.5 (–1.8 to –1.2)
Difference in adjusted change from baseline vs placebo, mean (95% CI)[c]		–0.4 (–0.8 to 0.0)	–0.5 (–0.9 to –0.1)
Week 30 EQ-5D VAS Score	n=119	n=125	n=120
Adjusted mean change from baseline (95% CI)[b]	16.9 (13.7 to 20.1)	19.9 (16.8 to 23.1)	18.0 (14.8 to 21.2)
Difference in adjusted change from baseline vs placebo, mean (95% CI)[c]		3.1 (–1.4 to 7.5)	1.1 (–3.4 to 5.6)
Week 52 EQ-5D VAS Score	n=81	n=89	n=79
Adjusted mean change from baseline (95% CI)[b]	14.2 (10.4 to 18.0)	24.2 (20.6 to 27.8)	26.6 (22.8 to 30.4)
Difference in adjusted change from baseline vs placebo, mean (95% CI)[c]		10.0 (4.8 to 15.2)	12.4 (7.0 to 17.8)

Abbreviations: CI=confidence interval; EQ=EuroQoL; LOCF=last observation carried forward.
a Lower EQ-5D scores and higher EQ-5D VAS scores indicate less severe disease.
b Mean changes were adjusted for individual baseline measurements.
c Difference = adjusted mean change for Vedolizumab – adjusted mean change for placebo.

Clinical meaningful improvement in HRQL

A higher proportion of Vedolizumab-treated patients compared to placebo patients had clinically meaningful improvements in some HRQL endpoints at Week 52 (Table 6.5.3.10, (Takeda Data on File, 2012a)).

Table 6.5.3.10: Proportion of patients with clinically meaningful improvement difference from baseline compared to placebo at Week 52 (GEMINI II)

	Placebo	Vedolizumab Q8W	Vedolizumab Q4W
IBDQ Total Score	n=82	n=79	n=92
Number (%) Achieving Clinically Meaningful Improvement	54(65.9)	59(74.7)	73(79.3)
95% CI	(55.6 to 76.1)	(65.1 to 84.3)	(71. to 87.6)
Difference from Placebo	---	8.8	**13.5***
95% CI for Difference from Placebo	---	(-5.2, 22.9)	(0.3, 26.7)
P-value for Difference from Placebo	---	0.2222	0.0460
SF 36 Physical Component Summary	n=82	n=79	n=91
Number (%)Achieving Clinically Meaningful Improvement	46(56.1)	57(72.2)	56 (61.5)
95% CI	(45.4 to 66.8)	(62.3 to 82.0)	(51.5 to 71.5)
Difference from Placebo	---	**16.1***	5.4
95% CI for Difference from Placebo	---	(1.5 to 30.7)	(-9.2 to 20.1)
P-value for Difference from Placebo	---	0.0345	0.4689
SF-36 Mental Component Summary	n=82	n=79	n=91
Number (%)Achieving Clinically Meaningful Improvement	44(53.7)	52(65.8)	55(60.4)
95% CI	(42.9 to 64.5)	(55.4 to 76.3)	(50.4 to 70.5)
Difference from Placebo	---	12.2	6.8
95% CI for Difference from Placebo	---	(-2.9 to 27.2)	(-8.0 to 21.5)
P-value for Difference from Placebo	---	0.1169	0.3694
EQ-5D VAS Score	n=81	n=79	n=89
Number (%)Achieving Clinically Meaningful Improvement	53(65.4)	62(78.5)	71(79.8)
95% CI	(55.1 to 75.8)	(69.4 to 87.5)	(71.4 to 88.1)
Difference from Placebo	---	13.0	**14.3***
95% CI for Difference from Placebo	---	(-0.7 to 26.8)	(1.0 to 27.6)
P-value for Difference from Placebo	---	0.0673	0.0361

Abbreviations: SE = Standard Error; CI=confidence interval; EQ=EuroQol; HRQL=health-related quality of life; IBDQ=Inflammatory Bowel Disease Questionnaire; SF-36=Short Form-36; VAS=visual analog scale.
a Higher IBDQ, SF-36, and EQ-5D VAS scores indicate improvements in HRQL; lower EQ-5D scores indicate improvements in HRQL.
b Mean changes were adjusted for individual baseline measurements.
c Difference = adjusted mean change for Vedolizumab – adjusted mean change for placebo.
* denotes statistically significant results.

GEMINI III (C13011)

A total of 416 patients were enrolled and included in the analysis of which 76% (315 patients) had previous failure of at least one TNF antagonist. All randomized patients received at least 1 dose of blinded study drug and are included in the ITT population.

Primary efficacy endpoints: Clinical remission (CDAI score ≤150 points) at Week 6 for the TNF antagonist failure population

There was no statistically significant difference between Vedolizumab and placebo in the primary endpoint of the proportion of patients achieving clinical remission at week 6 in the TNF antagonist failure population (Table 6.5.3.11); therefore, statistical evaluation of the secondary endpoints is considered exploratory (Sands et al., 2014). Nominal P values, relative risks, and 95% CIs are presented for descriptive purposes to fully characterize the effect of Vedolizumab induction treatment in this population.

Secondary efficacy endpoints:

- *Clinical remission at week 10, enhanced clinical response at week 6 and 10 and sustained remission in the TNF antagonist failure population*
- *Clinical remission and enhanced clinical response at week 6 and 10 and sustained remission in the overall population*

As shown in Table 6.5.3.11, compared to placebo, Vedolizumab was associated with a higher number of patients achieving clinical remission at week 10 and an enhanced clinical response (CDAI-100 response) at week 6 and 10 in the TNF antagonist failure population. These results suggest that a potential treatment benefit for Vedolizumab in the TNF antagonist failure population may be achieved beyond the 6-week period used to evaluate the primary endpoint in this study (Takeda Data on File, 2012b). In the overall population, Vedolizumab-treated patients had higher rates of clinical remission, and enhanced clinical response (CDAI-100) response at weeks 6 and 10 and sustained remission compared to placebo-treated patients (Table 6.5.3.12).

Table 6.5.3.11: Efficacy outcomes in TNF antagonist failure population in GEMINI III – ITT population

	Clinical remission[a]				Enhance clinical response[b]				Sustained Remission[c]	
	Week 6		Week 10		Week 6		Week 10			
	Placebo n=157	**VDZ n=158**	**Placebo n=157**	**VDZ n=158**	**Placebo n=157**	**VDZ n=158**	**Placebo n=157**	**VDZ n=158**	**Placebo n=157**	**VDZ n=158**
Number (%)	19 (12.1)	24 (15.2)	9 (12.1)	42 (26.6)	35 (22.3)	62 (39.2)	39 (24.8)	74 (46.8)	13 (8.3)	19 (12.0)
95% CI	(7.0, 17.2)	(9.6, 20.8)	(7.0, 17.2)	(19.7, 33.5)	(15.8, 28.8)	(31.6, 46.9)	(18.1, 31.6)	(39.1, 54.6)	(4.0, 12.6)	(7.0, 17.1)
Difference from placebo[d]		3.0		14.4		16.9		22		3.7
95% CI		(-4.5, 10.5)		(5.7, 23.1)		(6.7, 27.1)		(11.4, 32.6)		(-2.9, 10.3)
P-value[e]		0.433		0.0012		n/a		n/a		0.2755
Relative risk[f]		1.2		2.2		1.8		1.9		1.4
95% CI		(0.7, 2.2)		(1.3, 3.6)		(1.2, 2.5)		(1.4, 2.6)		(0.7, 2.8)

Abbreviations: CI = confidence interval; n/a, not available; TNF=tumour necrosis factor; VDZ, Vedolizumab
a Clinical remission is defined as CDAI score ≤ 150 points.
b Sustained remission is defined as CDAI score ≤ 150 points at both Week 6 and Week 10
c Enhanced clinical response is defined as a ≥100-point reduction in CDAI score from baseline.
d Difference and 95% CI: adjusted percent Vedolizumab - adjusted percent placebo and its 95% CI.
e P-value is based on the CMH chi-square test, with stratification according to: 1) concomitant use of oral corticosteroids (yes/no); 2) previous exposure to TNF antagonists and/or concomitant immunomodulatory use (yes/no).
f Adjusted Relative Risk and its 95% CI.

Table 6.5.3.12: Efficacy outcomes in overall population in GEMINI III – ITT population

	Clinical remission[a]				Enhance clinical response[b]				Sustained Remission[c]	
	Week 6		Week 10		Week 6		Week 10			
	Placebo n=207	VDZ n=209	Placebo n=207	VDZ n=209	Placebo n=207	VDZ n=209	Placebo n=207	VDZ n=209	Placebo n=207	VDZ n=209
Number (%)	25 (12.1)	40 (19.1)	27 (13.0)	60 (28.7)	47 (22.7)	82 (39.2)	50 (24.2)	100 (47.8)	17 (8.2)	32 (15.3)
95% CI	(7.6, 16.5)	(13.8, 24.5)	(8.5, 17.6)	(22.6, 34.8)	(17.0, 28.4)	(32.6, 45.9)	(18.3, 30.0)	(41.1, 54.6)	(4.5, 12.0)	(10.4, 20.2)
Difference from placebo[d]		6.9		15.5		16.4		23.7		7.0
95% CI		(0.1, 13.8)		(7.8, 23.3)		(7.7, 25.2)		(14.5, 32.9)		(0.9, 13.1)
P-value[e]		0.0478		< 0.0001		n/a		n/a		0.0249
Relative risk[f]		1.6		2.2		1.7		2.0		1.9
95% CI		(1.0, 2.5)		(1.4, 3.3)		(1.3, 2.3)		(1.5, 2.6)		(1.1, 3.2)

Abbreviations: CI = confidence interval; n/a not available; TNF=tumour necrosis factor; VDZ, Vedolizumab
a Clinical remission is defined as CDAI score ≤ 150 points.
b Sustained remission is defined as CDAI score ≤ 150 points at both Week 6 and Week 10
c Enhanced clinical response is defined as a ≥100-point reduction in CDAI score from baseline.
d Difference and 95% CI: adjusted percent Vedolizumab - adjusted percent placebo and its 95% CI.
e P-value is based on the CMH chi-square test, with stratification according to: 1) concomitant use of oral corticosteroids (yes/no); 2) previous exposure to TNF antagonists and/or concomitant immunomodulatory use (yes/no).
f Adjusted Relative Risk and its 95% CI.

Key efficacy endpoints in sub-groups

Key efficacy endpoints in the TNF naïve population

- Proportions of patients were greater with Vedolizumab than with placebo for the following outcomes: clinical remission at week 6 (Vedolizumab, 31.4%; placebo, 12.0%; P=0.012; relative risk, 2.6 [95% CI: 1.1, 6.2]); remission at week 10 (Vedolizumab, 35.3%; placebo, 16.0%; P=0.025; relative risk, 2.2 [95% CI: 1.1, 4.6]); remission at both weeks 6 and 10 (Vedolizumab, 25.5%; placebo, 8.0%; P=0.018; relative risk, 3.2 [95% CI: 1.1, 9.1]); CDAI-100 response at week 6 (Vedolizumab, 39.2%; placebo, 24.0%; P=0.088; relative risk, 1.6 [95% CI: 0.9, 2.9]); and CDAI-100 response at week 10 (Vedolizumab, 51.0%; placebo, 22.0%; P=0.002; relative risk, 2.3 [95% CI: 1.3, 4.2]).

C-reactive protein and faecal calprotectin concentrations

- Among patients in the TNF antagonist failure and overall populations with elevated baseline CRP levels, median changes in CRP concentration were modestly improved from baseline to Weeks 6 and 10; these improvements were more pronounced at Week 10 than at Week 6

HRQL outcomes

Changes from week 6 and 10 HRQL outcomes are summarized by treatment group in Table 6.5.3.13, 6.5.3.14, and 6.5.3.15 (Takeda Data on File, 2012b).

IBDQ

An increase of ≥ 16 points in the IBDQ Total score, ≥ 5 in IBDQ Bowel Function domain scores, ≥ 6 in IBDQ Emotional Function domain scores, or ≥ 2.5 in IBDQ Systemic and Social Function domain scores, represents clinically meaningful improvements in HRQL for patients.

Patients receiving induction therapy with Vedolizumab in both the TNF antagonist failure sub-population and the overall 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 6.5.3.13). The improvements in HRQL in the Vedolizumab groups were considered to be clinically meaningful improvements (Takeda Data on File, 2012b).

Table 6.5.3.13: Overall observed changes in IBDQ score from baseline to Week 6 and 10 in GEMINI III

	TNF Antagonist Failure Population		Overall Population	
IBDQ Total Score[a]	**Placebo**	**Vedolizumab**	**Placebo**	**Vedolizumab**
Week 6	n=150	n=154	n=198	n=202
Adjusted mean change from baseline (95% CI)[b]	14.6 (9.7 to 19.4)	24.0 (19.2 to 28.7)	14.9 (10.7 to 19.2)	24.1 (19.8 to 28.3)
Difference in adjusted change from baseline vs placebo, mean (95% CI)[c]		9.4 (2.6 to 16.2)		9.1 (3.1 to 15.1)
Week 10	n=144	n=152	n=192	n=197
Adjusted mean change from baseline (95% CI)[b]	15.4 (10.2 to 20.6)	28.3 (23.3 to 33.3)	15.0 (10.5 to 19.5)	28.6 (24.2 to 33.1)
Difference in adjusted change from baseline vs placebo, mean (95% CI)[c]		12.9 (5.7 to 20.1)		13.6 (7.3 to 19.9)

Abbreviations: CI=confidence interval; HRQL=health-related quality of life; IBDQ=Inflammatory Bowel Disease Questionnaire.
a Higher IBDQ scores indicate improvements in HRQL.
b Mean changes were adjusted within the ANCOVA model with factors for treatment and baseline measurement.
c Difference = adjusted mean change for Vedolizumab – adjusted mean change for placebo.

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 HRQL for patients.

For both the TNF antagonist failure sub-population and the overall population, although the Vedolizumab treatment groups achieved greater increases in the Week 6 and Week 10 SF-36 physical and mental component summary scores compared to the placebo group, the 95% CIs for the treatment differences included 0 except for the Week 10 SF-36 mental component summary score (Table 6.5.3.14, (Takeda Data on File, 2012b)).

Table 6.5.3.14: Overall observed changes in SF-36 scores from baseline to Week 6 and 10 in GEMINI III

	TNF Antagonist Failure Population		Overall Population	
SF-36 Summary Scores[a]	**Placebo**	**Vedolizumab**	**Placebo**	**Vedolizumab**
Week 6 Physical Component Summary Score	n=150	n=154	n=198	n=202
Adjusted mean change from baseline (95% CI)[b]	2.2 (1.2 to 3.3)	3.3 (2.3 to 4.3)	2.2 (1.3 to 3.2)	3.3 (2.4 to 4.3)
Difference in adjusted change from baseline vs placebo, mean (95% CI)[c]		1.1 (–0.4 to 2.5)		1.1 (–0.2 to 2.4)
Week 6 Mental Component Summary Score	n=150	n=154	n=198	n=202
Adjusted mean change from baseline (95% CI)[b]	3.0 (1.5 to 4.6)	4.1 (2.6 to 5.7)	3.3 (2.0 to 4.7)	3.9 (2.6 to 5.3)
Difference in adjusted change from baseline vs placebo, mean (95% CI)[c]		1.1 (–1.1 to 3.3)		0.6 (–1.3 to 2.6)
Week 10 Physical Component Summary Score	n=144	n=152	n=192	n=197
Adjusted mean change from baseline (95% CI)[b]	3.4 (2.2 to 4.5)	4.6 (3.5 to 5.7)	3.3 (2.3 to 4.3)	4.7 (3.7 to 5.7)
Difference in adjusted change from baseline vs placebo, mean (95% CI)[c]		1.2 (–0.4 to 2.8)		1.5 (0.0 to 2.9)
Week 10 Mental Component Summary Score	n=144	n=152	n=192	n=197
Adjusted mean change from baseline (95% CI)[b]	1.7 (0.1 to 3.4)	5.3 (3.7 to 6.9)	1.6 (0.2 to 3.1)	5.3 (3.8 to 6.7)
Difference in adjusted change from baseline vs placebo, mean (95% CI)[c]		3.5 (1.2 to 5.8)		3.6 (1.6 to 5.7)

Abbreviations: CI=confidence interval; HRQL=health-related quality of life; SF-36=Short Form-36.
a Higher SF-36 scores indicate improvements in HRQL.
b Mean changes were adjusted within the ANCOVA model with factors for treatment and baseline measurement.
c Difference = adjusted mean change for Vedolizumab – adjusted mean change for placebo.

EQ-5D and EQ-5D VAS

A decrease of ≥ 0.3 points in the EQ-5D score represents a clinically meaningful improvement in HRQL for patients. An increase of ≥ 7 points in the EQ-5D VAS score represents a clinically meaningful improvement in HRQL for patients.

For the TNF antagonist failure sub-population that received Vedolizumab treatment, the decreases in the EQ-5D scores and the increases in the EQ-5D VAS scores were considered clinically meaningful improvements in HRQL at both Week 6 and Week 10 (Table 6.5.3.15). The 95% CIs for the differences between Vedolizumab and placebo in the EQ-5D scores included 0 at Week 6 but not at Week 10, demonstrating improvements in HRQL over placebo (Table 6.5.3.15). Compared to patients receiving placebo, patients receiving Vedolizumab demonstrated greater improvements on the EQ-5D VAS scores at both Week 6 and Week 10. Similar results were seen in the overall study population (Takeda Data on File, 2012b).

Table 6.5.3.15: Overall observed changes in SF-36 scores from baseline to Week 6 and 10 in GEMINI III

	TNF Antagonist Failure Population		Overall Population	
	Placebo	**Vedolizumab**	**Placebo**	**Vedolizumab**
Week 6 EQ-5D Score[a]	n=149	n=158	n=197	n=201
Adjusted mean change from baseline (95% CI)[b]	–0.1 (–0.3 to 0.1)	–0.4 (–0.6 to –0.2)	–0.2 (–0.4 to 0.0)	–0.4 (–0.5 to –0.2)
Difference in adjusted change from baseline vs placebo, mean (95% CI)[c]		–0.2 (–0.5 to 0.1)		–0.2 (–0.5 to 0.1)
Week 10 EQ-5D Score[a]	n=143	n=152	n=191	n=197
Adjusted mean change from baseline (95% CI)[b]	–0.1 (–0.4 to 0.1)	–0.6 (–0.8 to –0.4)	–0.1 (–0.3 to 0.1)	–0.6 (–0.8 to –0.4)
Difference in adjusted change from baseline vs placebo, mean (95% CI)[c]		–0.5 (–0.8 to –0.2)		–0.5 (–0.8 to –0.2)
Week 6 EQ-5D VAS Score[a]	n=148	n=152	n=196	n=199
Adjusted mean change from baseline (95% CI)[b]	3.9 (0.8 to 7.0)	9.7 (6.7 to 12.8)	4.8 (2.1 to 7.5)	9.6 (6.9 to 12.2)
Difference in adjusted change from baseline vs placebo, mean (95% CI)[c]		5.8 (1.4 to 10.2)		4.8 (1.0 to 8.6)
Week 10 EQ-5D VAS Score[a]	n=141	n=148	n=188	n=192
Adjusted mean change from baseline (95% CI)[b]	2.6 (–0.6 to 5.8)	12.7 (9.6 to 15.8)	3.8 (1.0 to 6.6)	13.0 (10.3 to 15.8)
Difference in adjusted change from baseline vs placebo, mean (95% CI)[c]		10.1 (5.6 to 14.5)		9.2 (5.3 to 13.1)

Abbreviations: CI=confidence interval; EQ=EuroQol; HRQL=health-related quality of life; VAS=visual analog scale.
a Lower EQ-5D scores and higher EQ-VAS scores indicate improvements in HRQL.
b Mean changes were adjusted within the ANCOVA model with factors for treatment and baseline measurement.
c Difference = adjusted mean change for Vedolizumab – adjusted mean change for placebo.

6.6 Meta-analysis

6.6.1	**The following steps should be used as a minimum when presenting a meta-analysis.**

- Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.
- Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving 4 combinations in all).
- Provide an adequate description of the methods of statistical combination and justify their choice.
- Undertake sensitivity analysis when appropriate.
- Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).

Please see section 6.7

6.6.2	**If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.**

Please see section 6.7

6.6.3	**If any of the relevant RCTs listed in response to section 6.2.4 (Complete list of relevant RCTs) are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored.**

6.7 Indirect and mixed treatment comparisons

6.7.1	**Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.4, Appendix 4.**

The systematic review strategies described in section 6.1 are applicable for this section. A single systematic review and MTC were undertaken to calculate the relative treatment effect estimates of efficacy and safety among Vedolizumab and other biologic therapies indicated for the treatment of moderate to severe CD, using indirect comparisons. As mentioned above, the review and MTC includes treatments licenced in other countries besides the UK. However the result with respect to relevant comparators for the UK (Adalimumab and Infliximab) are presented here. Full details of the analyses can be found in the accompanying report (Takeda Data on File, 2014), if required. The inclusion of appropriate evidence for treatments in the network not licenced in the UK is not expected to affect the integrity of the analyses.

6.7.2	**Please follow the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 10.5, Appendix 5, a complete quality assessment for each comparator RCT identified.**

Please see section 6.1 to 6.5 for this section.

6.7.3	**Provide a summary of the trials used to conduct the indirect comparison. A suggested format is presented below. Network diagrams may be an additional valuable form of presentation.**

Ten studies were identified which provided information on Infliximab, Adalimumab and Vedolizumab. The main analysis included six of these studies since four were not felt to be comparable, exploratory secondary analysis was performed including these studies, a brief summary of these results are presented in section 6.7.6 and 6.7.8.

All the studies were randomized, placebo-controlled, double-blind trials, details of these studies are provided in Table 6.7.3.1. Several differences can be seen in the characteristics of the patients which could affect outcome, the most significant of which is prior anti-TNF exposure. Patients who have previously received treatment with anti-TNFs may be a more difficult-to-treat population than those who are anti-TNF–naïve; therefore, it is important to compare similar populations.

The trials did not all provide the same level of information on the prior anti-TNF exposure of their patient populations. Several studies (CLASSIC-I, CLASSIC-II, Targan 1997 & ACCENT I) provided information on patients who were anti-TNF naïve. The Vedolizumab trials (GEMINI II & III), provided information on both patients who were anti-TNF naïve and patients who had failed previous anti-TNF therapy. Only one comparator study (Sandborn 2007) provided information on a population of anti-TNF experienced patients. The anti-TNF-Failure population represents patients with inadequate response, loss of response or intolerance to anti-TNF. Unlike the anti-TNF-failure population the anti-TNF–experienced population included those patients who may have had a partial response or relapse following anti-TNF therapy. Our analyses used the anti-TNF-Failure population in the Vedolizumab studies versus the anti-TNF–experienced population in the comparator study. It is likely that the anti-TNF-Failure population is more difficult to treat than the anti-TNF–experienced population so conclusions from these analyses should be made with caution. Table 6.7.3.2 shows the definitions of the anti-TNF experienced/failure sub-populations.

Additionally some studies did not provide data sub-divided by prior TNF exposure (Watanabe, 2012, CHARM, Extend), these studies were excluded from the primary analysis, however a secondary analysis with the entire population was performed the results of which was presented in Takeda Data on File MTC report (2014).and will be presented briefly in this document.

Similarly, although the CLASSIC II study of Adalimumab was identified in the literature searches, patients were re-randomized on the basis of remission (rather than on response, which was the basis for re-randomization in GEMINI-II and ACCENT I presented here), and therefore it was not considered appropriate for the MTC since patients that met the remission criteria are likely to have experienced a much bigger drop in CDAI compared to those patients that were only classified as responders. This study was used therefore only in an exploratory analysis presented in Takeda Data on File MTC report (2014).

A summary of the trials/treatments included in the MTC can be found in Table 6.7.3.3. The studies were analysed in groups depending upon anti-TNF exposure and whether they were reporting on the induction or maintenance phase, giving the following comparisons:

- anti-TNF–naïve, induction (Figures 6.7.3.1 - 6.7.3.2)
- anti-TNF–naïve, maintenance (Figure 6.7.3.3)
- anti-TNF–experienced/failure, induction (Figure 6.7.3.4)
- anti-TNF– experienced/failure, maintenance (No network possible)
- entire population (secondary analysis)

Table 6.7.3.1: Details of studies which provided information on Infliximab, Adalimumab and Vedolizumab

Study Name	Interventions	Study phase	Number Randomized	Week of Analysis	Mean Age (years)	%Male	% Naïve	Mean Baseline CDAI	Mean Disease Duration (Years)
ACCENT I (S. B. Hanauer et al., 2002)	Placebo	Maintenance	188	54	NR	39	100	299	NR
	Infliximab 5 mg		192	54	NR	39	100	299	NR
	Infliximab 10 mg		193	54	NR	38	100	299	NR
CHARM (Jean-Frédéric Colombel et al., 2007)	Placebo	Maintenance	170	56	36.7	37.7	49.6	316.6	NR
	Adalimumab 40 mg ew		157	56	36.7	37.7	49.6	316.6	NR
	Adalimumab 40 mg eow		172	56	36.7	37.7	49.6	316.6	NR
CLASSIC-I (S. B. Hanauer et al., 2006)	Adalimumab 40 mg/20 mg	Induction	74	4	39	53	100	299	NR
	Adalimumab 80 mg/40 mg		75	4	38	33	100	301	NR
	Adalimumab 160 mg/80 mg		76	4	39	47	100	295	NR
	Placebo		74	4	37	50	100	296	NR
CLASSIC-II (W J Sandborn et al., 2007a)	Placebo	Maintenance	18	56	36	33	100	107	8.24
	Adalimumab 40 mg eow		19	56	34	37	100	106	7.73
	Adalimumab		18	56	38	50	100	88	9.13

Study Name	Interventions	Study phase	Number Randomized	Week of Analysis	Mean Age (years)	%Male	% Naïve	Mean Baseline CDAI	Mean Disease Duration (Years)
	40 mg ew								
EXTEND (P. Rutgeerts et al., 2012)	Placebo	Induction	65	12	37.2	37	43.1	321.1	9.8
	Adalimumab 40 mg/20 mg		64	12	37.1	38	53.1	318.7	10.4
EXTEND (P. Rutgeerts et al., 2012)	Placebo	Maintenance	65	52	37.2	37	43.1	321.1	9.8
	Adalimumab 40 mg ew		64	52	37.1	38	53.1	318.7	10.4
GEMINI-II (Takeda Data on File, 2012a)	Placebo	Induction	148	6	38.6	47	51	324.6	8.2
	Vedolizumab		220	6	36.3	48	50	327.3	9.2
GEMINI-II (Takeda Data on File, 2012a)	Placebo	Maintenance	153	52	37.2	47	46	325.2	9.6
	Vedolizumab Q4W		154	52	34.9	53	46	317	8.4
	Vedolizumab Q8W		154	52	35.1	44	43	325.5	7.7
GEMINI-III (Takeda Data on File, 2012b)	Placebo	Induction	207	10	37.1	43	24	297.4	NR
	Vedolizumab		209	10	38.6	44	24	311.4	NR
Sandborn, 2007	Placebo	Induction	166	4	37	39	0	313	NR

Study Name	Interventions	Study phase	Number Randomized	Week of Analysis	Mean Age (years)	%Male	% Naïve	Mean Baseline CDAI	Mean Disease Duration (Years)
(Sandborn et al., 2007b)	Adalimumab 160 mg/80 mg		159	4	39	31	0	313	NR
Targan, 1997 (Targan et al., 1997)	Placebo	Induction	25	4	38.5	60	100	288	10.4
	Infliximab 5 mg		27	4	37	52	100	312	12.5
	Infliximab 10 mg		28	4	39.3	46	100	318	11.5
	Infliximab 20 mg		28	4	36	46	100	307	13.5
Watanabe, 2012 (Watanabe et al., 2012)	Adalimumab 160 mg/80 mg	Induction	33	4	32	60.6	42.4	300.5	11
	Adalimumab 80 mg/40 mg		34	4	30.6	47.1	41.2	302.7	9.2
	Placebo		23	4	30.4	69.6	43.5	308.1	7.9
Watanabe, 2012 (Watanabe et al., 2012)	Placebo	Maintenance	25	52	30.8	60	44	296.7	8.2
	Adalimumab 40 mg eow		25	52	31.6	64	48	325.5	9.9

NR=not reported eow = every other week; ew = every week; NR = not reported; Q4W = every 4 weeks; Q8W = every 8 weeks.

Table 6.7.3.2: Definition of Anti-TNF Experienced/Failure population

Trial	Biologic Studied	Anti-TNF Experienced/Failure Sub-population	Sub-population Definition
GEMINI II	Vedolizumab 300 mg, Q4W, Q8W	Failure	Sub-group of patients defined as having previously failed TNF antagonist therapy
GEMINI III	Vedolizumab 300 mg	Failure	Sub-group of patients defined as having previously failed TNF antagonist therapy
(Sandborn et al., 2007b)	Adalimumab 160 mg/80 mg	Experienced	To be included, patients must have been intolerant of Infliximab or must have previously responded to Infliximab and then lost response The authors excluded patients who had a primary non response to Infliximab as defined by the investigator, received Infliximab or another TNF antagonist within the past 8 weeks, previously received Adalimumab (Humira, Abbott Laboratories, Abbott Park, Illinois), or participated in an Adalimumab clinical trial

anti-TNF = tumour necrosis factor antagonist; Q4W = every 4 weeks; Q8W = every 8 weeks

Table 6.7.3.3: Summary of the trials/treatments included in the MTC

Trials included in the MTC presenting anti-TNF exposure sub-population data							
No. trials	**Trial reference**	**Sub-population**	**Study phase**	**Adalimumab**	**Infliximab**	**Placebo**	**Vedolizumab**
1	CLASSIC-I	Naïve	Induction	✓		✓	
1	Sandborn, 2007	Experienced	Induction	✓		✓	
1	Targan, 1997	Naïve	Induction		✓	✓	
1	GEMINI-II	Naïve + Failure	Both			✓	✓
1	GEMINI-III	Naïve + Failure	Induction			✓	✓
1	ACCENT I	Naïve	Maintenance		✓	✓	
Trials included in the MTC but excluded from primary analysis for only presenting mixed anti-TNF exposure data							
No. trials	**Trial reference**	**Sub-population**	**Study phase**	**Adalimumab**	**Infliximab**	**Placebo**	**Vedolizumab**
1	Watanabe, 2012	Mixed	Induction + Maintenance	✓		✓	
1	CHARM	Mixed	Maintenance	✓		✓	
1	Extend	Mixed	Induction + Maintenance	✓		✓	
Trials included in the MTC but excluded from primary analysis for presenting data re-randomised on remission							
No. trials	**Trial reference**	**Sub-population**	**Study phase**	**Adalimumab**	**Infliximab**	**Placebo**	**Vedolizumab**
1	CLASSIC-II	Naïve	Maintenance	✓		✓	

GEMINI II & III presents mixed data which is also available by sub-population (Naïve + Failure),
Mixed data presented in these studies did provide the data by sub-population

Figure 6.7.3.1: Network diagram of the interventions compared for the outcomes of clinical remission and clinical response (drop in CDAI ≥ 70) in the Anti-TNF–Naïve sub-population in induction treatment

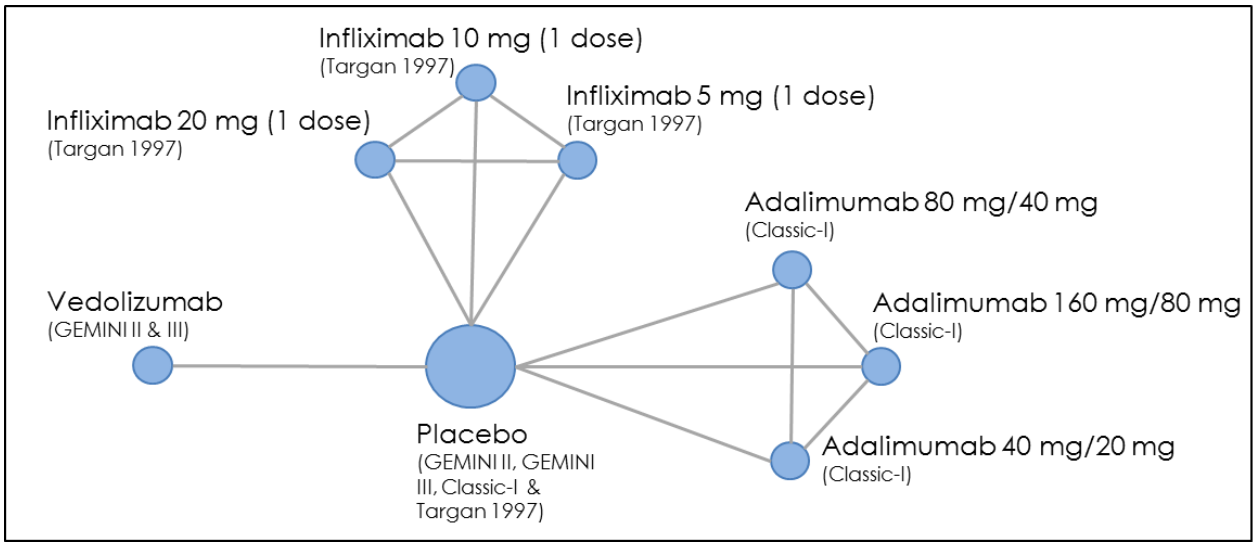


Figure 6.7.3.2: Network diagram of the interventions compared for the outcomes of enhanced clinical response (drop in CDAI ≥ 100) and discontinuation due to AE in the Anti-TNF–Naïve sub-population in induction treatment

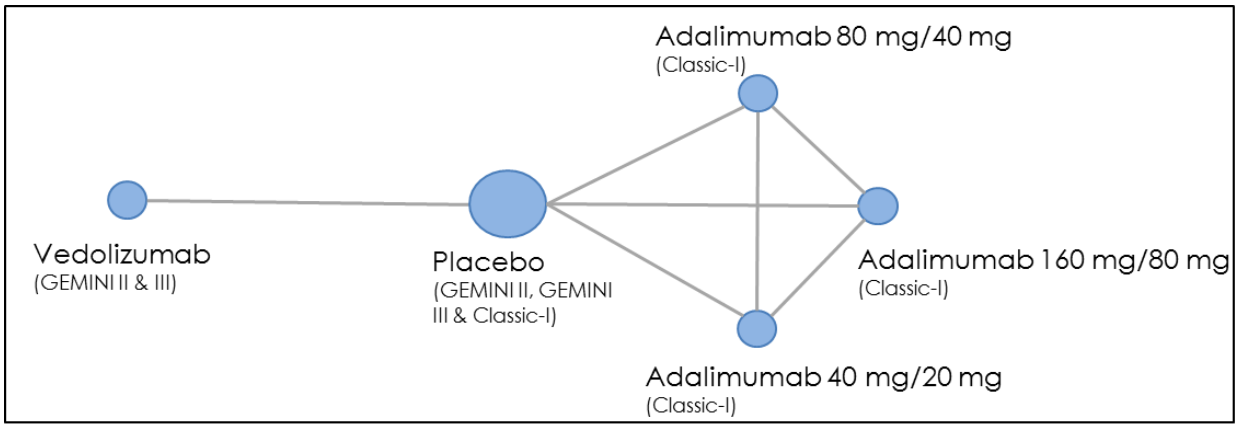


Figure 6.7.3.3: Network diagram of the interventions compared for the outcomes of clinical remission, clinical response (drop in CDAI ≥ 70) and discontinuation due to AE in the Anti-TNF–Naïve sub-population in maintenance treatment

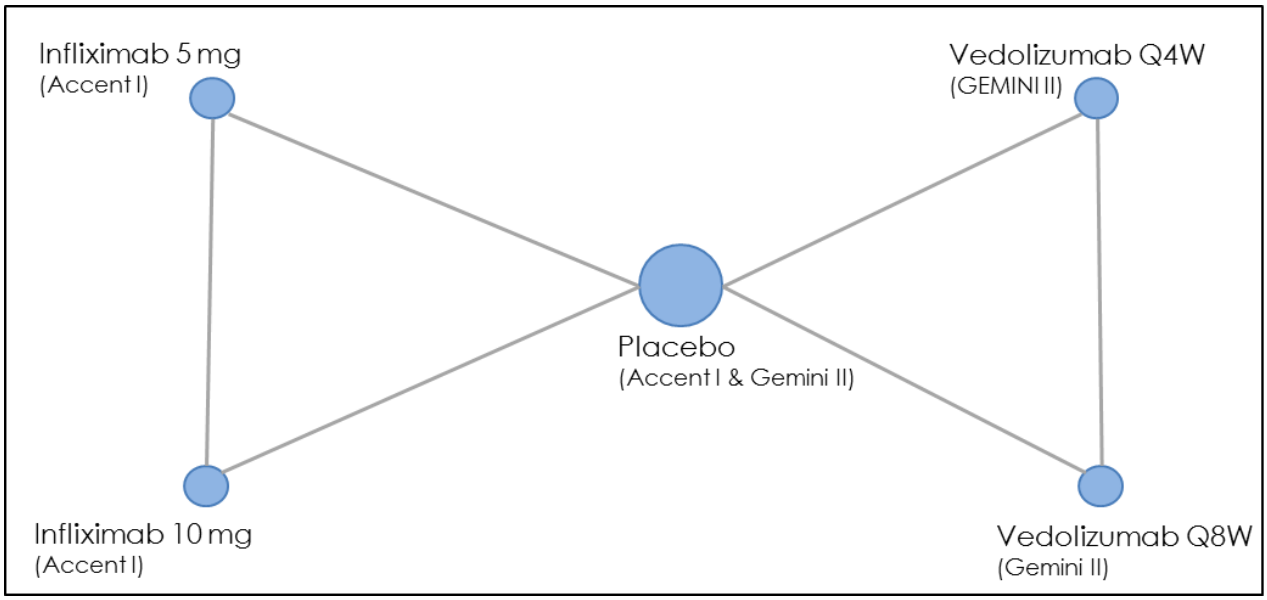
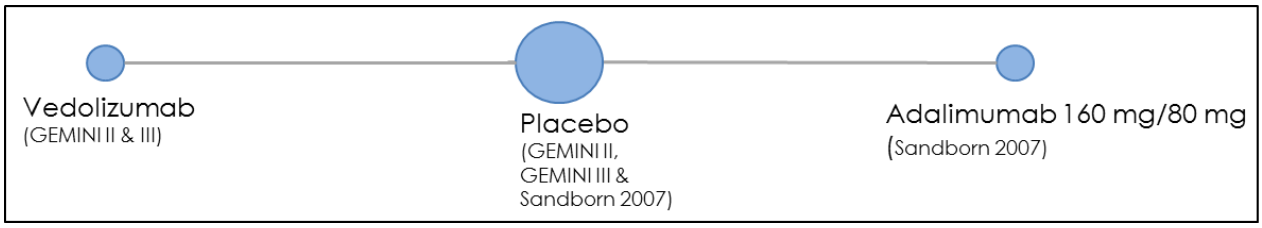


Figure 6.7.3.4: Network diagram of the interventions compared for the outcomes of clinical response (drop in CDAI ≥ 70), enhanced clinical response (drop in CDAI ≥ 100), clinical remission and discontinuation due to AEs in the Anti-TNF–Experienced/Failure sub-population in induction treatment



6.7.4 For the selected trials, provide a summary of the data used in the analysis.

Detailed tables of the data used in the analyses are presented in Appendix 6. Table 6.7.4.1 summarises the data that has been extracted from the RCTs considered relevant for this MTC, and which are used in the cost-effectiveness model presented in section 7. Data were lacking for some outcomes in either induction or maintenance; as a result not all treatments were represented in all analyses. Furthermore, in some analyses, the number of patients experiencing outcomes was very low, which means results can be affected by small changes. For example, the numbers of patients discontinuing due to AEs is very low, particularly in the short-term induction studies. This means that one or two patients experiencing one of these events can result in significant results. Where possible, MTCs have been conducted however the results should be interpreted with caution.

Table 6.7.4.1: Summary of data available for the analyses that are presented in Appendix 5

Study Population (Study Phase)	Clinical Response (drop in CDAI ≥70)	Enhanced Clinical Response (drop in CDAI ≥100)	Clinical Remission	Discontinuation due to AEs
TNF Naïve (Induction)	√	√	√	√
TNF Naïve (Maintenance)	√		√	√
TNF Experienced/Failure (Induction)	√	√	√	√
Entire population (Induction)	√	√	√	√
Entire population (Maintenance)	√	√	√	√

Entire population also reported the outcomes of serious adverse events (SAE) and CSF remission

6.7.5	**Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate Appendix.**

The methods used to fit the Bayesian MTCs follow that of Lu and Ades (2004). However, instead of the models being run directly from within WinBUGS or OpenBUGS (Lunn, 2000), the R package R2WinBUGS (Sturtz et al., 2005) was used to run OpenBUGS. Therefore, the data were set up in R format instead of the more commonly seen rectangular format in order for the models to be run from R. These models assumed binomial distributions and used a logistic link function. For all the analysis conducted using OpenBUGS, the following model specifications were used:

- chains
- Burn-in of 20,000 iterations
- Total of 60,000 iterations
- Thin rate of 50

Bayesian Fixed Effects MTC

Fairly informative priors were needed for the models to run. Different runs with different priors showed that the choice of prior had little effect on the results. It also was observed that the point estimates and credible intervals matched very closely those from the frequentist MTCs. Treatments were coded numerically and placebo used as treatment 1. The code used to run the Bayesian fixed effects MTCs are presented in Appendix 15.

Bayesian Random Effects MTC

Fairly informative priors were needed for the models to run. Different runs with different priors showed that the choice of prior had little effect on the results. It was also observed that the point estimates and credible intervals matched very closely those from the frequentist MTCs. The code used to run the random effects MTCs are presented in Appendix 15.

In addition to the binomial MTCs conducted, a complementary log-log binomial model was fitted to one of the MTCs to see whether this made any difference to the results. The complementary log-log model was considered to be more appropriate for the network of evidence since different studies used different lengths of time for the induction phase. Initially, this was not considered to be a problem since length of

induction was a deliberate part of the study designs and the length of induction is reflected in the label, so if the treatments are considered as a treatment regimen (which includes a stated induction time), then the results from a standard binomial MTC should be valid. However, if comparisons are desired that more closely reflect the treatment differences after adjustment to length of induction, then a complementary log-log model might be considered to be more appropriate. In order to assess whether the choice of model had any influence on the results, the number of serious adverse events was chosen as an endpoint, and both models were run on these data.

The complementary log-log model takes into account length of time by assuming an underlying Poisson process for each trial arm, with a constant event rate, so that the time until an event occurs in each trial arm has an exponential distribution. The full model is shown below.

$$\mathbf{cloglog}(p_{ik}) = \mathbf{log}(f_i) + \delta_{i,bk} I_{(k \neq 1)}$$

Where p_{ik} is the probability of an event in arm k of trial I, f_i accounts for the different follow-up times, and $\delta_{i,bk}$ represents the treatment effects as log-hazard ratios. This model and its assumptions are described by Dias et al. (2013). The WinBUGS code used to run this model is shown in Appendix 15. And the the results of this analysis are presented in the accompanying report (Takeda Data on File, 2014).

6.7.6 Please present the results of the analysis.

The principal summary measure for all analyses is the odds ratio. The primary analysis presented here is the subgroup analyses by prior anti-TNF experience. Undertaking the subgroup analyses ensures that similar patient populations are compared.

Summary of the results MTC of treatments in the anti-TNF-Naive sub-population, induction stage

The main findings of the MTC can be seen in Table 6.7.6.1 and are summarised below:

In the analysis using primary time points, Infliximab 5 mg showed significantly better clinical response (drop in CDAI ≥ 70) rates than Vedolizumab. However, data for Infliximab at the induction time point are available from only one study: Targan et al., 1997. This study has been excluded from previous reviews for the following reasons:

- A nonstandard dose was used
- There was a low placebo rate meaning active treatment (Infliximab) was more likely to demonstrate a significant effect
- Population sizes were small (fewer than 30 patients in each arm)

Therefore, there is good rationale to exclude this study and results are presented both with and without the Targan et al., 1997 study.

There was no evidence to suggest differences in clinical response (drop in CDAI ≥ 100 or ≥ 70) between Vedolizumab and other biologics, if Targan et al. (1997) is not included in the CDAI ≥ 70 analysis.

When Targan et al., 1997, was excluded from the analysis, there was no evidence to suggest differences in remission rates between Vedolizumab and Adalimumab 80 mg/40 mg, Adalimumab 160 mg/80 mg, or Adalimumab 40 mg/20 mg.

Analyses using week 6 for Vedolizumab and week 10 for Vedolizumab for clinical response (drop in CDAI ≥ 100 or ≥ 70) or remission had consistent results.

There was no evidence to suggest differences in results for discontinuation due to AEs between Vedolizumab and Adalimumab 80 mg/40 mg, Adalimumab 40 mg/20 mg.

Table 6.7.6.1: Summary of mixed treatment comparisons induction anti-TNF-Naïve sub-population (odds ratio vs. placebo [95% CrI])

		Comparator							
Outcome Measured		**Vedolizumab 300 mg**	**Adalimumab 80/40**	**Adalimumab 160/80**	**Adalimumab 40/20**	**Infliximab 5**	**Infliximab 10a**	**Infliximab 20a**	**Conclusion**
Clinical response (drop in CDAI ≥ 70)	Week 6 for Vedolizumab	1.8* (1.1, 3.0)	2.5* (1.3, 4.8)	2.6* (1.3, 4.8)	2.0* (1.1, 4.0)	25.0* (6.2, 128.0)	5.3* (1.5, 23.0)	9.8* (2.6, 41.0)	Infliximab significantly better than Vedolizumab
	Week 6 for Vedolizumab (Targan et al., 1997 removed)	1.8* (1.1, 3.0)	2.5* (1.3, 5.0)	2.5* (1.3, 5.0)	2.1* (1.1, 3.9)	NA	NA	NA	Vedolizumab not significantly different from Adalimumab
	Week 10 for Vedolizumab	1.9* (1.2, 3.1)	2.5* (1.3, 4.9)	2.5* (1.4, 4.9)	2.1* (1.1, 4.0)	25.0* (6.3, 118.0)	5.3* (1.5, 22.0)	9.7* (2.6, 42.0)	Infliximab significantly better than Vedolizumab
Enhanced clinical response (drop in CDAI ≥ 100)	Week 6 for Vedolizumab	1.9* (1.1, 3.1)	1.9 (0.9, 4.0)	2.9* (1.4, 5.9)	1.5 (0.7, 3.1)	NA	NA	NA	Vedolizumab not significantly different from Adalimumab
	Week 10 for Vedolizumab	2.3* (1.4, 3.8)	1.9 (0.9, 4.0)	2.9* (1.4, 5.9)	1.5 (0.7, 3.0)	NA	NA	NA	Vedolizumab not significantly different from Adalimumab
Clinical remission	Week 6 for Vedolizumab	2.9* (1.5, 6.0)	2.3* (1.0, 6.2)	4.1* (1.8, 10.0)	1.5 (0.6, 4.0)	26.0* (4.0, 425.0)	8.4* (1.3, 148.0)	8.7* (1.4, 160.0)	Infliximab significantly better than Vedolizumab
	Week 6 for Vedolizumab (Targan et al., 1997 removed)	3.0* (1.6, 6.2)	2.4* (1.0, 5.8)	4.1* (1.9, 10.0)	1.6 (0.6, 4.2)	NA	NA	NA	Vedolizumab not significantly different from Adalimumab
	Week 10 for Vedolizumab	2.7* (1.4, 5.4)	2.3* (1.0, 5.9)	4.1* (1.8, 10.0)	1.5 (0.6, 4.1)	25.0* (4.1, 451.0)	8.7* (1.4, 156.0)	8.8* (1.4, 180.0)	Infliximab significantly better than Vedolizumab
Discontinuation due to AEs		1.4 (0.3, 7.4)	0.4 (0.0, 5.6)	0.0* (0.0, 0.7)	0.5 (0.0, 5.9)	NA	NA	NA	Adalimumab 160 mg/80 mg significantly better than Vedolizumab

AE = adverse event; CDAI = Crohn's Disease Activity Index; CrI=credible interval; NA = not applicable. * = significant vs. placebo. [a] = non-standard dose, should not be included in comparisons

Summary of the results of the MTC of treatments in the anti-TNF Naïve sub-population, maintenance stage

The main findings of the MTC can be seen in Table 6.7.6.2 and are summarised below:

- There was no evidence to suggest differences in clinical response (drop in CDAI ≥ 70) between Vedolizumab Q8W and Infliximab (5 mg or 10 mg).
- There was no evidence to suggest differences between Vedolizumab Q4W and Infliximab 5 mg. However, Infliximab 10 mg showed significantly better clinical response (drop in CDAI ≥ 70) than Vedolizumab Q4W, although 95% credible intervals were wide.
- Analysis of enhanced clinical response (drop in CDAI ≥ 100) for the anti-TNF-Naïve sub-population was not possible, as no data other than for Vedolizumab were available.
- There was no evidence to suggest differences in remission rates between Vedolizumab (Q4W or Q8W) and Infliximab (5 mg or 10 mg).
- Vedolizumab (Q4W and Q8W) showed significantly better results for discontinuation due to AEs than for Infliximab 5 mg.
- Vedolizumab Q8W showed significantly better results for discontinuations due to AEs than Infliximab 10 mg.

Table 6.7.6.2: Summary of mixed treatment comparisons maintenance anti-TNF-Naïve sub-population (odds ratio vs. placebo [95% CrI])

Outcome Measured	Comparator				Conclusion
	Vedolizumab Q4W	Vedolizumab Q8W	Infliximab 5 mg/kg	Infliximab 10 mg/kg	
Clinical response (drop in CDAI ≥ 70)	1.8 (0.9, 3.5)	2.6* (1.3, 5.0)	3.4* (1.9, 6.5)	5.0* (2.6, 9.4)	Infliximab 10 mg significantly better than Vedolizumab Q4W
Clinical remission	2.4* (1.2, 4.9)	2.9* (1.4, 6.1)	2.5* (1.3, 5.2)	4.0* (2.1, 8.1)	Vedolizumab not significantly different
Discontinuation due to AEs	0.8 (0.3, 2.7)	0.5 (0.1, 1.8)	6.6* (2.8, 20.0)	3.4* (1.3, 10.0)	Vedolizumab significantly better than Infliximab

AE = adverse event; anti-TNF = tumor necrosis factor antagonist; CDAI = Crohn's Disease Activity Index; CrI=credible interval; Q4W = every 4 weeks; Q8W = every 8 weeks.
* = significant vs. placebo.

Summary of the results of the MTC of treatments in the anti-TNF-Failure/Experienced sub-population, induction and maintenance stage

Induction stage

The main findings of the MTC can be seen in Table 6.7.6.3 and are summarised below:

- Analyses compared anti-TNF-failure patients treated with Vedolizumab to anti-TNF–experienced patients treated with Adalimumab. Thus, the patients in the Adalimumab studies may have had a primary response to the prior anti-TNF. The Adalimumab study (Sandborn, 2007) included patients who had previously received Infliximab, but those with a primary non response were excluded. This population does not therefore overlap with the Vedolizumab treatment failure population.
- There was no evidence to suggest differences in enhanced clinical response (drop in CDAI ≥ 100) between Vedolizumab and Adalimumab 160 mg/80 mg using either week 6 or week 10 data for Vedolizumab.
    - Results were consistent when clinical response was defined as a drop in CDAI ≥ 70.
- Adalimumab 160 mg/80 mg showed significant benefit in terms of remission over Vedolizumab at week 6; however:
    - Patients with a primary non response to prior anti-TNF were excluded from the Adalimumab study.
    - There were large 95% credible intervals and a very small network of evidence.
- Full benefit of Vedolizumab was not evident by Week 6.
- By Week 10, there was no evidence to suggest differences in remission rates between Vedolizumab and Adalimumab 160 mg/80 mg.
- There was no evidence to suggest differences in results for discontinuations due to AEs between Vedolizumab and Adalimumab 160 mg/80 mg.

Maintenance stage

- Analyses were not possible at the maintenance time point for the anti-TNF–experienced/failure sub-population, as no data other than for Vedolizumab was available.

Table 6.7.6.3: Summary of mixed treatment comparisons induction anti-TNF-Experienced/Failure sub-population (odds ratio vs. placebo [95% CrI])

Outcome Measured		Comparator		Conclusion
		Vedolizumab 300 mg	Adalimumab 160 mg/80mg	
Clinical response (drop in CDAI ≥ 70)	Week 6 for Vedolizumab	1.9* (1.3, 2.8)	2.1* (1.4, 3.3)	Vedolizumab not significantly different from Adalimumab
	Week 10 for Vedolizumab	1.9* (1.3, 2.8)	2.1* (1.4, 3.3)	Vedolizumab not significantly different from Adalimumab
Enhanced clinical response (drop in CDAI ≥ 100)	Week 6 for Vedolizumab	1.7* (1.2, 2.6)	1.9* (1.2, 3.1)	Vedolizumab not significantly different from Adalimumab
	Week 10 for Vedolizumab	2.0* (1.3, 3.0)	1.9* (1.2, 3.1)	Vedolizumab not significantly different from Adalimumab
Clinical remission	Week 6 for Vedolizumab	1.4 (0.8, 2.6)	3.6* (1.8,7.1)	Adalimumab significant benefit over Vedolizumab
	Week 10 for Vedolizumab	2.5* (1.5, 4.3)	3.5* (1.8, 7.4)	Vedolizumab not significantly different from Adalimumab
Discontinuation due to AEs		0.4* (0.1, 0.9)	0.5 (0.1, 2.4)	Vedolizumab not significantly different from Adalimumab

AE = adverse event; anti-TNF = tumor necrosis factor antagonist; CDAI = Crohn's Disease Activity Index; CrI=credible interval; Q4W = every 4 weeks; Q8W = every 8 weeks.* = significant vs. placebo.

Brief summary of the results of the MTC of treatments in the entire population

Induction

The results for the entire population at induction were broadly consistent with those for the anti-TNF–naïve sub-population analysis. The full results can be found in Takeda data on file MTC report 2014, in summary, the results for the entire population at induction show the following:

- There was no evidence to suggest difference in enhanced clinical response (drop in CDAI ≥ 100), using either week 10 or primary time point data, for Vedolizumab, between Vedolizumab and Adalimumab 80 mg/40 mg, Adalimumab 160 mg/80 mg, Adalimumab 40 mg/20 mg.
- There was no evidence to suggest significant differences in clinical response (drop in CDAI ≥ 70), using week 10 data for Vedolizumab, between Vedolizumab and Adalimumab 80 mg/40 mg, Adalimumab 160 mg/80 mg, Adalimumab 40 mg/20 mg.
- Infliximab 5 mg and Infliximab 20 mg showed significantly better clinical response (drop in CDAI ≥ 70), using Week 10 data for Vedolizumab, than Vedolizumab. Results using primary time point data were consistent with results using Week 10 data for Vedolizumab.
- Infliximab 5 mg showed significantly better remission, using Week 10 data for Vedolizumab, than Vedolizumab.
- There was no evidence to suggest differences in remission, using Week 10 data for Vedolizumab, between Adalimumab 80 mg/40 mg, Adalimumab 160 mg/80 mg, Adalimumab 40 mg/20 mg.
- Results using primary time point data were broadly consistent with results using Week 10 data for Vedolizumab.
- There was no evidence to suggest differences in results for discontinuations due to AEs between Vedolizumab and Adalimumab 80 mg/40 mg, Adalimumab 160 mg/80 mg, Adalimumab 40 mg/20 mg.
- For the entire population, analysis of SAEs was carried out no significant differences were found.

Maintenance

The results for the entire population at the maintenance stage were not consistent with those for the anti-TNF–naïve sub-population analysis. The Vedolizumab results observed in the entire population were inferior to the results observed in the anti-TNF–naïve sub-population analysis, perhaps as a result of the high proportion of anti-TNF-failure patients in the Vedolizumab trials, but other unknown factors could also be responsible. The full results can be found in Takeda data on file MTC report 2014, in summary, the results for the entire population at maintenance show the following:

- Adalimumab 40 mg eow showed a significant benefit over Vedolizumab Q8W and Adalimumab 40 mg QW showed a significant benefit over Vedolizumab (Q4W or Q8W) in terms of enhanced clinical response (drop in CDAI ≥ 100).
- Adalimumab 40 mg eow, Adalimumab 40 mg QW, and Infliximab 10 mg all showed a significant benefit over Vedolizumab (Q4W or Q8W) in terms of clinical response (drop in CDAI ≥ 70). Infliximab 5 mg showed a significant benefit over Vedolizumab Q4W.
- There was no evidence to suggest differences in clinical response (drop in CDAI ≥ 70) between Vedolizumab Q8W and Infliximab 5 mg or between Vedolizumab Q4W and placebo.
- Adalimumab 40 mg eow, Adalimumab 40 mg QW, and Infliximab 10 mg showed a significant benefit over Vedolizumab (Q4W or Q8W) in terms of remission. Infliximab 5 mg showed a significant benefit over Vedolizumab Q4W.
- There was no evidence to suggest a difference in remission rates between Vedolizumab Q8W and Infliximab 5 mg or between Vedolizumab Q4W and placebo.
- There was no evidence to suggest differences in CSF remission between Vedolizumab (Q4W or Q8W) and Adalimumab 40 mg eow, Adalimumab 40 mg QW, or Natalizumab 300 mg.
- Vedolizumab (Q4W or Q8W) showed significantly better results for discontinuations due to AEs than Infliximab 5 mg and Infliximab 10 mg.
- There was no evidence to suggest differences in discontinuations due to AEs between Vedolizumab (Q4W or Q8W) and Adalimumab 40 mg eow, Adalimumab 40 mg QW, Natalizumab 300 mg, or placebo.

- Adalimumab 40 mg eow showed a significant benefit over Vedolizumab Q8W. No other differences were significant.
- The serious AE rates for Vedolizumab (Q4W or Q8W) were not significantly different from placebo.

It is clear from these results, that in the entire population analysis of the maintenance period, results for Vedolizumab are poorer than are seen when the data are analyzed by prior anti-TNF experience, although the data for the ant-TNF experienced population are more limited. As the heterogeneity analysis did not identify prior anti-TNF experience as a significant source of heterogeneity, there may be other differences between the studies. However, due to the limited amount of available information this test was underpowered and so may not be able to detect important differences. The more conservative approach was therefore used: focusing on the results of the sub-populations instead of making the assumption that the different patient populations could be combined.

It appears that the response rates for Vedolizumab are similar to those for the competitors. However, the placebo response rates in the GEMINI II study were substantially higher than those in the other studies. A high placebo rate can have a ceiling effect on odds ratios and so result in a lower odds ratio which means that the results may be biased against Vedolizumab for this patient population. As it is not clear what is causing this difference in placebo response rates between studies, it is more appropriate to use the sub-population analyses, rather than the entire population ones which may be affected by some confounding factors.

6.7.7	**Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.**

There are three main ways to look for and investigate heterogeneity in MTCs (differences in a common control, consistency check using closed loops, and exploring heterogeneity using meta-regression techniques). A description of how each method was applied to this MTC can be found in the Takeda Data on File MTC report (2014) provided and a summary of the finding are presented below.

Where there were closed loops in the network, consistency analyses were performed and studies were found to be consistent unless otherwise stated.

6.7.8	**If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.**

Where the above analyses, that investigated heterogeneity, indicated that a study was different to the rest of the studies in the network of evidence then the analysis was repeated with that study excluded and both sets of results reported.
The main outliers identified as being relevant in this appraisal were as follows:

- Watanabe 2011 – Adalimumab: low placebo rate; odds ratios not significantly different to 2 other studies.
- Targan 1997 – Infliximab (1 dose): low placebo rate, with high active treatment response.

The Targan 1997 study also was identified as one in which odds ratios appear to be biased by placebo rates. It was also a study for nonstandard doses on Infliximab. This study as discussed above did not influence the odds-ratios of other treatments because there were no direct connections in the network to other active treatments; the active treatments only connected to placebo.

However, the Targan (1997) paper was the only example for Infliximab where response rates were recorded for a drop in CDAI ≥ 70. So this was the only way a connection could be made for Vedolizumab and Infliximab. A sensitivity analysis was therefore performed by repeating these analyses with and without the Targan (1997) paper. It could also be argued that the presence Targan 1997 study provides more information about the placebo distribution, in actual fact, it had negligible effect on the placebo distribution which was probably due to the very small samples. Results from the MTC with and without Targan 1997 are presented above.

Additionally as mentioned in section 6.7.3 the CLASSIC-II study was excluded from the analysis due to not re-randomizing based on response. An additional analysis was performed on the anti-TNF naïve population in the maintenance stage including the classic data. This result is presented fully in the MTC report (Takeda Data on File, 2014). Assumptions were necessary to combine the CLASSIC-II data into to allow it to be included in the analysis, both of which are thought to bias the results.

6.7.9 Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

The clinical trials conducted varied in terms of study design (i.e., length of induction phase, randomization of responders for the maintenance phase, and different endpoint definitions) and in terms of patient populations (i.e., data were collected from different countries for each trial and contained differing proportions of treatment-naïve and treatment-experienced patients). Therefore, there was heterogeneity among trials, necessitating examination of the effects of this heterogeneity; where possible, only robust studies of similar design have been included.

Randomization of responders for the maintenance phase

All of the included maintenance studies re-randomized patients based on response criteria after induction treatment. Re-randomization ensured that all of the studies included a similar patient population in terms of response to induction. Only one study was excluded because it did not re-randomize based on response; in the CLASSIC II

study, only patients who met remission criteria after induction were included in the maintenance phase. As this population is more likely to have a positive outcome following maintenance therapy, the study was not included in the MTC of maintenance treatments.

Patient Population

- Patient populations also differed between studies. The proportion of patients who are anti-TNF–naïve may affect results, and it is important to compare similar populations.
- Data for patients with prior anti-TNF-Failure were only available for Vedolizumab. To perform this subgroup analysis, anti-TNF–experienced population data were taken in lieu of failure data for other biologics. These populations are likely to be different. For example, the anti-TNF–failure group would not include partial responders to prior anti-TNF therapy; indeed, the Adalimumab study (Sandborn, 2007) excluded patients with a primary nonresponse to prior anti-TNF. Again, the results from these analyses should be interpreted with caution, as it is difficult to assess the impact of these differences on the results.
- Based on an assessment of the baseline CDAI scores, it appears that patients enrolled in the GEMINI II study had more severe disease than in the other studies (mean baseline CDAI of 324.6 and 327.3 in the two treatment arms, compared with means of around 300 in the majority of other studies). Nonetheless, this was not significant in the assessments of heterogeneity.

Anti-TNF-Failure and Anti-TNF Naïve

- The primary analysis presented here is the subgroup analysis by prior anti-TNF experience. This is because the patient populations differed between studies and the proportion of patients who are anti-TNF–naïve may affect results as stated above. Undertaking the subgroup analysis ensured that similar patient populations were compared but also reduced the size of the networks analyzed.
- In terms of the anti-TNF–failure/experienced population, limited data were available. Although data on the group of patients with prior anti-TNF-Failure are key to Vedolizumab, these data were not available for any comparators. In fact, the only comparator with any similar data was Adalimumab and the data

available were for the anti-TNF–experienced population (who in the Adalimumab study must have responded to prior anti-TNF therapy to meet inclusion criteria). Despite this difference, Vedolizumab did not show significant differences in efficacy when compared with Adalimumab in this population.

Study Duration; Length of Induction and Maintenance Studies

- Duration of induction studies varies. In the base-case analysis, the primary time point for Vedolizumab (6 weeks) was used, along with comparable primary time points for the other biologics. This time point may not have allowed sufficient time for patients to respond to Vedolizumab. However, analysis of post hoc 10-week Vedolizumab data also was conducted and showed broadly consistent results.
- The impact of timing of induction outcome assessment on odds ratios was assessed in a time series analysis. This justified our approach of using the primary time point, as no significant relationship between time point and odds ratio was seen.
- In the maintenance studies, the time point for primary efficacy analyses was over 52 weeks; no studies relied on data from an earlier time point (e.g., 26 weeks), when previous (or induction) therapy may still affect results. The Vedolizumab study is of the shortest duration included (52 weeks), while some studies extend to 56 weeks (CHARM). We have no reason to suspect that these differences in study period would be sufficient to influence the results observed.

Trial Outcomes

- Different definitions (e.g., of response in CDAI) have been used in studies. The primary outcome for Vedolizumab is “enhanced response,” defined as an improvement in CDAI ≥ 100. Other studies only present data on “response,” defined as an improvement in CDAI ≥ 70. Analyses were conducted for both definitions to allow wider comparison, but use of the primary time point was preferred.

Use of Sub-populations

- Although results for the analysis of induction treatment are similar whether the entire population or sub-populations are used, the maintenance analysis results

for the entire population are quite different to those seen in either sub-population. This is largely due to the high placebo response rate in the GEMINI II study which may have lead to lower odds ratios for Vedolizumab compared with Infliximab and Adalimumab, even though the response rates in the active arm are similar. The reason for the high placebo response rate in GEMINI II is not clear, and the heterogeneity analysis did not identify previous therapy as a significant factor. None the less, this difference between studies means the results for the entire population are not reliable and reiterate the validity of the primary analysis, according to prior anti-TNF experience.

Summary

In summary, levels of heterogeneity in analyses have been tested and although the analysis to detect and explore heterogeneity suggested that some differences were present, they were not able to explain the cause of the heterogeneity. This was probably due to the small number of studies in the network resulting in a lack of power when regression models were fitted. Data were lacking for some outcomes in either induction or maintenance; therefore, not all treatments were represented in all analyses.

6.8 Non-RCT evidence

6.8.1	**If non-RCT evidence is considered (see section 6.2.7), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.6 and 10.7, appendices 6 and 7.**

Non-RCT, both experimental and observational, evidence will be required, not just for those situations in which RCTs are unavailable, but also to supplement information from RCTs when they are available. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3.2.8 to 3.2.10.

Not applicable as there was no non-RCT evidence of relevance to include.

6.9 Adverse events

6.9.1	**If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.8 and 10.9, appendices 8 and 9.**

Safety data included in this section

GEMINI II and III: The safety profile of Vedolizumab has been determined by analysis of adverse event rates reported in the published clinical trials referred to in this submission (William J Sandborn et al., 2013a; Sands et al., 2014). Safety was a secondary outcome of the GEMINI II and III study so no separate search was undertaken for safety.

Three further key sources of evidence on the safety profile of Vedolizumab will be presented in this section in addition to results from GEMINI II and GEMINI III:

- GEMINI LTS (C13008): interim results from an ongoing Phase III, single-arm, open-label study where the objective is to determine the long-term safety and efficacy of Vedolizumab in patients with ulcerative colitis and CD will be presented (J Colombel, Sands, Fox, & Feagan, 2013)

- GEMINI I (ulcerative colitis) and GEMINI II (Crohn's disease) pooled safety analysis (Jean-frédéric Colombel, Sands, & Feagan, 2012)

- Results from an integrated safety analysis of six Vedolizumab randomised placebo-controlled in IBD (ulcerative colitis and Crohn's disease) which includes data from the GEMINI LTS trial plus from patients enrolled in randomized studies who did not enrol into the open-label extension (J Colombel, Sands, Rutgeerts, et al., 2013)

6.9.2	**Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.**

GEMINI II

The safety population in the GEMINI II trial included all enrolled patients, including both Cohort 1 and Cohort 2 (See Figure 6.3.8.1).

- The placebo safety group (n=301) includes patients who received placebo in Cohort 1 (n=148) and patients who responded to Vedolizumab in the induction phase (up to week 6) and were randomized to placebo in the maintenance phase (up to week 52).
- The Vedolizumab safety group (n=814) includes patients from Cohort 1 and Cohort 2 who responded to Vedolizumab in the induction phase (up to week 6) and were randomized to Vedolizumab (Q4W, n=154 or Q8W, n=154) in the maintenance phase (up to week 52) and patients from Cohort 1 and Cohort 2 who received but did not respond to Vedolizumab in the induction phase (up to week 6) and received Vedolizumab (Q4W, n=506) in the maintenance phase (up to week 52).

The overall incidence of AEs was similar across treatment groups in both the induction and maintenance studies (William J Sandborn et al., 2013b; Takeda Data on File, 2012a). At least one AE was reported in 59% of patients receiving placebo, 56% of patients receiving double-blind Vedolizumab, and 57% of patients receiving open-label Vedolizumab in the induction study; and 84% of patients receiving placebo, 88% of

patients receiving Vedolizumab every 8 weeks, and 84% of patients receiving Vedolizumab every 4 weeks in the maintenance study. Table 6.9.1.1 provides the most common AEs reported in at least 5% of Vedolizumab-treated patients (William J Sandborn et al., 2013b). Nasopharyngitis occurred more frequently, while headache and abdominal pain occurred less frequently in the Vedolizumab patients compared with the placebo patients.

Serious AEs occurred more frequently in the Vedolizumab groups (24.4%) than in the placebo group (15.3%) (William J Sandborn et al., 2013b). In the maintenance study, one case each of latent tuberculosisTB, carcinoid tumour in the Appendix, squamous-cell carcinoma, and basal-cell skin carcinoma were diagnosed in the Vedolizumab groups, and a borderline ovarian tumour developed in one placebo patient. Five deaths occurred during the study period: 4 in the Vedolizumab group (one death each from Crohn's disease with sepsis, intentional overdose of prescription medication, myocarditis, and septic shock) and one in the placebo group (from bronchopneumonia). Only one patient discontinued the study because of a serious infusion reaction, and no cases of anaphylaxis were reported. The rates of infections and serious infections (5.5% vs 3.0%) were higher with Vedolizumab than with placebo. No cases of PML were identified.

Table 6.9.2.1: Treatment-emergent adverse events in the overall safety population in the GEMINI II trial

Event, n (%)	Placebo[a] (n=301)	Vedolizumab[b] (n=814)
Any AEs	246 (82)	706 (87)
Serious AEs	46 (15.3)	199 (24.4)
Serious infection	9 (3.0)	45 (5.5)
Any cancer	1 (0.3)	4 (0.5)
Adverse events occurring in >5% of Vedolizumab patients, categorized by preferred term		
CD exacerbation	65 (21.6)	164 (20.1)
Arthralgia	40 (13.3)	110 (13.5)
Pyrexia	40 (13.3)	103 (12.7)
Nasopharyngitis	24 (8.0)	100 (12.3)
Headache	47 (15.6)	97 (11.9)
Nausea	30 (10.0)	90 (11.1)
Abdominal pain	39 (13.0)	79 (9.7)
Upper respiratory tract infection	17 (5.6)	54 (6.6)
Fatigue	14 (4.7)	53 (6.5)
Vomiting	23 (7.6)	49 (6.0)
Back pain	12 (4.0)	38 (4.7)

a The placebo group includes patients who did not receive maintenance therapy with Vedolizumab (i.e., those who were randomly assigned to placebo during the induction phase plus those who had had a response to Vedolizumab induction therapy and were randomly assigned to placebo for the maintenance trial). † A serious infection was defined as a SAE of infection according to the classification for adverse event reporting in MedDRA.
b The Vedolizumab group includes patients who received maintenance therapy with Vedolizumab (i.e., those who had had a response to Vedolizumab induction therapy and were randomly assigned to receive Vedolizumab every 8 weeks or every 4 weeks as maintenance therapy plus those who did not have a response to Vedolizumab induction therapy and continued to receive Vedolizumab every 4 weeks during the maintenance trial);
c A serious infection was defined as a serious adverse event of infection according to the classification for adverse event reporting in MedDRA.
d The cancer in the placebo group was a borderline ovarian carcinoma, which is defined as a subset of epithelial ovarian tumours that are considered to be of low malignant potential. The cancers in the Vedolizumab group included one case each of basal-cell skin carcinoma, breast cancer, carcinoid tumour in the Appendix, and squamous-cell carcinoma of the skin.

GEMINI III

The overall safety population was defined as all patients who received any amount of study drug (Sands et al., 2014; Takeda Data on File, 2012b). The Overall Safety

Population was used for all safety analyses; patients in this population were analysed according to the treatment they received.

The incidence of AEs was similar between the treatments (Sands et al., 2014; Takeda Data on File, 2012b). Treatment-emergent AEs were reported in 56% and 60% of the Vedolizumab and placebo patients, respectively. The most common AEs in the Vedolizumab group are reported in Table 6.9.2.2. Among these events, the Vedolizumab group had higher incidences of nausea (6% vs. 2%), upper respiratory tract infection (4% vs. 2%), vomiting (4% vs. 2%), fatigue (3% vs. < 1%), and urinary tract infection (3% vs. 0%) compared with the placebo group, whereas the placebo group had higher incidences of Crohn's disease (10% vs. 3%) and pyrexia (6% vs. 3%) compared with the Vedolizumab group.

A higher number of placebo-treated patients (4%) prematurely discontinued from the study due to AEs than Vedolizumab-treated patients (2%), with gastrointestinal disorders the most common AE resulting in study discontinuation in both treatment groups (Sands et al., 2014; Takeda Data on File, 2012b).

Serious AEs were reported in 6% of patients receiving placebo and 8% of patients receiving Vedolizumab. Serious infection AEs occurred in 2 patients in the Vedolizumab group and no patients in the placebo group . No cases of PML were reported. No deaths occurred and no serious infusion-related or anaphylactic reactions were reported (Sands et al., 2014; Takeda Data on File, 2012b).

Table 6.9.2.2: Treatment-emergent adverse events in the overall safety population in the GEMINI III trial

Event, n (%)	Placebo n=207	Vedolizumab n=209
Any AEs	124 (60)	117 (56)
Drug-related AEs	34 (16)	34 (16)
Discontinued because of AEs	8 (4)	4 (2)
Serious AEs	16 (8)	13 (6)
Serious infection	0	2 (<1)
Drug-related SAEs	1 (<1)	1 (<1)
Discontinued because of SAEs	5 (2)	4 (2)
Adverse events occurring in >1% of Vedolizumab patients, categorized by preferred term		
Nausea	5 (2)	12 (6)
Headache	15 (7)	11 (5)
Arthralgia	9 (4)	10 (5)
Nasopharyngitis	8 (4)	9 (4)
Abdominal pain	6 (3)	9 (4)
Upper respiratory tract infection	5 (2)	9 (4)
Vomiting	5 (2)	9 (4)
Pyrexia	13 (6)	7 (3)
Crohn's disease	21 (10)	6 (3)
Fatigue	2 (< 1)	6 (3)
Urinary tract infection	0	6 (3)
Dizziness	4 (2)	5 (2)
Anaemia	1 (< 1)	5 (2)
Aphthous stomatitis	3 (1)	4 (2)
Musculoskeletal pain	0	4 (2)
Diarrhoea	4 (2)	3 (1)
Back pain	3 (1)	3 (1)
Insomnia	3 (1)	3 (1)
Oedema peripheral	2 (< 1)	3 (1)
Oropharyngeal pain	2 (< 1)	3 (1)
Asthenia	1 (< 1)	3 (1)
Decreased appetite	1 (< 1)	3 (1)
Erythema nodosum	1 (< 1)	3 (1)
Hypertension	1 (< 1)	3 (1)
Hypoaesthesia	1 (< 1)	3 (1)
Muscular weakness	1 (< 1)	3 (1)
Dyspepsia	0	3 (1)
Gastroenteritis	0	3 (1)

GEMINI LTS

The GEMINI LTS trial is a Phase III, open-label, multicentre, long-term safety study is ongoing and evaluating Vedolizumab in patients with ulcerative colitis and Crohn's disease (J Colombel, Sands, Fox, et al., 2013). The objective of this study is to collect

and characterise important clinical safety events resulting from chronic Vedolizumab administration.

The primary outcome measures are safety parameters: AEs, serious AEs, results of standard laboratory tests and ECGs, time to major IBD-related events (i.e., hospitalisations, surgeries, or procedures) and improvements in quality of life.

Study Design

Patients enrolled in this trial will receive Vedolizumab every 4 weeks for up to a maximum of 7 years (or until Vedolizumab becomes available in the US, whichever occurs first). The dosing period will be followed by a 16-week post-treatment observation period and safety assessment period. Patients will receive follow-up safety phone assessments every 6 months for 2 years following receipt of their final dose.

Patient Eligibility Criteria

Eligible patients included individuals' ≥18 years of age, who participated in previous Vedolizumab trials and who tolerated Vedolizumab treatment in the opinion of the investigator, or who had moderate to severe Crohn's disease or ulcerative colitis that had not previously received Vedolizumab. Therapeutic doses of conventional therapies for Crohn's disease or ulcerative colitis were permitted. Patients were excluded for development of any new, unstable, or uncontrolled disease.

Interim Results (as of July 2012)

Mean age was 41.3 years (SD 13.30) for patients with ulcerative colitis and 37.7 years (SD 12.52) for those with Crohn's disease. Vedolizumab exposure was ≥6, ≥12, and ≥24 months for 1534, 1149, and 502 patients, respectively.

The safety profile of Vedolizumab in this study was similar to that observed in the prior 12-month Phase III trials. Drug-related AEs were similar between Crohn's disease and ulcerative colitis patients with the most common AEs being headache 6%, nasopharyngitis 4%, nausea 4%, arthralgia 4%, upper respiratory infection 3%, and fatigue 3%.

Table 6.9.2.3: GEMINI LTS - interim safety results (as of July 2012)

AE Category, n (%)	UC Patients (n=704)	CD Patients (n=1118)
Drug-related AE	258 (37%)	447 (40%)
AE leading to discontinuation	61 (9%)	108 (10%)
SAE	127 (18%)	285 (25%)
Serious infection	30 (4%)	74 (7%)
Drug related	15 (2%)	51 (5%)
Leading to discontinuation	23 (3%)	65 (6%)
Death	3 (<1)[a]	3 (<1)[b]

AE, adverse event; CD, Crohn's disease; SAE, serious adverse event; UC, ulcerative colitis
a Respiratory failure, acute stroke, pulmonary embolism
b Septicaemia, traumatic intracranial haemorrhage, suicide

SAEs occurred in <1% of patients, both overall and by indication, except for anal abscess, which occurred in 2% of CD patients. No cases of systemic candidiasis, disseminated herpes zoster, cytomegalovirus hepatitis or encephalitis, pneumocystis pneumonia or PML were reported.

AEs that most commonly led to discontinuation were gastrointestinal, with exacerbations of ulcerative colitis and Crohn's disease most commonly reported (5% each). Malignancies were observed in <1% of patients (two cases of colon cancer and two malignant melanomas).

GEMINI I and GEMINI II pooled safety analysis

Both studies had a similar design and included adults with moderately to severely active UC or CD despite previous anti-TNF and/or other therapy (Jean-frédéric Colombel et al., 2012).

This analysis concluded that patients receiving Vedolizumab had higher rates of overall AEs and SAEs versus placebo; however, the overall incidence of AEs adjusted for patient-years was higher for placebo compared to the Vedolizumab groups. Data from this integrated safety analysis support the safety of Vedolizumab for the treatment of moderately to severely active ulcerative colitis and Crohn's disease. The incidence of AEs occurring in ≥10% of patients is shown in the table below.

Table 6.9.2.4: Incidence of AEs in >10% of patients: pooled analysis of GEMINI I and GEMINI II

Preferred Term	ITT-Placebo[a] n=279		Non-ITT Placebo[b] n=297		Vedolizumab n=1434	
	Pts n (%)	Events (per 100 PY)	Pts n (%)	Events (per 100 PY)	Pts n (%)	Events (per 100 PY)
Any AE	234 (84)	1180 (611.7)	232 (78)	1082 (692.3)	1203 (84)	6161 (623.1)
Nasopharyngitis	29 (10)	38 (19.7)	21 (7)	23 (14.7)	180 (13)	232 (23.5)
Headache	43 (15)	76 (39.4)	32 (11)	55 (35.2)	177 (12)	287 (29.0)
Arthralgia	36 (13)	45 (23.3)	29 (10)	36 (23.0)	166 (12)	210 (21.2)
Crohn's disease	29 (10)	32 (16.6)	36 (12)	41 (26.2)	164 (11)	194 (19.6)
Nausea	26 (9)	33 (17.1)	23 (8)	31 (19.8)	128 (9)	175 (17.7)
Pyrexia	30 (11)	33 (17.1)	22 (7)	29 (18.6)	127 (9)	156 (15.8)
Abdominal pain	20 (7)	29 (15.0)	29 (10)	36 (23.0)	114 (8)	148 (15.0)
Upper respiratory infection	19 (7)	25 (13.0)	19 (6)	23 (14.7)	106 (7)	134 (13.6)
Ulcerative colitis	29 (10)	29 (15.0)	29 (10)	33 (21.1)	97 (7)	119 (12.0)

Abbreviations: ITT=intent to treat; P-Y=person-years; PT=preferred term; Pts=patients; TPY=total person years
* ITT placebo=2 Vedolizumab induction doses, then placebo maintenance
† non-ITT placebo=placebo in induction and maintenance

Integrated safety analysis of six Vedolizumab randomised placebo-controlled trials in IBD

This analysis includes trials in ulcerative colitis and Crohn's disease. The safety population included all patients in the long term safety study (C13008) and those patients from the randomised clinical trials who did not enter in the open label extension study (J Colombel, Sands, Rutgeerts, et al., 2013).

The safety population were comparable between studies, with average age 36–40 years, approximately 70% of patients with disease activity of >3 years and anti-TNF-Failure ranging from 41% to 75%. More than 2800 patients with ulcerative colitis or Crohn's disease have received ≥1 infusion of Vedolizumab and the median duration of Vedolizumab exposure was approximately 1 year.

Across the integrated safety population, Vedolizumab demonstrated a tolerable safety profile for the treatment of adults with moderately to severely active CD or ulcerative colitis. Table 6.9.2.5 summarises the most common AEs observed. The incidence rate of serious infections of interest was low with Vedolizumab and consistent with the purported mechanism of action, there were no cases of PML.

Table 6.9.2.5: Incidence of AEs: pooled analysis of six Vedolizumab trials in UC and CD

AE Preferred term	UC n=1107		CD n=1723		UC and CD n=2830	
	n	Events (per 1000 PY)	n	Events (per 1000 PY)	n	Events (per 1000 PY)
Nasopharyngitis	211	13.2	300	14.2	511	13.8
Headache	168	10.1	289	13.7	457	12.1
Arthralgia	145	8.4	294	13.9	439	11.4
CD[a]	n/a	n/a	457	20.9	n/a	n/a[b]
Abdominal pain	85	4.7	263	11.9	348	8.6
UC[a]	266	15.4	n/a	n/a	n/a	n/a[b]
Serious adverse events						
CD[a]	n/a	n/a	243	10.2	n/a	n/a[b]
UC[a]	117	6.2	0	n/a	n/a	n/a[b]
Abdominal pain	3	0.2	31	1.3	34	0.8
Anal Abscess	2	0.1	31	1.3	33	0.8

[a]Exacerbation of disease.
[b]Incidence rate for exacerbation of disease in the integrated Vedolizumab population would be an underestimation. Most common SAEs are defined as those with an exposure-adjusted incidence rate of ≥10 patients/100 person years.

Tuberculosis

All patients entering Vedolizumab studies were pre-screened for TB by either skin testing (where clinically acceptable) or by interferon-gamma release assay. Across the integrated safety population, tuberculosis was reported in a total of 4 patients (3 with Crohn's disease, 1 with ulcerative colitis). All cases occurred within the first 18 months of Vedolizumab treatment and no extrapulmonary manifestations or dissemination reported

Progressive Multifocal Leukoencephalopathy

As of June 2013, no PML cases have been reported in any of the >2700 patients treated with VEDOLIZUMAB during the entire development program, including approximately 900 patients with ≥24 months exposure. Since 2007, dedicated risk assessment and minimisation plan using stepwise algorithm-based approach is included in all studies. Applying established Natalizumab PML incidence rates and risk stratification factors (i.e., >24 months exposure, use of prior immunosuppressants, % with JC virus antibodies) (Biogen, 2013) between 6 to 7 cases would have been observed by now if Vedolizumab carried similar risk.

Malignancies

As of June 2013, a total of 26 VEDOLIZUMAB-treated patients had been diagnosed with malignancy, of which 18 met severe adverse event criteria: Skin cancers (n=5) and colon cancer (n=4) were most common.

6.9.3 Give a brief overview of the safety of the technology in relation to the decision problem.

Vedolizumab is a safe and tolerable treatment option for patients with Crohn's disease and has no identified systemic immunosuppressive activity.

Safety and tolerability of Vedolizumab have been evaluated in a robust clinical development program. Overall median exposure was approximately one year (range, 1 day to 5 years) with more than 900 people treated with Vedolizumab for ≥2 years. Across the integrated safety population, Vedolizumab demonstrated a tolerable safety profile for the treatment of adults with moderately to severely active Crohn's disease and ulcerative colitis. The incidence rate of serious infections of interest was low with Vedolizumab and consistent with the mechanism of action, there were no cases of PML reported in the context of substantial exposure.

6.10 Interpretation of clinical evidence

6.10.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

The principal findings from the GEMINI II and III studies related to remission and response. The safety profile of Vedolizumab was determined in both these studies as well as in and open-label long term safety study (interim data only. In addition, Vedolizumab was compared to TNF-alpha antagonists in a meta-analysis. The clinical benefit and harms from these studies are described below.

GEMINI II

The study met the primary endpoint of clinical remission at Week 6 demonstrating the efficacy of Vedolizumab in the treatment of patients with moderately to severely active Crohn's disease. A statistically significantly greater proportion of Vedolizumab-treated patients achieved the primary efficacy endpoint of clinical remission at Week 6, with a treatment difference from placebo of 7.8% (95% CI: 1.2, 14.3), P=0.0206. The relative risk of achieving clinical remission at Week 6 was 2.1 (95% CI: 1.1, 4.2). The Vedolizumab treatment benefit as assessed by clinical remission was observed in the majority of patient sub-groups according to demographic characteristics, geographic region, and severity of disease.

Although a trend in favour of Vedolizumab was observed for the other primary endpoint of enhanced clinical response at Week 6, differences between the Vedolizumab and placebo groups did not reach statistical significance.

In the maintenance phase, both Vedolizumab dosing regimens (Q8W and Q4W) were effective as demonstrated by highly significant results in the primary efficacy endpoint of clinical remission at Week 52 (39.0% in the Q8W group [treatment difference from placebo 17.4%; 95% CI: 7.3, 27.5; P=0.0007], 36.4% in the Q4W group [treatment difference 14.7%; 95% CI: 4.6, 24.7; P=0.0042] versus 21.6% in the placebo-treated group). Similar findings were observed for enhanced clinical response at Week 52, a key secondary endpoint.

In GEMINI II, approximately 50% of patients were taking corticosteroids at baseline. Although corticosteroids are an effective option for treatment, they are associated with undesirable side effects. Examples of toxicities and severe adverse events include those associated with short-term use (hypertension, infection, acne, ecchymosis, moon face, hirsutism, petechial bleeding, and striae) and those resulting from prolonged use (new onset diabetes mellitus, steroid associated osteoporosis, osteonecrosis, myopathy, psychosis, cataracts, and glaucoma).

Among patients receiving corticosteroids at the start of the maintenance phase, statistically significantly greater proportions of Vedolizumab-treated patients in both treatment groups achieved corticosteroid-free clinical remission at Week 52 compared with patients who received placebo. In addition, greater proportions of Vedolizumab-treated patients achieved corticosteroid-free clinical remission at Week 52 and had been corticosteroid-free for 90 days and 180 days compared with patients who received placebo.

In GEMINI II, as rated by IBDQ, SF-36 (physical and mental components), and EQ-5D instruments, improvements in HRQL at Week 6 and 52 were consistently greater for patients who received Vedolizumab compared to patients who received placebo (Takeda Data on File, 2012a).

GEMINI III

The primary endpoint of clinical remission at Week 6 in the TNF-alpha antagonist failure ITT sub-population was not met. However, a potential treatment benefit of Vedolizumab versus placebo was reflected in the induction of clinical remission at Week 10 in this sub-population, the difference from placebo being 14.4%. The potential treatment benefit of Vedolizumab in inducing clinical remission at Week 10 was also seen in TNF-alpha-naïve patients and in patients who had failed 2 or more TNF-alpha antagonists.

In the overall ITT population, a treatment difference favouring Vedolizumab was reflected as a difference from placebo of 6.9% in the secondary efficacy endpoint of clinical remission at Week 6. A difference from placebo for Vedolizumab was also observed in clinical remission at Week 10 in the overall ITT population, the difference from placebo being 15.5%.

A potential treatment benefit for Vedolizumab versus placebo was also seen in the secondary efficacy endpoint of enhanced clinical response at Week 6 in the TNF-alpha antagonist failure ITT sub-population, the difference from placebo being 16.9%. Similar findings were observed for enhanced clinical response at Week 10.

The treatment difference of Vedolizumab compared with placebo in inducing an enhanced clinical response was observed in the overall ITT population in a pre-specified exploratory endpoint, the difference from placebo being 16.4%. Similar findings were observed for enhanced clinical responses at Week 10.

The potential treatment benefit was demonstrated at Weeks 6 and 10 in the subgroup of patients who were TNF-alpha antagonist naïve. Greater proportions of Vedolizumab-treated patients achieved clinical remission at Week 6 (31.4%) and at Week 10 (35.3%) compared with those who received placebo (12.0% and 16.0%, respectively). The treatment difference from placebo was 19.2% at Week 6 and 19.1% at Week 10. Treatment differences favouring Vedolizumab were also observed in sub-groups according to demographic factors and disease characteristics, such as measures of severity of disease.

In GEMINI III, improvement in IBDQ was consistently greater for patients who received Vedolizumab compared with 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 cutoffs (Takeda Data on File, 2012b).

Vedolizumab compared to TNF-alpha antagonists in a meta-analysis

The results from the meta-analyses are presented in Section 6.6 and 6.7. In the treatment of anti-TNF–naïve patients with Crohn's disease, Vedolizumab did not show significant differences in the efficacy endpoints studied, when compared with other biologics in the induction setting. Results were consistent regardless of whether the week 6 or week 10 data for Vedolizumab were used in analyses. In the maintenance setting, data for anti-TNF–naïve patients were available only for Vedolizumab and Infliximab. Vedolizumab did not show significant differences in efficacy results when compared with Infliximab, and rates of discontinuation due to adverse events were significantly better for Vedolizumab.

Data for the anti-TNF–failure population were available only for Vedolizumab. Data were available for Adalimumab in the anti-TNF–experienced population. In induction therapy, Vedolizumab did not show significant differences in most efficacy endpoints when compared with Adalimumab. However, Adalimumab had significantly higher rates of clinical remission when week 6 data for Vedolizumab were analyzed but not when the 10-week data for Vedolizumab were analyzed.

Safety profile of Vedolizumab

Safety and tolerability of Vedolizumab have been evaluated in a robust clinical development program (See Section 6.9.2). Overall median exposure to Vedolizumab was approximately one year (range, 1 day to 5 years) with more than 900 people treated with Vedolizumab for ≥2 years. Across the integrated safety population, Vedolizumab demonstrated a tolerable safety profile for the treatment of adults with moderately to severely active Crohn's disease and ulcerative colitis. The incidence rate of serious infections of interest was low with Vedolizumab and consistent with the mechanism of action, there were no cases of PML reported and Vedolizumab did not have any systemic effects in the context of substantial exposure.

6.10.2 Please provide a summary of the strength and limitations of the clinical evidence base of the intervention.

The evidence base supporting this submission for reimbursement for the use of Vedolizumab in patients with moderate to severe Crohn's disease comes from two placebo-controlled, randomised clinical trials, GEMINI II and GEMINI III. Together, they demonstrate a good level of efficacy and safety, per the EMA regulatory approval leading to Vedolizumab being indicated for the treatment of the aforementioned patient group.

GEMINI II

Strengths

- GEMINI II was a multicentre, multinational, randomised, double-blind, placebo-controlled trial designed to establish the efficacy and safety of Vedolizumab for

both induction and maintenance therapy in 1115 patients with moderately to severely active Crohn's disease.

- The trial design, sample size determinations, and statistically methodology allowed for independent assessments of efficacy in induction and maintenance therapy, and, in maintenance therapy, the evaluation of 2 different dosing regimens at 52 weeks. The primary efficacy endpoints – clinical remission and enhanced clinical response at Week 6 (induction phase) and clinical remission at Week 52 (maintenance phase) using definitions based on the CDAI score – are standard accepted endpoints for the evaluation of treatment benefit.
- The study met its objective of enrolling a population of patients with moderately to severely active Crohn's disease who may benefit from pharmacologic therapy, i.e., those who had failed 1 or more standard therapies for Crohn's disease, including TNF-alpha antagonists, immunomodulators, and corticosteroids. The baseline demographic and disease characteristics, including response to previous Crohn's disease treatments, were consistent with this target population.

Limitations

- In the maintenance study, there was an imbalance across the treatment groups in the proportion of patients who had achieved clinical remission at Week 6 because randomisation at Week 6 was not stratified by remission status. Only 27.9% of Vedolizumab Q4W patients and 33.8% of Vedolizumab Q8W patients had achieved clinical remission compared with 36.6% of placebo patients. This imbalance may have affected the analyses of the primary endpoint as well as the secondary and exploratory endpoints. Despite this imbalance most key endpoints were met.
- The modest efficacy of Vedolizumab in Crohn's disease may also be due to the severity of disease in the study populations of both registration studies, which may have precluded a robust inductive effect. In GEMINI II, patients had a mean baseline CDAI score of 324 points, a median CRP concentration of 11.5 mg/l, and a median faecal calprotectin value of 686 µg/g. In addition, 37% had a history of fistulising disease, and 42% had undergone at least one previous surgery for Crohn's disease. Approximately 50% of patients had had treatment failure (defined in the protocol as a lack of initial response, LOR, or unacceptable

side effects) with one or more TNF-alpha antagonists. Half of these patients did not have an initial response to Vedolizumab. Approximately 30% of patients had had treatment failure with 2 or more TNF-alpha antagonists. A population with such refractory disease has not been evaluated in previous trials of TNF-alpha antagonists.

GEMINI III

Strengths

- GEMINI III was a randomised, blinded, placebo-controlled study in 416 patients with moderately to severely active Crohn's disease, and was designed to establish the efficacy and safety of Vedolizumab for the induction of clinical remission in a broad population of patients including a substantial proportion of patients who had previously failed TNF-alpha antagonists and could therefore be considered hard to treat. By design, approximately 75% of the overall population had failed TNF-alpha antagonists; the remaining 25% were naïve to TNF-alpha antagonist therapy. Standard safety assessments were utilized, as well as assessments to evaluate potential immunogenicity, such as HAHA status and the occurrence of infusion-related reactions.
- Additionally, an active screening program (the Risk Assessment and Minimization for PML program) was utilized to detect and manage potential cases of PML, with specific follow-up information requirements, and, if appropriate, referral to neurologists for neurological examination and further diagnostic testing.
- The study met its objective of enrolling patients with moderately to severely active Crohn's disease who had limited treatment options.

In GEMINI III, the mean and median duration of disease was 10.3 and 8 years for the overall ITT population and 11.6 and 9.5 years for the TNF-alpha antagonist failure ITT sub-population.

- More patients in the TNF-alpha antagonist failure ITT sub-population had a disease duration of more than 7 years than in the overall ITT population (64% vs. 57%).

- Mean baseline disease activity, as assessed by baseline CDAI score, was similar for both the overall ITT population (307.7) and the TNF-alpha antagonist failure ITT sub-population (311.1).
- Approximately, one-third of patients in both populations had a CDAI score of >330. In the overall ITT population, 50% of patients had CRP levels of >10 mg/L.
- Of the 416 patients in the overall ITT population, 25% had failed 1 TNF-alpha antagonist, 41% had failed 2, and 8% had failed 3 such agents (Adalimumab, Certolizumab, Infliximab). In patients who had experienced TNF-alpha antagonist failure, 43% had an inadequate response (i.e., primary treatment failures) and 45% had loss of response (i.e., secondary treatment failures). With respect to concomitant medication, more than 50% were treated with corticosteroids and approximately 30% were treated with immunomodulators.

In summary a substantial proportion of patients enrolled in this study represents patients who have not been evaluated in previous published pivotal trials in Crohn's disease. In the overall population, almost half the patients failed 2 or more TNF-alpha antagonists and this represent a population with more severe disease that is difficult to treat with currently available therapies. In addition, potential treatment benefit was also demonstrated in patients' naïve to TNF-alpha antagonist therapy. This trial suggests that Vedolizumab provides benefit for the overall population of patients who have moderately to severely active Crohn's disease and are candidates for biological therapies, as well as for those who have failed 1 or more TNF-alpha antagonists and have limited treatment options. The efficacy data, although not statistically significant, suggest that patients who have previously failed TNF-alpha antagonist treatment, may achieve remission beyond the 6-week period of treatment and evaluation used for the primary analysis in this study. Analyses of the safety data reveal an acceptable safety profile for the target population.

6.10.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice

Crohn's disease is a chronic, relapsing disease for which there is no current cure. In many cases, patients will inevitably require additional lines of treatment following failure on or non-response to current treatments.

- The efficacy of 5-ASAs in Crohn's disease has been called into question by a meta-analysis (Akobeng & Gardner, 2005). The authors found no evidence to suggest that 5-ASA preparations are superior to placebo for the maintenance of medically-induced remission in patients with Crohn's disease.
- Corticosteroids, often required for patients who fail to respond to 5-ASAs, are highly effective for induction of remission, corticosteroids are not useful for maintenance of remission and carry significant undesirable side effects, including osteoporosis, glucose intolerance, and increased risk of infection (Cunliffe & Scott, 2002; McLean LP, 2012; Ricart et al., 2008)
- Immunomodulatory agents, including 6-mercaptopurine (6-MP) and azathioprine, have a role in maintenance of remission in moderate to severe Crohn's disease (Kandiel, Fraser, Korelitz, Brensinger, & Lewis, 2005; McLean LP, 2012). Their relatively slow onset of action precludes their use during flares of disease, and the use of these agents has been reported to potentially increase the risk of lymphoma in patients with IBD (Kandiel et al., 2005)
- For patients unsuitable for surgery, biologic agents, TNF-alpha antagonists, Infliximab and Adalimumab, have been proven useful for induction of remission in Crohn's disease. However, 50% of patients experience primary or secondary response failure when treated with Infliximab for Crohn's disease (van Assche, 2007). In addition, treatment with TNF-α antagonists has been associated with a number of serious adverse events involving hypersensitivity and infection. Reactivations of latent tuberculosis (Keane et al., 2001) and disseminated histoplasmosis have been reported, and in some cases have been fatal (Jean-Frederic Colombel et al., 2004).

From the patient's perspective, lack of disease control amounts to disease flares, complications that may require frequent hospitalisations, need for aggressive treatment or surgeries and the need for re-operations.

Following failure of medications, surgical intervention is the only current option. However, surgical removal of highly diseased, strictured, or stenotic segments of bowel in Crohn's disease is not curative. Relapse occurs in a majority of patients with Crohn's disease who undergo segmental resections, and the need for reoperation is the rule rather than the exception (Travis et al., 2008).The limitations of current therapies for IBD indicate that there is a significant need for additional therapies.

Vedolizumab, a gut-selective integrin inhibitor with a unique mode of action, has demonstrated clinical benefit through its pivotal studies in the overall population of patients who have moderately to severely active Crohn's disease and are candidates for biologic therapies, as well as for those who have failed 1 or more TNF-alpha antagonists and have limited treatment options. The safety data reveal an acceptable safety profile for this group of patients.

In the third line setting (after failure of conventional and anti-TNF-alpha therapies), clinical remission and clinical enhanced response rates in the anti-TNF-alpha- failure populations in both the GEMINI II and GEMINI III studies were higher in Vedolizumab-treated patients than in placebo-treated patients at Week 10, Differences from placebo were 7.4% (C13007) and 14.4% (C13011) for achieving remission, and 16.3% (C13007) and 22% (C13011) for achieving enhanced response. In view of the recognised unmet need, and the absence of a therapeutic alternative at present in this anti-TNF-alpha-failed population, Vedolizumab represents and important and clinical relevant addition to the treatment options in Crohn's disease.

In summary, the favourable safety profile of Vedolizumab compared with anti-TNF agents (lack of systemic immunosuppression, with no cases of extra-pulmonary or systemic TB with Vedolizumab in contrast to anti-TNF-alpha agents), the similarity of the efficacy of Vedolizumab to that of anti-TNF-alpha drugs, the delayed action of Vedolizumab, and the long-lasting efficacy in those who respond, combine to make Vedolizumab a useful option for second-line Crohn's disease patients.

6.10.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SmPC?

The EMA-approved administration schedule for initiation involves up to 3 doses of Vedolizumab before response can be evaluated for a prerequisite for continuation as a maintenance treatment, and not 2 as in the GEMINI trials.

From the SmPC:

"The recommended dose regimen of Entyvio [Vedolizumab] is 300 mg administered by intravenous infusion at 0, 2 and 6 weeks and then every 8 weeks thereafter.

Patients with Crohn's disease, who have not shown a response may benefit from a dose of Entyvio at Week 10. Continue therapy every 8 weeks from Week 14 in responding patients. Therapy for patients with Crohn's disease should not be continued if no evidence of therapeutic benefit is observed by Week 14

As presented in section 6, induction of remission in Crohn's disease may take up to 14 weeks in some patients. Although not fully known, the reasons for this may be related to the mechanism of action. According to the SmPC, this should be taken into consideration, particularly in patients with severe active disease at baseline not previously treated with TNF-alpha antagonists.

The EMA-approved dosing schedule does not differentiate between induction and maintenance, which reflects standard clinical practice. The 4-dose stopping rule is a pragmatic solution that offers patients an opportunity to achieve remission at 10 weeks if they do not meet response criteria at Week 6."

7 Cost effectiveness

7.1 Published cost-effectiveness evaluations

Identification of studies

7.1.1 Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 10.10, Appendix 10.

A systematic literature review was performed in April 2013 and was updated in March 2014. Searches were conducted via electronic medical databases. Bibliographic reference lists of included studies and systematic reviews were also screened for relevant publications.

The two searches were designed to yield economic evaluations of treatments for CD as well as studies of costs, resource use and utility values for CD. The results in this section are focussed on the cost-effectiveness analyses that were identified. Additional information on studies that assessed utility values in CD is provided in Sections 7.4.5, 7.4.6 and 7.4.7. Additional information on studies that assessed costs associated with treatment for CD is provided in Sections 7.5.3.

Original Search, April 2013

The following electronic databases were searched on April 16, 2013:

- MEDLINE, including MEDLINE in process (using PubMed platform)
- Embase (using Elsevier Platform)
- EconLit (using dialog platform)

- The Cochrane Library (using the Wiley platform), including the following:
    - The National Health Service's Economic Evaluation Database
    - Health Technology Assessment database

Date and Language Limitations

Electronic database searches encompassed articles that were published between 2003 and April 16, 2013. Searches before 2003 were not performed because no relevant economic evaluations were expected to be published more than 10 years ago: before that date, biologic drugs used in the treatment of UC had not been approved for use in the UK. Furthermore, resource use and cost studies published more than 10 years ago would be out of date; the resource use might not represent current practice and unit costs might not represent current prices.

No language limits were placed on the database searches.

Search Terms

Search terms for databases included combinations of free text and Medical Subject Headings (MeSH). The following types of terms were used:

Health condition of interest: Terms for CD (e.g., "Crohn Disease"[MeSH], "crohn disease")

Study type of interest: Economic evaluations, including cost-effectiveness, cost-utility, cost-minimisation, and cost-benefit analyses using economic models or analysis alongside clinical trials

Search terms relating to utility studies (e.g., "Quality-Adjusted Life Years" [MeSH], "EQ-5D," "time trade-off")

Search terms relating to cost and resource use studies (e.g., "Costs and Cost Analysis" [MeSH], Economics, medical [MeSH], "resource use")

Interventions (applied to economic evaluations only): Terms for VEDOLIZUMAB, Certolizumab (Cimzia), Natalizumab (Tysabri, Antegren),

Infliximab (Remicade), and Adalimumab (Humira), as appropriate for the disease of interest **Exclusionary terms: Unwanted publication types, using terms for comments, editorials, letters, and studies in animals but not in humans**

Section 10.10.4 presents the specific search terms. Table 10.10.4.1 presents the MEDLINE search strategy. This search strategy was adapted to search other electronic databases, and the specific search strategies are presented in the appendix

Inclusion and Exclusion Criteria

The selection of studies was guided by a pre-specified inclusion and exclusion criteria. 0 presents the inclusion and exclusion criteria. Non-UK resource use and cost studies were excluded. The review excluded any non-UK studies reporting costs; however, studies reporting productivity losses were included, irrespective of the country of analysis.

Table 7.1.1.1: List of criteria for the inclusion and exclusion of studies during the screening process

Criteria	Included	Excluded
Study type	Economic analyses Utility studies (including studies where utility weights were mapped from other instruments [e.g., disease-specific patient-reported outcome measures]) Prospective studies reporting costs or resource utilisation (e.g., observational studies, clinical trials)[a] Retrospective studies reporting costs or resource utilisation (e.g., cost of illness)[a] Systematic reviews of economic analyses, utility, resource use, or cost studies[b]	Commentaries and letters (publication type) Consensus reports Non-systematic reviews Articles reporting cost estimates that are not based on data (e.g., commentaries making general reference to cost burden)
Population	Patients (treatment naïve and treatment experienced) with CD	Patients who do not have CD
Interventions (applied to economic evaluations only)[c]	▪ Vedolizumab ▪ Certolizumab (Cimzia) ▪ Natalizumab (Tysabri, Antegren) ▪ Infliximab (Remicade) ▪ Adalimumab (Humira)	Economic evaluations that do not investigate one of the interventions of interest in at least one of the arms
Outcomes	▪ Utilities and costs by health states ▪ Indirect cost parameters ▪ Cost-effectiveness and/or cost-utility results for the interventions of interest	Overall annual disease national or per-patient costs

UC, ulcerative colitis; UK, United Kingdom.
[a] Resource use and cost studies from other countries than UK were excluded.
[b] Systematic reviews were used to identify primary studies but were not included in their own right. Systematic reviews were included at the level 1 screen. The full texts were obtained, and references lists were reviewed for relevant studies.
[c] Utility, resource use, and cost studies that are relevant to UC were included, regardless of the line of therapy and/or intervention investigated.

Study Selection Process

The literature review study-selection process occurred in the following two phases:

Level 1 screening: Titles and abstracts of studies identified from the electronic databases were reviewed by one researcher to determine each study's eligibility according to the inclusion and exclusion criteria. A second researcher performed a quality check of 5% of the titles and abstracts to ensure that the inclusion criteria were applied correctly.

Level 2 screening: Full texts of studies selected at level 1 were obtained and independently reviewed by two researchers to determine eligibility, using the same inclusion and exclusion criteria as applied at the level 1 screening.

Data were extracted from full-text publications where available. When a full-text journal publication was not available, the source used (e.g., abstract or poster) was noted.

Quality Control

Quality-control procedures for inclusion and exclusion of articles included the following:

At level 1 screening, a random selection (5%) of studies was checked by a second researcher. Some discrepancies were identified by this check; therefore, screening was performed by a second researcher on all of the abstracts. Any disagreements were resolved by consensus.

Full texts of studies selected at level 1 were reviewed by one researcher to determine eligibility at level 2 screening. Any uncertainties about inclusion were checked by a second researcher. A random selection (10%) of studies was checked by a second researcher. No discrepancies were identified by this check.

All extracted data were checked against the original sources.

Hand Search

The reference lists of five relevant systematic reviews (Liu et al., 2012; Binion et al., 2011; Yu et al., 2009; Kitchen et al., 2012; Tang et al., 2012), identified in the database searches, were searched for any potentially relevant articles that may have been

missed. Bibliographies of the economic evaluations also were searched for any relevant articles. Twenty-six articles potentially relevant to the economic review were identified from the bibliographies (systematic reviews = 11; economic evaluations = 15), of which 13 were not previously identified in the database searches and were selected for detailed screening (systematic reviews = 5; economic evaluations = 8). Therefore, the hand searches identified a total of 13 studies for level 1 screening.

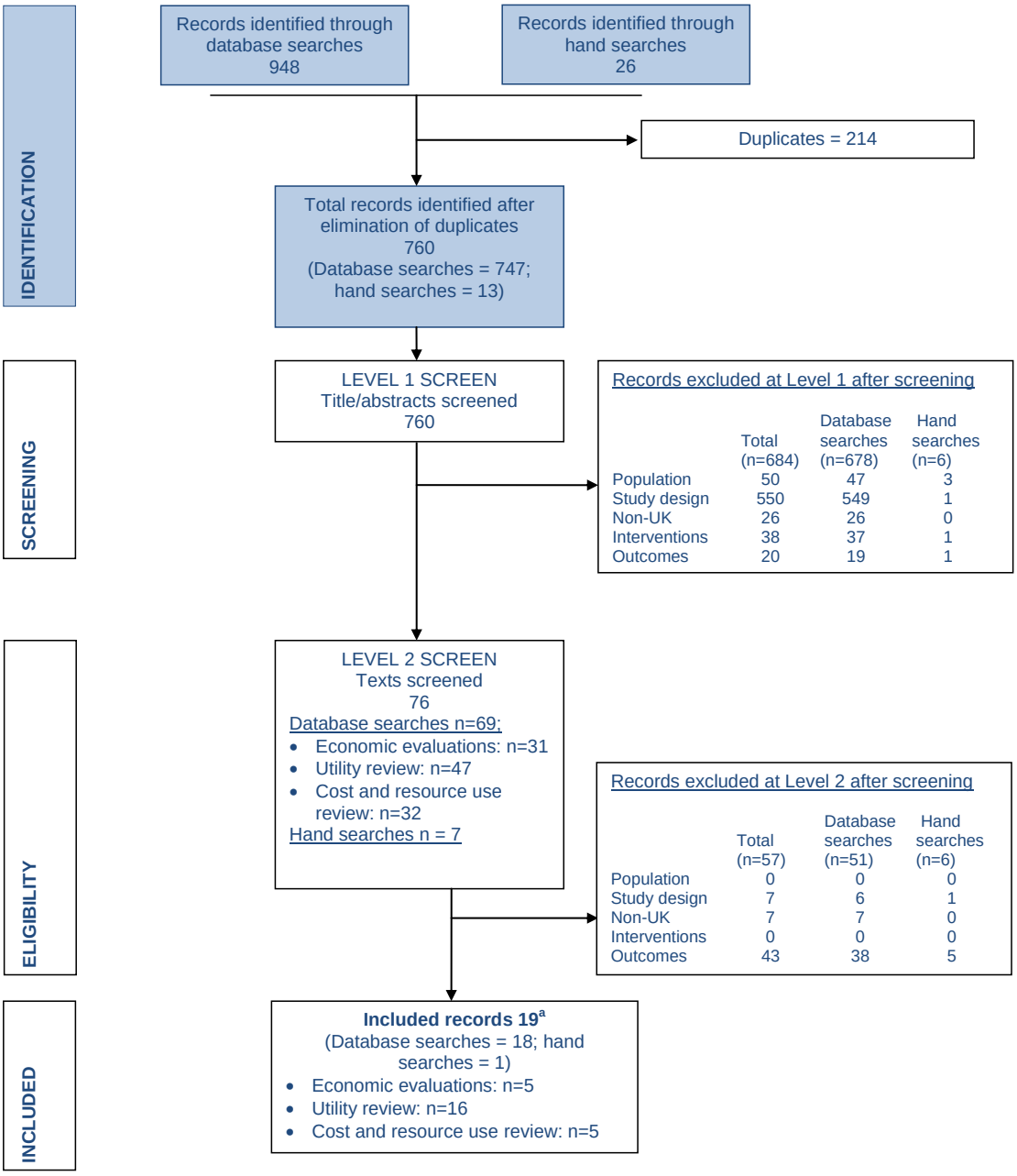
In the original search, a total of 760 records (titles and abstracts) were selected for level 1 screening (databases = 747; hand searches = 13). After the initial manual screening of titles and abstracts, 76 publications (database searches = 69; hand searches = 7) were progressed for level 2 screening of full-text articles. After the level 2 screening, 19 publications (database searches = 18; hand searches = 1) were selected for inclusion in the review.

In addition to these articles, one non-English article (Burgdorf et al., 2007) was identified. After consulting with Takeda Pharmaceuticals International, Inc., it was agreed that only English-language papers would be included in the data extraction.

Identified Studies in the Original Search (April 2013)

The number of studies included and excluded at each stage, the reasons for exclusion, and the study type are shown in the PRISMA flow diagram presented in 0.1.1.

Figure 1.1.1.1: PRISMA diagram for study inclusion and exclusion for the original search of economic evaluations, utility studies and cost and resource use studies, April 2013



PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Note: In the boxes labelled “Level 2 screen,” “Records excluded at Level 2 after screening,” and “Included records,” the number of economic evaluations, utility studies, and cost studies sum to more than the total for the database searches.

Second Search, March 2014

The literature search was updated in March, 2014 to ensure that additional economic evaluations, cost studies and utility studies published since April, 2013 would be included.

Criteria for considering studies for this review

The systematic review searched for economic evaluations as well as studies of the costs, resource use and utilities associated with UC and its treatment. The search strategy was based on the following PICOS elements:

- Participants: adults patients with CD (both treatment naive and treatment experienced)
- Intervention: VEDOLIZUMAB
- Comparators: Adalimumab, Infliximab and conventional therapy.
- Outcomes: humanistic burden (includes utility studies, PROs), direct costs, indirect costs, economic evaluations, resource utilisation
- Study design: all (excludes case studies and non-systematic reviews).

Inclusion criteria

- Economic analyses
- Utility studies (including studies where utility weights were mapped from other instruments [e.g., disease-specific patient-reported outcome measures])
- Prospective studies reporting costs or resource utilisation (e.g., observational studies, clinical trials)
- Retrospective studies reporting costs or resource utilisation (e.g., cost of illness)
- Systematic reviews of economic analyses, utility, resource use, or cost studies.

Exclusion criteria

- Commentaries and letters (publication type)
- Consensus reports
- Non-systematic reviews
- Articles reporting cost estimates that are not based on data (e.g., commentaries making general reference to cost burden)
- Cost studies reporting non-UK resource use estimates or costs.

Electronic searches

The key characteristics of the searches are listed below:

- Language: English
- Scope countries: No restrictions
- Time frame: April 2013 to March 2014, this includes both the hand search and the electronic search; the time frame is updated from an existing report which covers published material from 2003.
- Publication type/status: Publications excluded electronically if they were indexed as editorials, letters, case reports, commentaries, interview-based research, legal cases, newspaper articles or patient education handouts.

The specific search terms are based on EMTREE and MeSH. The search strategies are provided in Section 10.10, Appendix 10.

The databases searched for the literature review were:

- MEDLINE (Ovid SP) (searched 18/03/14)
- MEDLINE (R) In-Process Citations and Daily Updates (Ovid SP) (searched 18/03/14)
- EMBASE (Ovid SP) (searched 18/03/14)
- Econlit (searched 18/03/14)
- The Cochrane Library (searched 18/03/14)

The search strategies specific to each database were designed to focus retrieval on the published articles most likely to be relevant to the review questions. The search strategies and the searches were designed and performed by an experienced medical librarian.

Searching other resources

The electronic search was supplemented by hand searching in order to identify other published or unpublished material. Additional internet searches included a general internet search, and searches of the following websites for abstracts, slide presentations, and posters from relevant conferences:

- NICE Website
- Cost effectiveness analysis registry

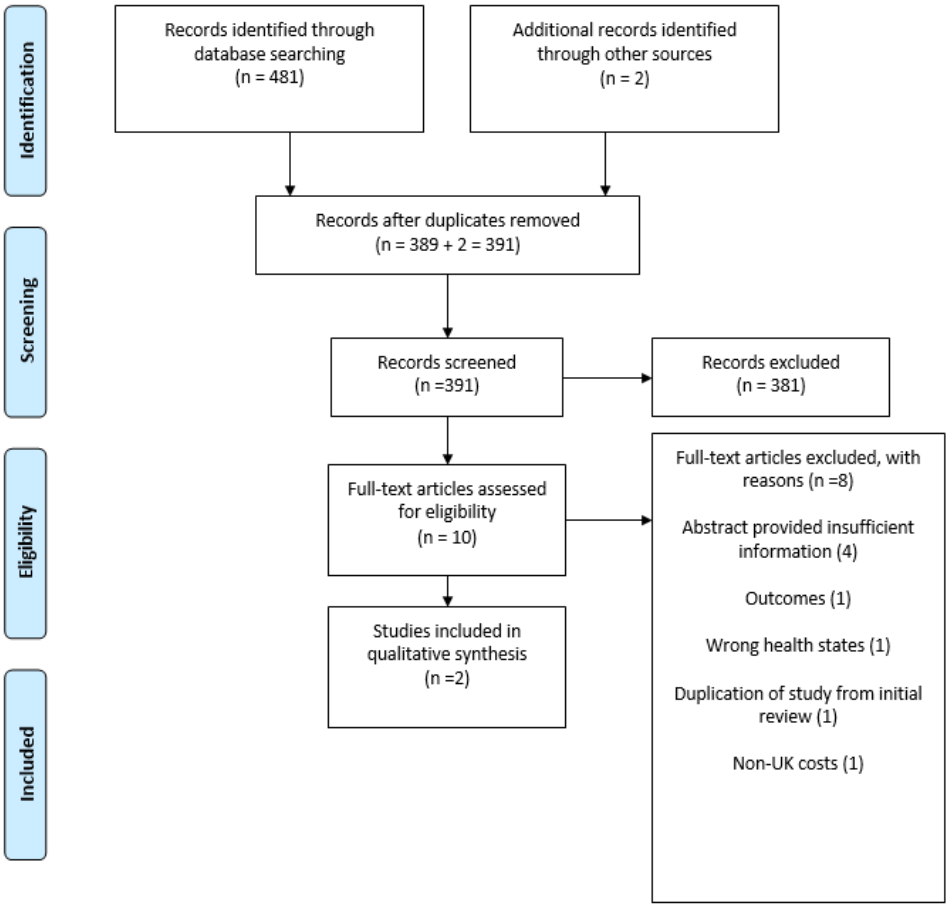
- International Society for Pharmacoeconomics and Outcomes Research: Research Digest, at http://www.ispor.org/research_study_digest/research_index.asp
- European Crohn's and Colitis Organisation, at https://www.ecco-ibd.eu/
- Digestive Disease Week
- United European Gastroenterology Week
- American College of Gastroenterology.

The search yielded 481 records. Of these, 92 were duplicates leaving 389 titles eligible for screening (Figure 1.1.1). A hand search of other resources, to identify any papers that may not have shown up in the database search, yielded 2 relevant titles. A total of 391 papers were therefore eligible for screening.

Of the 391 eligible papers, 381 were excluded on preliminary examination because they did not meet the inclusion criteria. This left 10 articles eligible for full text assessment. On full text assessment, 8 of the 10 articles were excluded; 5 were abstract only and contained insufficient information, 1 did not contain any relevant outcomes, 1 had already been identified in the initial systematic review, 1 was non-UK costs.

2 studies containing information relating to cost and resource use were found and met the inclusion criteria for the update to the systematic review. These two studies were costing studies, not cost-effectiveness analyses.

Figure 7.1.1.2: PRISMA diagram for study inclusion and exclusion for the second search of economic evaluations, utility studies and cost and resource use studies, March 2014



7.1.2	**Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.**

Table 7.1.2.1: Summary of economic analyses identified in the literature search

First Author (Year)	Publication Type, Country, Cost Year	Analysis or Model Type	Patient Population	Results			
				Interventions	**Cost**	**Outcome**	**ICER**
Dretzke (2011)	NICE Assessment Group model report, UK, 2005-2006	Cost-utility analysis; perspective = NHS and PSS Markov model; time horizon = 1 year, cycle length = 4 weeks The model states: remission, relapse, surgery, postsurgery remission Efficacy data derived from ACCENT I and CHARM. Transition probabilities for the SC states were the Olmstead County cohort study (Silverstein et al., 1999) Resource use and cost estimates were derived from the literature Where possible, health-state costs were taken from the NHS reference cost database Health-state utilities were derived from a widely cited study of HRQL (Gregor et al., 1997). Utility for surgery health state was assumed to be equivalent to EQ-5D state 22222 with utility weight of 0.516 One-way and probabilistic sensitivity analyses were conducted	Patients with moderate to severe, active CD (severe disease: CDAI > 300, moderate disease: 220 < CDAI ≤ 300)	**Cost-effectiveness over 1 year**	**Mean costs (£)**	**Mean QALYs**	**ICER (£ per QALY)**
				Infliximab, severe			
				MNT[a]	19,143	0.8957	£5.03M
				IND[a]	12,051	0.8943	Baseline
				Standard care	13,415	0.8119	Dominated
				Infliximab, moderate			
				MNT[a]	16,751	0.9245	£13.9M
				IND[a]	9573	0.9240	£94,321
				Standard care	6615	0.8926	Baseline
				Adalimumab, severe			
				MNT[b]	14,047	0.8956	£4.98M
				IND[b]	7053	0.8942	Baseline
				Standard care	13,421	0.8118	Dominated
				Adalimumab, moderate			
				MNT[b]	11,657	0.9236	£13.9M
				IND[b]	4583	0.9231	Baseline
				Standard care	6615	0.8922	Dominated

Bodger (2009)	Full article, UK, 2006-2007	Cost-utility analysis; perspective = NHS and PSS Markov model; time horizon = lifetime, cycle length = 8 weeks Health states: full response (CDAI score < 150), partial response (CDAI between 150 and 220), non response (CDAI score of between 220 and 600), surgery, and death SC transition probabilities were derived from the Olmstead County cohort study (Silverstein et al., 1999) Efficacy data were derived from ACCENT I (Infliximab) and CHARM (Adalimumab) trials Resource use and cost estimates were derived from a published UK study (Bassi et al., 2004) Utility weights for full, partial, and non response were based on EQ-5D utility scores calculated from midpoint CDAI scores using the algorithm developed by Buxton et al., 2007, where EQ-5D = 0.9168 – 0.0012 × CDAI Costs and QALYs were discounted at 3.5% per annum Probabilistic sensitivity analyses (1,000 simulations) were performed	Adult patients with moderate to severely active CD At model entry: 35-40 years of age, 40% men, at least 3 months since confirmed diagnosis of CD, CDAI score above 220	**Cost-effectiveness, lifetime analysis**	**Mean costs (£)**	**Mean QALYs**	**ICER vs. standard care (per QALY gained) (£)**
				Standard care	43,490	14.209	—
				Infliximab 5 mg/kg, 1 year	50,330	14.568	19,050
				Infliximab 5 mg/kg, 2 years	58,230	14.901	21,300
				Adalimumab 80 mg, 1 year	46,730	14.682	7,190
				Adalimumab 80 mg, 2 years	53,090	15.156	10,310

Loftus (2009)	Full article, UK, 2006	Cost-utility analysis; perspective = NHS and PSS Model does not appear to be Markov but has health states; time horizon = 1 year (base case) The model states: remission (< 150), moderate (≥ 150 to < 300), severe (≥ 300 to < 450), and very severe (≥ 450) Treatment efficacy and use for the Adalimumab arm were based on observations from CHARM A regression model used data from CLASSIC I to predict efficacy in patients who received non biologic pharmacotherapy Direct medical costs were derived from the literature (Bassi et al., 2004) Utilities were derived from the literature (Gregor et al., 1997) Univariate and multivariate analyses were conducted to determine the sensitivity of the model results Multivariate probabilistic analyses also were estimated	Patients with severe CD	**Cost-effectiveness at 56 weeks**	**Costs (£)**	**QALYS**	**ICER per QALY gained (£)**
				Adalimumab EOW	10,882	0.8516	16,064
				Non biologic	8,992	0.7339	—
			Patients with moderate-to-severe CD	**Cost-effectiveness at 56 weeks**	**Costs (£)**	**QALYS**	**ICER per QALY gained (£)**
				Adalimumab EOW	9,696	0.8647	33,731
				Non biologic	6,649	0.7743	—

Lindsay (2008)	Full article, UK, 2005-2006	Cost-utility analysis; perspective = NHS and PSS; Markov model; time horizon = 5 years, cycle length was selected to match the assessment visits in the ACCENT I and II trials[c] Health states: active, remission, non responding active, surgery, postsurgery remission, postsurgery complications, and death Efficacy sources: Targan et al., 1997, and ACCENT I (luminal); Present et al., 1999, and ACCENT II (fistulising). The transitions observed in the last assessment cycle in ACCENT trials (weeks 46-54) were used to extrapolate the analysis up to 5 years Transition probabilities for surgery and postsurgical states were obtained from the published literature Utilities were derived from the literature (Casellas et al., 2005) Costs and outcomes were discounted to present values at 3.5% per annum One-way and probabilistic sensitivity analyses were conducted	**Severe, active luminal CD** CDAI score between 220 and 400; history of CD for at least 3 months	**Cost-effectiveness at 5 years**	**Mean costs (£)**	**Mean QALYs**	**ICER per QALY gained (£)**
				Infliximab 5 mg/kg	31,499	2.145	26,128
				Standard care	26,627	1.959	—
			Fistulising CD Patients with a history of CD with single or multiple draining fistulae, including perianal fistulae and entero-cutaneous fistulae, for at least 3 months	**Cost-effectiveness at 5 years**	**Mean costs (£)**	**Mean QALYs**	**ICER per QALY gained (£)**
				Infliximab 5 mg/kg	37,488	2.449	29,752
				Standard care	31,490	2.247	—

Clark (2003)	Health technology assessment report, UK, cost year: NR	Cost-utility analysis; perspective = NHS and PSS; Markov model; time horizon = lifetime, cycle length = 8 weeks The health states: drug-dependent severe disease, drug-refractory disease state, drug responsive, medical remission, mild disease surgical remission, surgery, death Efficacy data were based on the 2 relevant published trials Utility values were based on a study by Gregor et al., 1997 Using the CDAI scores, these utility values were applied with interpolation to the 7 health states in the Olmstead County data Health-state costs estimated from an unpublished study of 38 UK patients for whom an average cost over 12 months was estimated. To make the results relevant to the UK, UK life tables were applied to the US data Costs and benefits were discounted at 6% and 1.5%, respectively A scenario analysis was used to test the results of an increased relapse rate	Chronic, active CD; mean start age: 37 years	**Cost-effectiveness over lifetime**	**Cost (£)**	**QALYs**	**Cost (£) per QALY**
				Infliximab compared with placebo (5 mg/kg)	NR	NR	93,244 (single dose) 62,016 (episodic)
				Infliximab compared with placebo (all doses)	NR	NR	135,333 (single dose) 72,261 (episodic)

7.1.3	**Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996) (Drummond & Jefferson, 1996) or Philips et al. (2004) (Philips et al., 2004). For a suggested format based on Drummond and Jefferson (1996), please see section 10.11, Appendix 11.**

Table 7.1.3.1: Quality assessment of economic analyses identified in the literature searches (Bodger, Clark and Dretzke studies)

Study identification Include author, title, reference, year of publication	**Bodger, K., Kikuchi, T., & Hughes, D. Cost-effectiveness of biological therapy for Crohn's disease: Markov cohort analyses incorporating United Kingdom patient-level cost data. (2009).**		**Clark, W., Raftery, J., & Barton, P. (n.d.). treatment of Crohn ' s disease, 2003**		**Dretzke J., Edlin. R., Round, J., Connock, M., Hulme, C., Czeczot, J., Meads, C. A systematic review and economic evaluation of the use of tumour. 2011**	
Section 1: Applicability (relevance to specific guideline review question(s) and the NICE reference case[a])		**Comments**		**Comments**		**Comments**
Is the study population appropriate for the guideline?	Yes	Adult patients with moderate to severely active Crohn's disease.	Yes	CD patients chronic active or fistulising disease	Yes	Patients with 'moderate-to-severe' CD
Are the interventions and services appropriate for the guideline?	Yes	Relevant for guidelines	Yes	Relevant for guidelines	Yes	Relevant for guidelines
Is the healthcare system in which the	Yes	N/A	Yes	N/A	Yes	N/A

study was conducted sufficiently similar to the current UK NHS context?						
Are costs measured from the NHS and personal social services (PSS) perspective?	Yes	UK NHS perspective	Yes	UK NHS perspective	Yes	UK NHS perspective
Are non-direct health effects on individuals excluded?	Unclear	No mention made of non direct health effects in the analysis	Yes	N/A	Yes	N/A
Are both costs and health effects discounted at an annual rate of 3.5%?	Yes	Cost and QALY both discounted at 3.5%	No	Discount rate of discounted at 6% and 1.5% respectively.	No	1 Year cycle, discounting therefore not applied.
Is the value of health effects expressed in terms of quality-adjusted life years (QALYs)?	Yes	N/A	Yes	N/A	Yes	N/A
Are changes in health-related quality of life (HRQL) reported	Yes	N/A	Yes	N/A	Yes	N/A

directly from patients and/or carers?						
Is the valuation of changes in HRQL (utilities) obtained from a representative sample of the general public?	Yes	N/A	Yes	N/A	Yes	N/A
Overall judgement: Directly applicable/Partially applicable/Not applicable	Directly applicable	Study meets all the above applicability criteria.	Directly applicable	Study meets all the above applicability criteria.	Directly applicable	Study meets all the above applicability criteria.
Other comments	.					
Section 2: Study limitations (the level of methodological quality)		**Comments**		**Comments**		**Comments**
Does the model structure adequately reflect the nature of the health condition under evaluation?	Yes	Typical patient profile used in developing the model	Yes	Reflects health condition.	Yes	Typical patient profile used in developing the model. Moderate to severe CD

Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	Lifetime horizon used to reflect possible differences between treatment	Yes	Life time horizon used	No	1 year time frame (with sensitivity analysis for 5 and 10 year time frames)
Are all important and relevant health outcomes included?	Unclear	No mention made of non direct health effects in the analysis	Unclear	Not much detail given as figures used copied from company submission	Partly	No mentions of adverse events
Are the estimates of baseline health outcomes from the best available source?	Yes	Extracted from existing literature	Yes	Formal search method used	Yes	N/A
Are the estimates of relative treatment effects from the best available source?	Yes	Systematic review conducted to determine best values to be used.	Unclear	No mention is made about how	Yes	Systematic review conducted to determine best values to be used.
Are all important and relevant costs included?	Partly	No mention of adverse events is made(Cost of managing adverse events might affect cost-effectiveness)	Unclear	Not much detail given as figures used copied from company submission	Partly	No mention of adverse events is made(Cost of managing adverse events might affect cost-effectiveness)

Are the estimates of resource use from the best available source?	Unclear	Although resource use is calculated, the source of this data is not explicitly mentioned.	Unclear	Not much detail given as figures used copied from company submission	Unclear	Although resource use is calculated, the source of this data is not explicitly mentioned.
Are the unit costs of resources from the best available source?	Partly	Only source of drug cost is mentioned	Unclear	Not much detail given as figures used copied from company submission	Yes	NHS national schedule of reference cost database 2005–6
Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	The ICER is calculated and reported.	Yes	The ICER is calculated and reported.	Yes	The ICER is calculated and reported.
Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Partly	Only deterministic sensitivity analysis carried out.	Partly	Only deterministic sensitivity analysis carried out.	Yes	Deterministic and PSA carried out
Is there no potential conflict of interest?	Yes	No conflict of interest declared	Unclear	No mention is made of conflict of interest	Yes	No conflict of interest declared

Overall assessment: Minor limitations/ Potentially serious limitations/ Very serious limitations	Potentially serious limitations	A broader range of sensitivity analysis required to test the robustness of input parameters	Potentially serious limitations	Additional sensitivity analysis will be useful. Also most of the figures used in the economic evaluation are extracted from an existing company submission without any clear reason given.	Minor limitations	N/A

Table 7.1.3.2: Quality assessment of economic analyses identified in the literature searches (Lindsay and Loftus studies)

Study identification Include author, title, reference, year of publication	**Lindsay, J., Punekar, Y. S., Morris, J., & Chung-Faye, G.,Health-economic analysis: cost-effectiveness of scheduled maintenance treatment with Infliximab for Crohn's disease--modelling outcomes in active luminal and fistulising disease in adults. Alimentary Pharmacology & Therapeutics, 2008.**		**Loftus, E. V, Johnson, S. J., Yu, A. P., Wu, E. Q., Chao, J., & Mulani, P. Cost-effectiveness of Adalimumab for the maintenance of remission in patients with Crohn's disease. European Journal of Gastroenterology & Hepatology, 2009**	
Section 1: Applicability (relevance to specific guideline review question(s) and the NICE		**Comments**		**Comments**

reference case[a])				
Is the study population appropriate for the guideline?	Yes	Patients suffering from active luminal or fistulising Crohn's disease.	Yes	N/A
Are the interventions and services appropriate for the guideline?	Yes	Relevant for guidelines	Yes	Relevant for guidelines
Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?	Yes	N/A	Yes	N/A
Are costs measured from the NHS and personal social services (PSS) perspective?	Yes	UK NHS perspective	Yes	UK NHS perspective
Are non-direct health effects on individuals excluded?	Unclear	No mention made of non direct health effects in the analysis	Yes	N/A
Are both costs and health effects discounted at an annual rate of 3.5%?	Yes	Cost and QALY both discounted at 3.5%	Yes	Cost and QALY both discounted at 3.5%

Is the value of health effects expressed in terms of quality-adjusted life years (QALYs)?	Yes	N/A	Yes	N/A
Are changes in health-related quality of life (HRQL) reported directly from patients and/or carers?	Yes	N/A	Yes	N/A
Is the valuation of changes in HRQL (utilities) obtained from a representative sample of the general public?	Yes	Obtained from Spanish public (n=200) and converted to utilities using a UK tariff	Yes	N/A
Overall judgement: Directly applicable/Partially applicable/Not applicable	Directly applicable	Study meets all the above applicability criteria.	Directly applicable	Study meets all the above applicability criteria.
Other comments				
Section 2: Study limitations (the level of methodological quality)		**Comments**		**Comments**
Does the model structure adequately reflect the nature of the health condition under evaluation?	Yes	Reflects health condition.	Yes	N/A

Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	5 year time frame	Yes	Lifetime horizon used to reflect possible differences between treatment
Are all important and relevant health outcomes included?	Partly	No mentions of adverse events	Yes	N/A
Are the estimates of baseline health outcomes from the best available source?	Yes	N/A	Unclear	No mention made of method used to select article
Are the estimates of relative treatment effects from the best available source?	Unclear	No mention is made about how	Unclear	No mention made of method used to select article
Are all important and relevant costs included?	Partly	No mention of adverse events is made(Cost of managing adverse events might affect cost-effectiveness)	Yes	N/A
Are the estimates of resource use from the best available source?	Yes	NHS national schedule of reference cost	Unclear	Although resource use is calculated, the source of this data is not explicitly mentioned.
Are the unit costs of resources from the best available source?	Yes	NHS national schedule of reference cost	Unclear	Source of data not mentioned

Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	The ICER is calculated and reported.	Yes	The ICER is calculated and reported.
Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	Deterministic and PSA carried out	Partly	Only deterministic sensitivity analysis carried out.
Is there no potential conflict of interest?	Yes	No conflict of interest declared	Yes	No conflict of interest declared
Overall assessment: Minor limitations/ Potentially serious limitations/ Very serious limitations	Minor limitations	N/A	Potentially serious limitations	A broader range of sensitivity analysis required to test the robustness of input parameters

7.2 De novo analysis

Patients

7.2.1 What patient group(s) is(are) included in the economic evaluation? Do they reflect the licenced indication/CE marking or the population from the trials in sections 1.3 and 6.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SmPC/IFU and included in the trials.

The population included in the model reflects the licensed population for Vedolizumab. Specifically, it includes patients with moderately to severely active CD (defined as a Crohn's Disease Activity Index [CDAI] score of 220 to 600) who have had an inadequate response with, lost response to, or are intolerant to either a conventional therapy or anti-TNFs. A series of analyses are conducted in various sub-groups of this patient population:

- Mixed population (includes both anti-TNF–naive and anti-TNF–failure patients, representing the intention to treat [ITT] population of the Vedolizumab trials)
- Anti-TNF–naive population
- Anti-TNF–failure population (both primary failure [no response] and secondary failure [loss of response after initially responding]). According to the GEMINI II and III trials, failure was defined as:
  - Signs and symptoms of persistently active disease despite a history of at least one 4-week induction regimen of Infliximab 5 mg/kg IV, two doses at least 2 weeks apart

    OR
  - Recurrence of symptoms during maintenance dosing following prior clinical benefit (discontinuation despite clinical benefit does not qualify)

    OR
  - History of intolerance of Infliximab (including, but not limited to, infusion-related reaction, demyelination, congestive heart failure, and infection)

The clinical trial for Infliximab included in the MTC was conducted in an anti-TNF–naive population only. Adalimumab has clinical data in both an anti-TNF–naive and an experienced (secondary failure) population, though the experienced population in Adalimumab clinical trials was not comparable to the Vedolizumab trial as it only included secondary failure patients (primary failure patients were excluded). Given the lack of data for Infliximab and the lack of comparable data for Adalimumab, we only compare Vedolizumab to other biologics in an anti-TNF–naive population. As such, the anti-TNF–failure and mixed populations are only used for comparison with conventional therapy.

In addition to these primary analyses, the model allows assessment of the cost-effectiveness of Vedolizumab, based on disease severity, defined by CDAI score:

- Moderate disease (CDAI 220-330) at baseline
- Severe disease (CDAI > 330) at baseline
- Severe disease at baseline, anti-TNF-Naïve
- Severe disease at baseline, anti-TNF-Failure
- Moderate disease at baseline, anti-TNF naïve
- Moderate disease at baseline, anti-TNF-Failure

7.2.2 Please provide a diagrammatical representation of the model you have chosen.

The model is in two parts: a decision-tree followed by a Markov model (as a cohort transition model). The decision-tree is used to capture the induction phase of treatment, in which patients are given a dosage of Vedolizumab (or a TNF-antagonist) so as to induce a response to treatment. The Markov model is used to capture the maintenance phase in which responding patients are treated to maintain that response. The chosen structure is consistent with recent modelling efforts (Bodger et al., 2009).

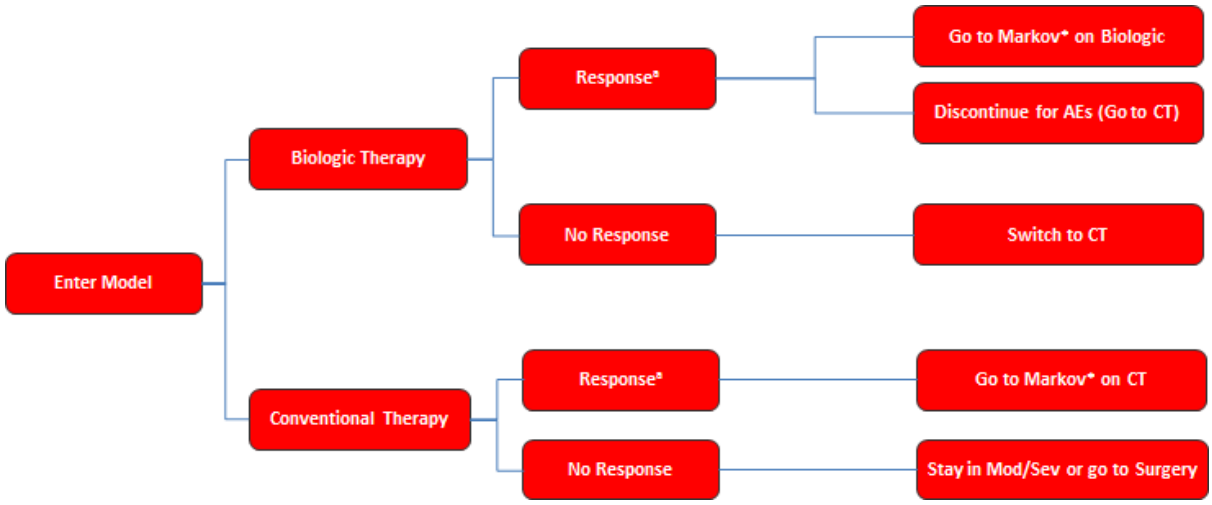
Previous models have been based upon health states of remission and relapse and did not consider partial response (Dretzke et al., 2011). We chose, instead, to use the structure outlined by Bodger and colleagues so as to better capture the treatment-

related impact on CD severity based on the CDAI, as recommended by the NICE Decision Support Unit (Wailoo et al., 2009). We adapted this model structure to include a decision tree for the induction phase and a Markov structure for the maintenance phase so as to most closely reflect the clinical trials.

Induction Phase (Decision Tree)

The induction phase of the model is intended to represent the induction phase of the clinical trials. During this phase, patients initiate treatment with Vedolizumab or one of the comparators: conventional therapy, Infliximab or Adalimumab (0).

Figure 7.2.2.1: Decision-tree for induction phase



AE = adverse event; CDAI = Crohn's Disease Activity Index; CT = conventional therapy.
[a] Response is defined as a drop in CDAI of 70 points or more. This includes patients who also achieve remission, as remission is a subset of response. Remission is defined as a CDAI score less than 150.
* The Markov structures can be seen in 0 below. The structures for biologic therapies and conventional therapies are similar, with differences arising in transition probabilities.

Patients who begin the model on a biologic therapy are monitored for response to the drug at the end of the 6-week induction phase. This duration was chosen to mirror the Vedolizumab clinical trials, which included a 6-week induction period. In a scenario analysis, we consider the impact of a 14-week induction period for Vedolizumab to reflect the license for the product. Patients who respond during the induction period and who do not discontinue due to adverse event intolerability then continue on maintenance therapy and enter the Markov model for maintenance therapy (0). Patients who fail to

respond to a biologic during the induction phase or who discontinue due to adverse events then switch to conventional therapy and then remain on conventional therapy for the remainder of the model.

Patients who enter the induction phase on conventional therapy may respond to treatment, in which case they enter the Markov model for conventional therapy (0). Patients who fail to respond are assumed to remain in moderate-severe disease for the remainder of the model time horizon or until they transition to surgery. Regardless of response status at the end of the induction phase, patients on conventional therapy remain on conventional therapy for the remainder of the model time horizon.

The 6-week duration of the induction phase was chosen to be consistent with the Vedolizumab clinical trials. However, it is important to note that not all of the biologics share the same duration of induction in their trials. Infliximab and Adalimumab, for example, measured response at week 8 in their trials. 0 presents the induction schedules for each of the biologic therapies

Table 7.2.2.1: Induction schedules for biologic therapies

Treatment	Trial Measurement of Response	Label Indication
Adalimumab[a]	▪ Week 4 (after doses at weeks 0 and 2) ▪ Week 8 (after doses at weeks 0, 2, 4, and 6)	• Induction: weeks 0 and 2 • Maintenance: starts at week 4, every other week thereafter • If no response at week 12, treatment should not be continued
Infliximab[b]	▪ Week 6 (after doses at weeks 0 and 2)	• Induction: weeks 0 and 2 • Maintenance: starts at week 6, every 8 weeks thereafter • If no response at week 6, treatment should not be continued
Vedolizumab[c]	▪ Induction response measured prior to week 6 dose (after doses at week 0 and 2) ▪ Week 10 (after doses at week 0 and 2, and 6) (in C13011 trial)	• Induction: weeks 0, 2, and 6 • Maintenance: starts at week 14, every 8 weeks thereafter • If no response at week 14, treatment should not be continued (differs from trial design: if no response at week 6, patients did not enter the induction phase)

[a] Week-4 data from CLASSIC-I (Hanauer et al., 2006), Sandborn et al. (2007a), and Watanabe et al. (2012). Week-8 data from ENACT-I trial (Sandborn et al., 2005).
[b] Based on the ACT-1 trial (Rutgeerts et al., 2004).

[c] Week-6 response data based on GEMINI II and GEMINI III trials (CSR C13007; CSR C13011). Week-10 data come from the GEMINI III trial (CSR C13011).

The model is based upon induction efficacy data as reported from the clinical trials. For Infliximab and Adalimumab, this means that patients received their dose at week 6 prior to assessment at week 8. For Vedolizumab, within the GEMINI II trial, patients received only their week 0 and week 2 doses before assessment at week 6. This is reflected in the model. In a sensitivity analysis, the proportion of patients at week 14 with response and remission who were treated with Vedolizumab or placebo is used in the model. It is assumed that these patients received Vedolizumab doses at weeks 0, 2, 6 and 10 and were assessed for response before receiving the dose at week 14.

For cost purposes, we assumed patients receive the following dosing in the induction phase:

- Vedolizumab: 300 mg at weeks 0 and 2
- Infliximab: 5 mg/kg at weeks 0, 2 and 6
- Adalimumab: 80 mg at week 0, 40 mg at week 2, 40 mg at weeks 4 and 6

These dosing assumptions are consistent with the trial-based doses from which the efficacy data were obtained.

Maintenance Phase

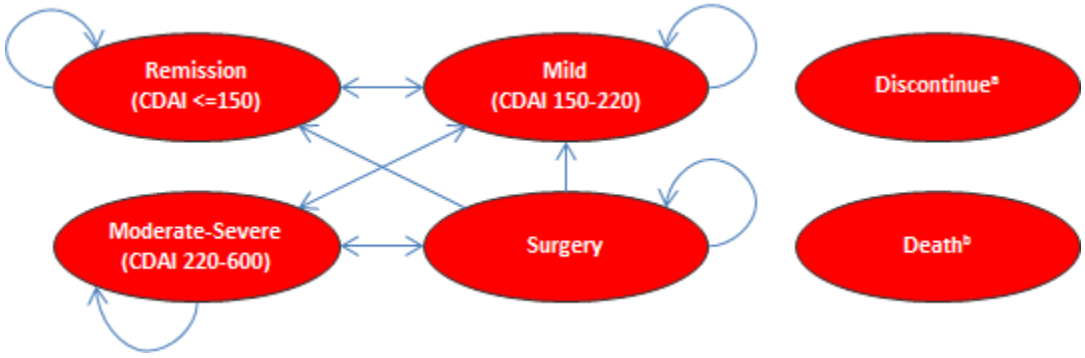
Patients on biologic therapy (Vedolizumab, Infliximab or Adalimumab) who respond to therapy enter the Markov model for maintenance treatment with the biologic. The underlying structure was adapted from a recently published UK economic analysis in CD (Bodger et al., 2009). The modelled health states are defined according to CDAI scores (0):

- Remission (CDAI < 150), which is equivalent to full response
- Mild (CDAI 150≤220)
- Moderate-Severe (CDAI 220-600)

Surgery, a mix of surgical procedures including panproctocolectomy with ileostomy or anal pouch formation, extended right hemicolectomy, drainage procedures, sigmoid colectomy, and ileal resection.

- Death

Figure 7.2.2.2: Markov model schematics for CD maintenance phase and beyond



[a] Reasons for discontinuation include lack of response and adverse events. Discontinuation due to adverse events is applicable only to responders on biologic treatments, because non responders on biologics switch to conventional therapy and continue receiving such until the end of the model's time horizon.
[b] Patients may transition to death from any health state during any cycle.

In the Markov model, patients may transition between each of the four health states (remission, mild, moderate-severe, and surgery). The probability of transition to each health state will depend on the patient's current health state as well as the current treatment.

In addition to these transitions among the disease severity health states, patients may experience death or (for those taking biologics) discontinue due to loss of response or adverse events. Patients may transition to death from any model health state in any cycle. Patients in the moderate-severe health state after 1 year on treatment will discontinue due to lack of response and switch to conventional therapy or surgery. Patients may experience death from any health state in the model. The model uses an age- and sex-specific mortality risk that increases with time. A mortality risk adjustment for time spent in each health state is also. The mortality inputs are described in more detail in Section 7.3.2.

Unlike economic models of ulcerative colitis, postsurgical health states (such as postsurgical remission and postsurgical complications) are not included in this model.

The reason for this is that surgery is curative in ulcerative colitis and patients do not take biologic therapy after surgery. In CD, surgery is palliative, not curative. As such, patients must continue to take therapy following surgery in order to manage their disease. Therefore, rather than having postsurgical health states, patients transition from surgery back onto active treatment in one of the CDAI-based health states.

7.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.5.

The model is intended to capture the relevant aspects of the clinical pathway: induction and maintenance treatment. The model makes appropriate comparisons with conventional therapy for patients that are anti-TNF naïve and / or anti-TNF-Failures. The model also makes comparison with biologics (Infliximab and Adalimumab) in patients that are anti-TNF naïve. These therapies represent the likely treatments that will be displaced by VEDOLIZUMAB and the therapies that patients may have received before being considered for treatment with VEDOLIZUMAB.

The severity of the disease as measured by the CDAI is the primary source for the health states as this is related to disease severity and quality of life and is considered the gold standard disease assessment tool (Yoshida et al. 1999). The CDAI was routinely measured within the trial, helped to determine entry to the maintenance phase of the GEMINI III trial and allows comparison with data from clinical trials of other biologics.

In addition, the model assesses the impact of different therapies on the probability of using surgery and the downstream impacts on costs and patient quality of life.

Finally, the model has a structure that is very similar to other models in the disease area that have been published or submitted to health technology assessment agencies

7.2.4 Please define what the health states in the model are meant to capture.

In the induction period, a decision tree is used to reflect the clinical problem: whether to continue therapy or not into the maintenance phase. The “health state” in this part of the

model is response (a drop of 70 or more points of the CDAI). This reflects the decision rule that was used in the GEMINI II clinical trial in order to re-randomise patients into the maintenance phase and allows comparison with Infliximab and Adalimumab which used this definition of response in clinical trials.

To model the maintenance period a Markov model is used. Three health states in the Markov model are based upon the CDAI. The CDAI is an index of eight factors, measuring disease severity: stool frequency, abdominal pain, an assessment of general well being, complications, medication use to control CD, presence of abdominal mass, haematocrit and deviation from standard weight. The model has health states for remission (CDA<150), mild disease (CDAI 150≤220) and moderate to severe disease (CDAI 220 - 600). These represent increasing severity of disease.

In addition to Mayo score, the model includes a surgery health state. In the model, surgery is defined as a mix of several procedures: including panproctocolectomy with ileostomy or anal pouch formation, extended right hemicolectomy, drainage procedures, sigmoid colectomy, and ileal resection. The costs of surgery are based upon the model by Bodger et al., 2009. Patients within the surgery health state may experience complications but do not enter specific post-surgical health states, as surgery is not curative, and the model captures patients returning to drug treatment for CD.

The model allows for patients to switch from a biologic to conventional therapy: as indicated by the “Discontinue” health state shown in Figure 11. Within the model, patients treated with Vedolizumab or another biologic that discontinue due to adverse events or a lack of response switch to conventional therapy.

Death is the absorbing health state of the model.

7.2.5	**How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.**

The model is primarily built upon patients transitioning through different health states of disease severity (defined by Mayo scores). The model is not progressive as CD is not a strictly progressive disease: in the model patients can transition to and from more severe health states. In addition to health states based upon the CDAI, the model captures patients moving to surgery and death.

7.2.6 Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

Table 7.2.6.1: Key feature of analysis

Factor	Chosen Values	Justification
Time Horizon	10 years	Previous models have used time horizons between 1 year and lifetime. 10 year time-horizon chosen to balance the lifetime nature of CD and 1-year clinical trial data. Other time horizons are used in scenario analyses.
Cycle Length	Induction (decision tree): 6 weeks Maintenance (Markov model): 8 weeks	6 weeks was the induction period of the GEMINI II trial. CDAI scores are likely to be relatively stable over an 8 week period
Half-cycle correction	Applied	Matches the reference case
Were health effects measured in QALYs; if not, what was used?	QALYs were used, as measured by the EQ-5D within the GEMINI III study	Matches the reference case
Discount of 3.5% for utilities and costs	Applied	Matches the reference case
Perspective (NHS)	An NHS perspective was used	Costs to PSS are likely to be minimal in this patient population

7.2.7 Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

Doses of Infliximab and Adalimumab are included in the model in line with their marketing authorisation. The treatment mix of conventional therapy is based upon the report of the IBD Audit Steering Group (Royal College of Physicians, 2013). Standard doses for conventional therapy are used in the model, as described in 0.

In the GEMINI II and III studies, patients randomised to receive Vedolizumab were allowed to receive conventional therapy. In the model it is assumed that patients that receive Vedolizumab, Infliximab or Adalimumab incur 50% of the costs of conventional therapy, as compared with patients that receive only conventional therapy.

Table 7.2.7.1: Treatment regimens for comparators of Crohn's disease treatment

Comparator	Regimens	
Vedolizumab	300 mg intravenous infusions at weeks 0, 2, and 6, and every 8 weeks thereafter	
Adalimumab	80 mg at week 0, 40 mg at week 2, and 40 mg on alternate weeks thereafter	
Infliximab	5 mg/kg intravenous infusions at weeks 0, 2, and 6, every 8 weeks thereafter	
Conventional therapy		
Treatment	**Dose and Frequency**	**% Use**
Aminosalicylates		
Balsalazide	1.5 g twice daily, adjusted according to response (maximum: 6 g daily)	5%
Mesalazine	1.2-2.4 g daily in divided doses	5%
Olsalazine	500 mg twice daily	5%
Sulfasalazine	500 mg 4 times daily	5%
Corticosteroids		
Budesonide	3 mg 3 times daily for up to 8 weeks	6%
Prednisolone	1 metered application (20 mg prednisolone) once or twice daily for 2 weeks	19%
Immunomodulators		
Azathioprine	1-3 mg/kg daily	57%
Mercaptopurine	Initially 2.5 mg/kg, adjusted according to response	10%
Methotrexate	10-25 mg once weekly	11%

7.2.8	**Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SmPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.**

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the 'response' criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology is particularly cost effective.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

The license for Vedolizumab states:

"Patients with Crohn's disease, who have not shown a response may benefit from a dose of Entyvio at Week 10 (see section 4.4). Continue therapy every eight weeks from Week 14 in responding patients. Therapy for patients with Crohn's disease should not be continued if no evidence of therapeutic benefit is observed by Week 14 (see section 5.1)."

The GEMINI II clinical trial was designed with an induction period of 6 weeks and patients enrolled in the maintenance phase of the trial based upon a CDAI response (a drop in the CDAI of 70 or more) at that time point. Patients that did not respond in the induction period continued to receive their original treatment: either Vedolizumab every four weeks or placebo. Response was assessed in these patients at week 10, although it

should be noted that response at this time point is based upon the partial Mayo score (i.e. without an endoscopy).

For the base case analysis of the model, and in line with the design of the GEMINI II trial, there is a treatment continuation rule at week 6 for Vedolizumab. But, in addition, a scenario analysis was conducted with the model, with the proportion of patients responding (and continuing treatment) and in remission being set to those observed at week 14.

Infliximab and Adalimumab have different continuation rules in their licensed indications: week 6 for Infliximab and week 12 for Adalimumab. Given the variety of assessment time points that could be chosen (weeks 6, 10, 12 and 14) and to simplify the model, one assessment point was chosen for the model (at week 6) for every comparator. In addition, in the scenario using a 14-week continuation rule, the patients that responded at week 14 were assumed to all be responders at week 6 (i.e. the proportion of patients that responded at week 14 was actually applied at week 6 within the model). However, it was also assumed in this scenario analysis that the Vedolizumab-treated patients received four doses before response assessment at week 14 (at baseline, week 2, Week 6 and Week 10).

Implementing the continuation rule requires a physician visit and a blood test (for haematocrit). To avoid potential double-counting the cost of implementing the continuation rule is assumed to be included within the health state costs of the model. For example, a patient in remission incurs costs of £236.52 per cycle (8 weeks). Within the model, it is assumed that this includes routine monitoring of CD.

The use of the CDAI is common in UC patients and predicts disease severity and quality of life. The CDAI score has been incorporated into clinical practice and is very similar to other disease severity scores used by clinicians. The additional burden to the NHS should be minimal.

Using a 6- or 14-week continuation rule limits the number of doses of Vedolizumab that patients will receive. In the case of a 6-week rule, patients would receive two doses at treatment start and 2 weeks later and would not be offered the 6-week dose if they have not responded at that time point. Similarly, in the case of a 14-week rule, patients would receive four doses, at weeks 0, 2, 6 and 10. Within the GEMINI II trial, 47.1% of patients responded at week 6 (106 patients of 225 randomised to Vedolizumab), and amongst the non-responders at week 6, an additional x patients responded at week 10 for an

overall response rate of x% at week 14 (x patients of y randomised to Vedolizumab). Therefore, approximately x-y% of patients would receive 2 or 4 doses of Vedolizumab, depending upon the different decision rule adopted.

Please see Section 7.7.9 for results of the cost-effectiveness of Vedolizumab using a scenario of a 14-week continuation rule.

7.3 Clinical parameters and variables

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical evidence section of the submission (section 6). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as a justification for the approach.

7.3.1 Please demonstrate how the clinical data were implemented into the model.

Population Baseline Characteristics

Patient baseline characteristics for age, sex and body weight in the model were the mean values from the pooled data of the trials included in the mixed treatment comparison. Within the model, age and sex are used to estimate the background mortality rate, while weight is used to estimate weight-based drug dosing.

Table 7.3.1.1: Patient characteristics

Parameter	Estimate
Age (years)	36.57
Percentage male	43.9%
Weight (kg)	68.89

Source: Pooled data from clinical trials in MTC. This MTC included the following studies: GEMINI III (2012); GEMINI II (2012); Hanauer et al. (2002); Colombel et al. (2007); Hanauer et al. (2006); Sandborn et al. (2007a); Sandborn et al. (2007b); Sandborn et al. (2007c) Sandborn et al. (2005); Rutgeerts et al. (2012); Schreiber et al. (2007); Schreiber et al. (2005); Watanabe et al. (2012); Winter et al. (2004); Sandborn et al. (2011); Sands et al. (2007); Ghosh et al. (2003); Targan et al. (1997).

Clinical Outcomes Data

Treatment efficacy includes response and remission data for the induction phase as well as the probability of being in remission or mild disease at the end of one year (the maintenance phase of the GEMINI II study).

The definitions of response and remission are as follows:

- Response: a decrease in CDAI score of 70 or more from baseline
- Remission: a CDAI score of 150 or less
- The modelled health states are defined as:
- Remission: a CDAI score of 150 or less
- Mild: a CDAI score of 150-220
- Moderate-severe: a CDAI score of greater than 220 (220-600)
- Surgery: a surgical intervention to resolve active CD symptoms

The following subsections outline the sources of clinical parameter estimates used in the model.

Response and Remission

For head-to-head comparisons between Vedolizumab and conventional therapy, the results of the Vedolizumab clinical trials, GEMINI III and GEMINI II, were used to estimate the response and remission percentages for each treatment.

For the comparison of Vedolizumab against Infliximab and Adalimumab, in the TNF-Naïve patient population, an indirect comparison was necessary as there are non head-to-head trial data. Hence, the clinical parameters for the comparisons with Infliximab and Adalimumab were drawn from the MTC, with the placebo arm of the clinical trials (which represents conventional therapy in the model) as the common comparator.

To estimate the efficacy of each biologic treatment, we estimated odds ratios using the response and remission data from the MTC (see Section 6.7). These odds ratios were then used to estimate the percentage of patients in each health state at the end of the induction period and at the end of the maintenance period for each of the treatment comparators.

The MTC generated odds ratios compared with placebo for response and remission in induction and maintenance separately for naive, experienced, and overall populations. The odds ratios were used to derive probabilities relative to a common comparator (conventional therapy), based on the odds ratio:

$$\frac{p2/(1-p2)}{p1/(1-p1)}$$

where *p2* is the probability of response or remission, respectively, for the biologic treatment and *p1* is the corresponding probability for conventional therapy. Given the probability of response or remission for conventional therapy, we solve for *p2* by rearranging the formula for the odds ratio.

0 and 0 present the odds ratios and the derived probability estimates of response and remission during the induction and maintenance phases using the MTC approach.

Table 7.3.1.2: Probability of achieving response/remission for naive patients during the induction period based on network meta-analysis

Treatment	Response		Remission	
	Odds ratio	**Probability**	**Odds ratio**	**Probability**
Vedolizumab[a]	1.82	53.01%	2.89	34.89%
Infliximab[b]	N/A	63.50%	N/A	37.00%
Adalimumab[a]	2.46	60.43%	2.31	29.92%
Conventional therapy[a]	1.00	38.33%	1.00	15.63%

[a] Estimated using a network meta-analysis including the studies listed in Appendix D. Odds ratios correspond to Figure 14 (Section 8.3.1.1) and Figure 19 (Section 8.3.1.6) of the MTC report (Ling et al., 2014).

[b] Due to an insufficient sample size in the Infliximab placebo-controlled trial (Targan et al., 1997), the averages of the week-2 and week-10 assessments from the ACT-1 trial were used to estimate a week-6 response for Infliximab (Rutgeerts et al., 2004).

Table 7.3.1.3: Probability of achieving response/remission for naive patients during the maintenance period based on network meta-analysis

Treatment	Response		Remission	
	Odds ratio	**Probability**	**Odds ratio**	**Probability**
Vedolizumab[a]	2.61	63.45%	2.95	49.37%
Infliximab[a]	3.42	69.44%	2.55	45.72%
Adalimumab[a]	1.47	49.35%	5.22	63.29%[b]
Conventional therapy[a]	1.00	39.91%	1.00	24.81%

[a] Estimated using a network meta-analysis including the studies listed in Appendix D. Odds ratios correspond to Figure 24 (Section 8.3.2.1) and Figure 25 (Section 8.3.2.3) of the MTC report (Ling et al., 2014).
[b] Note: Due to differences in the trial design for the Adalimumab maintenance trials, the odds ratio for remission is higher than the odds ratio for response for Adalimumab. As such, in the model we assume remission to be equal to response (49.35%).

0 presents the proportion of patients in response and remission for each treatment in the induction and maintenance phases. The data for the mixed population and the anti-TNF–failure population are based on the Vedolizumab clinical trials (GEMINI III and GEMINI II). Data for the naive population are based on the MTC (see Section 6.7).

Table 7.3.1.4: Probability of response and remission for each treatment

	Induction Phase Among Patients Who Enter the Model in Moderate-Severe Disease		End-of-Maintenance Phase Among Patients Who Responded in Induction Phase	
	Response	**Remission**	**Response**	**Remission**
Mixed population[a]				
Conventional therapy	33.80%	9.86%	35.29%	21.57%
Vedolizumab	48.02%	16.78%	47.40%	38.96%
Naive population				
Conventional therapy	38.33%	15.63%	39.91%	24.81%
Vedolizumab	53.01%	34.89%	63.45%	49.37%
Infliximab[b]	63.50%	34.50%	69.44%	45.71%
Adalimumab	60.43%	29.92%	49.35%	49.35%
Failure population[c]				
Conventional therapy	30.97%	10.18%	26.92%	12.82%
Vedolizumab	44.62%	13.08%	29.27%	28.05%

[a] Mixed population refers to a combination of anti-TNF–naive patients and anti-TNF–failure patients. For Vedolizumab, this is the intention to treat population of the clinical trial. Because Infliximab does not have a trial in anti-TNF–failure patients and because Adalimumab's trials with failure patients were only secondary failures, we only present the comparison with conventional therapy based on the GEMINI trial data.
[b] Infliximab data for the induction period is obtained from the ACCENT-1 trial (Rutgeerts et al., 2004), because the placebo-controlled Infliximab trial (Targan et al., 1997) included a very small sample size and did not measure a standard dosage of Infliximab.
[c] The anti-TNF–failure population includes both primary and secondary failure patients as reported in the GEMINI trials. Because Infliximab does not have a trial in anti-TNF–failure patients and because Adalimumab's trials with failure patients were only secondary failures, we only present the comparison with conventional therapy based on the GEMINI trial data.
Source: Response/remission probabilities for the mixed and anti-TNF–failure populations are obtained from the Studies C13007 and C13011 clinical study reports (CSR C13007, 2012; CSR C13011, 2012). Response/remission probabilities for the naive population are derived from odds ratios estimated in the mixed-treatment comparison (Ling et al., 2014). The odds ratios are applied relative to a pooled placebo estimate. As such, the probabilities do not mirror those from the clinical trials. See Appendix A for more details on these calculations.

Patients may respond to treatment without transitioning out of the moderate-severe health state. Data on the proportion of responders in moderate-severe disease for all therapies are not available. To estimate the percentage of patients who respond but remain in the moderate-severe health state during the induction phase, patient-level data from the Vedolizumab trials were used. Data from all patients who responded in the Vedolizumab trials were pooled and the proportion of responders whose CDAI score fell within each health state (remission, mild, and moderate-severe) was calculated. After

subtracting out the patients in remission, we were then able to estimate the percentage of responders in the mild and moderate-severe health states. The percentage of responders in the moderate-severe health state for each model population (mixed, anti-TNF-Naïve, anti-TNF-Failure) are provided in 0.

Table 7.3.1.5: Percentage of moderate-severe responders

Treatment	Mixed	Naive	Failure
All treatments	21.2%	17.8%	24.3%

Source: Calculated from pooled patient-level trial data from GEMINI III and GEMINI II. Due to lack of data for all comparators, we assumed the same percentages for all treatments.

Discontinuation

Within the model discontinuation of treatment can occur due to a lack of response in the induction phase or due to adverse events. In addition, it is assumed in the model that treatment with a biologic (Vedolizumab, Infliximab or Adalimumab) is limited to one year and all patients on therapy at week 5 of the model switch to conventional treatment.

Discontinuation due to adverse events is applicable only to responders on biologic treatments. Patients on conventional therapy are assumed to continue receiving conventional therapy until the end of the model's time horizon or until the patient transitions to the surgery health state. The data for discontinuation were obtained from those publications identified for the MTC (0). As not all of these trials reported discontinuation data, the data used in the model reflect those trials that did report discontinuation due to adverse events.

Table 7.3.1.6: Probability of discontinuation

Treatment	Mixed	Naive	Failure
Induction			
Vedolizumab	3.03%	3.07%	2.69%
Infliximab[a]	—	1.33%	—
Adalimumab	—	1.33%	—
Maintenance			
Vedolizumab	8.89%	6.06%	8.54%
Infliximab[a]	—	5.26%	—
Adalimumab	—	5.26%	—

Source: Data were obtained from those publications identified for the mixed-treatment comparison. However, not all of these trials reported discontinuation data. Data used in the model were from Final CSR C13007 (2012), Final CSR C13011 (2012), Hanauer et al. (2006), and Sandborn et al. (2007a).
[a] Due to lack of data, Infliximab discontinuation rates were assumed to be similar to Adalimumab.

Adverse Events

Unlike previous economic models, we have included the impact of adverse events. Adverse events for inclusion in the economic model were selected based on the opinion of two clinical experts selected based on their area of expertise and geographical location (one English-based consultant gastroenterologist and one Scottish-based consultant gastroenterologist). The corresponding treatment-specific adverse-event rates for the selected events were estimated from each relevant clinical trial. Specifically, data on the rates of adverse events for the ITT population of the induction and maintenance trials identified in the MTC were used. Any of these trials that reported adverse event data were included, although not all trials did report adverse events (0) presents the included adverse events and the corresponding probability of occurrence for each treatment.

Table 7.3.1.7: Probability of adverse events, by treatment

Adverse Event	Vedolizumab[a]	Infliximab[b]	Adalimumab[c]	Conventional Therapy[d]
Serious infection	1.54%	4.49%	1.80%	1.89%
Tuberculosis	0.00%	0.28%	0.00%	0.00%
Lymphoma	0.00%	0.00%	0.00%	0.08%
Acute hypersensitivity reactions	0.00%	0.00%	0.00%	0.74%
Skin Reactions	0.34%	0.00%	0.00%	0.16%

The trials included for adverse event estimates were those trials identified for the mixed-treatment comparison that included adverse event data. Specifically, these include [a] CSR C13007 (2012), CSR C13011 (2012); [b] Hanauer et al. (2002), Colombel et al. (2010); [c] Colombel et al. (2007), Hanauer et al. (2006), Rutgeerts et al. (2012), Sandborn et al. (2007a), and Watanabe et al. (2011).
[d] Pooled placebo data from the trials listed above (a-c).

Surgical Complications

Because surgery is modelled as a health state and postsurgical health states are not modelled, the incidence and cost of surgical complications is included within the surgery health state. Additional resource-use costs associated with surgical complications are included as one-time costs occurring during the same cycle in which the surgery occurred. The probabilities of various surgical complications are estimated from pooled data from systematically identified published literature on surgical intervention (0). The complications were included based on expert clinical opinion.

Table 7.3.1.8: Probabilities of surgery-related complications

Adverse Event	Proportion
Wound infection	8.13%
Prolonged ileus/bowel obstruction	4.52%
Intra-abdominal abscess	1.61%
Anastomotic leak	4.27%

Source: Pooled estimates from the following studies: McLeod et al. (2009), Milsom et al. (2001), Zurbuchen et al. (2013), Kusunoki et al. (1998), Fazio et al. (1996), Irvin et al. (1973), Eshuis et al. (2009), Maartenese et al. (2006), Ikeuchi et al. (2000), Cameron et al. (1992), Stocchi et al. (2008), Funayama et al. (2006).

7.3.2	**Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.**

To estimate transition probabilities used in the model, the percentage of patients in the remission and mild health states at the end of induction and at the end of 1 year were calibrated with the clinical trial data, and the transition probabilities were then calculated from that calibration. Linear programming was used to optimise the transition probabilities so as to minimise the sum of squared errors of the percentage of patients in remission and in mild disease at the end of one year. The procedure to calibrate the transition probabilities uses a Linear Programming solver engine provided within Microsoft Excel called Excel Solver. Details of the calculations are provided in Appendix 15, Section 10.15.

Results of this calibration procedure tend to show that the largest proportion of patients remain in their current state but that some patients transition into worsening and improving states in a manner that reflects general trends in bowel disease.

Transition probabilities from surgery to other health states were obtained from the study by Bodger et al., 2009. The probability of transitioning from surgery to surgery was quite high (33.75%) as reported in that study and, in a scenario analysis, the probability of transitioning from surgery to surgery is set to 0.072, proportionately adjusting the probabilities of transition from surgery to each other health state.

Table 7.3.2.1: Transition probabilities: mixed population

From/To	Remission	Mild	Moderate-Severe	Surgery
Vedolizumab				
Remission	0.994	0.006	0.000	0.000
Mild	0.049	0.593	0.358	0.000
Moderate-severe	0.000	0.063	0.910	0.027
Surgery	0.527	0.077	0.058	0.338
Conventional therapy				
Remission	0.833	0.167	0.000	0.000
Mild	0.000	0.566	0.434	0.000
Moderate-severe	0.000	0.000	0.973	0.027
Surgery	0.527	0.077	0.058	0.338

Source: Estimated based on response and remission data from the Vedolizumab clinical trials (CSR C13007, 2012; CSR C13011, 2012). Transition probabilities from surgery as reported in Bodger et al. (2009).

Table 7.3.2.2: Transition probabilities: naive population

From/To	Remission	Mild	Moderate-Severe	Surgery
Vedolizumab				
Remission	0.960	0.040	0.000	0.000
Mild	0.000	0.654	0.346	0.000
Moderate-severe	0.000	0.108	0.865	0.027
Surgery	0.527	0.077	0.058	0.338
Infliximab				
Remission	0.971	0.029	0.000	0.000
Mild	0.005	0.715	0.280	0.000
Moderate-severe	0.000	0.230	0.743	0.027
Surgery	0.527	0.077	0.058	0.338
Adalimumab				
Remission	0.995	0.005	0.000	0.000
Mild	0.013	0.494	0.494	0.000
Moderate-severe	0.000	0.000	0.973	0.027
Surgery	0.527	0.077	0.058	0.338
Conventional therapy				
Remission	0.882	0.118	0.000	0.000
Mild	0.001	0.603	0.396	0.000
Moderate-severe	0.000	0.033	0.940	0.027
Surgery	0.527	0.077	0.058	0.338

Source: Estimated based on response and remission data from the MTC (Ling et al., 2014). Transition probabilities from surgery as reported in Bodger et al. (2009).

Table 7.3.2.3: Transition probabilities: failure population

From/To	Remission	Mild	Moderate-Severe	Surgery
Vedolizumab				
Remission	0.983	0.017	0.000	0.000
Mild	0.000	0.500	0.500	0.000
Moderate-severe	0.000	0.000	0.973	0.027
Surgery	0.527	0.077	0.58	0.338
Conventional therapy				
Remission	0.784	0.216	0.000	0.000
Mild	0.000	0.598	0.402	0.000
Moderate-severe	0.000	0.015	0.958	0.027
Surgery	0.527	0.077	0.58	0.338

Source: Estimated based on response and remission data from the Vedolizumab clinical trials (CSR C13007, 2012; CSR C13011, 2012). Transition probabilities from surgery as reported in Bodger et al. (2009).

Mortality

Previous cost-effectiveness analyses have not incorporated mortality. However, given recent evidence on inflammatory bowel disease–related mortality (Button et al., 2010), deaths attributable to inflammatory bowel disease and other causes were considered in the model. To estimate this mortality, age- and sex-specific all-cause mortality was obtained for the UK (Office for National Statistics, 2011). The starting mortality rate in model cycle 1 is estimated based on the average age and sex distribution of the model's population. An exponential distribution was estimated to project mortality as the time horizon progressed. 0 shows the age- and sex-specific base mortality rate (based on UK data) used to estimate the initial mortality risk and the exponential rate of mortality increase over time.

Table 7.3.2.4: UK annual mortality rates (per 1,000 population)

Age (Years)	Annual Mortality Rate (per 1,000)	
	Males	Females
20-24	0.6	0.2
25-29	0.6	0.3
30-34	0.9	0.4
35-39	1.2	0.7
40-44	1.8	1.1
45-49	2.6	1.6
50-54	4.0	2.7
55-59	6.5	4.2
60-64	10.0	6.3
65-69	16.0	9.9
70-74	26.0	16.8
75-79	43.7	29.7
80-84	75.5	54.7
85 and over	152.7	136.9

UK, United Kingdom.
Source: Office for National Statistics (2011).

Using these data, an initial annual mortality rate of 0.0015 is estimated, which translates to a 6-week probability of 0.000174. Assuming an exponential function and fitting the curve to the data above, the per-cycle (8-week) mortality change factor was estimated to be 1.01385.

Mortality is then adjusted by health state based on available published literature. 0 shows the health-state–specific relative risk of mortality assumed for each health state. We also consider a scenario analysis in which no UC-related mortality is assumed.

Table 7.3.2.5: Relative mortality risk, by health state

Health state	Relative Risk
Remission[a]	1.00
Mild[a]	1.00
Moderate-severe[b]	1.90
Surgery[c]	1.30
Post surgery remission[c]	1.30
Post surgery complications[c]	1.30

[a] Assumed mortality risk similar to general population due to limited data availability.
[b] Button et al. (2010).
[c] Jess et al. (2007). Due to lack of available data, we assumed the same risk for patients in surgery and post surgery health states.

7.3.3	**Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.**

The first year of treatment is modelled in two parts: the first 6 weeks and the next 48 weeks. Thus, there are effectively different sets of transition probabilities for the induction and maintenance phase of the first year. After week 6, for the remainder of the ten years, transition probabilities are constant (with the exception of mortality). No formal assessment has been made of whether transition probabilities should vary with time thereafter. In line with previous models, and in the absence of any evidence to suggest that transition probabilities vary with time, it is assumed that after the induction phase, transition probabilities are constant.

7.3.4	**Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?**

Intermediate endpoints were not linked to final outcomes in the model.

7.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[1]:

- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

For purposes of validation, clinical experts reviewed a model specification document that outlined the structure of the model and the proposed calculations. This was to ensure that the proposed model structures closely reflected real-world clinical practice and that all model assumptions were clinically valid. The experts agreed with the model structure. In addition, the experts provided input on which adverse events to include in the model provided information on the treatment of surgical complications.

Clinical experts were selected based on their area of expertise and geographical location. One England-based consultant gastroenterologist and one Scotland-based consultant gastroenterologist were selected. Both participants declared no potential conflicts of interest.

The consultation process was threefold. The clinicians were first presented the model structure and its input parameters. A questionnaire was then distributed to the clinicians with the specific clinical questions required for the model development. The clinicians were then asked to review the final version of the model technical report and provide written comments, thereby validating the model assumptions. Some follow-up correspondence also took place via an email. Clinician expert opinion was used for validation purposes, to provide the list of important adverse events included in the model and to provide information on the treatment of surgical complications.

[1] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Summary of selected values

7.3.6	**Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.**

The table presented below provides a list of all the variables (including the values used, range (distribution)) that have been included in the cost effectiveness analysis.

Table 7.3.6.1: List of parameters

Parameter	Base Case Value	One-Way Sensitivity Analysis		Probabilistic Sensitivity Analysis			
		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	43.90%	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	0.79
Efficacy							
Efficacy –Initial response period							
Mixed Population (ITT)							
Conventional therapy (trial-based, 6-week data)		Conventional therapy efficacy - induction period (95% CI)			N		
Remission	9.86%	6.98%	13.16%	Beta	355	35	320
Response	33.80%	28.98%	38.80%	Beta	355	120	235

Vedolizumab (trial-based 6-week data)		Vedolizumab efficacy - induction period (95% CI)			N		
Remission	16.78%	13.40%	20.46%	Beta	429	72	357
Response	48.02%	43.31%	52.75%	Beta	429	206	223
Surgery		Percentage of patients requiring surgery (95% CI)					
Induction	2.03%	0.26%	5.55%	Beta	100	2	98
Maintenance	2.70%	0.50%	6.64%	Beta	100	3	97
Responders in moderate-severe		Percentage of responders in moderate-severe disease (95% CI)			**N**		
%f responders in MS	21.19%	16.22%	26.61%	Beta	236	50	186
TNF-Naive Population							
Conventional therapy (trial-based, 6-week data)		Conventional therapy efficacy - induction period (95% CI)			**N**		
Remission	9.45%	5.02%	15.08%	Beta	127	12	115
Response	38.71%	30.46%	47.30%	Beta	127	49	78
Vedolizumab (trial-based 6-week data)		Vedolizumab efficacy - induction period (95% CI)			N		
Remission	22.09%	16.08%	28.74%	Beta	163	36	127
Response	53.75%	46.09%	61.33%	Beta	163	88	75
Surgery		Percentage of patients requiring surgery (95% CI)					
Induction	2.03%	0.26%	5.55%	Beta	100	2	98
Maintenance	2.70%	0.50%	6.64%	Beta	100	3	97
Responders in moderate-severe		Percentage of responders in moderate-severe disease (95% CI)		N			

%f responders in MS	17.82%	11.03%	25.82%	Beta	101	18	83
Conventional therapy (MTC-based 6-week data)		Conventional therapy efficacy - induction period (95% CI)			N		
Remission	15.63%	11.68%	20.02%	Beta	286	45	244
Response	38.33%	32.81%	43.99%	Beta	286	111	178
Vedolizumab (MTC-based 6-week data)		Vedolizumab efficacy - induction period (95% CI)			N		
Remission	34.89%	27.78%	42.35%	Beta	163	57	106
Response	53.01%	45.34%	60.60%	Beta	163	86	77
Infliximab (MTC-based data)		Infliximab efficacy -initial response period (95% CI)			N		
Remission	34.50%	27.96%	41.35%	Beta	192	66	126
Response	63.50%	56.58%	70.15%	Beta	192	122	70
Adalimumab (MTC-based data)		Adalimumab efficacy -initial response period (95% CI)			N		
Remission	29.92%	20.17%	40.69%	Beta	75	22	53
Response	60.43%	49.21%	71.13%	Beta	75	45	30
Surgery (MTC-based data)		Percentage of patients requiring surgery (95% CI)					
Induction	2.03%	0.26%	5.55%	Beta	100	2	98
Maintenance	2.70%	0.50%	6.64%	Beta	100	3	97
Responders in moderate-severe		Percentage of responders in moderate-severe disease (95% CI)			N		
%f responders in MS	17.82%	11.03%	25.82%	Beta	101	18	83

TNF-Failure Population							
Conventional therapy (trial-based, 6-week data)		Conventional therapy efficacy - induction period (95% CI)			N		
Remission	10.18%	6.59%	14.43%	Beta	226	23	203
Response	30.97%	25.13%	37.14%	Beta	226	70	156
Vedolizumab (trial-based 6-week data)		Vedolizumab efficacy - induction period (95% CI)			N		
Remission	13.08%	9.27%	17.43%	Beta	260	34	226
Response	44.62%	38.63%	50.68%	Beta	260	116	144
Surgery		Percentage of patients requiring surgery (95% CI)					
Induction	2.03%	0.26%	5.55%	Beta	100	2	98
Maintenance	2.70%	0.50%	6.64%	Beta	100	3	97
Responders in moderate-severe							
%f responders in MS	24.26%	17.46%	31.78%	Beta	136	33	103
Mixed Moderate Population					N		
Conventional therapy (trial-based, 6-week data)		Conventional therapy efficacy - induction period (95% CI)					
Remission	7.25%	2.43%	14.38%	Beta	69	5	64
Response	31.88%	21.51%	43.26%	Beta	69	22	47
Vedolizumab (trial-based 6-week data)		Vedolizumab efficacy - induction period (95% CI)			N		
Remission	25.00%	17.33%	33.54%	Beta	108	27	81
Response	59.26%	49.89%	68.30%	Beta	108	64	44
Surgery		Percentage of patients requiring surgery (95% CI)			N		
Induction	2.03%	0.26%	5.55%	Beta	100	2	98

Maintenance	2.70%	0.50%	6.64%	Beta	100	3	97
Responders in moderate-severe					N		
%f responders in MS	0.00%	0.00%	0.00%	Beta	129	0	129
Mixed severe population							
Conventional therapy (trial-based, 6-week data)		Conventional therapy efficacy - induction period (95% CI)			N		
Remission	4.41%	0.93%	10.37%	Beta	68	3	65
Response	23.53%	14.31%	34.22%	Beta	68	16	52
Vedolizumab (trial-based 6-week data)		Vedolizumab efficacy - induction period (95% CI)		N			
Remission	10.19%	5.24%	16.52%	Beta	108	11	97
Response	38.89%	29.95%	48.22%	Beta	108	42	66
Surgery		Percentage of patients requiring surgery (95% CI)		N			
Induction	2.03%	0.26%	5.55%	Beta	100	2	98
Maintenance	2.70%	0.50%	6.64%	Beta	100	3	97
Responders in moderate-severe				N			
%f responders in MS	46.73%	37.40%	56.18%	Beta	107	50	57
Moderate Naive population							
Conventional therapy (trial-based, 6-week data)		Conventional therapy efficacy - induction period (95% CI)			N		
Remission	7.89%	1.70%	18.19%	Beta	38	3	35
Response	34.21%	20.21%	49.79%	Beta	38	13	25
Vedolizumab (trial-based 6-week data)		Vedolizumab efficacy - induction period (95% CI)					
Remission	33.33%	22.57%	45.05%	Beta	66	22	44

Response	66.67%	54.95%	77.43%	Beta	66	44	22
Surgery		Percentage of patients requiring surgery (95% CI)					
Induction	2.03%	0.26%	5.55%	Beta	100	2	98
Maintenance	2.70%	0.50%	6.64%	Beta	100	3	97
Responders in moderate-severe					N		
%f responders in MS	0.00%	0.00%	0.00%	Beta	49	0	49
Conventional therapy (MTC-based 6-week data)		Conventional therapy efficacy - induction period (95% CI)			N		
Remission	9.45%	5.02%	15.08%	Beta	127	12	115
Response	38.71%	30.46%	47.30%	Beta	127	49	78
Vedolizumab (MTC-based 6-week data)		Vedolizumab efficacy - induction period (95% CI)			N		
Remission	22.09%	16.08%	28.74%	Beta	163	36	127
Response	53.75%	46.09%	61.33%	Beta	163	88	75
Infliximab (MTC-based data)		Infliximab efficacy -initial response period (95% CI)			N		
Remission	0.00%	0.00%	0.00%	Beta	0	0	0
Response	0.00%	0.00%	0.00%	Beta	0	0	0
Adalimumab (MTC-based data)		Adalimumab efficacy -initial response period (95% CI)			N		
Remission	0.00%	0.00%	0.00%	Beta	0	0	0
Response	0.00%	0.00%	0.00%	Beta	0	0	0
Surgery (MTC-based data)		Percentage of patients requiring surgery (95% CI)			N		
Induction	2.03%	0.26%	5.55%	Beta	100	2	98
Maintenance	2.70%	0.50%	6.64%	Beta	100	3	97

Responders in moderate-severe		Percentage of responders in moderate-severe disease (95% CI)					
%f responders in MS	0.00%	0.00%	0.00%	Beta	49	0	49
Severe Naïve population							
Conventional therapy (trial-based, 6-week data)		Conventional therapy efficacy - induction period (95% CI)			N		
Remission	6.67%	0.85%	17.76%	Beta	30	2	28
Response	23.33%	10.30%	39.72%	Beta	30	7	23
Vedolizumab (trial-based 6-week data)		Vedolizumab efficacy - induction period (95% CI)					
Remission	13.79%	6.26%	23.68%	Beta	58	8	50
Response	43.10%	30.74%	55.92%	Beta	58	25	33
Surgery		Percentage of patients requiring surgery (95% CI)					
Induction	2.03%	0.26%	5.55%	Beta	100	2	98
Maintenance	2.70%	0.50%	6.64%	Beta	100	3	97
Responders in moderate-severe					N		
%f responders in MS	46.15%	30.98%	61.70%	Beta	49	18	21
Conventional therapy (MTC-based 6-week data)		Conventional therapy efficacy - induction period (95% CI)			N		
Remission	8.93%	6.31%	11.94%	Beta	392	35	357
Response	32.14%	27.61%	36.84%	Beta	392	126	266
Vedolizumab (MTC-based 6-week data)		Vedolizumab efficacy - induction period (95% CI)					
Remission	11.52%	7.94%	15.66%	Beta	260	30	230
Response	45.96%	39.95%	52.03%	Beta	260	119	141

Infliximab (MTC-based data)		Infliximab efficacy -initial response period (95% CI)					
Remission	0.00%	0.00%	0.00%	Beta	0	0	0
Response	0.00%	0.00%	0.00%	Beta	0	0	0
Adalimumab (MTC-based data)		Adalimumab efficacy -initial response period (95% CI)		N			
Remission	25.50%	19.05%	32.53%	Beta	159	41	118
Response	49.77%	42.04%	57.51%	Beta	159	79	80
Surgery (MTC-based data)		Percentage of patients requiring surgery (95% CI)		N			
Induction	2.03%	0.26%	5.55%	Beta	100	2	98
Maintenance	2.70%	0.50%	6.64%	Beta	100	3	97
Responders in moderate-severe		Percentage of responders in moderate-severe disease (95% CI)			N		
%f responders in MS	46.15%	30.98%	61.70%	Beta	39	18	21
Moderate TNF-Failure population					N		
Conventional therapy (trial-based, 6-week data)		Conventional therapy efficacy - induction period (95% CI)					
Remission	6.90%	0.88%	18.35%	Beta	29	2	27
Response	24.14%	10.69%	40.95%	Beta	29	7	22
Vedolizumab (trial-based 6-week data)		Vedolizumab efficacy - induction period (95% CI)					
Remission	12.82%	4.41%	24.80%	Beta	39	5	34
Response	46.15%	30.98%	61.70%	Beta	39	18	21
Surgery		Percentage of patients requiring surgery (95% CI)					
Induction	2.03%	0.26%	5.55%	Beta	100	2	98
Maintenance	2.70%	0.50%	6.64%	Beta	100	3	97

Responders in moderate-severe							
%f responders in MS	0.00%	0.00%	0.00%	Beta	80	0	80
Severe TNF-failure population					N		
Conventional therapy (trial-based, 6-week data)		Conventional therapy efficacy - induction period (95% CI)					
Remission	0.00%	0.00%	0.00%	Beta	29	0	29
Response	20.69%	8.30%	36.89%	Beta	29	6	23
Vedolizumab (trial-based 6-week data)		Vedolizumab efficacy - induction period (95% CI)					
Remission	7.50%	1.62%	17.32%	Beta	40	3	37
Response	35.00%	21.20%	50.22%	Beta	40	14	26
Surgery		Percentage of patients requiring surgery (95% CI)					
Induction	2.03%	0.26%	5.55%	Beta	100	2	98
Maintenance	2.70%	0.50%	6.64%	Beta	100	3	97
Responders in moderate-severe							
%f responders in MS	49.25%	37.43%	61.12%	Beta	67	33	34
Transition probabilities (post-induction)							
Mixed Population (ITT)							
Vedolizumab							
Remission to:		VDZ transition probabilities: remission (95% CI)			N		
Remission	99.36%	97.63%	99.98%	Dirichlet	154	153	138
Mild	0.64%	2.37%	0.02%	Dirichlet	154	1	0
Moderate-to-severe	0.00%	0.00%	0.00%	Dirichlet	154	0	0

Surgery	0.00%	0.00%	0.00%	Dirichlet	154	0	0
Mild to:		VDZ transition probabilities: mild (95% CI)					
Remission	4.90%	5.84%	3.98%	Dirichlet	154	8	6
Mild	59.31%	51.48%	66.92%	Dirichlet	154	91	74
Moderate-to-severe	35.79%	42.69%	29.10%	Dirichlet	154	55	49
Surgery	0.00%	0.00%	0.00%	Dirichlet	154	0	0
Moderate-to-severe to:		VDZ transition probabilities: moderate-severe (95% CI)					
Remission	0.00%	0.00%	0.00%	Dirichlet	154	0	0
Mild	6.34%	3.07%	10.68%	Dirichlet	154	10	11
Moderate-to-severe	90.96%	94.14%	86.75%	Dirichlet	154	140	132
Surgery	2.70%	2.79%	2.58%	Dirichlet	154	4	8
Conventional therapy							
Remission to:		CT transition probabilities: remission (95% CI)			N		
Remission	83.28%	76.99%	88.74%	Dirichlet	153	127	155
Mild	16.72%	23.01%	11.26%	Dirichlet	153	26	18
Moderate-to-severe	0.00%	0.00%	0.00%	Dirichlet	153	0	0
Surgery	0.00%	0.00%	0.00%	Dirichlet	153	0	0
Mild to:		CT transition probabilities: mild (95% CI)					
Remission	0.00%	0.00%	0.00%	Dirichlet	153	0	0
Mild	56.57%	48.67%	64.30%	Dirichlet	153	87	92
Moderate-to-severe	43.43%	51.33%	35.70%	Dirichlet	153	66	60

Surgery	0.00%	0.00%	0.00%	Dirichlet	153	0	0
Moderate-to-severe to:		CT transition probabilities: moderate-severe (95% CI)					
Remission	0.00%	0.00%	0.00%	Dirichlet	153	0	0
Mild	0.00%	0.00%	0.00%	Dirichlet	153	0	0
Moderate-to-severe	97.30%	97.30%	97.30%	Dirichlet	153	149	145
Surgery	2.70%	2.70%	2.70%	Dirichlet	153	4	3
Surgery							
Surgery to:		Surgery transition probabilities (95% CI)			N		
Remission	52.72%	44.81%	60.56%	Dirichlet	153	81	77
Mild	7.71%	9.00%	6.43%	Dirichlet	153	12	16
Moderate-to-Severe	5.82%	6.79%	4.85%	Dirichlet	153	9	8
Surgery	33.75%	39.39%	28.15%	Dirichlet	153	52	40
TNF-Naive Population							
Vedolizumab		VDZ transition probabilities: remission (95% CI)			N		
Remission to:	97.44%	92.53%	99.76%	Dirichlet	66	64	70
Remission	2.56%	7.47%	0.24%	Dirichlet	66	2	1
Mild	0.00%	0.00%	0.00%	Dirichlet	66	0	0
Moderate-to-severe	0.00%	0.00%	0.00%	Dirichlet	66	0	0
Surgery							

Mild to:		VDZ transition probabilities: mild (95% CI)					
Remission	14.13%	18.17%	10.25%	Dirichlet	66	9	4
Mild	57.95%	45.94%	69.50%	Dirichlet	66	38	40
Moderate-to-severe	27.92%	35.89%	20.25%	Dirichlet	66	18	16
Surgery	0.00%	0.00%	0.00%	Dirichlet	66	0	0
Moderate-to-severe to:		VDZ transition probabilities: moderate-severe (95% CI)					
Remission	0.00%	0.00%	0.00%	Dirichlet	66	0	0
Mild	15.12%	7.61%	24.63%	Dirichlet	66	10	11
Moderate-to-severe	82.18%	89.45%	72.98%	Dirichlet	66	54	47
Surgery	2.70%	2.94%	2.40%	Dirichlet	66	2	0
Conventional therapy							
Remission to:		CT transition probabilities: remission (95% CI)			N		
Remission	92.51%	85.40%	97.38%	Dirichlet	71	66	62
Mild	7.49%	14.60%	2.62%	Dirichlet	71	5	7
Moderate-to-severe	0.00%	0.00%	0.00%	Dirichlet	71	0	0
Surgery	0.00%	0.00%	0.00%	Dirichlet	71	0	0
Mild to:		CT transition probabilities: mild (95% CI)					
Remission	3.55%	4.52%	2.61%	Dirichlet	71	3	2
Mild	57.62%	46.03%	68.79%	Dirichlet	71	41	39
Moderate-to-severe	38.84%	49.45%	28.60%	Dirichlet	71	28	33

Surgery	0.00%	0.00%	0.00%	Dirichlet	71	0	0
Moderate-to-severe to:		CT transition probabilities: moderate-severe (95% CI)					
Remission	0.00%	0.00%	0.00%	Dirichlet	71	0	0
Mild	6.63%	2.12%	13.41%	Dirichlet	71	5	1
Moderate-to-severe	90.67%	95.05%	84.08%	Dirichlet	71	64	56
Surgery	2.70%	2.83%	2.50%	Dirichlet	71	2	0
Surgery							
Surgery to:		Surgery transition probabilities (95% CI)		N			
Remission	52.72%	41.15%	64.14%	Dirichlet	71	37	31
Mild	7.71%	9.60%	5.85%	Dirichlet	71	5	4
Moderate-to-Severe	5.82%	7.24%	4.41%	Dirichlet	71	4	4
Surgery	33.75%	42.01%	25.60%	Dirichlet	71	24	20
Vedolizumab (MTC-based data)							
Remission to:		VDZ transition probabilities: remission (95% CI)			N		
Remission	95.98%	90.12%	99.26%	Dirichlet	66	63	64
Mild	4.02%	9.88%	0.74%	Dirichlet	66	3	4
Moderate-to-severe	0.00%	0.00%	0.00%	Dirichlet	66	0	0
Surgery	0.00%	0.00%	0.00%	Dirichlet	66	0	0
Mild to:		VDZ transition probabilities: mild (95% CI)					
Remission	0.00%	0.00%	0.00%	Dirichlet	66	0	0

Mild	65.44%	53.65%	76.34%	Dirichlet	66	43	41
Moderate-to-severe	34.56%	46.35%	23.66%	Dirichlet	66	23	32
Surgery	0.00%	0.00%	0.00%	Dirichlet	66	0	0
Moderate-to-severe to:		VDZ transition probabilities: moderate-severe (95% CI)					
Remission	0.00%	0.00%	0.00%	Dirichlet	66	0	0
Mild	10.83%	4.59%	19.30%	Dirichlet	66	7	14
Moderate-to-severe	86.47%	92.52%	78.25%	Dirichlet	66	57	53
Surgery	2.70%	2.89%	2.44%	Dirichlet	66	2	1
Conventional therapy (MTC-based data)							
Remission to:		CT transition probabilities: remission (95% CI)			N		
Remission	88.16%	83.33%	92.26%	Dirichlet	199	175	182
Mild	11.84%	16.67%	7.74%	Dirichlet	199	24	26
Moderate-to-severe	0.00%	0.00%	0.00%	Dirichlet	199	0	0
Surgery	0.00%	0.00%	0.00%	Dirichlet	199	0	0
Mild to:		CT transition probabilities: mild (95% CI)					
Remission	0.10%	0.11%	0.08%	Dirichlet	199	0	0
Mild	60.31%	53.43%	66.98%	Dirichlet	199	120	134
Moderate-to-severe	39.60%	46.45%	32.94%	Dirichlet	199	79	92
Surgery	0.00%	0.00%	0.00%	Dirichlet	199	0	0

Moderate-to-severe to:		CT transition probabilities: moderate-severe (95% CI)					
Remission	0.00%	0.00%	0.00%	Dirichlet	199	0	0
Mild	3.26%	1.27%	6.13%	Dirichlet	199	6	6
Moderate-to-severe	94.04%	95.97%	91.25%	Dirichlet	199	187	176
Surgery	2.70%	2.76%	2.62%	Dirichlet	199	5	10
Infliximab							
Remission to:		IFX transition probabilities: remission (95% CI)			N		
Remission	97.12%	93.35%	99.34%	Dirichlet	113	110	120
Mild	2.88%	6.65%	0.66%	Dirichlet	113	3	2
Moderate-to-severe	0.00%	0.00%	0.00%	Dirichlet	113	0	0
Surgery	0.00%	0.00%	0.00%	Dirichlet	113	0	0
Mild to:		IFX transition probabilities: mild (95% CI)					
Remission	0.54%	0.70%	0.39%	Dirichlet	113	1	1
Mild	71.48%	62.85%	79.39%	Dirichlet	113	81	77
Moderate-to-severe	27.98%	36.45%	20.22%	Dirichlet	113	32	24
Surgery	0.00%	0.00%	0.00%	Dirichlet	113	0	0
Moderate-to-severe to:		IFX transition probabilities: moderate-severe (95% CI)					
Remission	0.00%	0.00%	0.00%	Dirichlet	113	0	0
Mild	23.35%	16.05%	31.54%	Dirichlet	113	26	27
Moderate-to-severe	73.95%	80.99%	66.05%	Dirichlet	113	84	93

Surgery	2.70%	2.96%	2.41%	Dirichlet	113	3	1
Adalimumab							
Remission to:		ADA transition probabilities: remission (95% CI)			N		
Remission	99.50%	95.02%	100.00%	Dirichlet	19	19	17
Mild	0.50%	4.98%	0.00%	Dirichlet	19	0	0
Moderate-to-severe	0.00%	0.00%	0.00%	Dirichlet	19	0	0
Surgery	0.00%	0.00%	0.00%	Dirichlet	19	0	0
Mild to:		ADA transition probabilities: mild (95% CI)					
Remission	1.28%	1.82%	0.73%	Dirichlet	19	0	1
Mild	49.36%	27.78%	71.07%	Dirichlet	19	9	9
Moderate-to-severe	49.36%	70.39%	28.20%	Dirichlet	19	9	12
Surgery	0.00%	0.00%	0.00%	Dirichlet	19	0	0
Moderate-to-severe to:		ADA transition probabilities: moderate-severe (95% CI)					
Remission	0.00%	0.00%	0.00%	Dirichlet	19	0	0
Mild	0.00%	0.00%	0.00%	Dirichlet	19	0	0
Moderate-to-severe	97.30%	97.30%	97.30%	Dirichlet	19	18	23
Surgery	2.70%	2.70%	2.70%	Dirichlet	19	1	0
Surgery:		Surgery Transition probabilities (95% CI)			N		
Remission	52.72%	45.78%	59.61%	Dirichlet	199	105	114
Mild	7.71%	8.84%	6.59%	Dirichlet	199	15	16

Moderate-to-Severe	5.82%	6.67%	4.97%	Dirichlet	199	12	9
Surgery	33.75%	38.70%	28.83%	Dirichlet	199	67	67
TNF-Failure Population							
Vedolizumab (trial-based 6 weeks data)							
Remission to:		VDZ transition probabilities: remission (95% CI)			N		
Remission	98.31%	94.63%	99.90%	Dirichlet	82	81	83
Mild	1.69%	5.37%	0.10%	Dirichlet	82	1	1
Moderate-to-severe	0.00%	0.00%	0.00%	Dirichlet	82	0	0
Surgery	0.00%	0.00%	0.00%	Dirichlet	82	0	0
Mild to:		VDZ transition probabilities: mild (95% CI)					
Remission	0.00%	0.00%	0.00%	Dirichlet	82	0	0
Mild	50.00%	39.27%	60.73%	Dirichlet	82	41	28
Moderate-to-severe	50.00%	60.73%	39.27%	Dirichlet	82	41	41
Surgery	0.00%	0.00%	0.00%	Dirichlet	82	0	0
Moderate-to-severe to:		VDZ transition probabilities: moderate-severe (95% CI)					
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	97.30%	97.30%	97.30%	Dirichlet	82	80	106
Surgery	2.70%	2.70%	2.70%	Dirichlet	82	2	3
Conventional therapy (trial-based 6							

weeks data)							
Remission to:		CT transition probabilities: remission (95% CI)			N		
Remission	78.43%	68.72%	86.77%	Dirichlet	78	61	75
Mild	21.57%	31.28%	13.23%	Dirichlet	78	17	14
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:		CT transition probabilities: mild (95% CI)					
Remission	0.00%	0.00%	0.00%	Dirichlet	78	0	0
Mild	59.80%	48.78%	70.34%	Dirichlet	78	47	40
Moderate-to-severe	40.20%	51.22%	29.66%	Dirichlet	78	31	24
Surgery	0.00%	0.00%	0.00%	Dirichlet	78	0	0
Moderate-to-severe to:		CT transition probabilities: moderate-severe (95% CI)					
Remission	0.00%	0.00%	0.00%	Dirichlet	78	0	0
Mild	1.49%	0.06%	5.10%	Dirichlet	78	1	1
Moderate-to-severe	95.80%	97.20%	92.29%	Dirichlet	78	75	71
Surgery	2.70%	2.74%	2.60%	Dirichlet	78	2	1
Surgery		Surgery Transition probabilities (95% CI)			**N**		
Remission	52.72%	41.68%	63.63%	Dirichlet	78	41	36
Mild	7.71%	9.51%	5.93%	Dirichlet	78	6	3
Moderate-to-Severe	5.82%	7.18%	4.48%	Dirichlet	78	5	7

Surgery	33.75%	41.63%	25.96%	Dirichlet	78	26	32
Mixed moderate population							
Vedolizumab (trial-based 6 weeks data)							
Remission to:		VDZ transition probabilities: remission (95% CI)			N		
Remission	99.50%	97.20%	100.00%	Dirichlet	78	78	72
Mild	0.50%	2.80%	0.00%	Dirichlet	78	0	0
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:		VDZ transition probabilities: mild (95% CI)					
Remission	7.56%	9.09%	6.01%	Dirichlet	78	6	3
Mild	46.22%	35.35%	57.27%	Dirichlet	78	36	31
Moderate-to-severe	46.22%	55.56%	36.72%	Dirichlet	78	36	29
Surgery	0.00%	0.00%	0.00%	Dirichlet	78	0	0
Moderate-to-severe to:		VDZ transition probabilities: moderate-severe (95% CI)					
Remission	0.00%	0.00%	0.00%	Dirichlet	78	0	0
Mild	0.00%	0.00%	0.00%	Dirichlet	78	0	0
Moderate-to-severe	97.30%	97.30%	97.30%	Dirichlet	78	76	91
Surgery	2.70%	2.70%	2.70%	Dirichlet	78	2	0
Conventional therapy (trial-based 6 weeks data)							

Remission to:		CT transition probabilities: remission (95% CI)					
Remission	94.65%	89.03%	98.32%	Dirichlet	86	81	73
Mild	5.35%	10.97%	1.68%	Dirichlet	86	5	2
Moderate-to-severe	0.00%	0.00%	0.00%	Dirichlet	86	0	0
Surgery	0.00%	0.00%	0.00%	Dirichlet	86	0	0
Mild to:		CT transition probabilities: mild (95% CI)					
Remission	2.70%	3.34%	2.08%	Dirichlet	86	2	2
Mild	55.35%	44.81%	65.65%	Dirichlet	86	48	48
Moderate-to-severe	41.94%	51.84%	32.27%	Dirichlet	86	36	43
Surgery	0.00%	0.00%	0.00%	Dirichlet	86	0	0
Moderate-to-severe to:		CT transition probabilities: moderate-severe (95% CI)					
Remission	0.00%	0.00%	0.00%	Dirichlet	86	0	0
Mild	0.00%	0.00%	0.00%	Dirichlet	86	0	0
Moderate-to-severe	97.30%	97.30%	97.30%	Dirichlet	86	84	79
Surgery	2.70%	2.70%	2.70%	Dirichlet	86	2	3
Surgery		Surgery Transition probabilities (95% CI)					
Remission	52.72%	42.20%	63.12%	Dirichlet	86	45	45
Mild	7.71%	9.43%	6.01%	Dirichlet	86	7	14
Moderate-to-Severe	5.82%	7.12%	4.54%	Dirichlet	86	5	8
Surgery	33.75%	41.26%	26.32%	Dirichlet	86	29	32

Mixed severe population							
Vedolizumab (trial-based 6 weeks data)							
Remission to:		VDZ transition probabilities: remission (95% CI)			N		
Remission	99.47%	97.06%	100.00%	Dirichlet	75	75	80
Mild	0.53%	2.94%	0.00%	Dirichlet	75	0	0
Moderate-to-severe	0.00%	0.00%	0.00%	Dirichlet	75	0	0
Surgery	0.00%	0.00%	0.00%	Dirichlet	75	0	0
Mild to:		VDZ transition probabilities: mild (95% CI)					
Remission	4.01%	5.14%	2.93%	Dirichlet	75	3	3
Mild	60.16%	48.93%	70.88%	Dirichlet	75	45	48
Moderate-to-severe	35.83%	45.93%	26.19%	Dirichlet	75	27	26
Surgery	0.00%	0.00%	0.00%	Dirichlet	75	0	0
Moderate-to-severe to:		VDZ transition probabilities: moderate-severe (95% CI)					
Remission	0.00%	0.00%	0.00%	Dirichlet	75	0	0
Mild	7.88%	2.96%	14.90%	Dirichlet	75	6	3
Moderate-to-severe	89.42%	94.20%	82.60%	Dirichlet	75	67	74
Surgery	2.70%	2.84%	2.49%	Dirichlet	75	2	2
Conventional therapy (trial-based 6 weeks data)							
Remission to:		CT transition probabilities:					

		remission (95% CI)					
Remission	82.47%	72.57%	90.53%	Dirichlet	67	55	60
Mild	17.53%	27.43%	9.47%	Dirichlet	67	12	12
Moderate-to-severe	0.00%	0.00%	0.00%	Dirichlet	67	0	0
Surgery	0.00%	0.00%	0.00%	Dirichlet	67	0	0
Mild to:		CT transition probabilities: mild (95% CI)					
Remission	0.00%	0.00%	0.00%	Dirichlet	67	0	0
Mild	59.92%	48.03%	71.24%	Dirichlet	67	40	41
Moderate-to-severe	40.08%	51.97%	28.76%	Dirichlet	67	27	29
Surgery	0.00%	0.00%	0.00%	Dirichlet	67	0	0
Moderate-to-severe to:		CT transition probabilities: moderate-severe (95% CI)					
Remission	0.00%	0.00%	0.00%	Dirichlet	67	0	0
Mild	1.82%	0.08%	6.08%	Dirichlet	67	1	1
Moderate-to-severe	95.48%	97.17%	91.34%	Dirichlet	67	64	56
Surgery	2.70%	2.75%	2.58%	Dirichlet	67	2	1
Surgery		Surgery Transition probabilities (95% CI)					
Remission	52.72%	42.20%	63.12%	Dirichlet	67	35	35
Mild	7.71%	9.43%	6.01%	Dirichlet	67	5	6
Moderate-to-Severe	5.82%	7.12%	4.54%	Dirichlet	67	4	3
Surgery	33.75%	41.26%	26.32%	Dirichlet	67	23	33
Moderate TNF-Naïve population							

Vedolizumab (trial-based 6 weeks data)							
Remission to:		VDZ transition probabilities: remission (95% CI)			N		
Remission	99.50%	96.20%	100.00%	Dirichlet	39	39	37
Mild	0.50%	3.80%	0.00%	Dirichlet	39	0	1
Moderate-to-severe	0.00%	0.00%	0.00%	Dirichlet	39	0	0
Surgery	0.00%	0.00%	0.00%	Dirichlet	39	0	0
Mild to:		VDZ transition probabilities: mild (95% CI)			N		
Remission	11.31%	14.37%	8.15%	Dirichlet	39	4	2
Mild	44.34%	29.31%	59.92%	Dirichlet	39	17	14
Moderate-to-severe	44.34%	56.32%	31.93%	Dirichlet	39	17	16
Surgery	0.00%	0.00%	0.00%	Dirichlet	39	0	0
Moderate-to-severe to:		VDZ transition probabilities: moderate-severe (95% CI)			N		
Remission	0.00%	0.00%	0.00%	Dirichlet	39	0	0
Mild	0.00%	0.00%	0.00%	Dirichlet	39	0	0
Moderate-to-severe	97.30%	97.30%	97.30%	Dirichlet	39	38	54
Surgery	2.70%	2.70%	2.70%	Dirichlet	39	1	0
Conventional therapy (trial-based 6 weeks data)							
Remission to:		CT transition probabilities: remission (95% CI)					

Remission	94.21%	86.42%	98.79%	Dirichlet	51	48	35
Mild	5.79%	13.58%	1.21%	Dirichlet	51	3	4
Moderate-to-severe	0.00%	0.00%	0.00%	Dirichlet	51	0	0
Surgery	0.00%	0.00%	0.00%	Dirichlet	51	0	0
Mild to:		CT transition probabilities: mild (95% CI)					
Remission	7.19%	9.22%	5.17%	Dirichlet	51	4	3
Mild	51.97%	38.37%	65.42%	Dirichlet	51	27	31
Moderate-to-severe	40.85%	52.41%	29.41%	Dirichlet	51	21	29
Surgery	0.00%	0.00%	0.00%	Dirichlet	51	0	0
Moderate-to-severe to:		CT transition probabilities: moderate-severe (95% CI)					
Remission	0.00%	0.00%	0.00%	Dirichlet	51	0	0
Mild	1.79%	0.03%	6.76%	Dirichlet	51	1	1
Moderate-to-severe	95.51%	97.22%	90.67%	Dirichlet	51	49	40
Surgery	2.70%	2.75%	2.56%	Dirichlet	51	1	2
Surgery		Surgery Transition probabilities (95% CI)					
Remission	52.72%	39.11%	66.13%	Dirichlet	51	27	41
Mild	7.71%	9.93%	5.52%	Dirichlet	51	4	3
Moderate-to-Severe	5.82%	7.50%	4.17%	Dirichlet	51	3	2
Surgery	33.75%	43.47%	24.18%	Dirichlet	51	17	21
Vedolizumab (MTC-based data)							

Remission to:		VDZ transition probabilities: remission (95% CI)					
Remission	95.98%	90.12%	99.26%	Dirichlet	66	63	65
Mild	4.02%	9.88%	0.74%	Dirichlet	66	3	1
Moderate-to-severe	0.00%	0.00%	0.00%	Dirichlet	66	0	0
Surgery	0.00%	0.00%	0.00%	Dirichlet	66	0	0
Mild to:		VDZ transition probabilities: mild (95% CI)					
Remission	0.00%	0.00%	0.00%	Dirichlet	66	0	0
Mild	65.44%	53.65%	76.34%	Dirichlet	66	43	47
Moderate-to-severe	34.56%	46.35%	23.66%	Dirichlet	66	23	25
Surgery	0.00%	0.00%	0.00%	Dirichlet	66	0	0
Moderate-to-severe to:		VDZ transition probabilities: moderate-severe (95% CI)					
Remission	0.00%	0.00%	0.00%	Dirichlet	66	0	0
Mild	10.83%	4.59%	19.30%	Dirichlet	66	7	5
Moderate-to-severe	86.47%	92.52%	78.25%	Dirichlet	66	57	58
Surgery	2.70%	2.89%	2.44%	Dirichlet	66	2	3
Conventional therapy (MTC-based data)							
Remission to:		CT transition probabilities: remission (95% CI)					
Remission	88.16%	79.75%	94.54%	Dirichlet	71	63	57
Mild	11.84%	20.25%	5.46%	Dirichlet	71	8	8

Moderate-to-severe	0.00%	0.00%	0.00%	Dirichlet	71	0	0
Surgery	0.00%	0.00%	0.00%	Dirichlet	71	0	0
Mild to:		CT transition probabilities: mild (95% CI)					
Remission	0.10%	0.13%	0.07%	Dirichlet	71	0	0
Mild	60.31%	48.77%	71.29%	Dirichlet	71	43	38
Moderate-to-severe	39.60%	51.11%	28.64%	Dirichlet	71	28	40
Surgery	0.00%	0.00%	0.00%	Dirichlet	71	0	0
Moderate-to-severe to:		CT transition probabilities: moderate-severe (95% CI)					
Remission	0.00%	0.00%	0.00%	Dirichlet	71	0	0
Mild	3.26%	0.50%	8.44%	Dirichlet	71	2	4
Moderate-to-severe	94.04%	96.72%	89.01%	Dirichlet	71	67	66
Surgery	2.70%	2.78%	2.56%	Dirichlet	71	2	0
Infliximab							
Remission to:		IFX transition probabilities: remission (95% CI)					
Remission	97.12%	97.12%	97.12%	Dirichlet	0	0	0
Mild	2.88%	2.88%	2.88%	Dirichlet	0	0	0
Moderate-to-severe	0.00%	0.00%	0.00%	Dirichlet	0	0	0
Surgery	0.00%	0.00%	0.00%	Dirichlet	0	0	0
Mild to:		IFX transition probabilities: mild (95% CI)					
Remission	0.54%	0.54%	0.54%	Dirichlet	0	0	0

Mild	71.48%	71.48%	71.48%	Dirichlet	0	0	0
Moderate-to-severe	27.98%	27.98%	27.98%	Dirichlet	0	0	0
Surgery	0.00%	0.00%	0.00%	Dirichlet	0	0	0
Moderate-to-severe to:		IFX transition probabilities: moderate-severe (95% CI)					
Remission	0.00%	0.00%	0.00%	Dirichlet	0	0	0
Mild	23.35%	23.35%	23.35%	Dirichlet	0	0	0
Moderate-to-severe	73.95%	73.95%	73.95%	Dirichlet	0	0	0
Surgery	2.70%	2.70%	2.70%	Dirichlet	0	0	0
Adalimumab							
Remission to:		ADA transition probabilities: remission (95% CI)					
Remission	99.50%	99.50%	99.50%	Dirichlet	0	0	0
Mild	0.50%	0.50%	0.50%	Dirichlet	0	0	0
Moderate-to-severe	0.00%	0.00%	0.00%	Dirichlet	0	0	0
Surgery	0.00%	0.00%	0.00%	Dirichlet	0	0	0
Mild to:		ADA transition probabilities: mild (95% CI)					
Remission	1.28%	1.28%	1.28%	Dirichlet	0	0	0
Mild	49.36%	49.36%	49.36%	Dirichlet	0	0	0
Moderate-to-severe	49.36%	49.36%	49.36%	Dirichlet	0	0	0
Surgery	0.00%	0.00%	0.00%	Dirichlet	0	0	0
Moderate-to-severe to:		ADA transition probabilities: moderate-severe (95% CI)					

Remission	0.00%	0.00%	0.00%	Dirichlet	0	0	0
Mild	0.00%	0.00%	0.00%	Dirichlet	0	0	0
Moderate-to-severe	97.30%	97.30%	97.30%	Dirichlet	0	0	0
Surgery	2.70%	2.70%	2.70%	Dirichlet	0	0	0
Surgery:		Surgery Transition probabilities (95% CI)					
Remission	52.72%	41.15%	64.14%	Dirichlet	71	37	36
Mild	7.71%	9.60%	5.85%	Dirichlet	71	5	6
Moderate-to-Severe	5.82%	7.24%	4.41%	Dirichlet	71	4	7
Surgery	33.75%	42.01%	25.60%	Dirichlet	71	24	25
Severe TNF-Naïve population							
Vedolizumab (trial-based 6 weeks data)							
Remission to:		VDZ transition probabilities: remission (95% CI)					
Remission	96.10%	87.31%	99.81%	Dirichlet	32	31	29
Mild	3.90%	12.69%	0.19%	Dirichlet	32	1	0
Moderate-to-severe	0.00%	0.00%	0.00%	Dirichlet	32	0	0
Surgery	0.00%	0.00%	0.00%	Dirichlet	32	0	0
Mild to:		VDZ transition probabilities: mild (95% CI)					
Remission	13.76%	19.63%	8.28%	Dirichlet	32	4	5
Mild	59.75%	42.56%	75.78%	Dirichlet	32	19	19
Moderate-to-severe	26.49%	37.81%	15.94%	Dirichlet	32	8	18

Surgery	0.00%	0.00%	0.00%	Dirichlet	32	0	0
Moderate-to-severe to:		VDZ transition probabilities: moderate-severe (95% CI)		N			
Remission	0.00%	0.00%	0.00%	Dirichlet	32	0	0
Mild	24.51%	11.50%	40.54%	Dirichlet	32	8	7
Moderate-to-severe	72.79%	85.34%	57.33%	Dirichlet	32	23	30
Surgery	2.70%	3.17%	2.13%	Dirichlet	32	1	1
Conventional therapy (trial-based 6 weeks data)							
Remission to:		CT transition probabilities: remission (95% CI)					
Remission	90.56%	76.37%	98.54%	Dirichlet	24	22	12
Mild	9.44%	23.63%	1.46%	Dirichlet	24	2	2
Moderate-to-severe	0.00%	0.00%	0.00%	Dirichlet	24	0	0
Surgery	0.00%	0.00%	0.00%	Dirichlet	24	0	0
Mild to:		CT transition probabilities: mild (95% CI)					
Remission	0.16%	0.25%	0.09%	Dirichlet	24	0	0
Mild	60.03%	40.24%	78.25%	Dirichlet	24	14	19
Moderate-to-severe	39.80%	59.52%	21.66%	Dirichlet	24	10	5
Surgery	0.00%	0.00%	0.00%	Dirichlet	24	0	0
Moderate-to-severe to:		CT transition probabilities: moderate-severe (95% CI)					
Remission	0.00%	0.00%	0.00%	Dirichlet	24	0	0

Mild	3.05%	0.02%	12.52%	Dirichlet	24	1	0
Moderate-to-severe	94.25%	97.19%	85.05%	Dirichlet	24	23	23
Surgery	2.70%	2.78%	2.44%	Dirichlet	24	1	0
Surgery		Surgery Transition probabilities (95% CI)					
Remission	52.72%	33.12%	71.89%	Dirichlet	24	13	12
Mild	7.71%	10.91%	4.58%	Dirichlet	24	2	4
Moderate-to-Severe	5.82%	8.23%	3.46%	Dirichlet	24	1	1
Surgery	33.75%	47.74%	20.07%	Dirichlet	24	8	7
Vedolizumab (MTC-based data)							
Remission to:		VDZ transition probabilities: remission (95% CI)					
Remission	95.98%	90.81%	99.06%	Dirichlet	82	79	64
Mild	4.02%	9.19%	0.94%	Dirichlet	82	3	8
Moderate-to-severe	0.00%	0.00%	0.00%	Dirichlet	82	0	0
Surgery	0.00%	0.00%	0.00%	Dirichlet	82	0	0
Mild to:		VDZ transition probabilities: mild (95% CI)					
Remission	0.00%	0.00%	0.00%	Dirichlet	82	0	0
Mild	65.44%	54.88%	75.28%	Dirichlet	82	54	40
Moderate-to-severe	34.56%	45.12%	24.72%	Dirichlet	82	28	23
Surgery	0.00%	0.00%	0.00%	Dirichlet	82	0	0
Moderate-to-severe to:		VDZ transition probabilities: moderate-severe (95% CI)					

Remission	0.00%	0.00%	0.00%	Dirichlet	82	0	0
Mild	10.83%	5.11%	18.36%	Dirichlet	82	9	13
Moderate-to-severe	86.47%	92.02%	79.17%	Dirichlet	82	71	79
Surgery	2.70%	2.87%	2.47%	Dirichlet	82	2	2
Conventional therapy (MTC-based data)							
Remission to:		CT transition probabilities: remission (95% CI)					
Remission	88.16%	80.17%	94.30%	Dirichlet	78	69	69
Mild	11.84%	19.83%	5.70%	Dirichlet	78	9	5
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:		CT transition probabilities: mild (95% CI)					
Remission	0.10%	0.12%	0.07%	Dirichlet	78	0	0
Mild	60.31%	49.30%	70.81%	Dirichlet	78	47	42
Moderate-to-severe	39.60%	50.58%	29.12%	Dirichlet	78	31	32
Surgery	0.00%	0.00%	0.00%	Dirichlet	78	0	0
Moderate-to-severe to:		CT transition probabilities: moderate-severe (95% CI)					
Remission	0.00%	0.00%	0.00%	Dirichlet	78	0	0
Mild	3.26%	0.57%	8.16%	Dirichlet	78	3	0
Moderate-to-severe	94.04%	96.66%	89.27%	Dirichlet	78	73	84
Surgery	2.70%	2.78%	2.56%	Dirichlet	78	2	1

Infliximab							
Remission to:		IFX transition probabilities: remission (95% CI)					
Remission	97.12%	97.12%	97.12%	Dirichlet	0	0	0
Mild	2.88%	2.88%	2.88%	Dirichlet	0	0	0
Moderate-to-severe	0.00%	0.00%	0.00%	Dirichlet	0	0	0
Surgery	0.00%	0.00%	0.00%	Dirichlet	0	0	0
Mild to:		IFX transition probabilities: mild (95% CI)					
Remission	0.54%	0.54%	0.54%	Dirichlet	0	0	0
Mild	71.48%	71.48%	71.48%	Dirichlet	0	0	0
Moderate-to-severe	27.98%	27.98%	27.98%	Dirichlet	0	0	0
Surgery	0.00%	0.00%	0.00%	Dirichlet	0	0	0
Moderate-to-severe to:		IFX transition probabilities: moderate-severe (95% CI)					
Remission	0.00%	0.00%	0.00%	Dirichlet	0	0	0
Mild	23.35%	23.35%	23.35%	Dirichlet	0	0	0
Moderate-to-severe	73.95%	73.95%	73.95%	Dirichlet	0	0	0
Surgery	2.70%	2.70%	2.70%	Dirichlet	0	0	0
Adalimumab							
Remission to:		ADA transition probabilities: remission (95% CI)					
Remission	99.50%	99.50%	99.50%	Dirichlet	0	0	0
Mild	0.50%	0.50%	0.50%	Dirichlet	0	0	0

Moderate-to-severe	0.00%	0.00%	0.00%	Dirichlet	0	0	0
Surgery	0.00%	0.00%	0.00%	Dirichlet	0	0	0
Mild to:		ADA transition probabilities: mild (95% CI)					
Remission	1.28%	1.28%	1.28%	Dirichlet	0	0	0
Mild	49.36%	49.36%	49.36%	Dirichlet	0	0	0
Moderate-to-severe	49.36%	49.36%	49.36%	Dirichlet	0	0	0
Surgery	0.00%	0.00%	0.00%	Dirichlet	0	0	0
Moderate-to-severe to:		ADA transition probabilities: moderate-severe (95% CI)					
Remission	0.00%	0.00%	0.00%	Dirichlet	0	0	0
Mild	0.00%	0.00%	0.00%	Dirichlet	0	0	0
Moderate-to-severe	97.30%	97.30%	97.30%	Dirichlet	0	0	0
Surgery	2.70%	2.70%	2.70%	Dirichlet	0	0	0
Surgery:		Surgery Transition probabilities (95% CI)					
Remission	52.72%	41.68%	63.63%	Dirichlet	78	41	35
Mild	7.71%	9.51%	5.93%	Dirichlet	78	6	7
Moderate-to-Severe	5.82%	7.18%	4.48%	Dirichlet	78	5	6
Surgery	33.75%	41.63%	25.96%	Dirichlet	78	26	22
Moderate TNF-failure population							
Vedolizumab (trial-based 6 weeks data)							
Remission to:		VDZ transition probabilities:					

		remission (95% CI)					
Remission	99.50%	96.20%	100.00%	Dirichlet	39	39	38
Mild	0.50%	3.80%	0.00%	Dirichlet	39	0	0
Moderate-to-severe	0.00%	0.00%	0.00%	Dirichlet	39	0	0
Surgery	0.00%	0.00%	0.00%	Dirichlet	39	0	0
Mild to:		VDZ transition probabilities: mild (95% CI)					
Remission	7.58%	9.72%	5.39%	Dirichlet	39	3	3
Mild	46.21%	31.03%	61.75%	Dirichlet	39	18	13
Moderate-to-severe	46.21%	59.25%	32.85%	Dirichlet	39	18	21
Surgery	0.00%	0.00%	0.00%	Dirichlet	39	0	0
Moderate-to-severe to:		VDZ transition probabilities: moderate-severe (95% CI)					
Remission	0.00%	0.00%	0.00%	Dirichlet	39	0	0
Mild	0.00%	0.00%	0.00%	Dirichlet	39	0	0
Moderate-to-severe	97.30%	97.30%	97.30%	Dirichlet	39	38	41
Surgery	2.70%	2.70%	2.70%	Dirichlet	39	1	1
Conventional therapy (trial-based 6 weeks data)							
Remission to:		CT transition probabilities: remission (95% CI)					
Remission	88.22%	75.85%	96.51%	Dirichlet	35	31	17
Mild	11.78%	24.15%	3.49%	Dirichlet	35	4	2

Moderate-to-severe	0.00%	0.00%	0.00%	Dirichlet	35	0	0
Surgery	0.00%	0.00%	0.00%	Dirichlet	35	0	0
Mild to:		CT transition probabilities: mild (95% CI)					
Remission	0.00%	0.00%	0.00%	Dirichlet	35	0	0
Mild	50.00%	33.77%	66.23%	Dirichlet	35	18	19
Moderate-to-severe	50.00%	66.23%	33.77%	Dirichlet	35	18	24
Surgery	0.00%	0.00%	0.00%	Dirichlet	35	0	0
Moderate-to-severe to:		CT transition probabilities: moderate-severe (95% CI)					
Remission	0.00%	0.00%	0.00%	Dirichlet	35	0	0
Mild	0.00%	0.00%	0.00%	Dirichlet	35	0	0
Moderate-to-severe	97.30%	97.30%	97.30%	Dirichlet	35	34	33
Surgery	2.70%	2.70%	2.70%	Dirichlet	35	1	0
Surgery		Surgery Transition probabilities (95% CI)					
Remission	52.72%	36.37%	68.78%	Dirichlet	35	18	18
Mild	7.71%	10.38%	5.09%	Dirichlet	35	3	3
Moderate-to-Severe	5.82%	7.83%	3.84%	Dirichlet	35	2	3
Surgery	33.75%	45.42%	22.29%	Dirichlet	35	12	13
Failure & severe population							
Vedolizumab (trial-based 6 weeks data)							
Remission to:		VDZ transition probabilities:					

		remission (95% CI)					
Remission	96.93%	90.16%	99.83%	Dirichlet	43	42	38
Mild	3.07%	9.84%	0.17%	Dirichlet	43	1	1
Moderate-to-severe	0.00%	0.00%	0.00%	Dirichlet	43	0	0
Surgery	0.00%	0.00%	0.00%	Dirichlet	43	0	0
Mild to:		VDZ transition probabilities: mild (95% CI)					
Remission	0.00%	0.00%	0.00%	Dirichlet	43	0	0
Mild	54.19%	39.36%	68.65%	Dirichlet	43	23	25
Moderate-to-severe	45.81%	60.64%	31.35%	Dirichlet	43	20	16
Surgery	0.00%	0.00%	0.00%	Dirichlet	43	0	0
Moderate-to-severe to:		VDZ transition probabilities: moderate-severe (95% CI)					
Remission	0.00%	0.00%	0.00%	Dirichlet	43	0	0
Mild	0.00%	0.00%	0.00%	Dirichlet	43	0	0
Moderate-to-severe	97.30%	97.30%	97.30%	Dirichlet	43	42	50
Surgery	2.70%	2.70%	2.70%	Dirichlet	43	1	0
Conventional therapy (trial-based 6 weeks data)							
Remission to:		CT transition probabilities: remission (95% CI)					
Remission	75.30%	61.54%	86.83%	Dirichlet	43	32	30
Mild	24.70%	38.46%	13.17%	Dirichlet	43	11	18

Moderate-to-severe	0.00%	0.00%	0.00%	Dirichlet	43	0	0
Surgery	0.00%	0.00%	0.00%	Dirichlet	43	0	0
Mild to:		CT transition probabilities: mild (95% CI)					
Remission	0.00%	0.00%	0.00%	Dirichlet	43	0	0
Mild	60.87%	46.05%	74.73%	Dirichlet	43	26	27
Moderate-to-severe	39.13%	53.95%	25.27%	Dirichlet	43	17	19
Surgery	0.00%	0.00%	0.00%	Dirichlet	43	0	0
Moderate-to-severe to:		CT transition probabilities: moderate-severe (95% CI)					
Remission	0.00%	0.00%	0.00%	Dirichlet	43	0	0
Mild	2.28%	0.06%	8.32%	Dirichlet	43	1	0
Moderate-to-severe	95.02%	97.18%	89.15%	Dirichlet	43	41	39
Surgery	2.70%	2.76%	2.53%	Dirichlet	43	1	1
Surgery		Surgery Transition probabilities (95% CI)					
Remission	52.72%	37.92%	67.28%	Dirichlet	43	23	21
Mild	7.71%	10.12%	5.34%	Dirichlet	43	3	2
Moderate-to-Severe	5.82%	7.64%	4.03%	Dirichlet	43	3	6
Surgery	33.75%	44.31%	23.36%	Dirichlet	43	15	16
Other Efficacy Parameters							
Mortality relative risks		Relative risk of all-cause mortality (+/- 20%)			% in tails		
Relative risk of mortality - R	1.0	0.81	1.21	Gamma	20%	96.04	0.01

Relative risk of mortality - M	1.3	1.03	1.53	Gamma	20%	96.04	0.01
Relative risk of mortality - MS	2.3	1.83	2.73	Gamma	20%	96.04	0.02
Relative risk of mortality - S	3.2	2.61	3.90	Gamma	20%	96.04	0.03
Costs							
Drug Costs	All drug costs were considered fixed and not included in the sensitivity analyses						
Vedolizumab							
Vedolizumab (Induction phase)	[redacted]						
Vedolizumab per cycle (maintenance phase)	[redacted]						
Cost of administration (induction phase)	£616.00						
Cost of administration per cycle (maintenance phase)	£308.00						
Infliximab							
Infliximab (Induction phase)	£5,035.44						
Infliximab per cycle (maintenance phase)	£1,678.48						
Cost of administration (induction phase)	£2,464.00						
Cost of administration per cycle (maintenance phase)	£308.00						
Adalimumab							
Adalimumab (Induction phase)	£1760.70.1						

	2						
Adalimumab per cycle (maintenance phase)	£1,408.56						
Cost of administration (induction phase)	£0.00						
Cost of administration per cycle (maintenance phase)	£0.00						
Conventional Therapy	% Use	Cost per day					
Balsalazide	5%	£0.94					
Mesalazine	5%	£1.47					
Olsalazine	5%	£0.71					
Sulfasalazine	5%	£0.29					
Budesonide	6%	£2.25					
Prednisolone	19%	£4.86					
Azathioprine	57%	£0.19					
Mercaptopurine	10%	£6.95					
Methotrexate	11%	£0.92					
Weighted average cost per cycle		**£119.49**					
Cost per cycle for patients treated with biologic		**£59.75**					
Health state Costs		Health state costs (-/+ 20%)			% in tails		
Remission	£109.80	£88.94	£132.82	Gamma	20%	96.04	1.14
Mild	£313.38	£253.85	£379.08	Gamma	20%	96.04	3.26
Moderate-to-Severe	£489.51	£396.52	£592.14	Gamma	20%	96.04	5.10

Surgery (with complications)	£10,945.95	£8,866.66	£13,240.97	Gamma	20%	96.04	113.97
Non-NHS government costs		Non-NHS government cost (+/- 20%)					
Remission	0	0	0	Gamma	20%	0	0
Mild	0	0	0	Gamma	20%	0	0
Moderate-to-Severe	168.00	136.09	203.22	Gamma	20%	96.04	1.75
Surgery	168.00	136.09	203.22	Gamma	20%	96.04	1.75
Indirect cost		Indirect costs (-/+ 20%)					
Hourly wage	£0.00	£0.00	£0.00	Gamma	20%	0.00	0.00
Remission	0.00	0.00	0.00	Gamma	20%	0.00	0.00
Mild	0.00	0.00	0.00	Gamma	20%	0.00	0.00
Moderate-to-Severe	0.00	0.00	0.00	Gamma	20%	0.00	0.00
Surgery	0.00	0.00	0.00	Gamma	20%	0.00	0.00
Health state utilities		Health state utilities (+/- 20%)			N		
Remission	0.820	0.74	0.89	Beta	100	82	18
Mild	0.730	0.64	0.81	Beta	100	73	27
Moderate-to-Severe	0.570	0.47	0.67	Beta	100	57	43
Surgery	0.570	0.47	0.67	Beta	100	57	43
Adverse Events							
Adverse Events: Incidence							
Vedolizumab		AE incidence - Vedolizumab (95% CI)			**N**		
Serious Infection	0.015	0.24%	4.00%	Beta	154	2	152
Tuberculosis	0.000	0.00%	0.00%	Beta	154	0	154

Lymphoma	0.000	0.00%	0.00%	Beta	154	0	154
Acute hypersensitivity reaction	0.000	0.00%	0.00%	Beta	154	0	154
Skin reactions	0.003	0.00%	1.67%	Beta	154	1	153
Infliximab		AE incidence - Infliximab (95% CI)			**N**		
Serious Infection	0.045	0.00%	0.00%	Beta	0	0	0
Tuberculosis	0.003	0.00%	0.00%	Beta	0	0	0
Lymphoma	0.000	0.00%	0.00%	Beta	0	0	0
Acute hypersensitivity reaction	0.000	0.00%	0.00%	Beta	0	0	0
Skin reactions	0.000	0.00%	0.00%	Beta	0	0	0
Adalimumab		AE incidence - Adalimumab (95% CI)			**N**		
Serious Infection	0.018	0.56%	3.75%	Beta	257	5	252
Tuberculosis	0.000	0.00%	0.00%	Beta	257	0	257
Lymphoma	0.000	0.00%	0.00%	Beta	257	0	257
Acute hypersensitivity reaction	0.000	0.00%	0.00%	Beta	257	0	257
Skin reactions	0.000	0.00%	0.00%	Beta	257	0	257
Conventional therapy		AE incidence - Conventional therapy (95% CI)			**N**		
Serious Infection	0.019	0.81%	3.41%	Beta	410	8	402
Tuberculosis	0.000	0.00%	0.00%	Beta	410	0	410
Lymphoma	0.001	0.00%	0.49%	Beta	410	0	410
Acute hypersensitivity reaction	0.007	0.16%	1.77%	Beta	410	3	407
Skin reactions	0.002	0.00%	0.71%	Beta	410	1	409
Cost per adverse event		Cost per adverse event (+/-			% in tails		

		20%)					
Serious Infection	£1,469.98	£1,190.74	£1,778.19	Gamma	20%	96.04	15.31
Tuberculosis	£2,271.94	£1,840.36	£2,748.29	Gamma	20%	96.04	23.66
Lymphoma	£14,974.67	£12,130.09	£18,114.38	Gamma	20%	96.04	155.92
Acute hypersensitivity reaction	£3,188.00	£2,582.41	£3,856.43	Gamma	20%	96.04	33.19
Skin reactions	£1,363.28	£1,104.31	£1,649.11	Gamma	20%	96.04	14.19
Adverse event disutilities		Adverse event disutilities (+/- 20%)			**N**		
Serious Infection	0.520	0.42	0.62	Beta	100	52	48
Tuberculosis	0.550	0.45	0.65	Beta	100	55	45
Lymphoma	0.195	0.12	0.28	Beta	100	20	81
Acute hypersensitivity reaction	0.110	0.06	0.18	Beta	100	11	89
Skin reactions	0.030	0.01	0.07	Beta	100	3	97
Proportion Discontinuing due to AEs							
Vedolizumab		Vedolizumab discontinuation rate (95% CI)			N		
Induction	0.03	1.63%	4.85%	Beta	429	13	416
Maintenance	0.09	4.94%	13.85%	Beta	154	14	140
Infliximab		Infliximab discontinuation rate (95% CI)					
Induction	0.00%	0.00%	0.00%	Beta	0	0	0
Maintenance	0.00%	0.00%	0.00%	Beta	0	0	0

Adalimumab		Adalimumab discontinuation rate (95% CI)					
Induction	0.06%	2.16%	11.30%	Beta	98	6	92
Maintenance	0.09%	5.81%	12.77%	Beta	257	23	234

7.3.7	**Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan–Meier plots.**

Costs and clinical outcomes are extrapolated in the model beyond one year which is the duration of the clinical trial data up to ten years in the base-case, based on assuming constant transition probabilities beyond 1 year for each biologic. It is assumed in the model that all patients receiving biologics (Vedolizumab, Infliximab, Adalimumab or golimumab) have one year of treatment (consistent with the duration of clinical trial data) and then switch to a conventional therapy. They are subject to the transition probabilities for conventional therapy after one year.

Within the model, more patients are in remission after treatment with Vedolizumab than conventional therapy, and therefore the starting distribution of patients in health states is different at 54 weeks. However, this is still likely to be a conservative assumption if there is any residual efficacy from treatment beyond one year for the biologic therapies.

7.3.8	**Provide a list of all assumptions in the de novo economic model and a justification for each assumption.**

- The base-case analysis calculates the drug costs based on whole units used and assumes unused drug in opened vials is wasted (no vial sharing is assumed).
- Due to a lack of clinical data for treatment duration beyond 1 year, we assumed only 1 years of biologic treatment.
- Patients on surgery as a first-line treatment progress to conventional therapy after surgery. Therefore, any costs of complications due to surgery are rolled into the cost of the surgical treatment and not explicitly modelled using health states.

- Reasons for discontinuation include lack of response and adverse events. Discontinuation due to adverse events is applicable only to responders on biologic treatments, because non responders on biologics switch to conventional therapy and continue receiving such until the end of the model's time horizon or until the patients require surgery.
- Adverse events of biologics can occur equally likely at any time during treatment.
- Patients may discontinue treatment due to intolerability to adverse events at any time during treatment.
- In a scenario analysis, where the duration of treatment is assumed to be 3 years, patients who respond to biologic treatment during the induction phase continue on treatment for at least 1 year. After 1 year, it is assumed that patients who are in mild disease or remission continue on treatment. Patients entering the moderate-severe disease state after 1 year on treatment discontinue treatment and switch to conventional therapy.
- We assumed that any dose-skipping (e.g., temporary discontinuation or drug holiday) will already be captured in the trial-based efficacy data; thus, we do not adjust the transition probabilities for patients on drug holiday. However, we assumed 100% compliance for drug cost purposes due to lack of available trial data on doses received for all comparators. As such, this is a conservative assumption with regard to comparison of a biologic to conventional therapy, as we are overestimating the costs.

7.4 Measurement and valuation of health effects

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.4.

The HRQL impact of adverse events should still be explored regardless of whether they are included in cost-effectiveness analysis.

All parameters used to estimate cost-effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

Patient experience

7.4.1	**Please outline the aspects of the condition that most affect patients' quality of life.**

Inflammatory bowel diseases have a deleterious effect on quality of life. Patients with CD generally find their disease more burdensome than patients with UC, owing to more frequent and longer flare-ups in CD, the greater risk of hospitalization, and the use of more aggressive medications or surgery (Lesage, Hagège, Tucat, & Gendre, 2011).

Patients with chronic CD have reduced HRQL compared with the general population, particularly in general health and vitality (Høivik et al., 2012). In general, HRQL worsens with worsening severity.

Aspects of physical life affected by IBD include daily functioning, energy/vitality and pain (cramping, joint pain, pain during sex) (Wolfe and Sirois, 2008). The physical aspects of IBD and perceived social repercussions result in intense emotional consequences, ranging from anxiety/depression to fear and loss of passion.

More detailed information on the burden to patients' quality of life is provided in Section 2.1.

7.4.2	**Please describe how a patient's HRQL is likely to change over the course of the condition.**

CD is a chronic disease with patients typically experiencing periods of active disease and remission. However, the disease is progressive, and although medical management is the preferred therapy for CD, some patients will receive surgery to induce a response and reduce the burden of CD complications.

Surgery in patients with CD is associated with substantial morbidity, with up to 22% of patients experiencing surgery-related complications (Kopylov et al., 2012). Ideally, initial and repeat surgery should be delayed as much as possible by optimizing medical management of CD (Gapasin et al., 2012). A recent audit of IBD cases in an Australian hospital revealed that 27% of CD surgeries were potentially avoidable with proper medical management. Even minor procedures such as limited resections for ileal disease may result in impaired body image and sexuality, particularly in younger patients. Surgical patients also face a high risk of clinical relapse (up to 75%) and re-intervention (up to 45% of patients require re-intervention by 10 years post-operatively).

HRQL data derived from clinical trials

7.4.3	**If HRQL data were collected in the clinical trials identified in section 6 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.**

- Method of elicitation.
- Method of valuation.
- Point when measurements were made.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.

HRQL data was collected in the GEMINI II and GEMINI III trials using the IBDQ, SF-36 and EQ-5D instruments. In the GEMINI II study, patients completed the quality of life scores at baseline, week 6 (the end of the induction period), week 30 and week 52 (the end of the trial). In the GEMINI III study, patients completed the quality of life scores at baseline, week 6 (the end of the induction period), and week 10 (the end of the trial). Using the EQ-5D data is consistent with the NICE reference case and these data were used in the model in the base-case. Alternative utility values identified in the systematic review were used in scenario analyses (see Sections 7.4.5, 7.4.6, 7.4.7 and 7.7.9).

Where appropriate, data from GEMINI II and GEMINI III were pooled together and a single dataset was created based on the same key variables from both trials.

The pooled dataset included CDAI health state at baseline, CDAI health state at each time point of observation, age, gender, trial ID and Patient ID. As the outcomes of interest for the economic model is health state utility weights independent of time, a dataset was created that contains a variable for CDAI health state. For patients who had more than one observation (i.e., data collected at multiple time points, data for each patient observation) received its own row in the dataset. We were only interested in EQ-5D and CDAI-based health state where these variables are collected at the same time point. As such, information was included for GEMINI II for 6, 30 and 52 weeks and for GEMINI III information at weeks 6 and 10 was utilized, as these represent the time points at which both EQ-5D and CDAI data were collected.

Patients were categorised as being in remission (CDAI<150), mild disease (CDAI 150-219) or moderate to severe disease (CDAI 220-600) regardless of study visit or treatment received. The mean utility values observed by health state, for the overall pooled population were used in the base-case of the model (these are the data in the first row of 0).

Table 7.4.3.1: Summary statistics of health-state utility weights, CD trials

Population	Remission (CDAI < 150) Mean (SD)	Mild-Moderate (150<CDAI<220) Mean (SD)	Moderate-Severe (CDAI 220-600) Mean (SD)
Pooled GEMINI II and III			
Overall population	0.82 (0.163)	0.73 (0.183)	0.57 (0.284)
Moderate health state at baseline	0.83 (0.174)	0.73 (0.183)	0.61 (0.261)
Severe health state at baseline	0.81 (0.155)	0.71 (0.178)	0.52 (0.306)
GEMINI II (Induction)			
Overall population	0.84 (0.152)	0.72 (0.196)	0.59 (0.279)
Moderate health state at baseline	0.84 (0.152)	0.73 (0.177)	0.63 (0.239)
Severe health state at baseline	0.84 (0.152)	0.72 (0.221)	0.55 (0.303)
GEMINI II (Maintenance)			
Overall population	0.84 (0.150)	0.73 (0.185)	0.56 (0.299)
Moderate health state at baseline	0.86 (0.150)	0.72 (0.190)	0.62 (0.257)
Severe health state at baseline	0.81 (0.165)	0.70 (0.191)	0.49 (0.325)
GEMINI III			
Overall population	0.80 (0.176)	0.73 (0.181)	0.59 (0.272)
Moderate health state at baseline	0.80 (0.188)	0.74 (0.177)	0.61 (0.264)
Severe health state at baseline	**0.80 (0.140)**	**0.71 (0.163)**	**0.55 (0.282)**

CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; SD = standard deviation. Moderate health state at baseline = CDAI 220-330; Severe health state at baseline CDAI>330. Note: these summary statistics do not control for the correlation between multiple observations from the same patient. As such, while the mean values will still be valid, the variance will be underestimated.

Mapping

7.4.4	**If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.**

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

Mapping was not used to transform quality of life data to utilities.

HRQL studies

7.4.5	**Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 10.12, Appendix 12.**

The literature was reviewed to identify any studies that provide information on utilities related to treatments for CD. The search was limited to utilities as opposed to general or disease-specific quality of life instruments, as the was to identify alternative utilities that could be used or contrasted with the base-case utility values in the model.

Please see Section 7.1.2 and Appendix 10, Section 10.10 for a description of the methods of the systematic review.

7.4.6	**Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.**

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.
- Appropriateness of the study for cost-effectiveness analysis.

Table 7.4.6.1 summarises the results of the literature search for utility studies. And Table 7.4.6.2 summarises the compliance of the studies with the NICE reference case.

Table 7.4.6.1: Summary of utility studies identified in the literature searches

First Author (Year)	Study Population[a]	Methods of Elicitation and Valuation[b]	Health-State Description	Appropriateness of Health states[c]	Mapping
Louis (2013) abstract	N = 1678 Patients with UC in France, Germany, Italy, and Spain Mean age, 40.8 years; 51% men Mild UC: 53.9% Moderate UC: 39.9% Severe UC: 6.1%	Data from patients collected July to September 2012 EQ-5D VAS Fisher's exact tests and analysis of variance were used to assess differences in categorical and continuous variables, respectively, among patients with current mild, moderate, and severe UC, as determined by their gastroenterologist	Mild Moderate Severe	To condition and treatment pathways: Health states appear appropriate, although, the definitions of these were not reported; no surgery-related health states To economic analysis: This study is unlikely to be appropriate to the economic analysis because the health states were different from those used in the economic model. In addition, this study is an abstract and does not present EQ-5D index score (only VAS).	None
Vaizey (2013) poster	N = 173 UC patients with median Mayo score 2.00, and with 58% in remission, 18% mild	Observational, cross-sectional study used a patient questionnaire to collect EQ-5D scores Clinical assessment of the	Remission (0-2 partial Mayo) Mild (3-4 partial Mayo) Moderate/ severe	To condition and treatment pathways: Health states appear appropriate; no surgery-related health states To economic analysis:	None

First Author (Year)	Study Population[a]	Methods of Elicitation and Valuation[b]	Health-State Description	Appropriateness of Health states[c]	Mapping
	activity, and 24% with moderate/severe	patients disease severity was measured using the partial Mayo score	(5+ partial Mayo)	This UK-based study was described in a conference abstract, so there is little information about the methods used. Utility values for the health states were based on partial Mayo scores and are not appropriate for the use in the economic analysis.	
Brown (2011)	N = 17 Physicians (gastroenterologists = 10, surgeons = 7) N = 69 UC patients living with moderate disease, defined by a SCCAI score between 4 and 9 N = 150 Postcolectomy	TTO method Subjects were asked to imagine themselves in each of the scenarios provided when completing the survey, as opposed to relying on specific personal or anecdotal experiences of either state. After reading each scenario, subjects were informed of their average remaining life expectancy according to data from the 2003	Moderate UC Postcolectomy	To condition and treatment pathways: Health states appear appropriate although are not reflective of all possible states, such as severe or mild UC To economic analysis: This US-based study collected utility values using the TTO method from both patients and physicians and does not conform to the NICE reference case.	None

First Author (Year)	Study Population[a]	Methods of Elicitation and Valuation[b]	Health-State Description	Appropriateness of Health states[c]	Mapping
	patients	US life tables. Responses were converted to a utility scale ranging from 0 to 1.		Postcolectomy utility value could be considered in the economic model as an alternative, e.g., as part of the sensitivity analyses.	
Waljee (2011)	N = 450 Non-UC patients (n = 150) UC patients (mild, moderate, or severe) who had not undergone colectomy (n = 150) UC patients who were postcolectomy (n = 150)	TTO method Subjects were informed of their actuarial remaining life expectancy based on age and gender. Several subjects experienced inflammatory bowel disease; gastroenterologists and surgeons developed standardised scenarios of life with moderate UC and life in a postcolectomy state. Responses were converted to a utility scale ranging from 0 to 1.	UC without colectomy: All Mild (0-3 SCCAI), Moderate (4-7 SCCAI), Severe (> 8 SCCAI) UC postcolectomy, including all, chronic activity, exacerbation of disease, dysplasia/ cancer, unknown	To condition and treatment pathways: Health states appear appropriate To economic analysis: This US-based study collected utility values using the TTO method from both patients and physicians and does not conform to the NICE reference case. In addition, the study provided utility values for only some of the health states relevant for the economic analysis.	None
Poole (2010)	PINCE study (n = 126): extensive	UC disease severity was classified according to the sum	Remission (UCDAI score 0-2)	To condition and treatment pathways:	Response mapping

First Author (Year)	Study Population[a]	Methods of Elicitation and Valuation[b]	Health-State Description	Appropriateness of Health states[c]	Mapping
	active UC; 59% male, median age 43.5 years PODIUM study (n = 359): mild to moderate UC, remission with a relapse within the past year; 53% male, median age 48 years	score with the UCDAI. Estimates of patients' HRQL for deriving health-state utility scores were evaluated using the EQ-5D at baseline, 2, 4, and 8 weeks. The study mapped UC severity categories of remission, mild-to-moderate, and severe, to establish their EQ-5D index.	Mild to moderate relapse (UCDAI score 3-8) Severe relapse (UCDAI score 9-12)	Health states appear appropriate; no surgery-related health states To economic analysis: The utility values were collected using the EQ-5D; however, the health states do not match those used in the economic analysis.	algorithm was used to predict EQ-5D domain response from UCDAI
Punekar (2010)	UC patients (N = NR)	The preferences for the health states used in this analysis were obtained from a patient survey carried out in Cardiff Hospital, using the EQ-5D and valued using UK tariffs, which reflect valuations of the UK population (Woehl et al., 2007). The utilities derived from these health-state preferences were further classified into individual	Remission (SCAI: 0-2) Active UC (SCAI: 3+) Surgical remission Surgical complications	To condition and treatment pathways: Health states appear appropriate for the population of patients undergoing surgery To economic analysis: The utility values are collected using the EQ-5D and values using UK tariffs as per the NICE recommendations. However, the health states do not	None

First Author (Year)	Study Population[a]	Methods of Elicitation and Valuation[b]	Health-State Description	Appropriateness of Health states[c]	Mapping
		presurgery health states by indexing them with a SCAI. The Woehl study did not capture utilities associated with post surgery complications. These utilities were adopted from a study conducted by Arseneau et al. (2006). Separate sets of utilities were available for IPAA and ileostomy; a weighted average based on the prevalence of these surgical techniques (29% IPAA, 71% ileostomy) was calculated for post surgery remission.		match all of the health states used in the economic analysis, which encompasses patients receiving medical treatment and patients undergoing surgery. Surgery-related utilities could be considered in the sensitivity analysis.	
Poole (2009) abstract	UC patients (N = 359)	Data were analysed from the phase 3 Pentasa Once Daily in UC for Maintenance of Remission trial Health-related utility was estimated by Monte Carlo	Remission (UCDAI score: ≤ 2) Mild/moderate relapse (UCDAI score: 3-8) Severe relapse	To condition and treatment pathways: Health states appear appropriate; no surgery-related health states To economic analysis: This study is not appropriate for	Response mapping algorithm was used to predict EQ-5D domain

First Author (Year)	Study Population[a]	Methods of Elicitation and Valuation[b]	Health-State Description	Appropriateness of Health states[c]	Mapping
		bootstrap simulation, using a response mapping algorithm to predict EQ-5D domain response from UCDAI item scores and applying the UK tariff for preference-based utility.	(UCDAI score: > 8)	use in the economic analysis because it used different health states than those used in the economic model.	response from UCDAI
Tsai (2008)	N = NR UC patients	The health-state utility values used in this economic analysis were obtained from a patient survey (Woehl et al., 2007)[d] carried out in Cardiff Hospital, using the EQ-5D and valued using UK tariffs. The utilities derived from these health state preferences were further classified into individual presurgery health states by indexing them with a SCAI. The Woehl study did not capture utilities associated with post	Remission (SCAI: 0-2) Mild (SCAI: 3-5) Moderate-severe (SCAI: 6+) Temporary discontinuers Surgery Post surgery remission Post surgery remission Post surgery complications	To condition and treatment pathways: Health states appear appropriate To economic analysis: This study is the most appropriate for use in the economic analysis because it used the same health states as those used in the model. Although, the health states were defined in the study by Woehl and colleagues (2007) using a SCAI (which encompasses only the clinical parameters), the Mayo measure (which	None

First Author (Year)	Study Population[a]	Methods of Elicitation and Valuation[b]	Health-State Description	Appropriateness of Health states[c]	Mapping
		surgery complications. These utilities were adopted from a study conducted by Arseneau et al. (2006).	Death	encompasses both clinical and endoscopic parameters) was used to define health states in the economic model by model by Tsai and colleagues (2008), as is the case in the current economic analysis.	
Arseneau (2006)	N = 48 UC patients	Utility weights obtained using a scripted structured review, which included written descriptions and visual aids for each health state. Health-state descriptions were developed using input from a nominal group process with health care professionals and several rounds of focus groups with UC patients. TTO and VAS were used to collect preference data.	Remission Active UC Infusion reaction Hypertension Pneumonia Ileostomy Surgical complications J pouch Misdiagnosed Crohn's disease (postcolectomy) Obstruction Pouchitis	To condition and treatment pathways: Health states appear appropriate, although no response/mild disease or postsurgical remission states To economic analysis: This study used TTO and VAS, rather than EQ-5D; therefore, it did not comply with the requirements of the NICE reference case. In addition, the utility weights did not match all of the health states	None

First Author (Year)	Study Population[a]	Methods of Elicitation and Valuation[b]	Health-State Description	Appropriateness of Health states[c]	Mapping
			Chronic pouchitis Stage III colorectal cancer Stage IV colorectal cancer Death	included in the economic analysis. Values for some states could be considered for use in the sensitivity analysis.	
Muir (2001)	Patients who underwent IPAA for UC	HRQL measures included the TTO, Rating Form of IBD Patient Concerns, and the Short-Form 36. Assessments occurred preoperatively and 1, 6, and 12 months postoperatively. Patients underwent a 2-stage procedure: the first stage was a proctocolectomy with formation of a J-pouch and a Brooke ileostomy; the second stage was takedown of the ileostomy.	Preoperative 1 month post operation 6 months post operation 12 months post operation	To condition and treatment pathways: Health states appear appropriate for the study population but not for the broader population To economic analysis: This study did not use EQ-5D. In addition, the utility weights did not match the health states included in the economic analysis.	None

EQ-5D, EuroQol 5 Dimensions; HRQL, health-related quality of life; IBD, inflammatory bowel disease; IPAA, ileal pouch anal anastomosis; NICE, National Institute for Health and Care Excellence; NR, not reported; SCAI, Simple Colitis Activity Index; SCCAI, Simple Clinical Colitis Activity Index; TTO, time trade-off; UC, ulcerative colitis; UCDAI, Ulcerative Colitis Disease Activity Index; UK, United Kingdom; US, United States; VAS, visual analog scale.

[a] Includes information about recruitment, sample size, response rate, and interventions received (as reported in the included studies; references to other publications within a study were not traced to original sources).

[b] Includes elicitation methods and valuation methods.

[c] The appropriateness of health states adapted by the analyses was evaluated both in terms of the condition and the established treatment pathway and in terms of the analyses' suitability for the current economic analysis. The economic analysis defines the modelled health states according to Mayo scores: "Remission" (Mayo = 0-2), equivalent to full response; "Mild-to-Moderate" (Mayo = 3-5), equivalent to partial response; "Moderate-to-Severe" (Mayo = 6-12), assumed to be equivalent to non response; "Surgery"; and "Death."

[d] The poster by Woehl and colleagues (2007) was not retrieved by the searches performed as part of this review but was examined along with other studies identified through hand searches. It was not included in the review because it did not report utility or cost estimates by health states. Therefore, it is unclear whether this source was correctly referenced by Tsai and colleagues (2008) as the primary source of the utility values applied in their economic model.

Table 7.4.6.2: Compliance of utility estimates with NICE reference case

First Author (Year)	Reported Directly From Patients?	Values = Public Preferences Using Choice-Based Method?	EQ-5D?	Utility Scale?[a]
Louis (2013) abstract	Yes	No	EQ-5D VAS	NR
Vaizey (2013)	Yes	Yes; tariff not reported	EQ-5D AQoL-8D	Yes
Brown (2011)	Yes	Choice-based method but did not reflect public preferences	No (TTO)	Yes
Waljee (2011)	Yes	Choice-based method but did not reflect public preferences	No (TTO)	Yes
Poole (2010)	Yes	Yes, EQ-5D index valued using UK tariff	Yes	Yes
Poole (2009) abstract	Yes	Yes, EQ-5D index valued using UK tariff	Yes	Yes
Punekar (2010) Referenced the Cardiff study (Woehl et al., 2007) and Arseneau et al., 2006	Yes	Yes, EQ-5D index valued using UK tariff (presurgery health states)	Yes	Yes
Tsai (2008) Referenced the Cardiff study (Woehl et al., 2007) and Arseneau et al., 2006	Yes	Yes, EQ-5D index valued using UK tariff (presurgery health states)	Yes	Yes
Arseneau (2006)	Yes	Choice-based method but did not reflect public preferences	No (TTO)	Yes
Muir (2001)	Yes	Choice-based method but did not reflect public preferences	No (TTO)	Yes

AQoL-8D, Assessment of Quality of Life; EQ-5D, EuroQol 5 Dimensions; NICE, National Institute for Health and Care Excellence; NR, not reported; TTO, time trade-off; UK, United Kingdom; VAS, visual analog scale.
[a] 1 = full or perfect health; 0 = dead.

7.4.7	**Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.**

Adverse events

7.4.8	**Please describe how adverse events have an impact on HRQL.**

An analysis of the impact of adverse events on patient reported quality of life in the GEMINI II and GEMINI III studies has not been conducted. See Section 6.9.2 for a summary of the safety data related to VEDOLIZUMAB in CD. Within the model, disutilities were applied for adverse events. The methods used to derive the proportion of patients with adverse events is described in Section 7.3.1.

Quality-of-life data used in cost-effectiveness analysis

7.4.9	**Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 7.4.3 to 7.4.8. Justify the choice of utility values, giving consideration to the reference case.**

For the “CDAI health states” (remission, mild disease, moderate to severe disease) the model uses the observed EQ-5D scores from the GEMINI II and GEMINI III studies (see Section 7.4.3). For the surgery health state, because patients in the GEMINI II and GEMINI III studies were not followed for surgery, it was assumed that the value was equal to that of the utility for the moderate-severe health state.

In a scenario analysis, we consider an alternative data source of the utilities referenced in the model by Bodger et al.: namely, the study by Buxton et al., 2007. Buxton and colleagues mapped EQ-5D utility weights to CDAI scores using a linear regression approach and derived a relationship of EQ-5D = 0.9168 – 0.0012CDAI. For the scenario analysis, the average of the CDAI range for each health state (e.g., 75 for remission; 185 for mild, 460 for moderate-severe) was used to estimate each health-state utility weight. Again, patients undergoing surgery were assumed to have the same utility as patients with moderate-severe disease. The utility estimates for the base-case and the scenario analysis are presented in the table below

Table 7.4.9.1: Health-state utility weights

Health state	Vedolizumab Trial Data (Base-Case)	Buxton et al. (2007)
Remission	0.820	0.827
Mild	0.730	0.695
Moderate-severe	0.570	0.425
Surgery	0.570*	0.425

Adverse Event Disutilities

Previous economic analyses in CD have not considered adverse events. Therefore, utility decrements for adverse events were identified through a targeted review of the available published literature . To incorporate these utility decrements into the model, we multiplied disutility estimates by the probability of experiencing each adverse event per cycle to estimate a per-cycle, adverse-event–adjusted, utility weight. This value was then multiplied by the health-state utility weight for the health-state failure in each cycle to estimate the utility value for each cycle. For example, a patient in remission, treated with Vedolizumab, would have a health-state utility of 0.880. Based on the probability of each adverse event and the disutility associated with that adverse event, a patient treated with Vedolizumab would have an adverse-event–adjustment of 0.999. Multiplying these two would give the overall (adverse-event–adjusted) utility value of 0.879 for a Vedolizumab patient in remission during that cycle.

Table 7.4.9.2: Utility estimates for adverse events

Adverse Event	Disutility Estimate	Source
Serious infection	-0.520	Brown et al. (2001) (= 1 − 0.48)
Tuberculosis	-0.550	Porco et al. (2006), Appendix Table 7 (= 1 − 0.45)
Malignancy (including Lymphoma)	-0.195	Hornberger et al. (2008) (= 1 − 0.805)
Acute hypersensitivity reactions	-0.110	Beusterien et al. (2010)[a]
Skin site reactions	-0.030	Beusterien et al. (2009)

7.4.10	**If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[2]:**

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Clinical experts did not assess the applicability of utility values for the model.

[2] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

7.4.11	**Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?**

Within the model, it is assumed that quality of life is constant within a health state. There could be patient variability in patients' experience of quality of life within health states, but the cycle length is 8 weeks and no formal analysis has been conducted to assess this possibility.

7.4.12	**Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?**

No health effects identified were excluded from the analysis.

7.4.13	**If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?**

The quality of life assumed in the analysis was capture within the health states.

7.4.14	**Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.**

Within a health state HRQL was assumed to be constant over time.

7.4.15	**Have the values in sections 7.4.3 to 7.4.8 been amended? If so, please describe how and why they have been altered and the methodology.**

The utility values have not been amended.

7.5 Resource identification, measurement and valuation

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.5.

All parameters used to estimate cost-effectiveness should be presented clearly in a table and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

NHS costs

7.5.1	**Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.**

Table 7.5.1.1 provides a summary of the sources of the costs that were used in the model. For most variables, NHS reference costs were used, in line with previous economic evaluations in the area. Further details of the units used to estimate the costs of treating adverse events are provided in the Appendix.

Table 7.5.1.1: Summary of cost sources used in the model

Cost Input	Source
Drug Costs	BNF, May 2013
IV drug administration	PbR mandatory tariff 2012/13 FZ37F
Health states	
Remission (Mayo = 0-2)	Bodger et al., 2009 (inflated to 2012 using Pay and Price Index from Curtis, 2012)
Mild (Mayo = 3-5)	Bodger et al., 2009 (inflated to 2012 using Pay and Price Index from Curtis, 2012)
Moderate-to-Severe (Mayo = 6-12)	Bodger et al., 2009 (inflated to 2012 using Pay and Price Index from Curtis, 2012)
Surgery	Bodger et al., 2009 (inflated to 2012 using Pay and Price Index from Curtis, 2012)
Adverse Events	
Serious infection	NHS Reference Costs 2011/12. Average of 5 different types of serious infections: sepsis, pneumonia, urinary tract infection, respiratory infection and bronchitis
Tuberculosis	NHS Reference Costs 2011/12. Average of non-elective short stay and long stay tuberculosis.
Lymphoma	NICE 2003, NICE 2012 and NICE 2011. Average of Lymphoma costs from three technological appraisal, TA65, TA243 and TA226
Acute hypersensitivity reactions	NHS Reference Costs 2011/12. Average of non-elective short stay and long stay pyrexia.
Skin reactions	NHS Reference Costs 2011/12. Average of procedures associated with skin disorders

7.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

Please see Section 7.5.1.

Resource identification, measurement and valuation studies

7.5.3 Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 10.13, Appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

- country of study
- date of study
- applicability to UK clinical practice
- cost valuations used in study
- costs for use in economic analysis
- technology costs

The literature was reviewed to identify any studies that provide information on costs or resource use related to treatments for UC. Please see Section 7.1.2 and Appendix 10, Section 10.10 for a description of the methods of the systematic review.

7.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[3]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique)

Clinical experts were selected based on their area of expertise and geographical location. One England-based consultant gastroenterologist and one Scotland-based consultant gastroenterologist were selected. Both participants declared no potential conflicts of interest.

The consultation process was threefold. The clinicians were first presented the model structure and its input parameters. A questionnaire was then distributed to the clinicians with the specific clinical questions required for the model development. The clinicians were then asked to review the final version of the model technical report and provide written comments, thereby validating the model assumptions. Some follow-up correspondence also took place via an email. Clinician expert opinion was used for validation purposes, to provide the list of important adverse events included in the model and to provide information on the treatment of surgical complications.

[3] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Please see section 7.5.6 for a summary of how surgical complications were costed within the model.

Intervention and comparators' costs

7.5.5	**Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.**

Cost of biologics: Vedolizumab, Infliximab, Adalimumab

For Vedolizumab and Infliximab, the induction phase consisted of two treatments at weeks 0 and 2 with patient assessment at week 6 and a dose only for patients with response. Patients were subsequently treatments every 8 weeks thereafter in the maintenance phase. For Adalimumab, the induction phase included a loading dose of 160 mg at week 0 and 80 mg at week 2, followed by 40 mg at weeks 4 and 6. During the maintenance phase, patients received 40 mg of Adalimumab every other week.

Table 7.5.5.1: Cost of biologics during induction phase

Treatment	Total Vials Used	Cost Per Vial[a]	Cost Per Cycle
Vedolizumab	2	[redacted]	[redacted]
Infliximab	8	£419.62	£3,356.96
Adalimumab	5[b]	£352.14	£1,760.70

[a] Source: British National Formulary (2013).
[b] Patients treated with Adalimumab receive 80 mg in week 0, 40 mg in week 2, and 40 mg every 2 weeks thereafter. As such, patients receive five 40-mg doses of Adalimumab in the induction phase: two doses at week 0, one dose at week 2, and one dose each at weeks 4 and 6.

Table 7.5.5.2: Per-cycle cost of biologics during 8-week cycle in the maintenance phase

Treatment	Administration	Vials/Admin	Total Vials	Cost per Cycle
Vedolizumab	1	1	1	[redacted]
Infliximab	1	4	4	£1,678.48
Adalimumab	4	1	4	£1,408.56

Cost of conventional therapy

The mix of treatments that compose conventional therapy is based the UK IBD Audit Steering Group Report (Royal College of Physicians, 2013). The estimated treatment cost of conventional therapy is based on the doses and unit costs reported in the British National Formulary (2013). The prices of treatment options, treatment costs, and estimated treatment mix are summarised in 0.

Patients on biologic therapy are also assumed to require conventional therapy use. We assumed that the resource-use cost of conventional therapy for patients taking biologics is half that of the costs of the conventional therapy strategy alone. We test this assumption in a scenario analysis in which we assumed the costs of conventional therapy to be the same regardless of strategy.

Table 7.5.5.3: Doses and unit costs of conventional therapy

Treatment	Dose and Frequency	Price	% Use
Aminosalicylates			
Balsalazide	1.5 g twice daily, adjusted according to response (maximum: 6 g daily)	750 mg, 130-cap pack at £30.42	5%
Mesalazine	1.2-2.4 g daily in divided doses	400 mg, 120-tab pack at £41.62	5%
Olsalazine	500 mg twice daily	250 mg, 112-cap pack at £19.77	5%
Sulfasalazine	500 mg 4 times daily	500 mg, 112-cap pack at £5.82	5%
Corticosteroids			
Budesonide	3 mg 3 times daily for up to 8 weeks	3 mg net price: 100-cap pack at £75.05	6%
Prednisolone	1 metered application (20 mg prednisolone) once or twice daily for 2 weeks	14-application canister at £48.00	19%
Immunomodulators			
Azathioprine	1-3 mg/kg daily	25 mg net price: 28-tab pack at £6.02; 50 mg, 56-tab pack at £5.04	57%
Mercaptopurine	Initially 2.5 mg/kg, adjusted according to response	50 mg net price: 25-tab pack at £22.54	10%
Methotrexate	10-25 mg once weekly	2.5 mg net price: 24-tab pack at £2.39; 28-tab pack at £3.27	11%

Source: British National Formulary (December 2013) for unit costs; UK IBD Audit Steering Group (Royal College of Physicians, 2013) for percentage use.

Health-state costs

7.5.6 Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 7.2.4.

As the health states in the model are consistent with those in the model of Bodger et al., those costs are used. The estimated per-cycle costs per health state are presented in 0.

Table 7.5.6.1: Per-cycle cost, by health state

Resource Item	Cost (in 2006-7 £)	Cost (Inflated to 2011-12 £)
Remission	£96	£109.80
Mild	£274	£313.38
Moderate-severe	£428	£489.51
Surgery	£9,251	£10,580.51

Source: Bodger et al. (2009) inflated to 2012 using the Pay and Price Index (Curtis, 2012)

In addition, for patients in the surgery health state, the costs of treating surgical complications are included (0). Surgery-related complication costs were estimated by applying NHS reference costs to resource use as reported by expert clinical opinion. Please see Sections 7.3.1 for information on the rate of complications in the model, Section 7.3.5 for information on how clinical expert opinion was derived.

Table 7.5.6.2: Costs of surgery-related complications

Adverse Event	Total Cost	Source
Wound infection	£1,724.87	NHS Reference Costs 2011/12. Assumed 4 additional hospital days and 1 outpatient visit according to expert clinical opinion
Prolonged ileus/ bowel obstruction	£1,609.39	NHS Reference Costs 2011/12. Assumed 4 additional hospital days according to expert clinical opinion
Intra-abdominal abscess	£2,011.73	NHS Reference Costs 2011/12. Assumed 5 additional hospital days according to expert clinical opinion
Anastomotic leak	£2,816.43	NHS Reference Costs 2011/12. Assumed 7 additional hospital days according to expert clinical opinion

NHS = National Health Service.

Adverse-event costs

7.5.7 Please summarise the costs for each adverse event listed in section 6.9 (Adverse events). These should include the costs of therapies identified in sections 2.7 and 2.8. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

The costs of adverse events were estimated as weighted averages using the relevant health care resource group codes in the NHS Reference Cost schedule (Department of Health, 2013) and the assumption that all patients are hospitalised with these adverse events (0).

Table 7.5.7.1: Costs of adverse events

Adverse Event	Total Cost	Source
Serious infection	£1,470.00	NHS Reference Costs 2011/12. Average of 5 different types of serious infections: sepsis, pneumonia, urinary tract infection, respiratory infection, and bronchitis
Tuberculosis	£2,272.00	NHS Reference Costs 2011/12. Average of non elective short-stay and long-stay tuberculosis
Lymphoma	£14,975.00	NICE (2003), NICE (2012), and NICE (2011). Average of lymphoma costs from three technological appraisals for rituximab (TA65, TA243, and TA226)
Hypersensitivity	£3,188.00	NHS Reference Costs 2011/12. Average of non elective short-stay and long-stay pyrexia
Injection site reactions	£1,363.28	NHS Reference Costs 2011/12. Average of procedures associated with skin disorders

NHS, National Health Service; NICE, National Institute for Health and Care Excellence.

Economic Model

Miscellaneous costs

7.5.8 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

No additional costs were included in the model.

7.6 Sensitivity analysis

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.1.11, 5.8, and 5.9.4 to 5.9.12.

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.

All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis (PSA) is preferred for translating the imprecision in

all input variables into a measure of decision uncertainty in the cost-effectiveness of the options being compared.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

7.6.1	**Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.**

Uncertainty around structural assumptions has not been investigated

7.6.2	**Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 7.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.**

With the exception of drug costs, all inputs to the model were included in a one-way sensitivity analysis. Drug costs were assumed to be fixed and excluded from the analysis. A list of the range used in the sensitivity analysis for each variable is provided in Section 7.3.6.

7.6.3	**Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 7.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).**

A probabilistic sensitivity analysis was undertaken. A list of the distributions used in the PSA for each variable is provided in Section 7.3.6. Drug costs were assumed to be fixed and excluded from the analysis.

7.7 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following.

- Link between clinical- and cost-effectiveness results.
- Costs, QALYs and incremental cost per QALY.
- Disaggregated results such as LYG, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment.
- A statement as to whether the results are based on a PSA.
- Cost-effectiveness acceptability curves, including a representation of the cost-effectiveness acceptability frontier.
- Scatter plots on cost-effectiveness quadrants.
- A tabulation of the mean results (costs, QALYs, ICERs), the probability that the treatment is cost effective at thresholds of £20,000–£30,000 per QALY gained and the error probability.

Clinical outcomes from the model

7.7.1	**For the outcomes highlighted in the decision problem (see section 5), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.**

The model was calibrated to estimate the same proportion of patients with remission and mild disease at the end of the maintenance phase as was observed in the GEMINI 2 trial.

Table 7.7.1.1: Summary of clinical endpoints from the GEMINI 2 and GEMINI 3 trials and the cost-effectiveness model

	Placebo / Conventional Therapy		Vedolizumab	
	Clinical Trial	**Model Result**	**Clinical Trial**	**Model Result**
Outcome				
End of induction[a]				
Proportion with response	33.80%	35.85%	48.02%	50.06%
Proportion in remission	9.86%	9.86%	16.78%	16.78%
End of maintenance[b]				
Proportion with mild disease[c]	3.15%	3.15%	4.05%	4.47%
Proportion in remission[d]	5.28%	5.28%	18.71%	18.46%

[a] The proportion of patients with response and remission at the end of the induction period, from the clinical trial, are pooled results from the GEMINI 2 and GEMINI 3 clinical trials. The model result provides the calculated proportion of patients in response and remission at the end of the induction period in the model.
[b] The proportion of patients with response and mild disease at the end of the maintenance period, from the clinical trial, are pooled results from the GEMINI 2 clinical trial. The model result provides the calculated proportion of patients in response and mild disease at the end of the maintenance period in the model.
[c] The proportion with mild disease from the clinical trial was calculated as the proportion that achieved response in the induction phase multiplied by the proportion of patients with response at the end of the maintenance phase that were not in remission.
[d] The proportion in remission at the end of the maintenance phase was calculated as the proportion that achieved response in the induction phase multiplied by the proportion of patients that were in remission at the end of the maintenance phase.

Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

7.7.2 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

Because data do not allow for a reasonable comparison of Vedolizumab with Infliximab and Adalimumab in TNF-failure patients, Markov traces are displayed by patient population and comparator, below. The graphs show the proportion of patients in each health state at each cycle of the model, describing the “flow” of patients through the model for each comparator.

Mixed Population (ITT)

Figure 7.7.2.1: Markov trace: Vedolizumab for the mixed patient population (ITT)

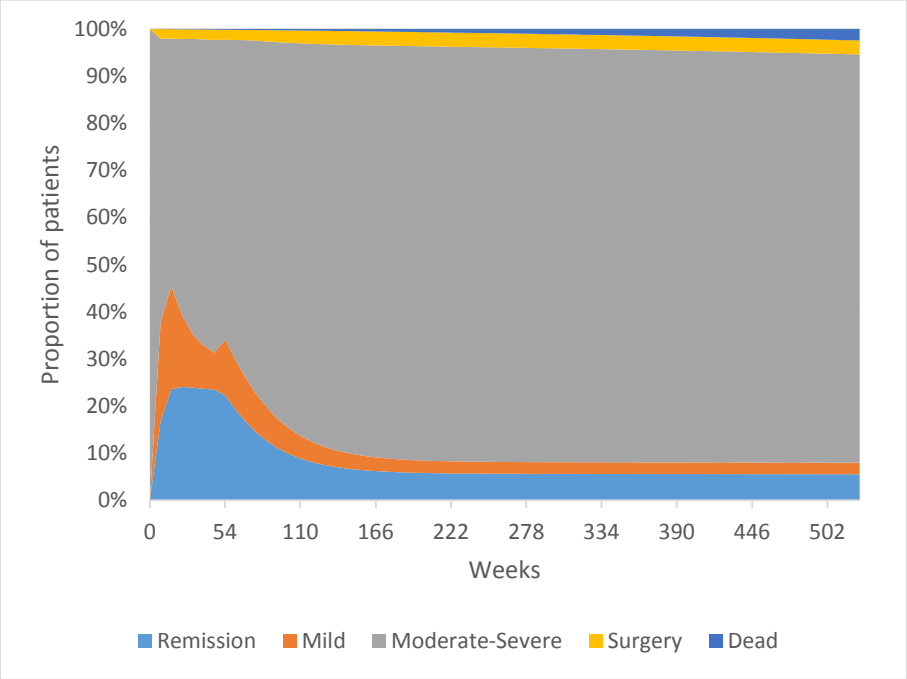
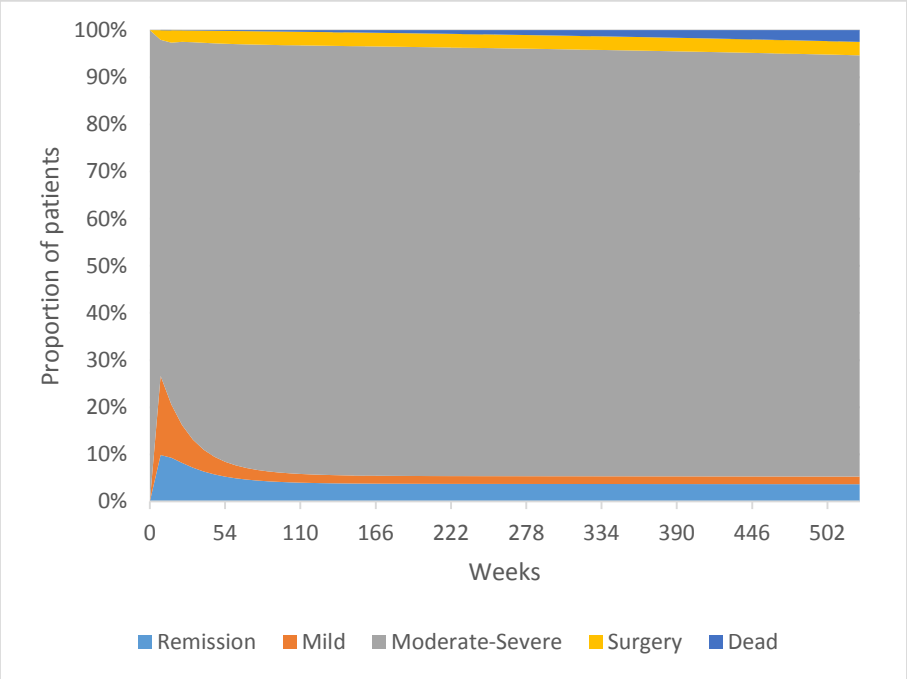


Figure 7.7.2.2: Markov trace: conventional therapy for the mixed patient population (ITT)



TNF-Naïve Population

Figure 7.7.2.3: Markov trace: Vedolizumab for the TNF-Naïve population (MTC-based estimates)

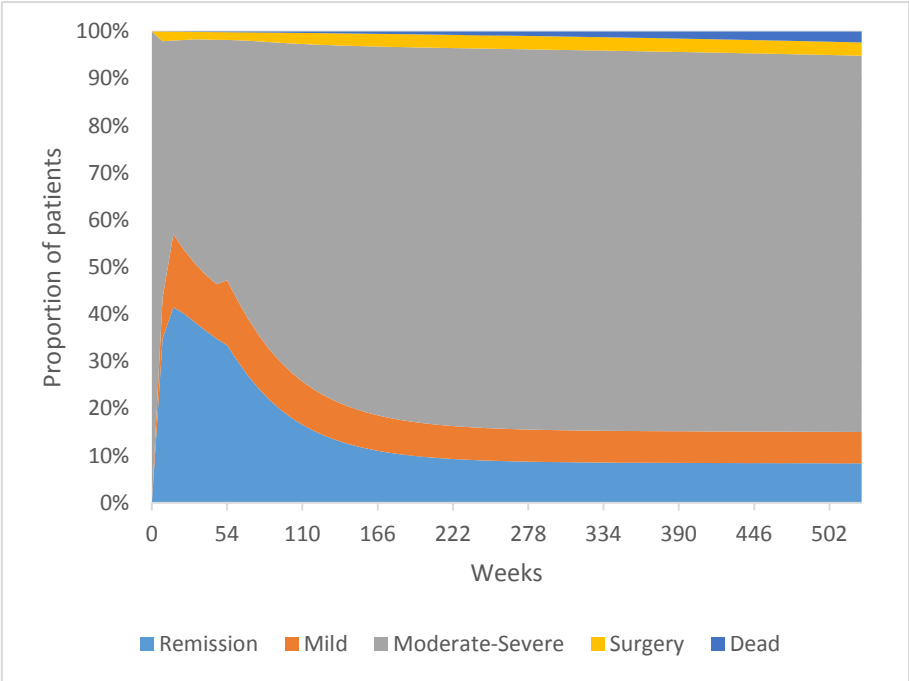


Figure 7.7.2.4: Markov trace: conventional therapy for the TNF-Naïve population (MTC-based estimates)

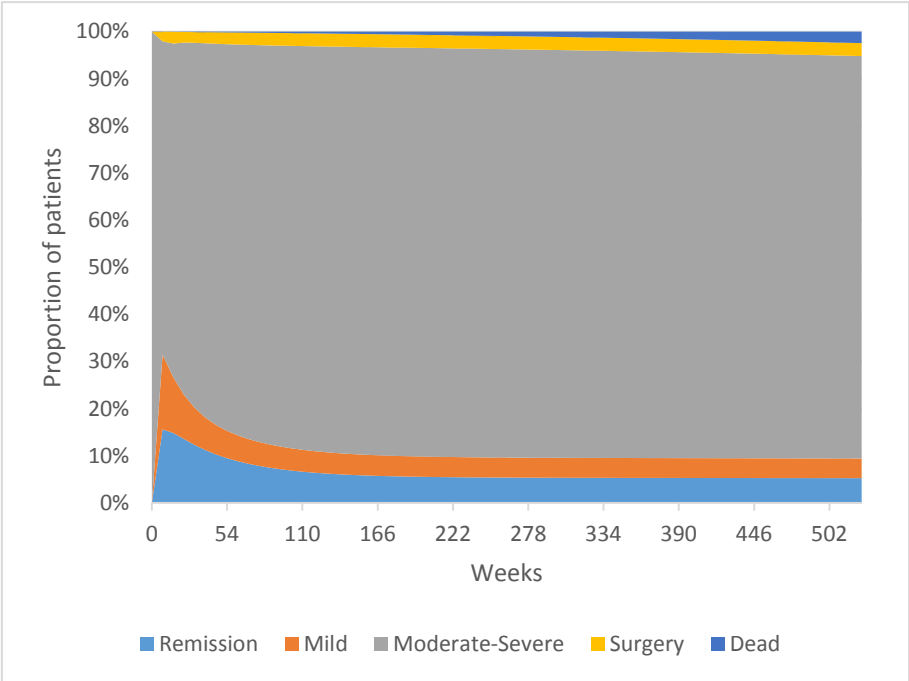


Figure 7.7.2.5: Markov trace: Infliximab for the TNF-Naïve population

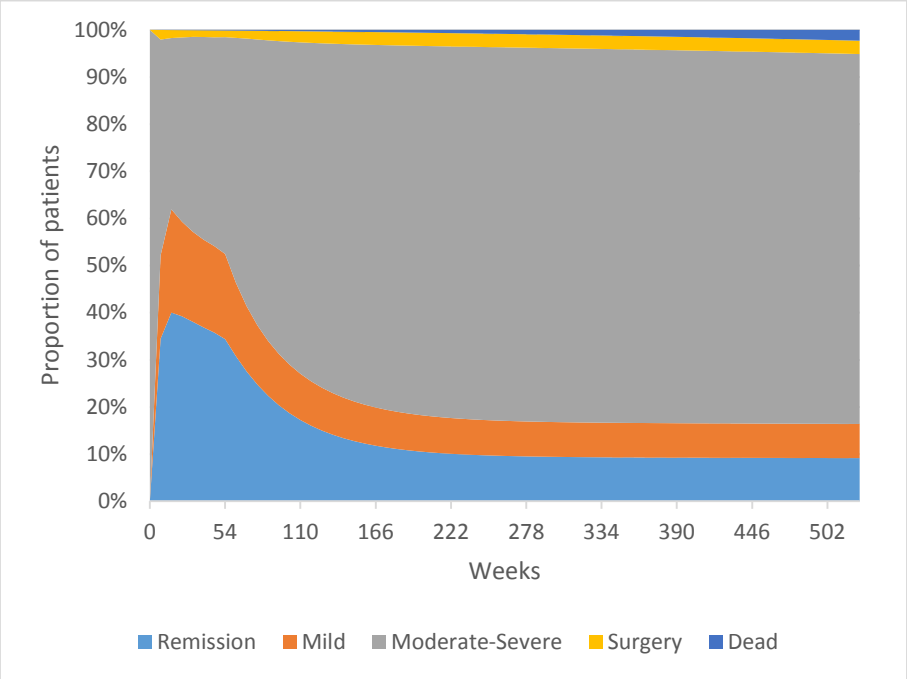
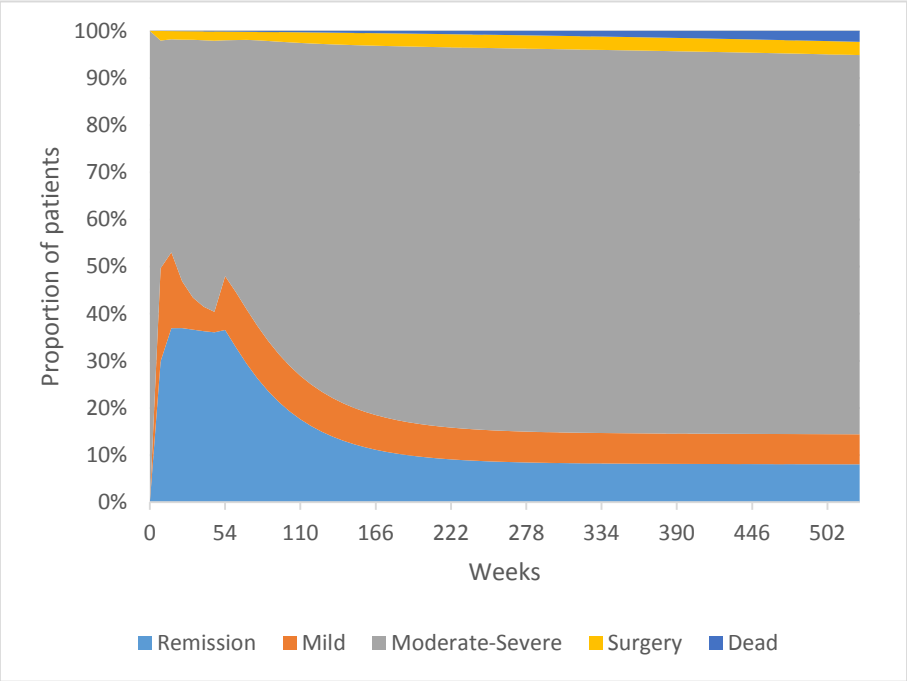


Figure 7.7.2.6: Markov trace: Adalimumab for the TNF-Naïve population



TNF-Failure Patients

Figure 7.7.2.7: Markov trace: Vedolizumab for the TNF-Failure population (clinical trial-based estimates)

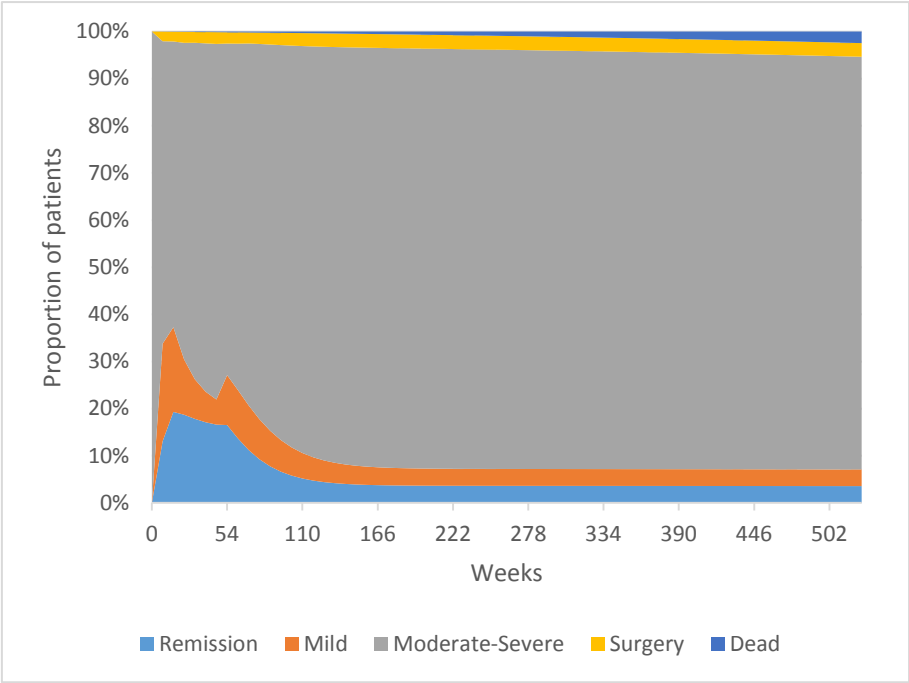
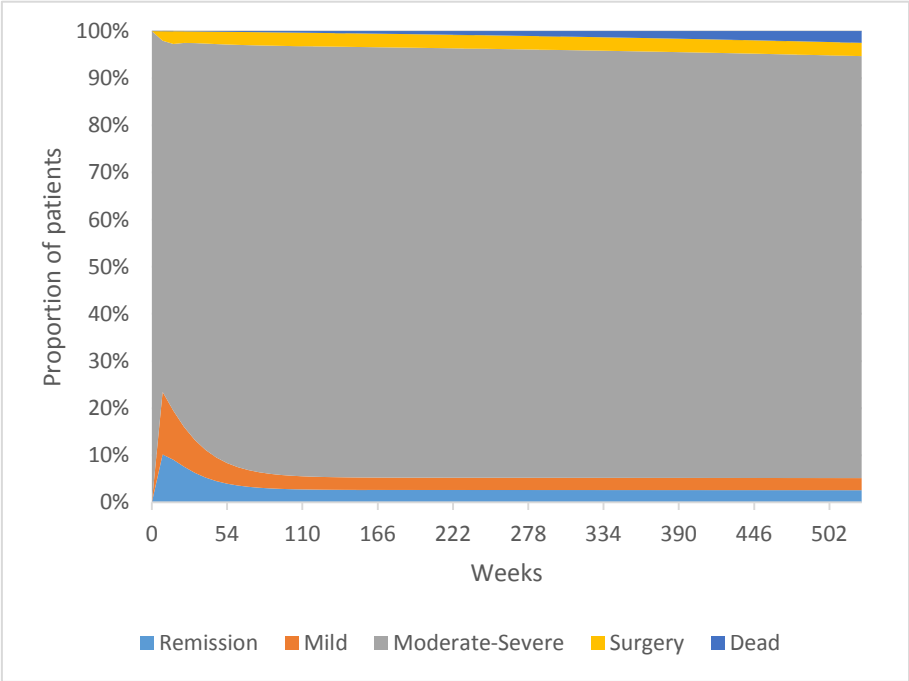


Figure 7.7.2.8: Markov trace: conventional therapy for the TNF-Failure population (clinical trial-based estimates)



Mixed Moderate Patients

Figure 7.7.2.9: Markov trace: Vedolizumab for the mixed patient population (ITT) with moderate disease at baseline

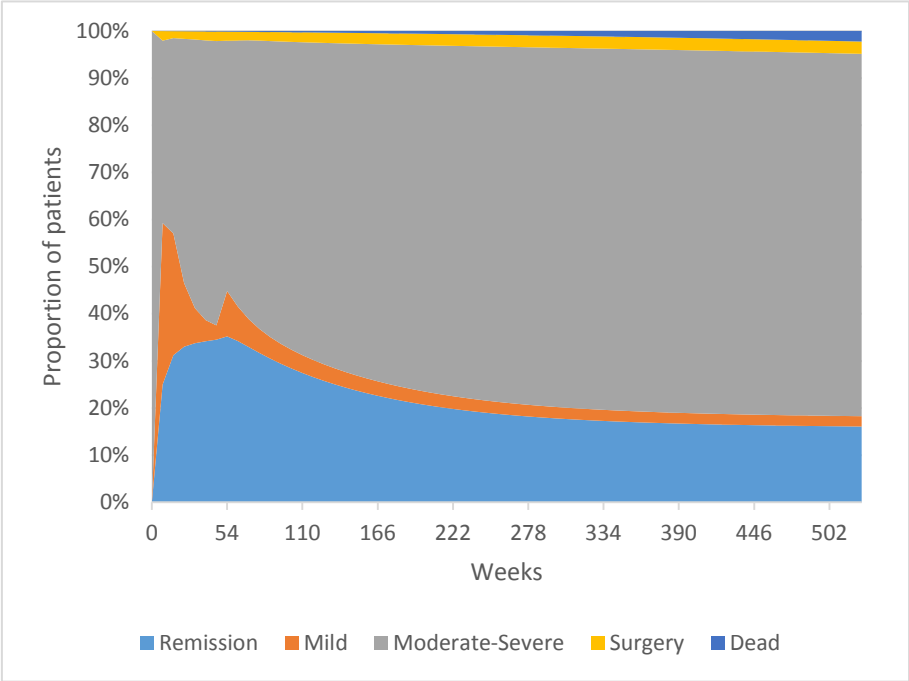
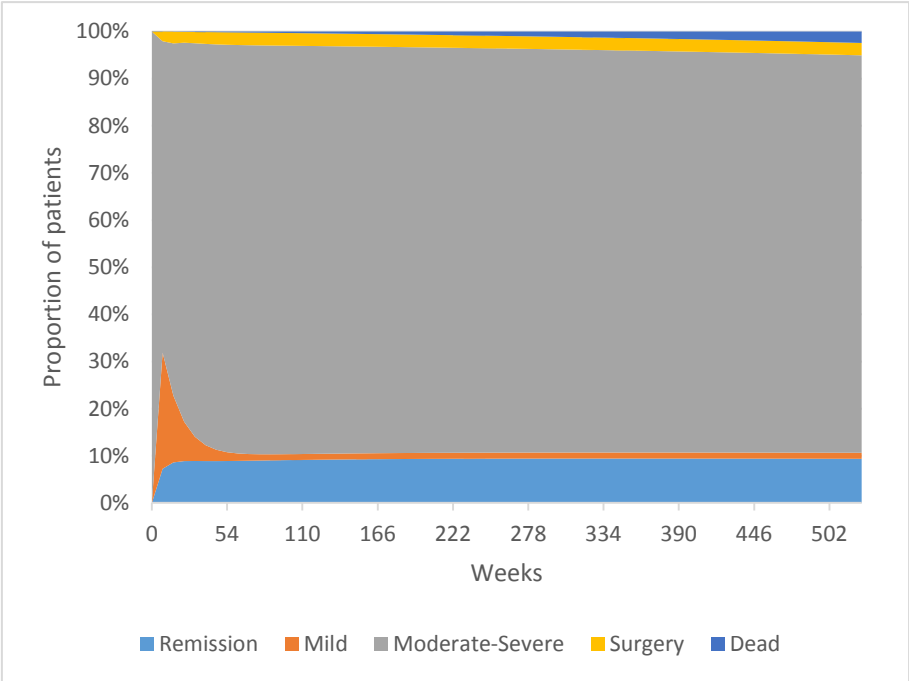


Figure 7.7.2.10: Markov trace: conventional Therapy for the mixed patient population (ITT) with moderate disease at baseline



Mixed Severe Patients

Figure 7.7.2.11: Markov trace: Vedolizumab for the mixed patient population (ITT) with severe disease at baseline

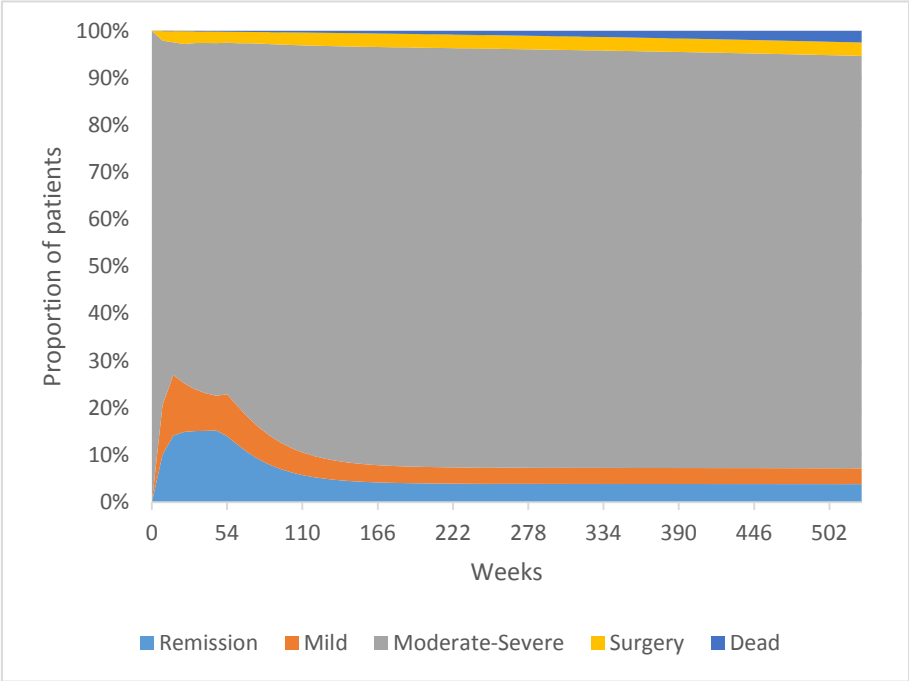
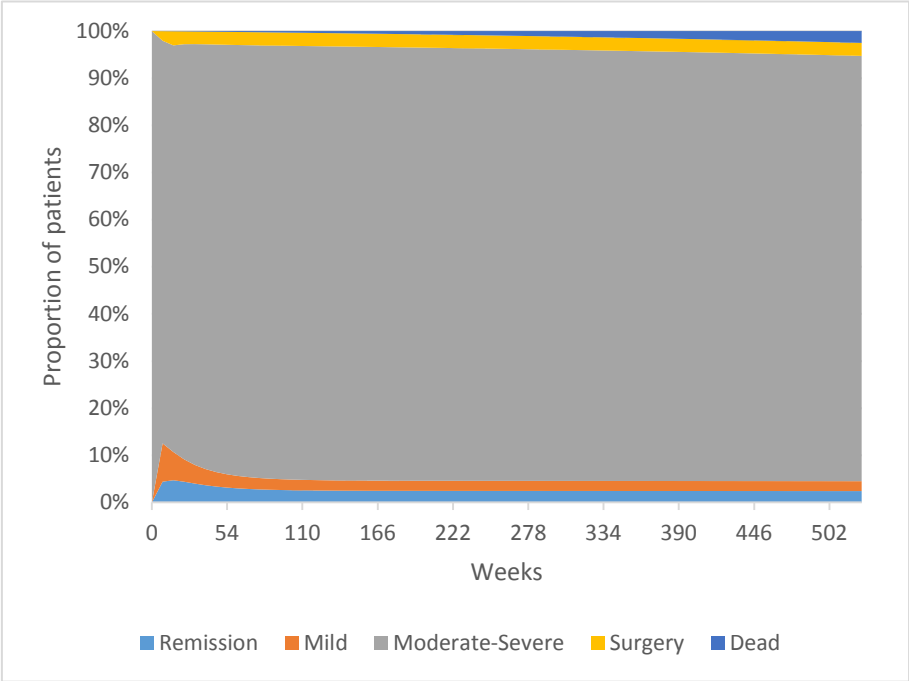


Figure 7.7.2.12: Markov trace: conventional therapy for the mixed patient population (ITT) with severe disease at baseline



TNF-Naïve Moderate Patients

Figure 7.7.2.13: Markov trace: Vedolizumab for the TNF-Naïve patient population (ITT) with moderate disease at baseline

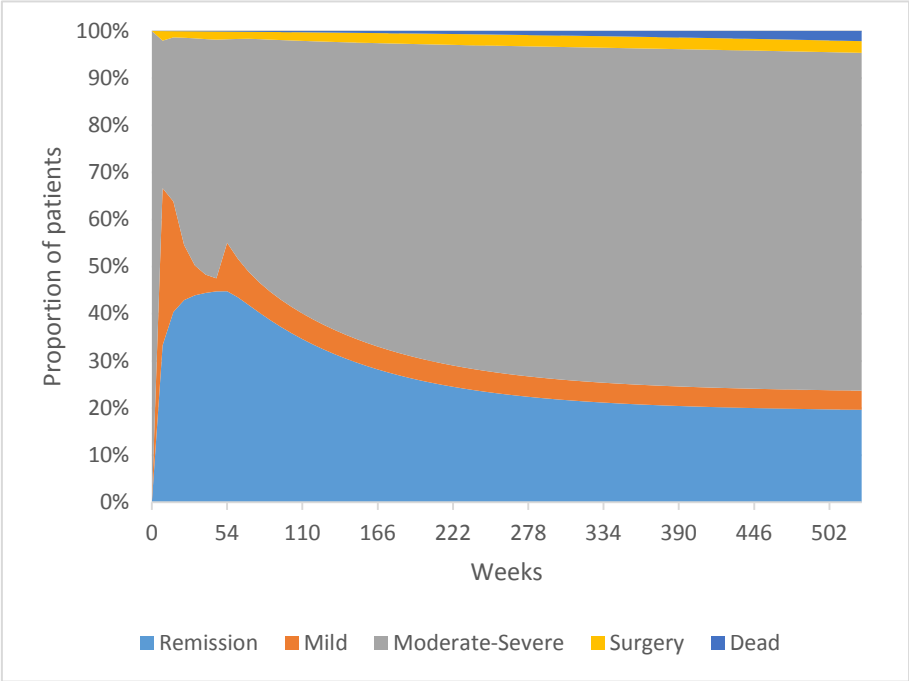
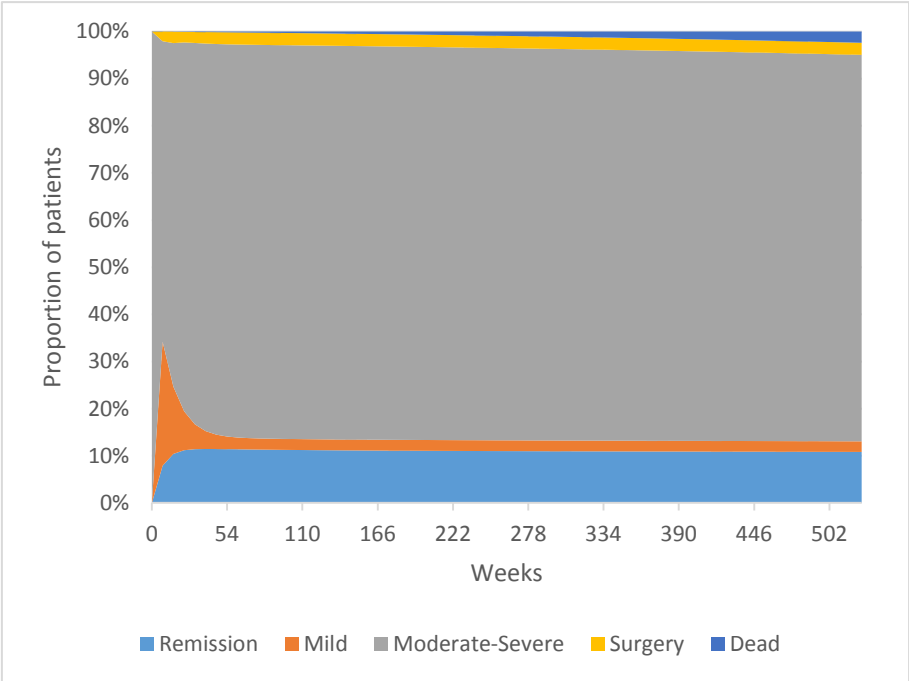


Figure 7.7.2.14: Markov trace: conventional therapy for the TNF-Naïve patient population (ITT) with moderate disease at baseline



TNF-Naïve Severe Patients

Figure 7.7.2.15: Markov trace: Vedolizumab for the TNF-Naïve patient population (ITT) with severe disease at baseline

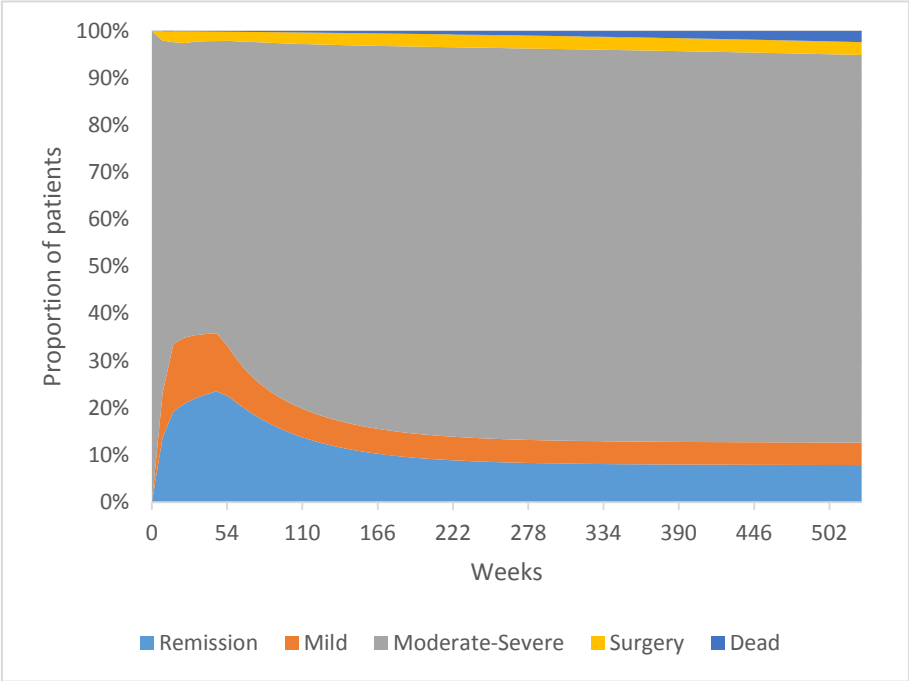
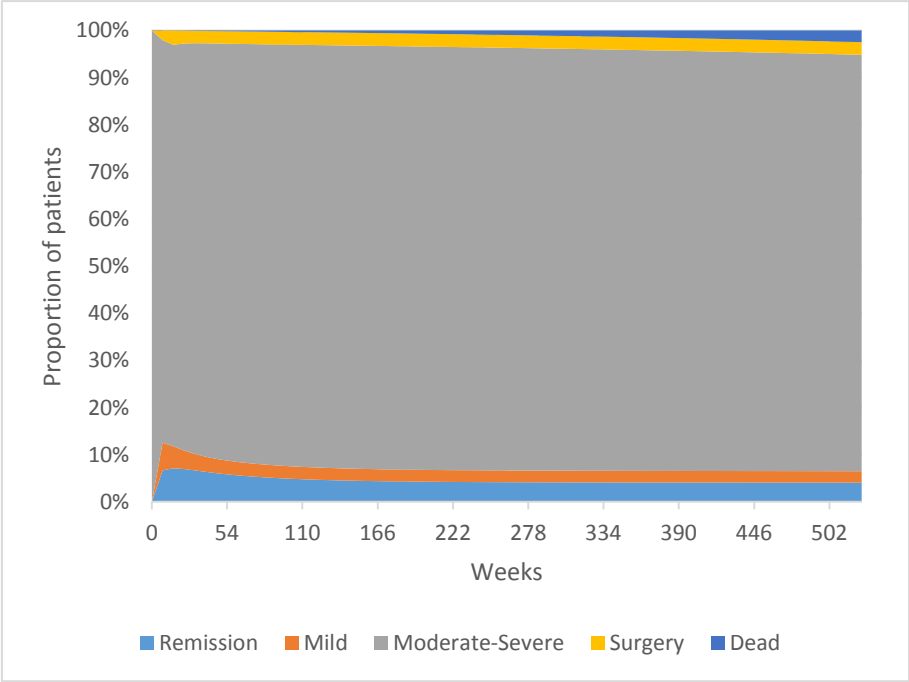


Figure 7.7.2.16: Markov trace: conventional therapy for the TNF-Naïve patient population (ITT) with severe disease at baseline



TNF-Failure Moderate Patients

Figure 7.7.2.17: Markov trace: Vedolizumab for the TNF-Failure patient population (ITT) with moderate disease at baseline

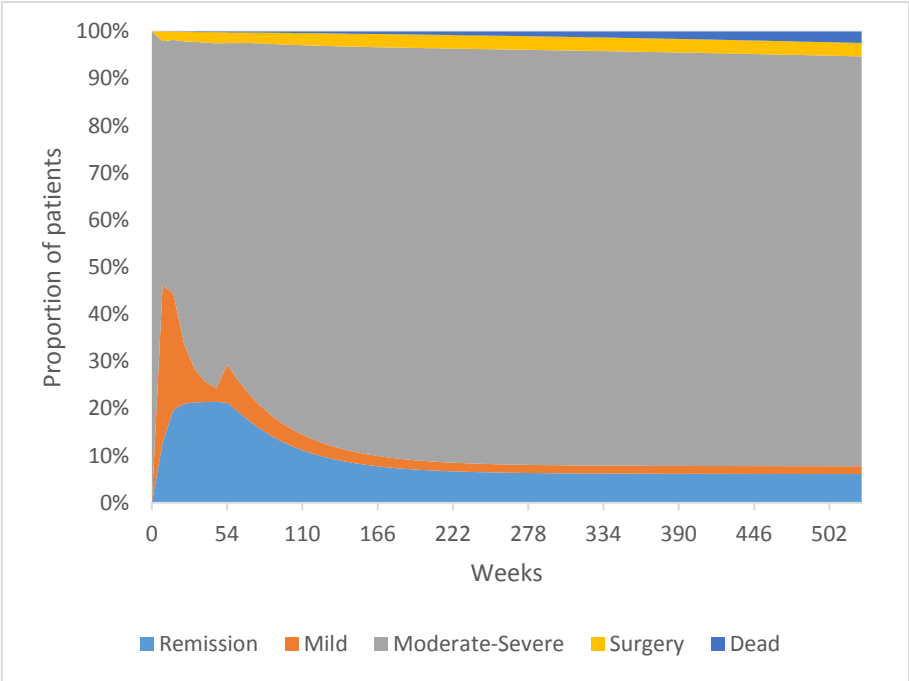
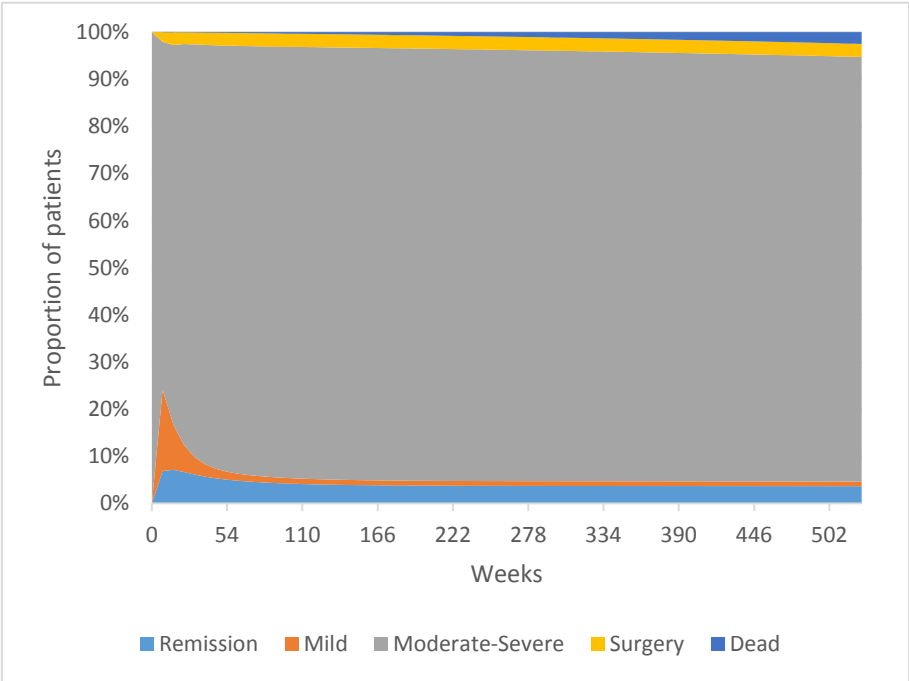


Figure 7.7.2.18: Markov trace: conventional therapy for the TNF-Failure patient population (ITT) with moderate disease at baseline



TNF-Failure Severe Patients

Figure 7.7.2.19: Markov trace: Vedolizumab for the TNF-Failure patient population (ITT) with severe disease at baseline

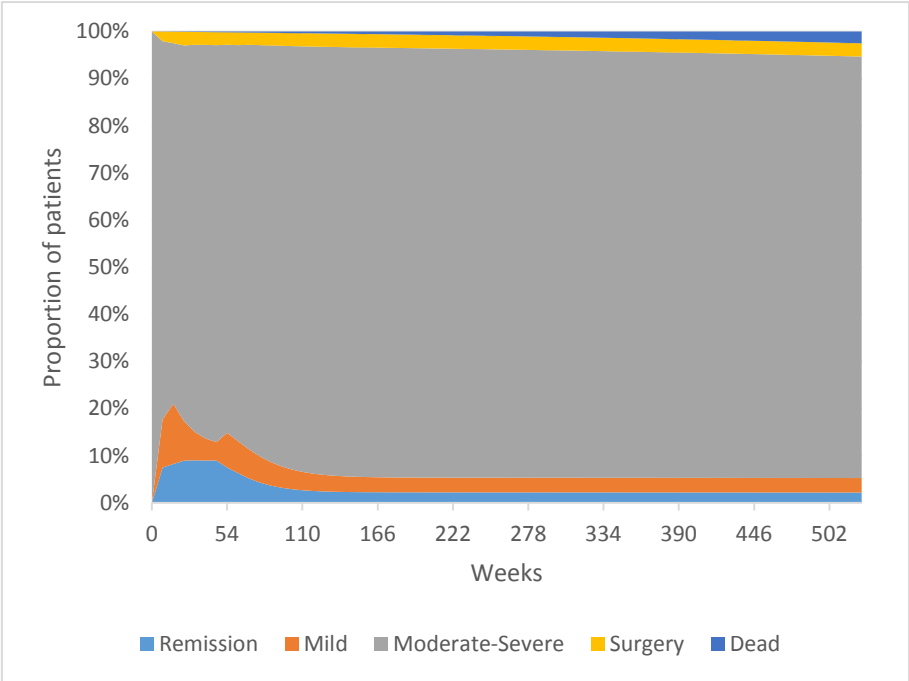
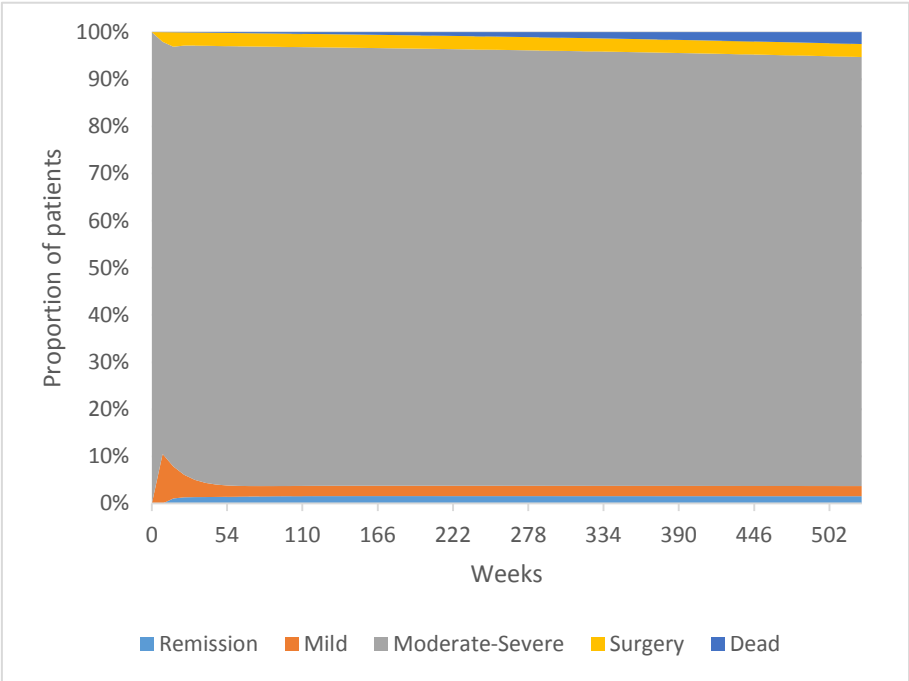


Figure 7.7.2.20: Markov trace: conventional therapy for the TNF-Failure patient population (ITT) with severe disease at baseline



7.7.3	**Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.**

Because data do not allow for a reasonable comparison of Vedolizumab with Infliximab and Adalimumab therapies in TNF-failure patients, Markov traces of utility values are displayed by patient population and comparator, below. The graphs show the total utility score for each cycle of the model, by health, describing the contribution of each health state to the overall utility for the cohort, cycle by cycle. The graphs diminish over time primarily as a result of mortality: patients who have died do not contribute to the overall utility score for the cohort.

Mixed Population (ITT)

Figure 7.7.3.1: Utility Markov trace: Vedolizumab for the mixed patient population (ITT). Modelled utility scores by Health state per cycle.

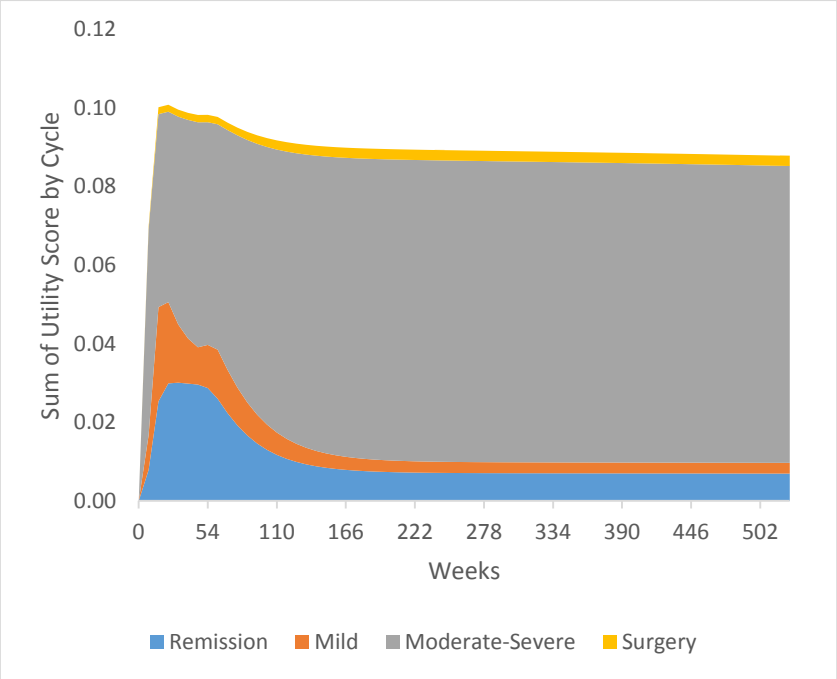
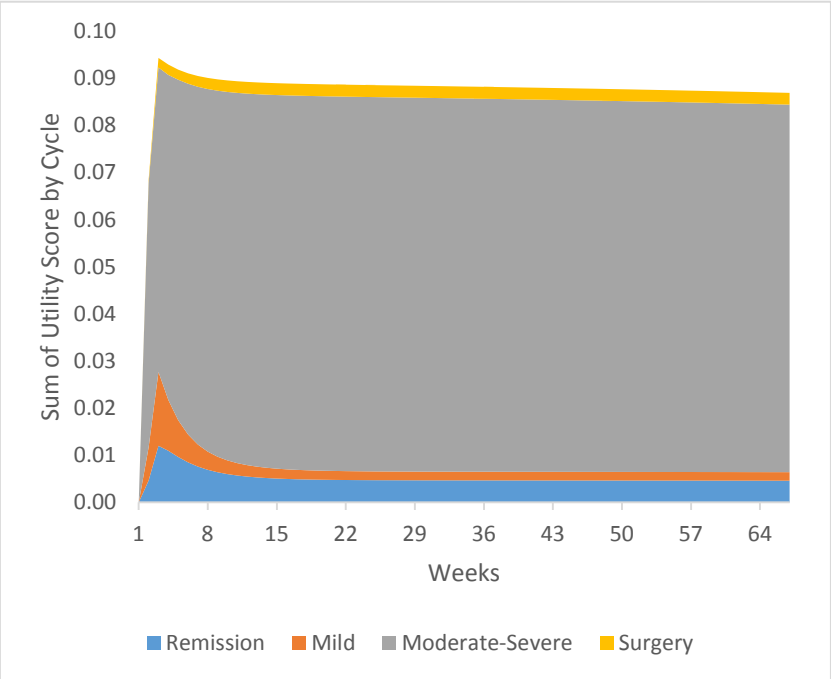


Figure 7.7.3.2: Utility Markov trace: conventional therapy for the mixed patient population (ITT). Modelled utility scores by Health state per cycle.



TNF-Naïve Population

Figure 7.7.3.3: Utility Markov trace: Vedolizumab for the TNF-Naive patient population (MTC-based estimates). Modelled utility scores by Health state per cycle.

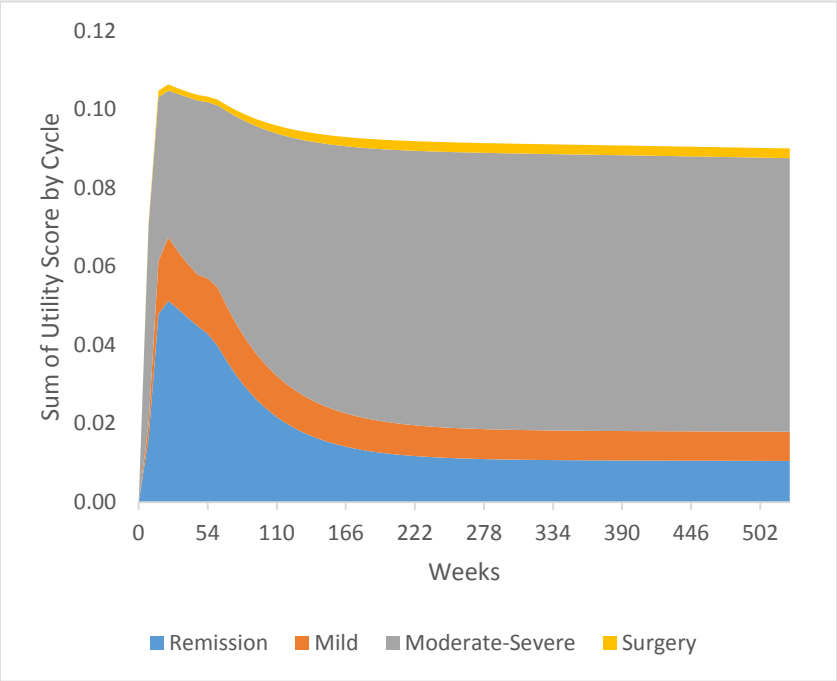


Figure 7.7.3.4: Utility Markov trace: conventional therapy for the TNF-Naive patient population (MTC-based estimates). Modelled utility scores by Health state per cycle.

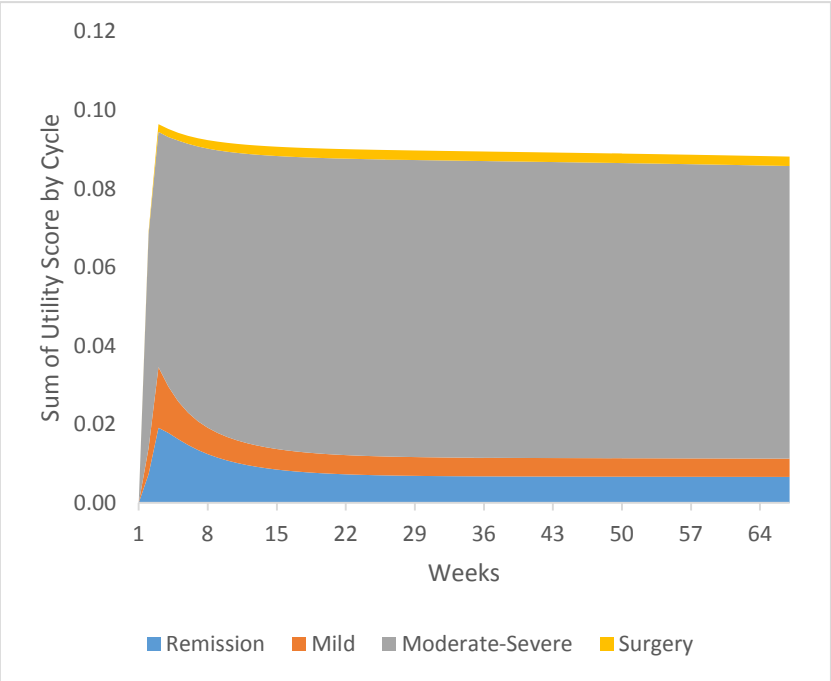


Figure 7.7.3.5: Utility Markov trace: Infliximab for the TNF-Naive patient population (MTC-based estimates). Modelled utility scores by Health state per cycle.

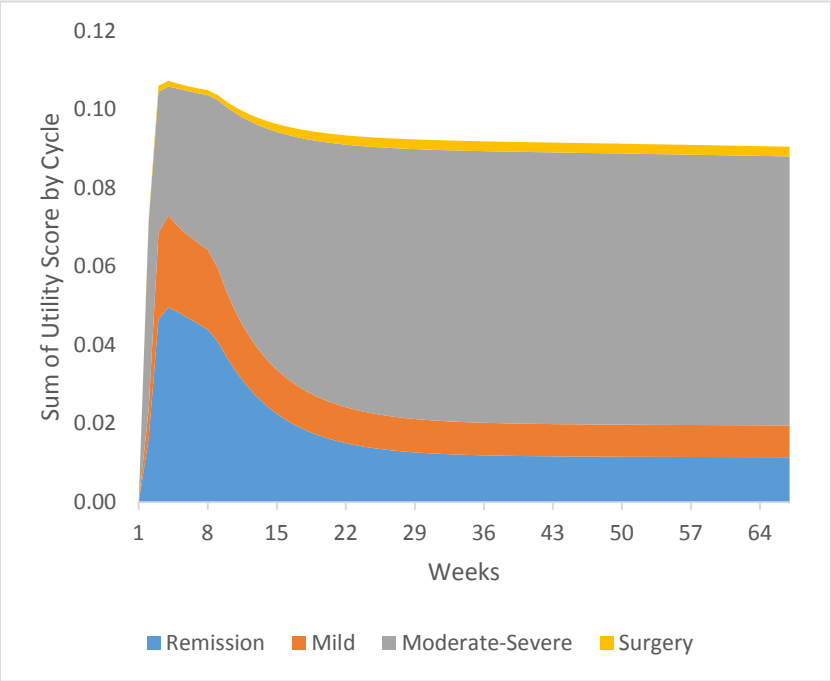
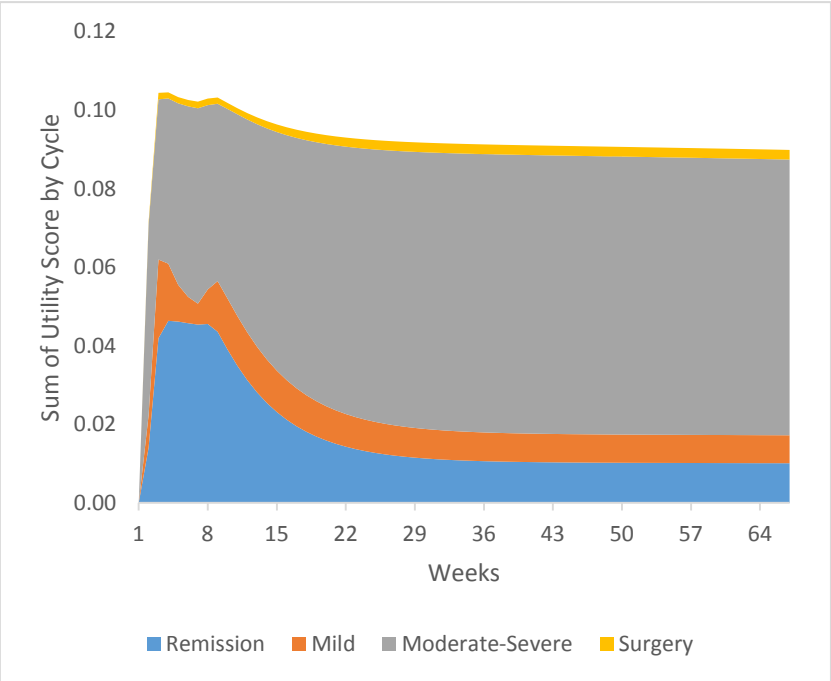


Figure 7.7.3.6: Utility Markov trace: Adalimumab for the TNF-Naive patient population (MTC-based estimates). Modelled utility scores by Health state per cycle.



7.7.4	**Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:**

The following tables present the life years, QALYs and costs accrued, by health state, by patient population and comparator.

Mixed Population (ITT)

Table 7.7.4.1: Life years estimated by the model by Health state for the mixed population (ITT)

	VDZ	Conventional therapy
Remission (CDAI < 150)	0.735	0.355
Mild (CDAI = 150-220)	0.385	0.204
Moderate-to-Severe (CDAI = 220-600)	6.956	7.511
Surgery	0.233	0.236
Total	8.310	8.306

Table 7.7.4.2: QALYs estimated by the model by Health state for the mixed population (ITT)

	VDZ	Conventional therapy
Remission (CDAI < 150)	0.602	0.291
Mild (CDAI = 150-220)	0.281	0.148
Moderate-to-Severe (CDAI = 220-600)	3.958	4.273
Surgery	0.133	0.135
Total	4.973	4.847

Table 7.7.4.3: Costs estimated by the model by Health state for the mixed population (ITT)

	Vedolizumab	Conventional therapy
Drug-related costs	£15,303.64	£6,289.48
Biologics	£9,212.59	£0.00
Conventional therapy	£6,091.04	£6,289.48
Non-drug related cost	£40,739.66	£42,114.60
Health-state costs	£40,156.62	£41,506.35
Adverse event costs	£583.03	£608.26
Total costs	£56,043.29	£48,404.09

TNF-Naïve Patients

Table 7.7.4.4: Life years estimated by the model by Health state for the TNF-Naïve population

	VDZ	Conventional therapy	Infliximab	Adalimumab
Remission (CDAI < 150)	1.687	0.817	0.843	0.843
Mild (CDAI = 150-220)	0.837	0.520	0.527	0.527
Moderate-to-Severe (CDAI = 220-600)	5.603	6.762	6.728	6.728
Surgery	0.189	0.211	0.211	0.211
Total	8.317	8.310	8.310	8.310

Table 7.7.4.5: QALYs estimated by the model by Health state for the TNF-Naïve population

	VDZ	Conventional therapy	Infliximab	Adalimumab
Remission (CDAI < 150)	1.381	0.669	0.690	0.690
Mild (CDAI = 150-220)	0.610	0.379	0.384	0.384
Moderate-to-Severe (CDAI = 220-600)	3.188	3.847	3.828	3.828
Surgery	0.108	0.120	0.120	0.120
Total	5.287	5.015	5.022	5.023

Table 7.7.4.6: Costs estimated by the model by Health state for the TNF-Naïve population

	Vedolizumab	Conventional therapy	Infliximab	Adalimumab
Drug-related costs	£15,905.54	£6,311.86	£16,877.97	£12,475.16
Biologics	£9,792.21	£0.00	£10,814.84	£6,403.99
Conventional therapy	£6,113.34	£6,311.86	£6,063.14	£6,071.17
Non-drug related cost	£34,916.14	£38,929.38	£37,596.72	£37,940.75
Health-state costs	£34,331.24	£38,318.97	£36,983.31	£37,360.81
Adverse event costs	£584.90	£610.41	£613.41	£579.93
Total costs	£50,821.68	£45,241.24	£54,474.69	£50,415.91

TNF-Failure Population

Table 7.7.4.7: Life years estimated by the model by Health state for the TNF-Failure population

	VDZ	Conventional therapy
Remission (CDAI < 150)	0.495	0.265
Mild (CDAI = 150-220)	0.428	0.275
Moderate-to-Severe (CDAI = 220-600)	7.153	7.532
Surgery	0.233	0.234
Total	8.308	8.306

Table 7.7.4.8: QALYs estimated by the model by Health state for the TNF-Failure population

	VDZ	Conventional therapy
Remission (CDAI < 150)	0.405	0.217
Mild (CDAI = 150-220)	0.312	0.201
Moderate-to-Severe (CDAI = 220-600)	4.069	4.285
Surgery	0.133	0.133
Total	4.919	4.836

Table 7.7.4.9: Costs estimated by the model by Health state for the TNF-Failure population

	Vedolizumab	Conventional therapy
Drug-related costs	£15,004.56	£6,290.88
Biologics	£8,905.11	£0.00
Conventional therapy	£6,099.45	£6,290.88
Non-drug related cost	£41,265.23	£42,120.34
Health-state costs	£40,681.23	£41,511.95
Adverse event costs	£583.99	£608.39
Total costs	£56,269.79	£48,411.22

Moderate Mixed Population

Table 7.7.4.10: Life years estimated by the model by Health state for the moderate mixed population

	VDZ	Conventional therapy
Remission (CDAI < 150)	1.834	0.769
Mild (CDAI = 150-220)	0.354	0.180
Moderate-to-Severe (CDAI = 220-600)	5.932	7.140
Surgery	0.196	0.219
Total	8.316	8.308

Table 7.7.4.11: QALYs estimated by the model by Health state for the moderate mixed population

	VDZ	Conventional therapy
Remission (CDAI < 150)	1.501	0.629
Mild (CDAI = 150-220)	0.258	0.131
Moderate-to-Severe (CDAI = 220-600)	3.375	4.062
Surgery	0.112	0.125
Total	5.246	4.947

Table 7.7.4.12: Costs estimated by the model by Health state for the moderate mixed population

	Vedolizumab	Conventional therapy
Drug-related costs	£16,279.58	£6,304.09
Biologics	£10,183.92	£0.00
Conventional therapy	£6,095.66	£6,304.09
Non-drug related cost	£35,540.86	£39,992.24
Health-state costs	£34,957.85	£39,382.58
Adverse event costs	£583.01	£609.66
Total costs	£51,820.43	£46,296.33

Severe Mixed Population

Table 7.7.4.13: Life years estimated by the model by Health state for the severe mixed population

	VDZ	Conventional therapy
Remission (CDAI < 150)	0.485	0.222
Mild (CDAI = 150-220)	0.383	0.205
Moderate-to-Severe (CDAI = 220-600)	7.209	7.647
Surgery	0.230	0.231
Total	8.308	8.305

Table 7.7.4.14: QALYs estimated by the model by Health state for the severe mixed population

	VDZ	Conventional therapy
Remission (CDAI < 150)	0.397	0.182
Mild (CDAI = 150-220)	0.279	0.149
Moderate-to-Severe (CDAI = 220-600)	4.102	4.350
Surgery	0.131	0.132
Total	4.909	4.813

Table 7.7.4.15: Costs estimated by the model by Health state for the severe mixed population

	Vedolizumab	Conventional therapy
Drug-related costs	£14,449.44	£6,292.52
Biologics	£8,331.13	£0.00
Conventional therapy	£6,118.31	£6,292.52
Non-drug related cost	£41,178.20	£42,118.13
Health-state costs	£40,592.12	£41,509.58
Adverse event costs	£586.09	£608.55
Total costs	£55,627.64	£48,410.65

Moderate TNF-Naïve Patients

Table 7.7.4.16: Life years estimated by the model by Health state for the moderate TNF-Naïve population

	VDZ	Conventional therapy	Infliximab	Adalimumab
Remission (CDAI < 150)	2.295	0.916	0.504	0.504
Mild (CDAI = 150-220)	0.473	0.258	0.455	0.455
Moderate-to-Severe (CDAI = 220-600)	5.370	6.922	7.123	7.123
Surgery	0.181	0.213	0.227	0.227
Total	8.319	8.309	8.308	8.308

Table 7.7.4.17: QALYs estimated by the model by Health state for the moderate TNF-Naïve population

	VDZ	Conventional therapy	Infliximab	Adalimumab
Remission (CDAI < 150)	1.878	0.749	0.412	0.412
Mild (CDAI = 150-220)	0.345	0.188	0.332	0.332
Moderate-to-Severe (CDAI = 220-600)	3.055	3.938	4.052	4.052
Surgery	0.103	0.121	0.129	0.129
Total	5.382	4.997	4.925	4.925

Table 7.7.4.18: Costs estimated by the model by Health state for the moderate TNF-Naïve population

	Vedolizumab	Conventional therapy	Infliximab	Adalimumab
Drug-related costs	£17,083.80	£6,309.96	£11,105.71	£8,644.41
Biologics	£10,998.26	£0.00	£4,880.49	£2,419.19
Conventional therapy	£6,085.53	£6,309.96	£6,225.22	£6,225.22
Non-drug related cost	£33,238.99	£39,110.19	£40,815.93	£40,805.92
Health-state costs	£32,657.36	£38,499.96	£40,208.03	£40,208.03
Adverse event costs	£581.64	£610.23	£607.89	£597.88
Total costs	£50,322.79	£45,420.15	£51,921.63	£49,450.32

Severe TNF-Naïve Patients

Table 7.7.4.19: Life years estimated by the model by Health state for the severe TNF-Naïve population

	VDZ	Conventional therapy	Infliximab	Adalimumab
Remission (CDAI < 150)	0.944	0.384	0.413	0.413
Mild (CDAI = 150-220)	0.515	0.223	0.234	0.234
Moderate-to-Severe (CDAI = 220-600)	6.637	7.475	7.435	7.435
Surgery	0.216	0.224	0.224	0.224
Total	8.311	8.306	8.307	8.307

Table 7.7.4.20: QALYs estimated by the model by Health state for the severe TNF-Naïve population

	VDZ	Conventional therapy	Infliximab	Adalimumab
Remission (CDAI < 150)	0.773	0.314	0.338	0.338
Mild (CDAI = 150-220)	0.375	0.163	0.171	0.171
Moderate-to-Severe (CDAI = 220-600)	3.776	4.253	4.230	4.230
Surgery	0.123	0.128	0.128	0.128
Total	5.047	4.857	4.866	4.866

Table 7.7.4.21: Costs estimated by the model by Health state for the severe TNF-Naïve population

	Vedolizumab	Conventional therapy	Infliximab	Adalimumab
Drug-related costs	£14,932.77	£6,298.78	£11,104.46	£11,838.63
Biologics	£8,814.90	£0.00	£4,880.49	£5,744.65
Conventional therapy	£6,117.87	£6,298.78	£6,223.97	£6,093.98
Non-drug related cost	£38,893.94	£41,222.22	£41,137.97	£38,856.60
Health-state costs	£38,308.13	£40,613.07	£40,530.20	£38,273.96
Adverse event costs	£585.81	£609.15	£607.77	£582.64
Total costs	£53,826.71	£47,521.00	£52,242.44	£50,695.23

Moderate TNF-Failure Population

Table 7.7.4.22: Life years estimated by the model by Health state for the moderate TNF-Failure population

	VDZ	Conventional therapy
Remission (CDAI < 150)	0.782	0.344
Mild (CDAI = 150-220)	0.298	0.138
Moderate-to-Severe (CDAI = 220-600)	7.004	7.594
Surgery	0.225	0.230
Total	8.309	8.306

Table 7.7.4.23: QALYs estimated by the model by Health state for the moderate TNF-Failure population

	VDZ	Conventional therapy
Remission (CDAI < 150)	0.640	0.282
Mild (CDAI = 150-220)	0.217	0.100
Moderate-to-Severe (CDAI = 220-600)	3.985	4.320
Surgery	0.128	0.131
Total	4.971	4.833

Table 7.7.4.24: Costs estimated by the model by Health state for the moderate TNF-Failure Population

	Vedolizumab	Conventional therapy
Drug-related costs	£15,080.09	£6,294.14
Biologics	£8,975.71	£0.00
Conventional therapy	£6,104.38	£6,294.14
Non-drug related cost	£40,172.56	£41,784.27
Health-state costs	£39,588.13	£41,175.56
Adverse event costs	£584.43	£608.71
Total costs	£55,252.65	£48,078.40

Severe TNF-Failure Population

Table 7.7.4.25: Life years estimated by the model by Health state for the severe TNF-Failure population

	VDZ	Conventional therapy
Remission (CDAI < 150)	0.270	0.125
Mild (CDAI = 150-220)	0.329	0.208
Moderate-to-Severe (CDAI = 220-600)	7.475	7.739
Surgery	0.233	0.232
Total	8.306	8.305

Table 7.7.4.26: QALYs estimated by the model by Health state for the severe TNF-Failure population

	VDZ	Conventional therapy
Remission (CDAI < 150)	0.221	0.103
Mild (CDAI = 150-220)	0.239	0.152
Moderate-to-Severe (CDAI = 220-600)	4.253	4.403
Surgery	0.133	0.132
Total	4.846	4.789

Table 7.7.4.27: Costs estimated by the model by Health state for the severe TNF-Failure population

	Vedolizumab	Conventional therapy
Drug-related costs	£14,080.91	£6,291.42
Biologics	£7,954.49	£0.00
Conventional therapy	£6,126.42	£6,291.42
Non-drug related cost	£41,942.30	£42,410.19
Health-state costs	£41,355.25	£41,801.75
Adverse event costs	£587.05	£608.44
Total costs	£56,023.21	£48,701.61

7.7.5	**Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.**

The following tables present details of the disaggregated incremental life years, QALYs and costs by health state, patient population and comparator.

Mixed Population (ITT)

Table 7.7.5.1: Disaggregated QALYs for Vedolizumab and conventional therapy estimated by the model for the mixed population (ITT)

	Vedolizumab	Conventional therapy	Increment	Absolute Increment	% Absolute Increment
Remission (CDAI < 150)	0.602	0.291	0.311	0.311	107.05%
Mild (CDAI = 150-220)	0.281	0.148	0.132	0.132	89.13%
Moderate-to-Severe (CDAI = 220-600)	3.958	4.273	-0.316	0.316	7.39%
Surgery	0.133	0.135	-0.002	0.002	1.31%
Total	4.973	4.847	0.126	0.761	205%

Table 7.7.5.2: Disaggregated costs for Vedolizumab and conventional therapy estimated by the model for the mixed population (ITT)

	Vedolizumab	Conventional therapy	Increment	Absolute Increment	% Absolute Increment
Drug-related costs	£15,303.64	£6,289.48	£9,014.15	£9,014.15	143.32%
Biologics	£9,212.59	£0.00	£9,212.59	£9,212.59	0.00%
Conventional therapy	£6,091.04	£6,289.48	-£198.44	£198.44	3.16%
Non-drug related cost	£40,739.66	£42,114.60	-£1,374.95	£1,374.95	3.26%
Health-state costs	£40,156.62	£41,506.35	-£1,349.72	£1,349.72	3.25%
Adverse event costs	£583.03	£608.26	-£25.22	£25.22	4.15%
Total costs	£56,043.29	£48,404.09	£7,639.21	£7,639.21	15.78%

TNF-Naïve Patients

Table 7.7.5.3: Disaggregated QALYs for Vedolizumab and conventional therapy estimated by the model for the TNF Naïve population (trial-based estimates)

	Vedolizumab	Conventional therapy	Increment	Absolute Increment	% Absolute Increment
Remission (CDAI < 150)	1.381	0.669	0.712	0.712	106.40%
Mild (CDAI = 150-220)	0.610	0.379	0.231	0.231	61.12%
Moderate-to-Severe (CDAI = 220-600)	3.188	3.847	-0.659	0.659	17.13%
Surgery	0.108	0.120	-0.012	0.012	10.35%
Total	5.287	5.015	0.272	1.615	195%

Table 7.7.5.4: Disaggregated costs for Vedolizumab and conventional therapy estimated by the model for the TNF-Naïve population (trial-based estimates)

	Vedolizumab	Conventional therapy	Increment	Absolute Increment	% Absolute Increment
Drug-related costs	£15,905.54	£6,311.86	£9,593.68	£9,593.68	151.99%
Biologics	£9,792.21	£0.00	£9,792.21	£9,792.21	0.00%
Conventional therapy	£6,113.34	£6,311.86	-£198.53	£198.53	3.15%
Non-drug related cost	£34,916.14	£38,929.38	-£4,013.24	£4,013.24	10.31%
Health-state costs	£34,331.24	£38,318.97	-£3,987.73	£3,987.73	10.41%
Adverse event costs	£584.90	£610.41	-£25.51	£25.51	4.18%
Total costs	£50,821.68	£45,241.24	£5,580.44	£5,580.44	12.33%

Table 7.7.5.5: Disaggregated QALYs for Vedolizumab and Infliximab estimated by the model for the TNF Naïve population (MTC-based estimates)

	Vedolizumab	Conventional therapy	Increment	Absolute Increment	% Absolute Increment
Remission (CDAI < 150)	0.987	1.029	-0.042	0.042	4.11%
Mild (CDAI = 150-220)	0.495	0.581	-0.086	0.086	14.81%
Moderate-to-Severe (CDAI = 220-600)	3.536	3.439	0.097	0.097	2.81%
Surgery	0.121	0.121	0.001	0.001	0.46%
Total	5.140	5.171	-0.031	0.226	22%

Table 7.7.5.6: Disaggregated costs for Vedolizumab and Infliximab estimated by the model for the TNF-Naïve population (MTC-based estimates)

	Vedolizumab	Conventional therapy	Increment	Absolute Increment	% Absolute Increment
Drug-related costs	£15,825.07	£16,877.97	-£1,052.90	£1,052.90	6.24%
Biologics	£9,730.86	£10,814.84	-£1,083.97	£1,083.97	10.02%
Conventional therapy	£6,094.21	£6,063.14	£31.07	£31.07	0.51%
Non-drug related cost	£37,896.87	£37,596.72	£300.15	£300.15	0.80%
Health-state costs	£37,313.79	£36,983.31	£330.48	£330.48	0.89%
Adverse event costs	£583.09	£613.41	-£30.32	£30.32	4.94%
Total costs	£53,721.95	£54,474.69	-£752.74	£752.74	1.38%

Table 7.7.5.7: Disaggregated QALYs for Vedolizumab and Adalimumab estimated by the model for the TNF Naïve population (MTC-based estimates)

	Vedolizumab	Conventional therapy	Increment	Absolute Increment	% Absolute Increment
Remission (CDAI < 150)	0.987	0.981	0.006	0.006	0.61%
Mild (CDAI = 150-220)	0.495	0.467	0.029	0.029	6.16%
Moderate-to-Severe (CDAI = 220-600)	3.536	3.563	-0.027	0.027	0.75%
Surgery	0.121	0.121	0.000	0.000	0.11%
Total	5.140	5.131	0.008	0.061	8%

Table 7.7.5.8: Disaggregated costs for Vedolizumab and Adalimumab estimated by the model for the TNF-Naïve population (MTC-based estimates)

	Vedolizumab	Conventional therapy	Increment	Absolute Increment	% Absolute Increment
Drug-related costs	£15,825.07	£12,475.16	£3,349.91	£3,349.91	26.85%
Biologics	£9,730.86	£6,403.99	£3,326.87	£3,326.87	51.95%
Conventional therapy	£6,094.21	£6,071.17	£23.04	£23.04	0.38%
Non-drug related cost	£37,896.87	£37,940.75	-£43.87	£43.87	0.12%
Health-state costs	£37,313.79	£37,360.81	-£47.03	£47.03	0.13%
Adverse event costs	£583.09	£579.93	£3.16	£3.16	0.54%
Total costs	£53,721.95	£50,415.91	£3,306.04	£3,306.04	6.56%

TNF-Failure Patients

Table 7.7.5.9: Disaggregated QALYs for Vedolizumab and Conventional therapy estimated by the model for the TNF-Failure population (trial-based estimates)

	Vedolizumab	Conventional therapy	Increment	Absolute Increment	% Absolute Increment
Remission (CDAI < 150)	0.405	0.217	0.188	0.188	86.90%
Mild (CDAI = 150-220)	0.312	0.201	0.111	0.111	55.39%
Moderate-to-Severe (CDAI = 220-600)	4.069	4.285	-0.215	0.215	5.03%
Surgery	0.133	0.133	-0.001	0.001	0.58%
Total	4.919	4.836	0.083	0.516	148%

Table 7.7.5.10: Disaggregated costs for Vedolizumab and conventional therapy estimated by the model for the TNF-Failure population (trial-based estimates)

	Vedolizumab	Conventional therapy	Increment	Absolute Increment	% Absolute Increment
Drug-related costs	£15,004.56	£6,290.88	£8,713.68	£8,713.68	138.51%
Biologics	£8,905.11	£0.00	£8,905.11	£8,905.11	0.00%
Conventional therapy	£6,099.45	£6,290.88	-£191.43	£191.43	3.04%
Non-drug related cost	£41,265.23	£42,120.34	-£855.11	£855.11	2.03%
Health-state costs	£40,681.23	£41,511.95	-£830.71	£830.71	2.00%
Adverse event costs	£583.99	£608.39	-£24.40	£24.40	4.01%
Total costs	£56,269.79	£48,411.22	£7,858.57	£7,858.57	16.23%

Mixed Moderate Patients

Table 7.7.5.11: Disaggregated QALYs for Vedolizumab and conventional therapy estimated by the model for the mixed moderate population (trial-based estimates)

	Vedolizumab	Conventional therapy	Increment	Absolute Increment	% Absolute Increment
Remission (CDAI < 150)	1.501	0.629	0.872	0.872	138.56%
Mild (CDAI = 150-220)	0.258	0.131	0.127	0.127	96.90%
Moderate-to-Severe (CDAI = 220-600)	3.375	4.062	-0.687	0.687	16.92%
Surgery	0.112	0.125	-0.013	0.013	10.76%
Total	5.246	4.947	0.298	1.700	263%

Total 7.7.5.12: Disaggregated costs for Vedolizumab and conventional therapy estimated by the model for mixed moderate population (trial-based estimates)

	Vedolizumab	Conventional therapy	Increment	Absolute Increment	% Absolute Increment
Drug-related costs	£16,279.58	£6,304.09	£9,975.49	£9,975.49	158.24%
Biologics	£10,183.92	£0.00	£10,183.92	£10,183.92	0.00%
Conventional therapy	£6,095.66	£6,304.09	-£208.43	£208.43	3.31%
Non-drug related cost	£35,540.86	£39,992.24	-£4,451.39	£4,451.39	11.13%
Health-state costs	£34,957.85	£39,382.58	-£4,424.73	£4,424.73	11.24%
Adverse event costs	£583.01	£609.66	-£26.66	£26.66	4.37%
Total costs	£51,820.43	£46,296.33	£5,524.10	£5,524.10	11.93%

Mixed Severe Patients

Table 7.7.5.13: Disaggregated QALYs for Vedolizumab and conventional therapy estimated by the model for the mixed severe population (trial-based estimates)

	Vedolizumab	Conventional therapy	Increment	Absolute Increment	% Absolute Increment
Remission (CDAI < 150)	0.277	0.106	0.170	0.170	159.81%
Mild (CDAI = 150-220)	0.185	0.091	0.094	0.094	103.93%
Moderate-to-Severe (CDAI = 220-600)	2.199	2.389	-0.189	0.189	7.92%
Surgery	0.070	0.072	-0.002	0.002	3.15%
Total	2.731	2.658	0.073	0.456	275%

Table 7.7.5.14: Disaggregated costs for Vedolizumab and conventional therapy estimated by the model for mixed severe population (trial-based estimates)

	Vedolizumab	Conventional therapy	Increment	Absolute Increment	% Absolute Increment
Drug-related costs	£11,628.68	£3,470.71	£8,157.97	£8,157.97	235.05%
Biologics	£8,331.13	£0.00	£8,331.13	£8,331.13	0.00%
Conventional therapy	£3,297.54	£3,470.71	-£173.16	£173.16	4.99%
Non-drug related cost	£22,124.25	£23,077.68	-£953.43	£953.43	4.13%
Health-state costs	£21,809.69	£22,740.76	-£931.07	£931.07	4.09%
Adverse event costs	£314.56	£336.92	-£22.36	£22.36	6.64%
Total costs	£33,752.92	£26,548.39	£7,204.54	£7,204.54	27.14%

Moderate TNF-Naïve Patients

Table 7.7.5.15: Disaggregated QALYs for Vedolizumab and conventional therapy estimated by the model for the moderate TNF-Naïve population (trial-based estimates)

	Vedolizumab	Conventional therapy	Increment	Absolute Increment	% Absolute Increment
Remission (CDAI < 150)	1.878	0.749	1.129	1.129	150.63%
Mild (CDAI = 150-220)	0.345	0.188	0.157	0.157	83.28%
Moderate-to-Severe (CDAI = 220-600)	3.055	3.938	-0.883	0.883	22.42%
Surgery	0.103	0.121	-0.018	0.018	15.21%
Total	5.382	4.997	0.384	2.187	272%

Table 7.7.5.16: Disaggregated costs for Vedolizumab and conventional therapy estimated by the model for moderate TNF-Naïve population (trial-based estimates)

	Vedolizumab	Conventional therapy	Increment	Absolute Increment	% Absolute Increment
Drug-related costs	£17,083.80	£6,309.96	£10,773.83	£10,773.83	170.74%
Biologics	£10,998.26	£0.00	£10,998.26	£10,998.26	0.00%
Conventional therapy	£6,085.53	£6,309.96	-£224.43	£224.43	3.56%
Non-drug related cost	£33,238.99	£39,110.19	-£5,871.20	£5,871.20	15.01%
Health-state costs	£32,657.36	£38,499.96	-£5,842.60	£5,842.60	15.18%
Adverse event costs	£581.64	£610.23	-£28.59	£28.59	4.69%
Total costs	£50,322.79	£45,420.15	£4,902.64	£4,902.64	10.79%

Table 7.7.5.17: Disaggregated QALYs for Vedolizumab and infliximab estimated by the model for the moderate TNF-Naïve population (MTC-based estimates)

	Vedolizumab	Conventional therapy	Increment	Absolute Increment	% Absolute Increment
Remission (CDAI < 150)	0.777	0.412	0.365	0.365	88.49%
Mild (CDAI = 150-220)	0.544	0.332	0.212	0.212	64.08%
Moderate-to-Severe (CDAI = 220-600)	3.641	4.052	-0.411	0.411	10.15%
Surgery	0.124	0.129	-0.005	0.005	4.16%
Total	5.086	4.925	0.161	0.994	167%

Table 7.7.5.18: Disaggregated costs for Vedolizumab and Infliximab estimated by the model for moderate TNF-Naïve population (MTC-based estimates)

	Vedolizumab	Conventional therapy	Increment	Absolute Increment	% Absolute Increment
Drug-related costs	£15,883.40	£11,105.71	£4,777.70	£4,777.70	43.02%
Biologics	£9,795.32	£4,880.49	£4,914.83	£4,914.83	100.70%
Conventional therapy	£6,088.09	£6,225.22	-£137.13	£137.13	2.20%
Non-drug related cost	£38,723.59	£40,815.93	-£2,092.34	£2,092.34	5.13%
Health-state costs	£38,141.12	£40,208.03	-£2,066.91	£2,066.91	5.14%
Adverse event costs	£582.47	£607.89	-£25.43	£25.43	4.18%
Total costs	£54,606.99	£51,921.63	£2,685.36	£2,685.36	5.17%

Table 7.7.5.19: Disaggregated QALYs for Vedolizumab and Adalimumab estimated by the model for the moderate TNF-Naïve population (MTC-based estimates)

	Vedolizumab	Conventional therapy	Increment	Absolute Increment	% Absolute Increment
Remission (CDAI < 150)	0.777	0.412	0.365	0.365	88.49%
Mild (CDAI = 150-220)	0.544	0.332	0.212	0.212	64.08%
Moderate-to-Severe (CDAI = 220-600)	3.641	4.052	-0.411	0.411	10.15%
Surgery	0.124	0.129	-0.005	0.005	4.16%
Total	5.086	4.925	0.160	0.994	167%

Table 7.7.5.20: Disaggregated Costs for Vedolizumab and Adalimumab estimated by the model for moderate TNF-Naïve population (MTC-based estimates)

	Vedolizumab	Conventional therapy	Increment	Absolute Increment	% Absolute Increment
Drug-related costs	£15,883.40	£8,644.41	£7,239.00	£7,239.00	83.74%
Biologics	£9,795.32	£2,419.19	£7,376.13	£7,376.13	304.90%
Conventional therapy	£6,088.09	£6,225.22	-£137.13	£137.13	2.20%
Non-drug related cost	£38,723.59	£40,805.92	-£2,082.33	£2,082.33	5.10%
Health-state costs	£38,141.12	£40,208.03	-£2,066.91	£2,066.91	5.14%
Adverse event costs	£582.47	£597.88	-£15.42	£15.42	2.58%
Total costs	£54,606.99	£49,450.32	£5,156.67	£5,156.67	10.43%

Severe TNF-Naïve Patients

Table 7.7.5.21: Disaggregated QALYs for Vedolizumab and conventional therapy estimated by the model for severe TNF-Naïve population (trial-based estimates)

	Vedolizumab	Conventional therapy	Increment	Absolute Increment	% Absolute Increment
Remission (CDAI < 150)	0.773	0.314	0.459	0.459	146.06%
Mild (CDAI = 150-220)	0.375	0.163	0.212	0.212	130.40%
Moderate-to-Severe (CDAI = 220-600)	3.776	4.253	-0.477	0.477	11.21%
Surgery	0.123	0.128	-0.005	0.005	3.91%
Total	5.047	4.857	0.189	1.153	292%

Table 7.7.5.22: Disaggregated costs for Vedolizumab and conventional therapy estimated by the model for TNF-Naïve population (trial-based estimates)

	Vedolizumab	Conventional therapy	Increment	Absolute Increment	% Absolute Increment
Drug-related costs	£14,932.77	£6,298.78	£8,633.99	£8,633.99	137.07%
Biologics	£8,814.90	£0.00	£8,814.90	£8,814.90	0.00%
Conventional therapy	£6,117.87	£6,298.78	-£180.91	£180.91	2.87%
Non-drug related cost	£38,893.94	£41,222.22	-£2,328.28	£2,328.28	5.65%
Health-state costs	£38,308.13	£40,613.07	-£2,304.94	£2,304.94	5.68%
Adverse event costs	£585.81	£609.15	-£23.34	£23.34	3.83%
Total costs	£53,826.71	£47,521.00	£6,305.70	£6,305.70	13.27%

Table 7.7.5.23: Disaggregated QALYs for Vedolizumab and Infliximab estimated by the model for the severe TNF-Naïve population (MTC-based estimates)

	Vedolizumab	Conventional therapy	Increment	Absolute Increment	% Absolute Increment
Remission (CDAI < 150)	0.593	0.367	0.227	0.227	61.81%
Mild (CDAI = 150-220)	0.399	0.243	0.156	0.156	64.03%
Moderate-to-Severe (CDAI = 220-600)	3.877	4.152	-0.275	0.275	6.62%
Surgery	0.127	0.130	-0.002	0.002	1.70%
Total	4.996	4.891	0.105	0.659	134%

Table 7.7.5.24: Disaggregated costs for Vedolizumab and Infliximab estimated by the model for TNF-Naïve population (MTC-based estimates)

	Vedolizumab	Conventional therapy	Increment	Absolute Increment	% Absolute Increment
Drug-related costs	£15,128.85	£11,104.46	£4,024.39	£4,024.39	36.24%
Biologics	£9,024.37	£4,880.49	£4,143.89	£4,143.89	84.91%
Conventional therapy	£6,104.47	£6,223.97	-£119.50	£119.50	1.92%
Non-drug related cost	£39,929.28	£41,137.97	-£1,208.70	£1,208.70	2.94%
Health-state costs	£39,344.86	£40,530.20	-£1,185.34	£1,185.34	2.92%
Adverse event costs	£584.42	£607.77	-£23.35	£23.35	3.84%
Total costs	£55,058.12	£52,242.44	£2,815.69	£2,815.69	5.39%

Table 7.7.5.25: Disaggregated QALYs for Vedolizumab and Adalimumab estimated by the model for the severe TNF-Naïve population (MTC-based estimates)

	Vedolizumab	Conventional therapy	Increment	Absolute Increment	% Absolute Increment
Remission (CDAI < 150)	0.593	0.837	-0.243	0.243	29.09%
Mild (CDAI = 150-220)	0.399	0.366	0.033	0.033	9.03%
Moderate-to-Severe (CDAI = 220-600)	3.877	3.738	0.139	0.139	3.72%
Surgery	0.127	0.124	0.003	0.003	2.64%
Total	4.996	5.064	-0.068	0.419	44%

Table 7.7.5.26: Disaggregated costs for Vedolizumab and Adalimumab estimated by the model for severe TNF-Naïve population (MTC-based estimates)

	Vedolizumab	Conventional therapy	Increment	Absolute Increment	% Absolute Increment
Drug-related costs	£15,128.85	£11,838.63	£3,290.22	£3,290.22	27.79%
Biologics	£9,024.37	£5,744.65	£3,279.72	£3,279.72	57.09%
Conventional therapy	£6,104.47	£6,093.98	£10.49	£10.49	0.17%
Non-drug related cost	£39,929.28	£38,856.60	£1,072.67	£1,072.67	2.76%
Health-state costs	£39,344.86	£38,273.96	£1,070.90	£1,070.90	2.80%
Adverse event costs	£584.42	£582.64	£1.77	£1.77	0.30%
Total costs	£55,058.12	£50,695.23	£4,362.89	£4,362.89	8.61%

Moderate TNF- Failure Patients

Table 7.7.5.27: Disaggregated QALYs for Vedolizumab and conventional therapy estimated by the model for the moderate TNF-Failure population (trial-based estimates)

	Vedolizumab	Conventional therapy	Increment	Absolute Increment	% Absolute Increment
Remission (CDAI < 150)	0.640	0.282	0.358	0.358	127.15%
Mild (CDAI = 150-220)	0.217	0.100	0.117	0.117	116.65%
Moderate-to-Severe (CDAI = 220-600)	3.985	4.320	-0.336	0.336	7.77%
Surgery	0.128	0.131	-0.003	0.003	2.11%
Total	4.971	4.833	0.137	0.814	254%

Table 7.7.5.28: Disaggregated costs for Vedolizumab and conventional therapy estimated by the model for moderate TNF-Failure population (trial-based estimates)

	Vedolizumab	Conventional therapy	Increment	Absolute Increment	% Absolute Increment
Drug-related costs	£15,080.09	£6,294.14	£8,785.95	£8,785.95	139.59%
Biologics	£8,975.71	£0.00	£8,975.71	£8,975.71	0.00%
Conventional therapy	£6,104.38	£6,294.14	-£189.76	£189.76	3.01%
Non-drug related cost	£40,172.56	£41,784.27	-£1,611.71	£1,611.71	3.86%
Health-state costs	£39,588.13	£41,175.56	-£1,587.44	£1,587.44	3.86%
Adverse event costs	£584.43	£608.71	-£24.27	£24.27	3.99%
Total costs	£55,252.65	£48,078.40	£7,174.24	£7,174.24	14.92%

Severe TNF-Failure Patients

Table 7.7.5.29: Disaggregated QALYs for Vedolizumab and conventional therapy estimated by the model for the severe TNF-Failure population (trial-based estimates)

	Vedolizumab	Conventional therapy	Increment	Absolute Increment	% Absolute Increment
Remission (CDAI < 150)	0.221	0.103	0.118	0.118	115.29%
Mild (CDAI = 150-220)	0.239	0.152	0.088	0.088	57.84%
Moderate-to-Severe (CDAI = 220-600)	4.253	4.403	-0.150	0.150	3.41%
Surgery	0.133	0.132	0.000	0.000	0.28%
Total	4.846	4.789	0.056	0.357	177%

Table 7.7.5.30: Disaggregated costs for Vedolizumab and conventional therapy estimated by the model for severe TNF-Failure population (trial-based estimates)

	Vedolizumab	Conventional therapy	Increment	Absolute Increment	% Absolute Increment
Drug-related costs	£14,080.91	£6,291.42	£7,789.49	£7,789.49	123.81%
Biologics	£7,954.49	£0.00	£7,954.49	£7,954.49	0.00%
Conventional therapy	£6,126.42	£6,291.42	-£165.00	£165.00	2.62%
Non-drug related cost	£41,942.30	£42,410.19	-£467.89	£467.89	1.10%
Health-state costs	£41,355.25	£41,801.75	-£446.50	£446.50	1.07%
Adverse event costs	£587.05	£608.44	-£21.39	£21.39	3.52%
Total costs	£56,023.21	£48,701.61	£7,321.60	£7,321.60	15.03%

Base-case analysis

7.7.6	**Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.**

Table 7.7.6.1 below presents Incremental Cost-Effectiveness Estimates for Vedolizumab compared with each alternative by patient sub-group. In the mixed population, Vedolizumab has greater incremental costs and QALYs than conventional therapy and derives an ICER of £60,661.

In the TNF Naïve population, Vedolizumab generates greater QALY's than all other comparators, and dependant on the acquisition cost of the medicine, either derives a low estimated ICER (£2,000 - £20,500 approx) or dominates.

In the mixed moderate group, Vedolizumab has greater incremental costs and QALYs than conventional therapy and derives an ICER of £18,531. In the mixed severe group, Vedolizumab has greater incremental costs and QALYs than conventional therapy and derives an ICER of £75,433.

In the moderate TNF Naïve population, Vedolizumab generates greater QALY's than all other comparators, and dependant on the acquisition cost of the medicine, either derives a low estimated ICER (£2,000 - £12,000 approx) or dominates.

In the severe TNF Naïve population, Vedolizumab does not generate greater QALY's than all other comparators, and dependant on the acquisition cost of the medicine, and derives ICER's of between £10,000 to £35,000.

In the moderate TNF-Failure group, Vedolizumab has greater incremental costs and QALYs than conventional therapy and derives an ICER of £52,311. In the severe TNF-Failure group, Vedolizumab has greater incremental costs and QALYs than conventional therapy and derives an ICER of £130,732.

Table 7.7.6.1: Base-case results

Population / Technology	Total Costs	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (Cost per QALY gained)
Mixed Population (ITT)							
Vedolizumab	£56,043	8.310	4.973				
Conventional Therapy	£48,404	8.306	4.847	£7,639	0.003	0.126	£60,661
TNF-Naïve Patients							
Vedolizumab	£50,821	8.317	5.287				
Conventional Therapy	£45,241	8.310	5.015	£5,580	0.007	0.272	£20,532
Infliximab (MTC data)	£54,474	8.315	5.171	-£3,653	-0.002	-0.116	Vedolizumab dominates
Adalimumab (MTC data)	£50,415	8.314	5.131	£406	0.003	0.156	£2,602
Mixed moderate Patients							
Vedolizumab	£51,820	8.316	5.246				
Conventional Therapy	£46,296	8.308	4.947	£5,524	0.008	0.298	£18,531
Mixed severe Patients							
Vedolizumab	£55,627	8.308	4.909				
Conventional Therapy	£48,410	8.305	4.813	£7,216	0.003	0.096	£75,433
Moderate TNF-Naïve Patients							
Vedolizumab	£50,322	8.319	5.382				
Conventional Therapy	£45,420	8.309	4.997	£4,902	0.010	0.384	£12,761
Infliximab (MTC data)	£51,921	8.308	4.925	-£1,599	0.011	0.457	Vedolizumab

Population / Technology	Total Costs	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (Cost per QALY gained)
							dominates
Adalimumab (MTC data)	£49,450	8.308	4.925	£872	0.011	0.457	£1,908
Severe TNF-Naïve Patients							
Vedolizumab	£53,826	8.311	5.047				
Conventional Therapy	£47,521	8.306	4.857	£6,305	0.005	0.189	£33,317
Infliximab (MTC data)	£52,242	8.307	4.891	£1,584	0.004	0.156	£10,153
Adalimumab (MTC data)	£50,695	8.312	5.064	£3,131	-0.001	-0.017	Ada dominates
Moderate TNF-Failure Patients							
Vedolizumab	£55,252.65	8.309	4.971				
Conventional Therapy	£48,078.40	8.306	4.833	£7,174.24	0.004	0.137	£52,311
Severe TNF-Failure Patients							
Vedolizumab	£56,023	8.306	4.846				
Conventional Therapy	£48,701	8.305	4.789	£7,321	0.002	0.056	£130,732

Sensitivity analyses

7.7.7	**Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.**

The one-way sensitivity analysis replaced each variable with the upper and lower value, listed in table 7.3.6.1 (Section 7.3.6) and ran the model with that value. This was repeated for every variable and those with the biggest impact on the cost-effectiveness ratio were plotted on tornado diagrams.

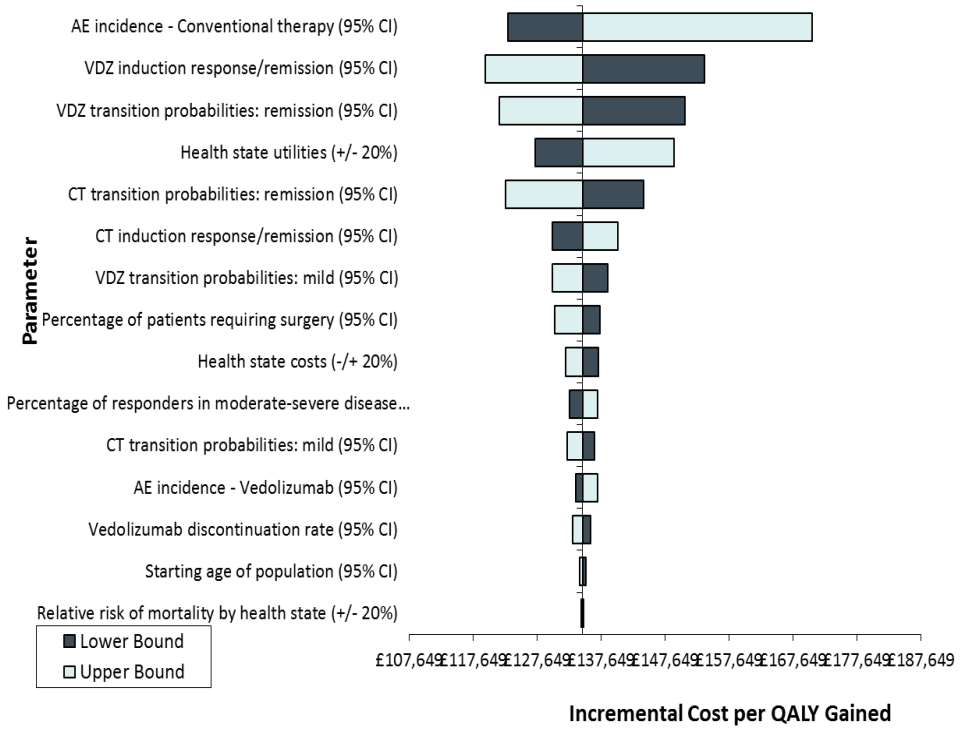
Tornado diagrams, by patient population and comparator, are presented below.

Mixed Population (ITT)

The figures below show that the variables with the biggest impact upon the ICER when comparing against conventional therapy are:

- Transition probabilities for remission related to conventional therapy.
- Vedolizumab efficacy.
- Health state costs.
- Transition probabilities for remission related to Vedolizumab.
- Surgery transition probabilities.

Figure 7.7.7.1: Tornado diagram: cost-effectiveness versus conventional therapy for the mixed patient population (ITT)



Anti-TNF-Naïve Population

Figure 7.7.7.2: Tornado diagram: cost-effectiveness versus conventional therapy for the Anti-TNF–Naïve patient population

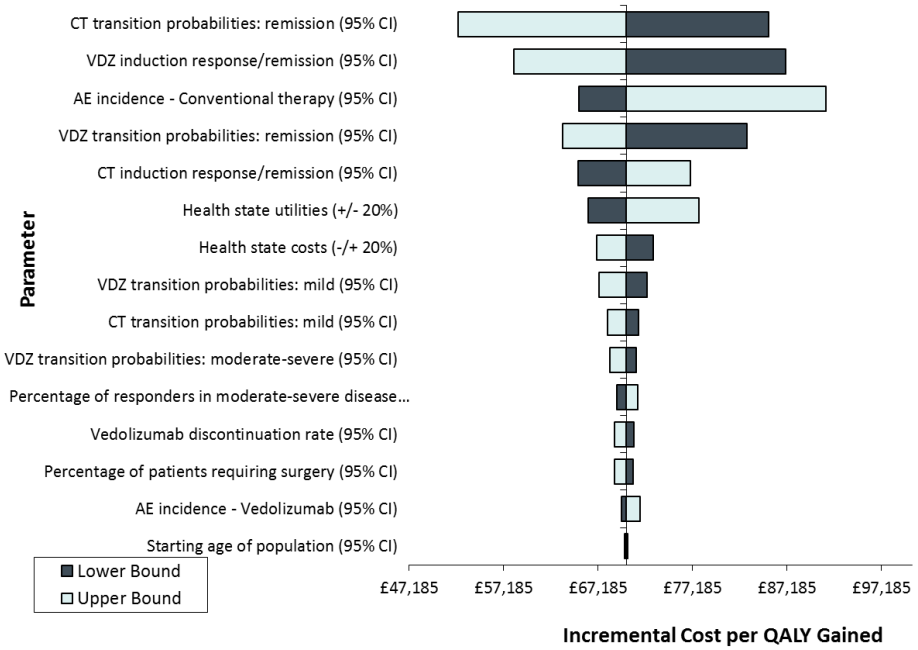


Figure 7.7.7.3: Tornado diagram: cost-effectiveness versus Infliximab for the Anti-TNF–Naïve patient population (ITT)

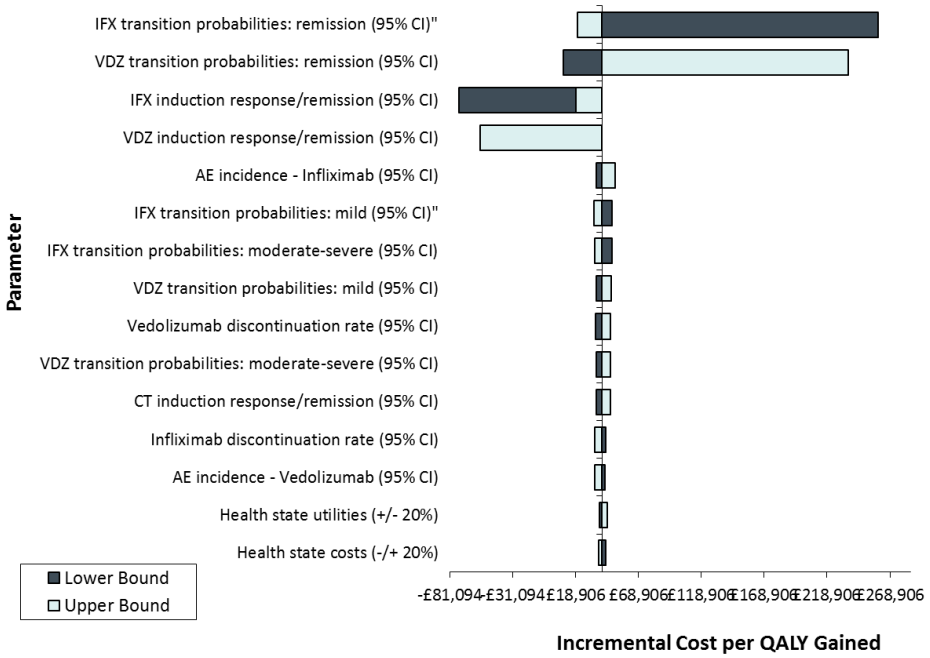
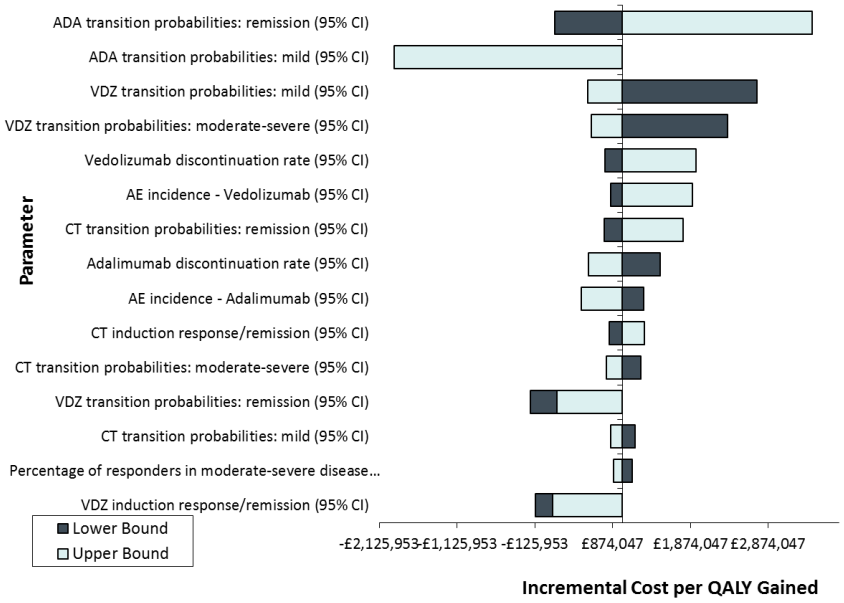
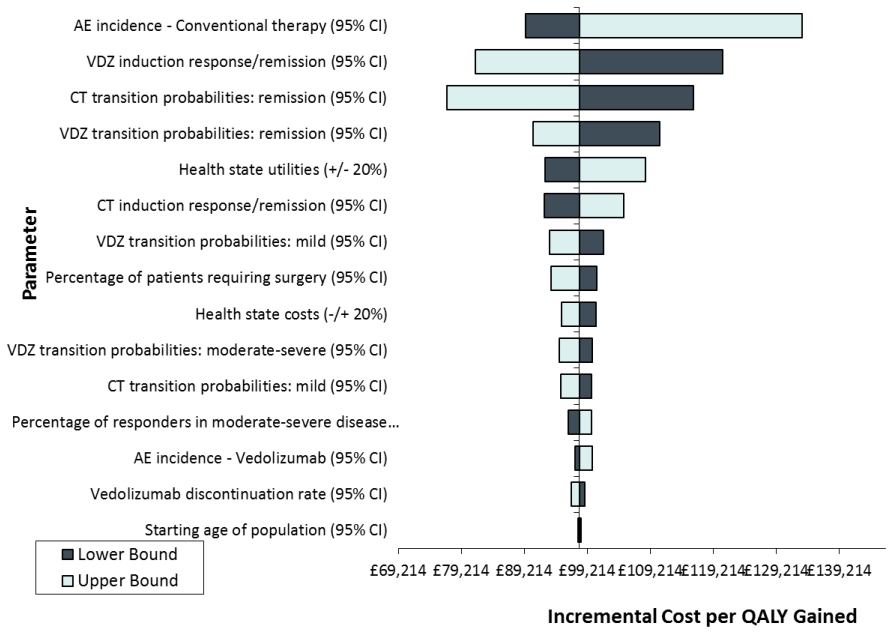


Figure 7.7.7.4: Tornado diagram: cost-effectiveness versus Adalimumab for the Anti-TNF–Naïve patient population (ITT)



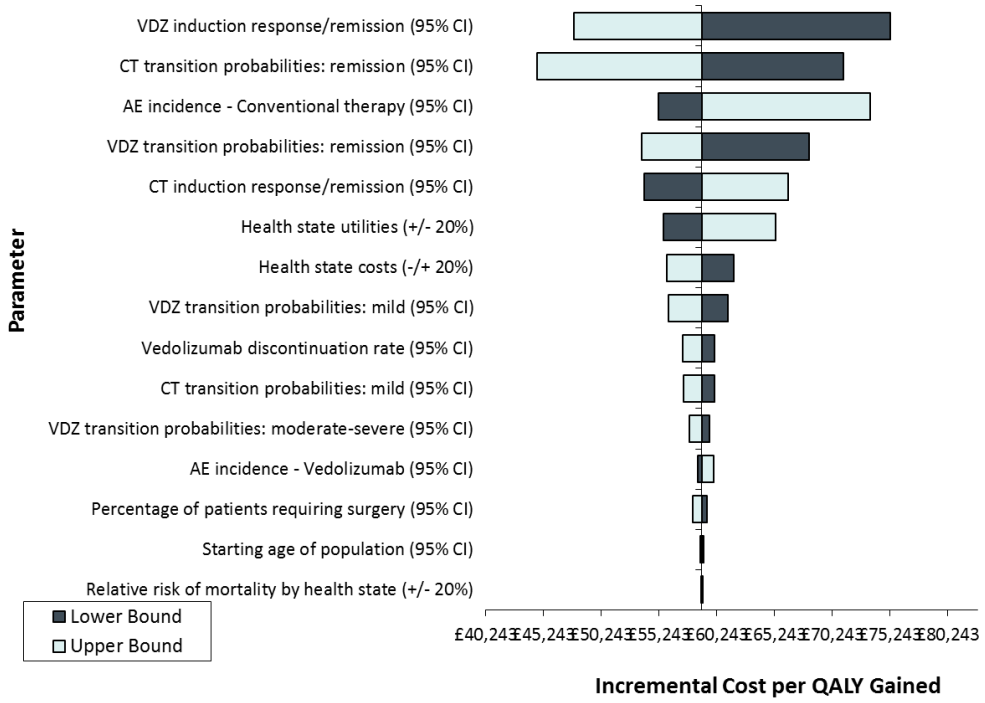
Anti-TNF-Failure Population

Figure 7.7.7.5: Tornado diagram: cost-effectiveness versus conventional therapy for the Anti-TNF-Failure patient population



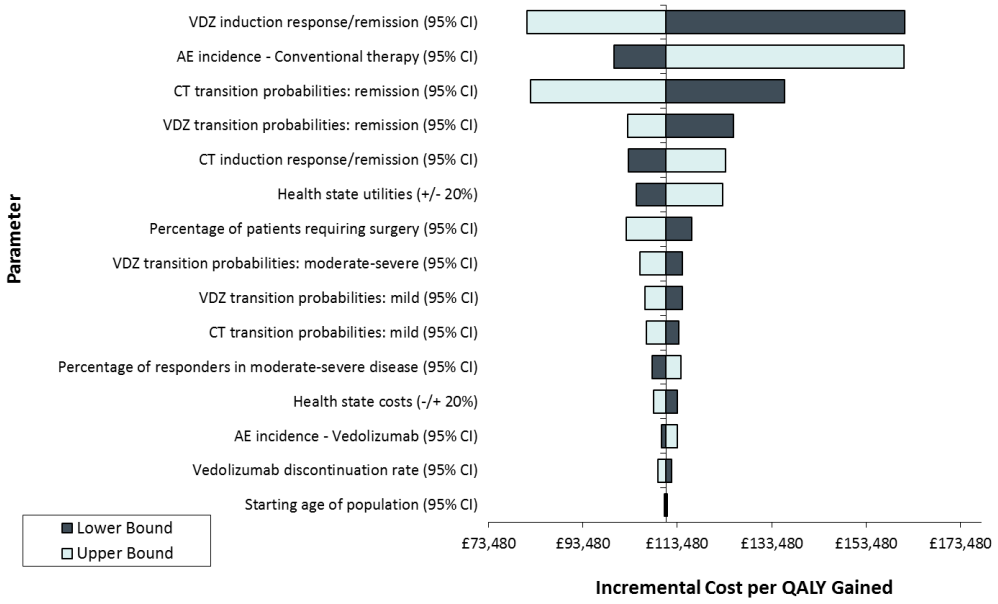
Mixed Moderate Population

Figure 7.7.7.6: Tornado diagram: cost-effectiveness versus conventional therapy for the mixed moderate patient population



Mixed Severe Population

Figure 7.7.7.7: Tornado diagram: cost-effectiveness versus conventional therapy for the mixed severe patient population



Moderate Anti-TNF Naïve Population

Figure 7.7.7.8: Tornado diagram: cost-effectiveness versus conventional therapy for the moderate Anti-TNF–Naïve patient population

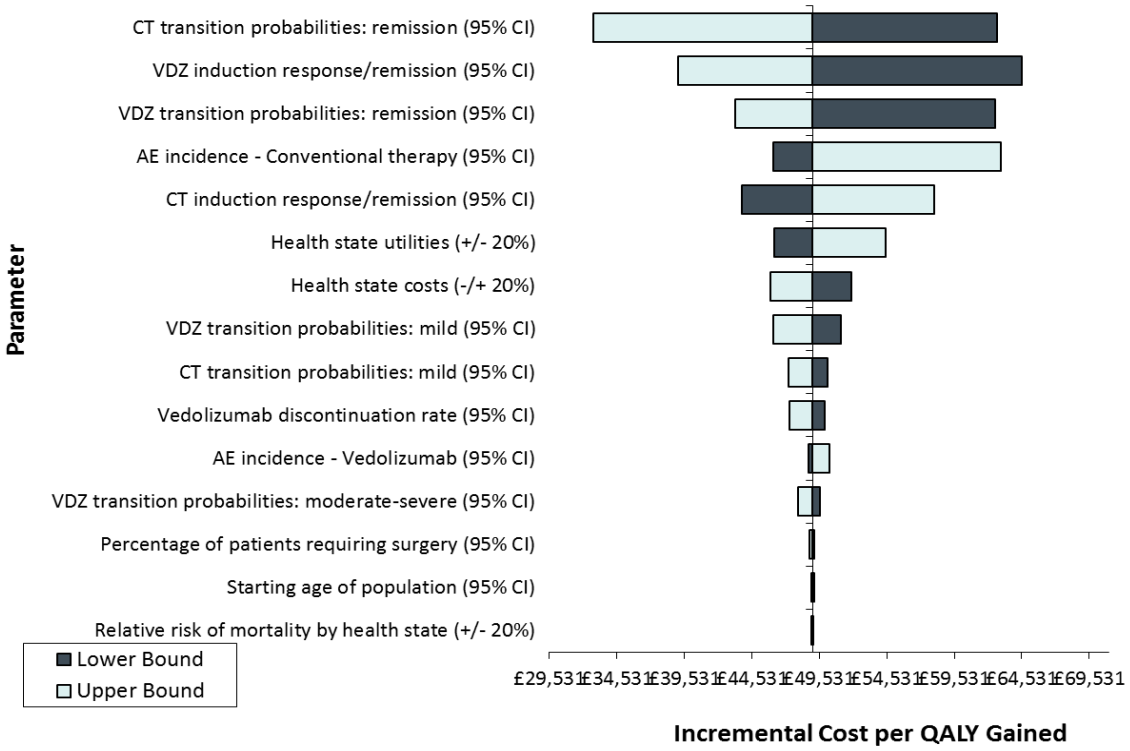


Figure 7.7.7.9: Tornado diagram: cost-effectiveness versus Infliximab for the moderate Anti-TNF–Naïve patient population

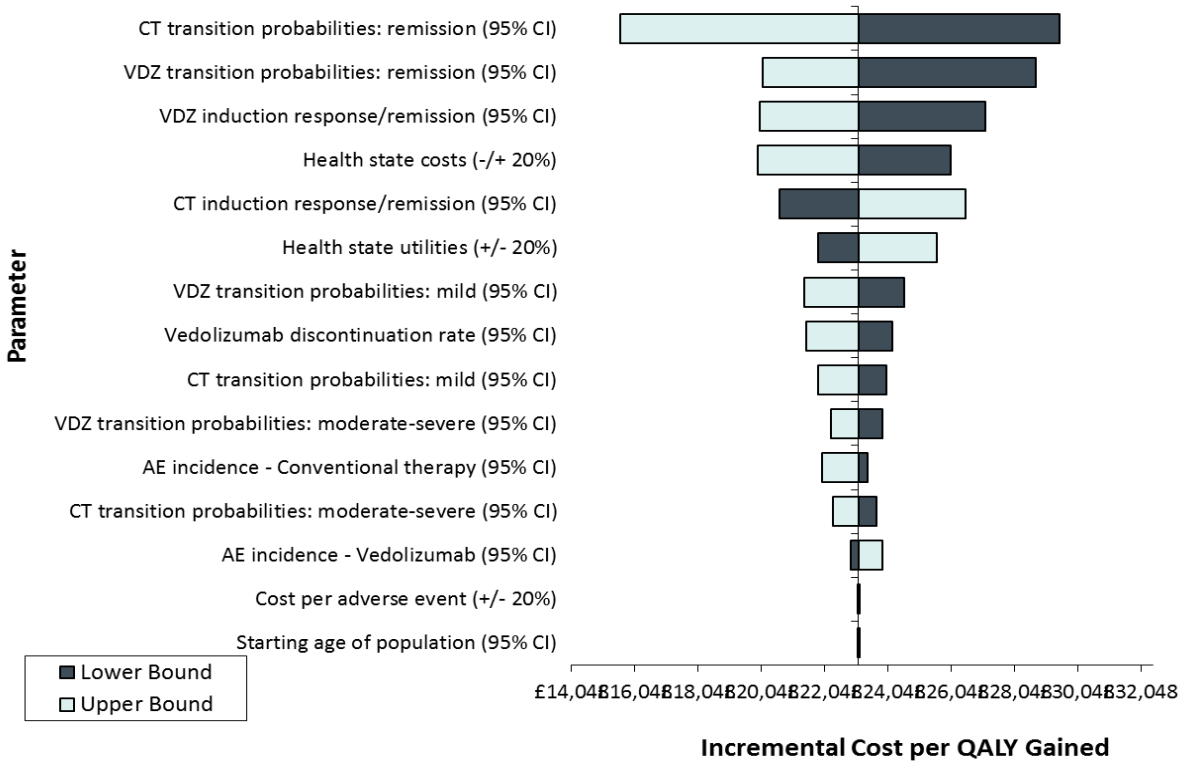
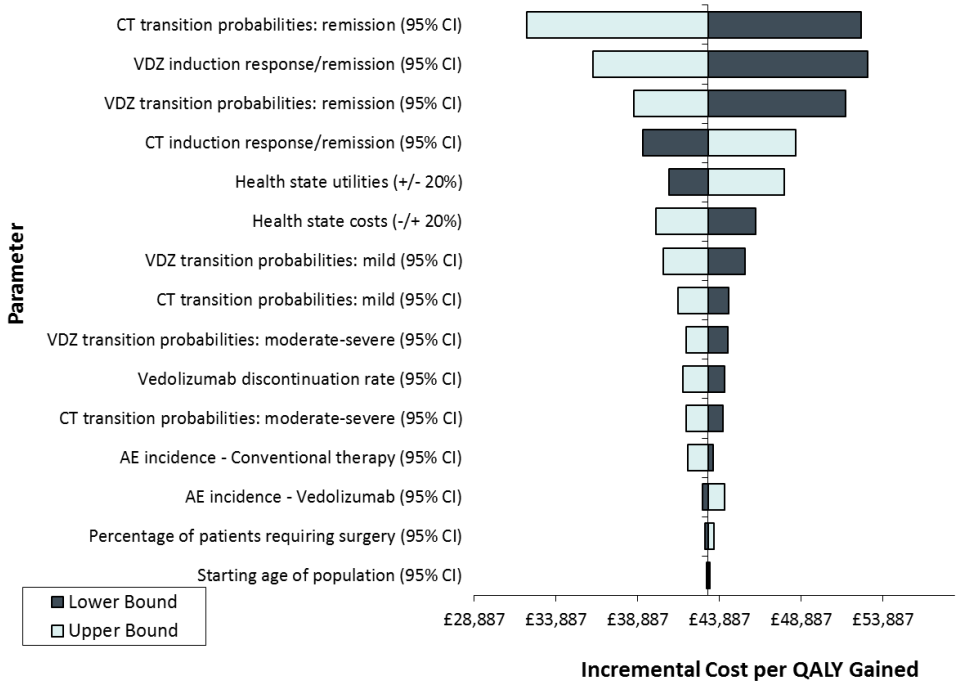


Figure 7.7.7.10: Tornado diagram: cost-effectiveness versus Adalimumab for the moderate Anti-TNF–Naïve patient population



Severe Anti-TNF Naïve Population

Figure 7.7.7.11: Tornado diagram: cost-effectiveness versus conventional therapy for the severe Anti-TNF–Naïve patient population

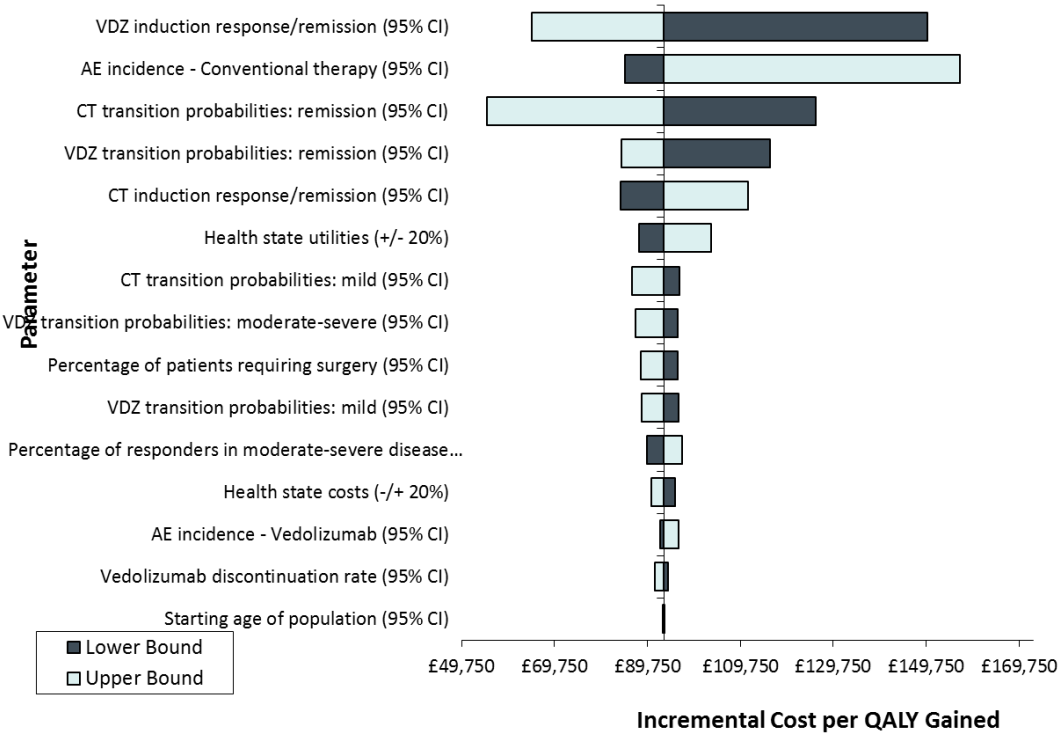


Figure 7.7.7.12: Tornado diagram: cost-effectiveness versus Infliximab for the severe Anti-TNF–Naïve patient population

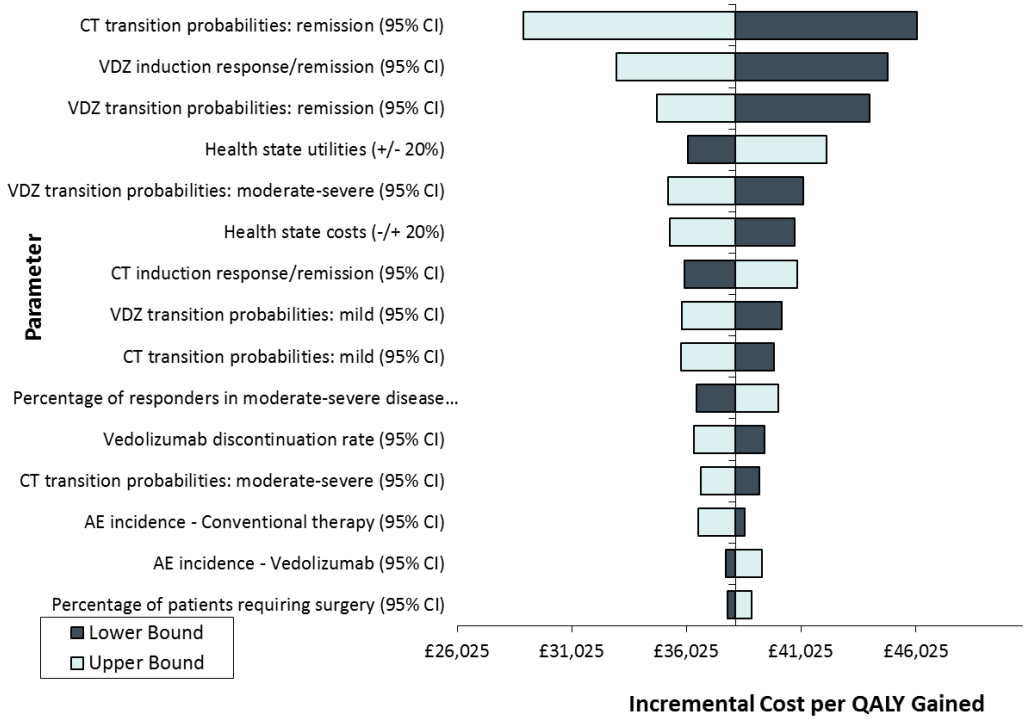
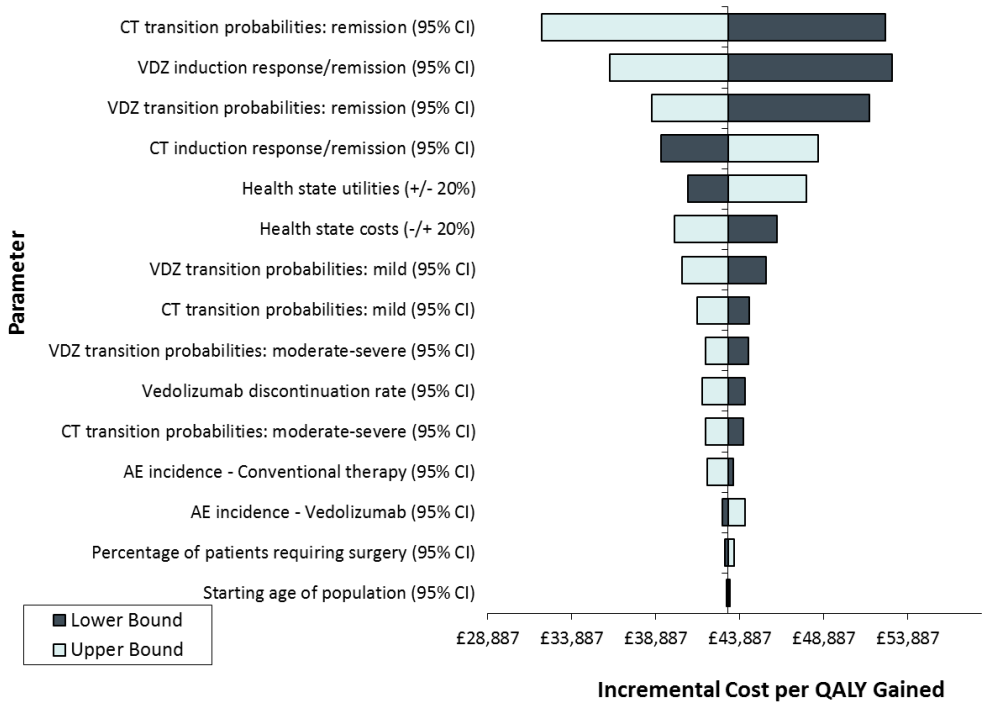
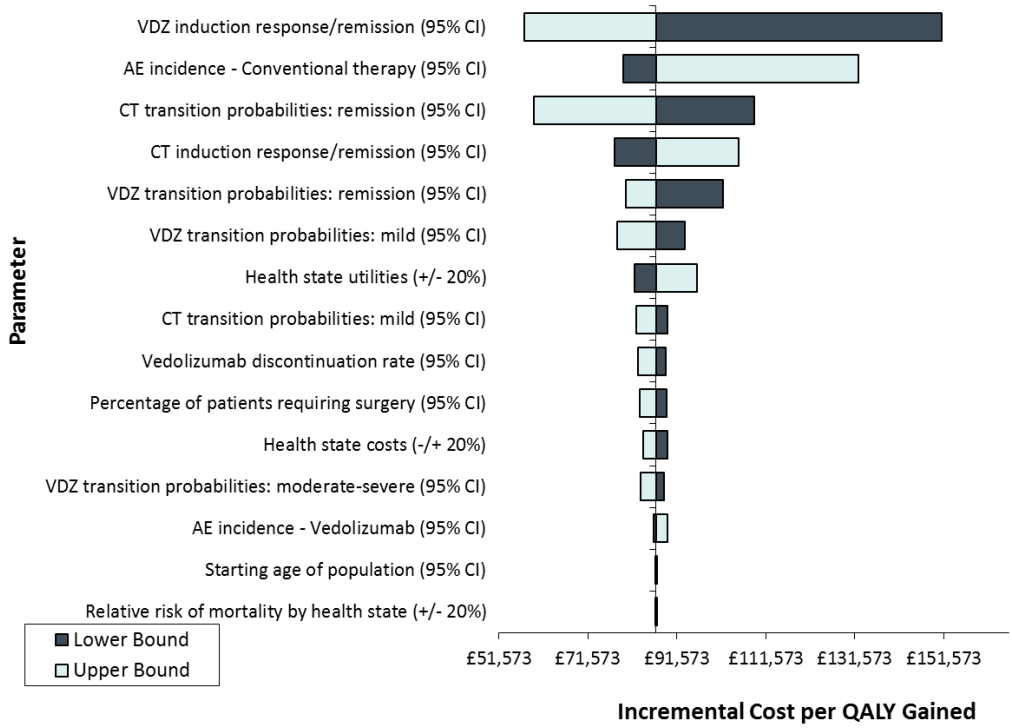


Figure 7.7.7.13: Tornado diagram: cost-effectiveness versus Adalimumab for the severe Anti-TNF–Naïve patient population



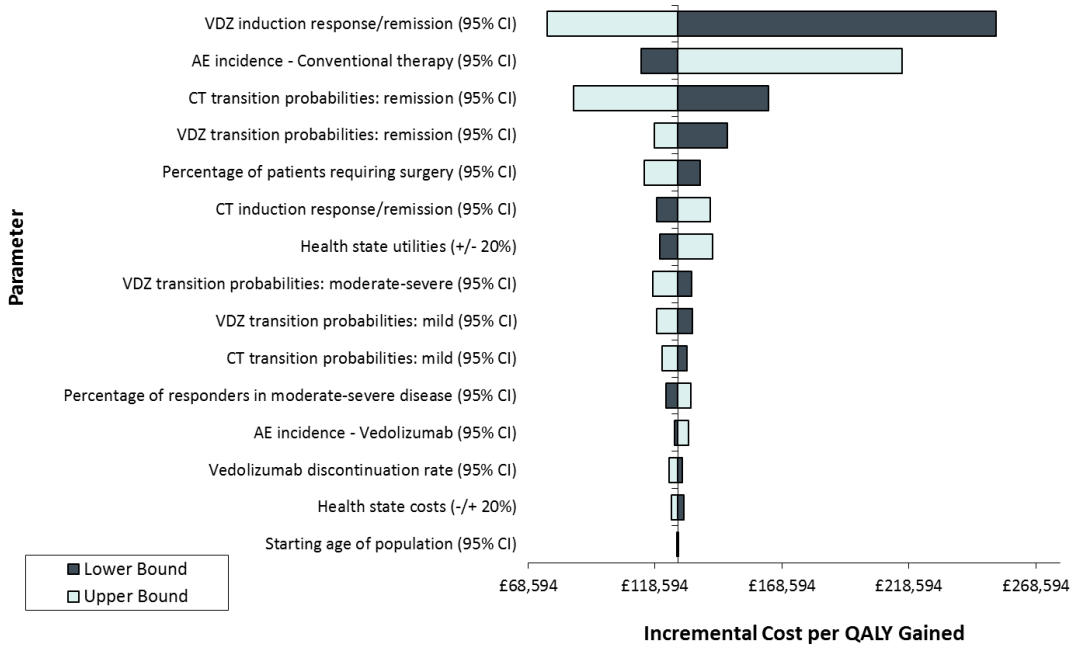
Moderate Anti-TNF-Failure Population

Figure 7.7.7.14: Tornado diagram: cost-effectiveness versus conventional therapy for the moderate Anti-TNF–Failure patient population



Severe Anti-TNF-Failure Population

Figure 7.7.7.15: Tornado diagram: cost-effectiveness versus conventional therapy for the severe Anti-TNF-Failure patient population

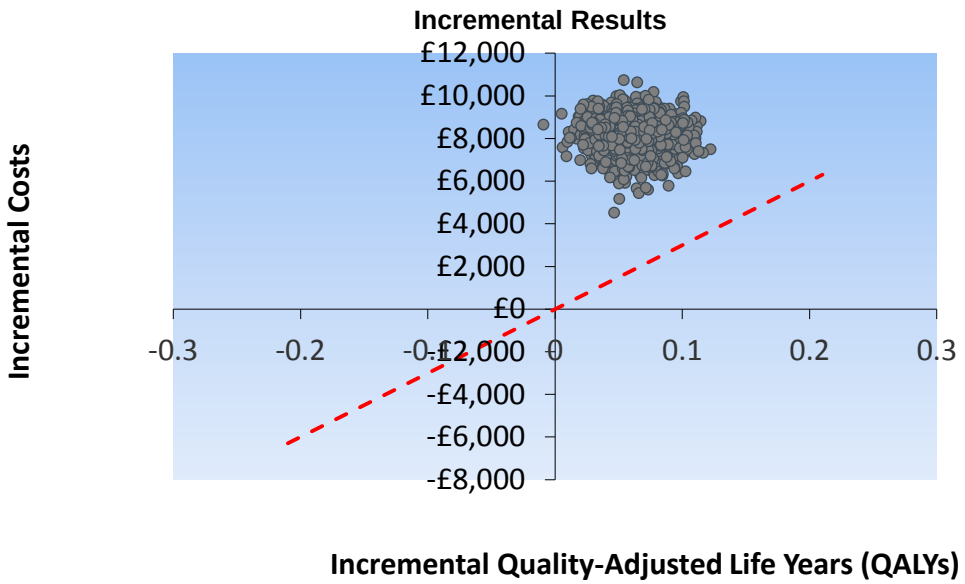


7.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

Probabilistic sensitivity analyses were run by patient population (for all patients, mixed TNF-Naïve, moderate and severe TNF naïve, mixed moderate patients, mixed severe patients, severe and moderate TNF-Failure, mixed TNF-Failure) and comparator, using the inputs listed in Table 7.3.6.1 (Section 7.3.6). 3,000 simulations were used for each comparison. Scatter plots on the cost-effectiveness plane and cost-effectiveness acceptability curves, by patient population and comparator, are presented below.

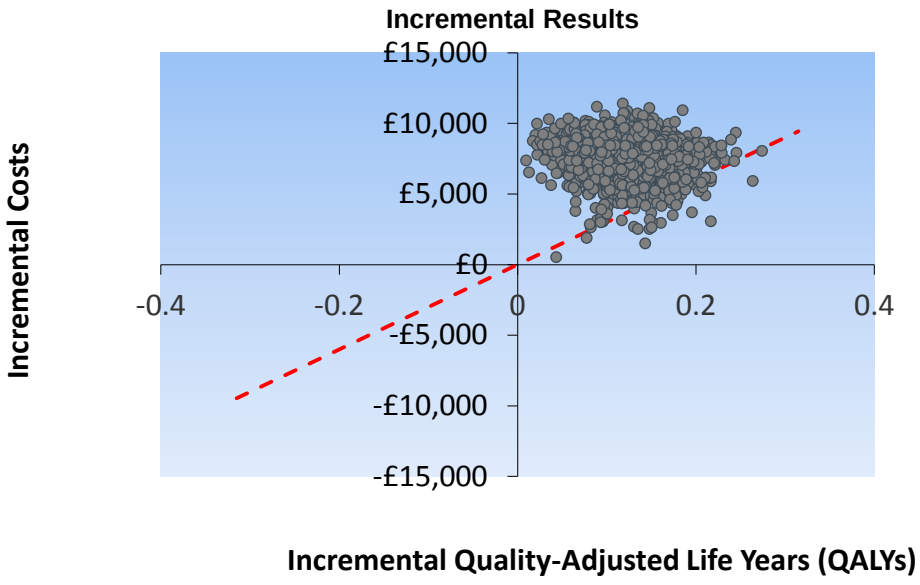
Mixed Population (ITT)

Figure 7.7.8.1: PSA: cost-effectiveness plane and CEAC for Vedolizumab versus conventional therapy for the mixed patient population (ITT)



Anti-TNF Naïve Population

Figure 7.7.8.2: PSA: cost-effectiveness plane and CEAC for Vedolizumab versus conventional therapy for the Anti-TNF–Naïve patient population



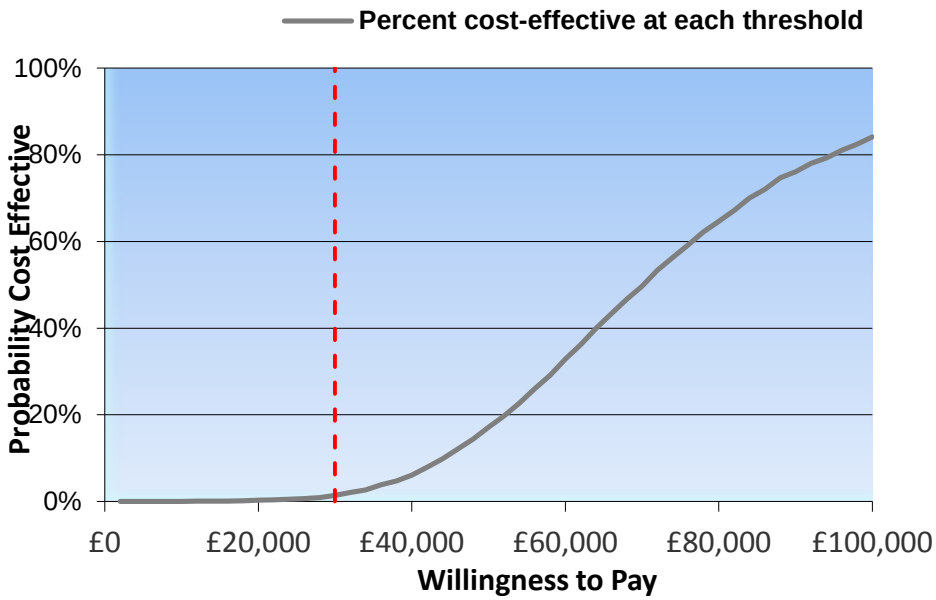
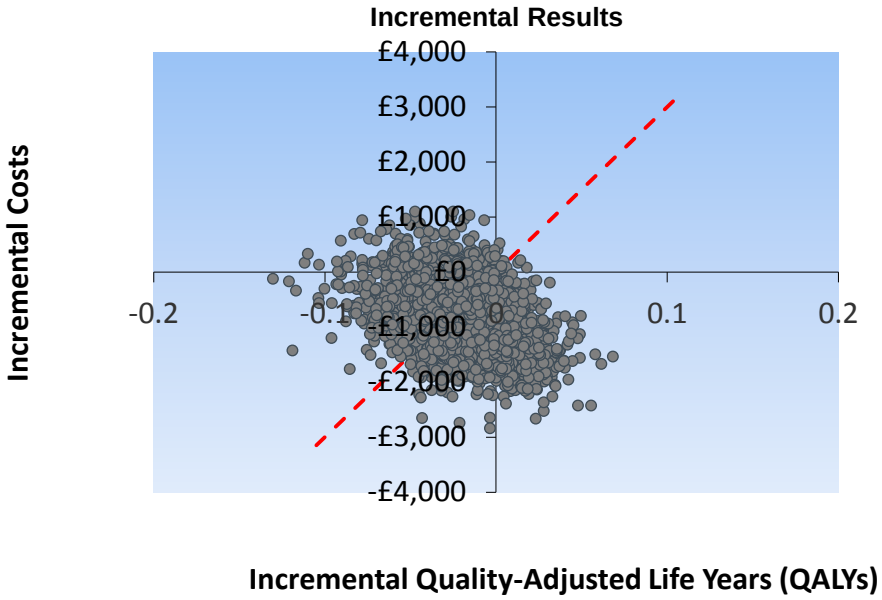


Figure 7.7.8.3: PSA: cost-effectiveness plane and CEAC for Vedolizumab versus Infliximab for the Anti-TNF–Naïve patient population


Incremental Results
£4,000
£3,000
£2,000
£1,000
£0
-£1,000
-£2,000
-£3,000
-£4,000
-0.2
-0.1
0
0.1
0.2
Incremental Costs
Incremental Quality-Adjusted Life Years (QALYs)

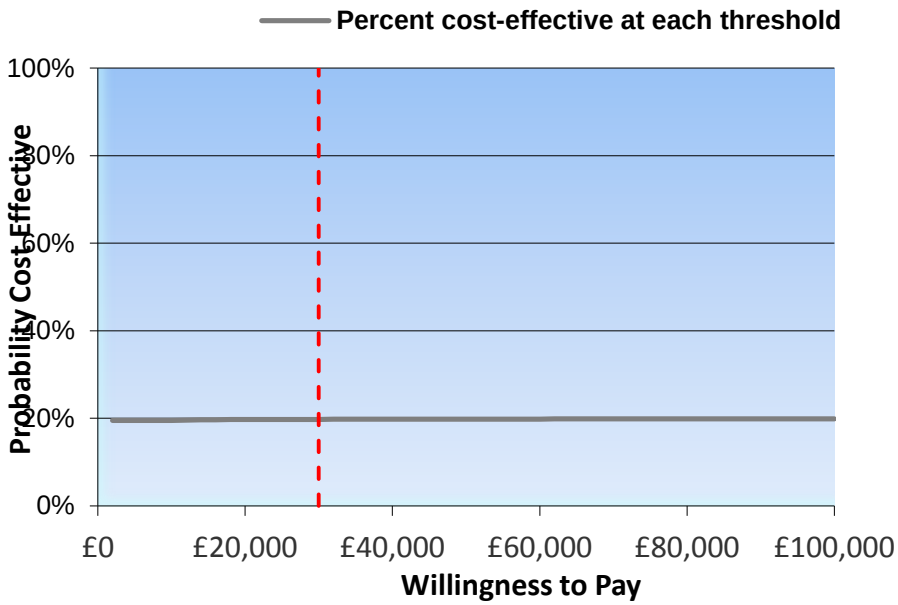
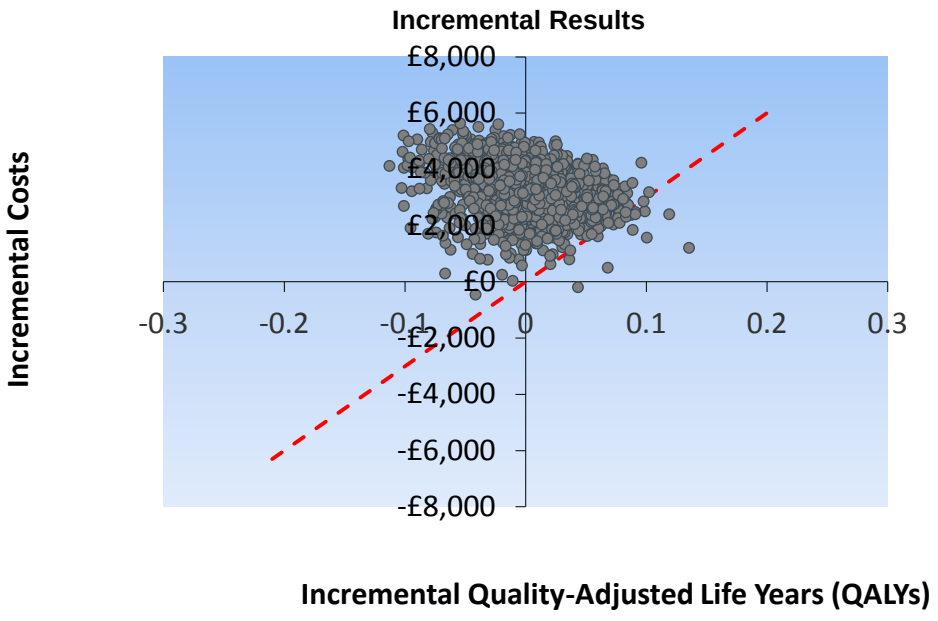
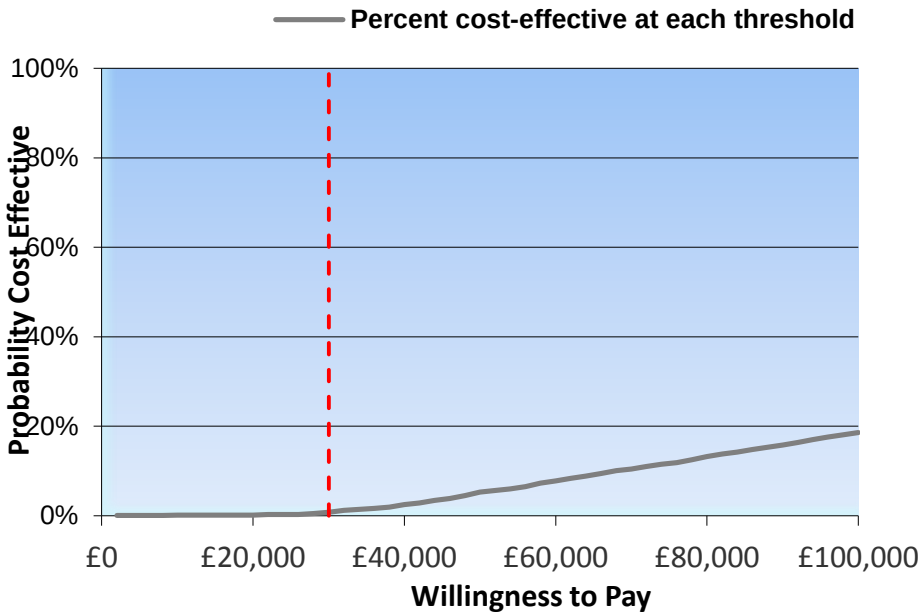

Percent cost-effective at each threshold
100%
80%
60%
40%
20%
0%
Probability Cost-Effective
£0
£20,000
£40,000
£60,000
£80,000
£100,000
Willingness to Pay

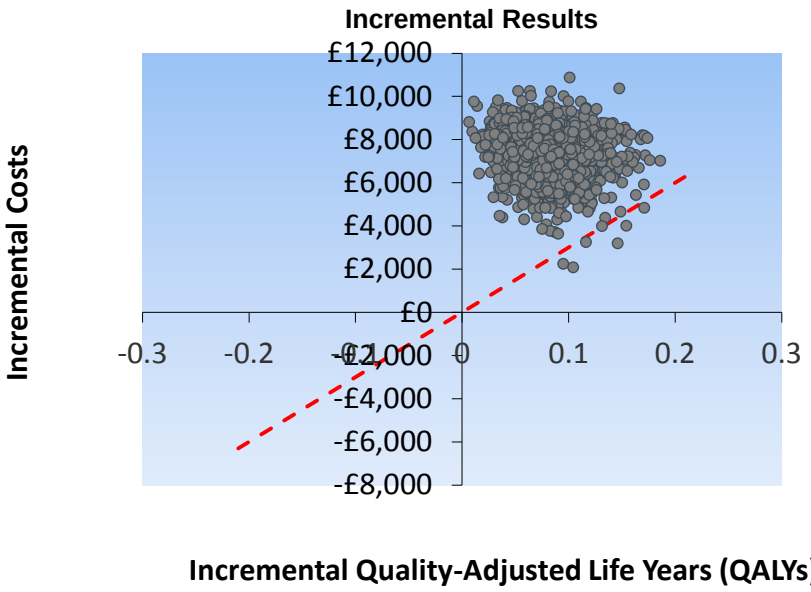
Figure 7.7.8.4: PSA: cost-effectiveness plane and CEAC for Vedolizumab versus Adalimumab for the Anti-TNF–Naïve patient population

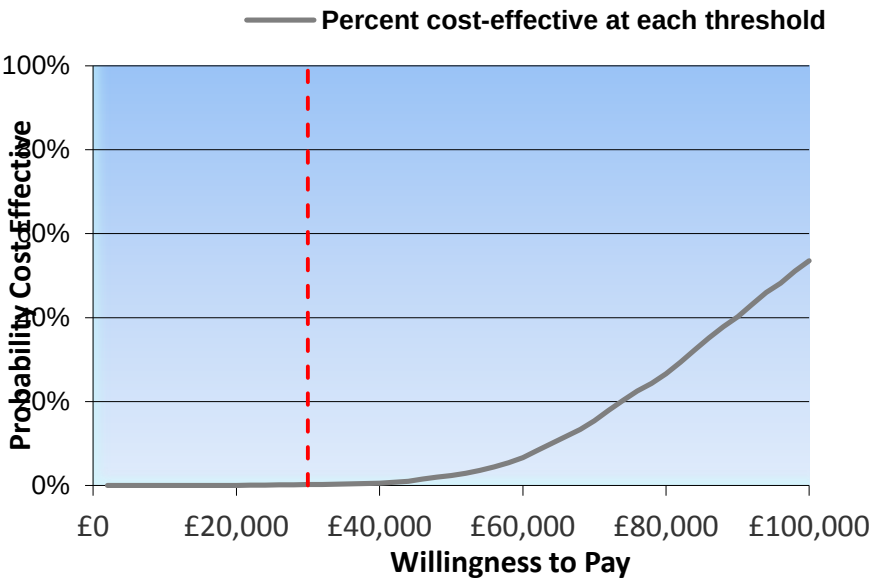




Anti-TNF-Failure Population

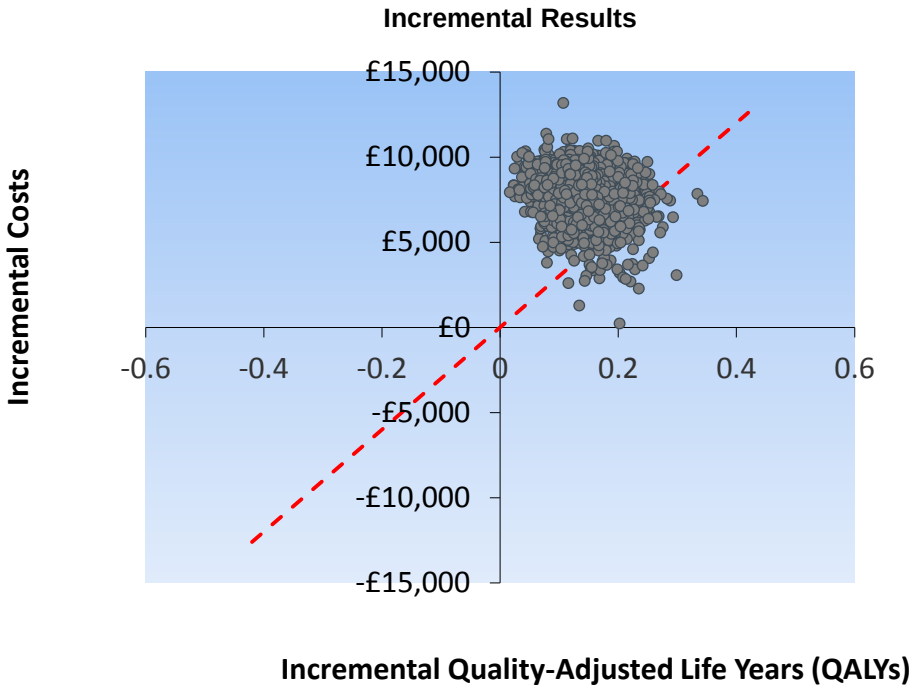
Figure 7.7.8.5: PSA: cost-effectiveness plane and CEAC for Vedolizumab versus conventional therapy for the Anti-TNF-Failure patient population

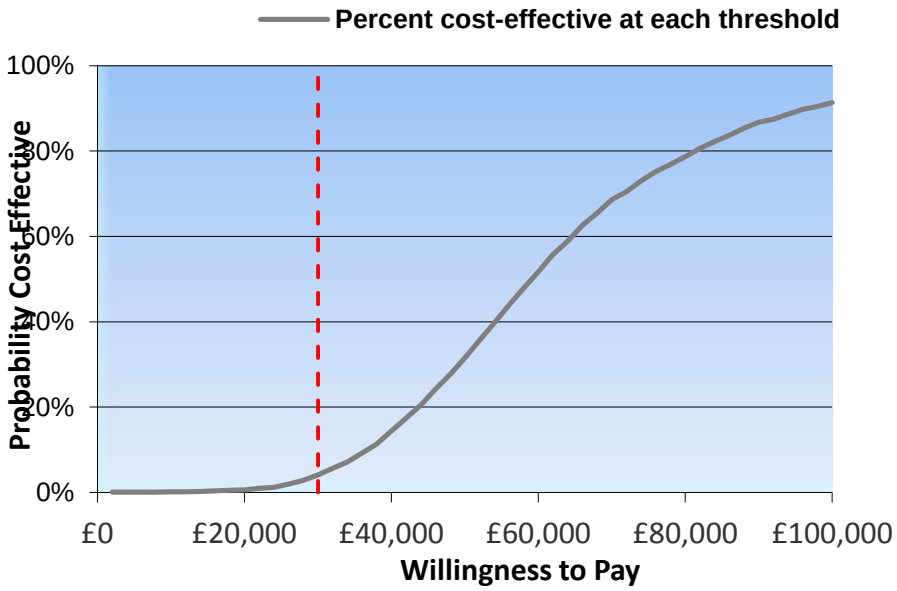




Mixed Moderate Population

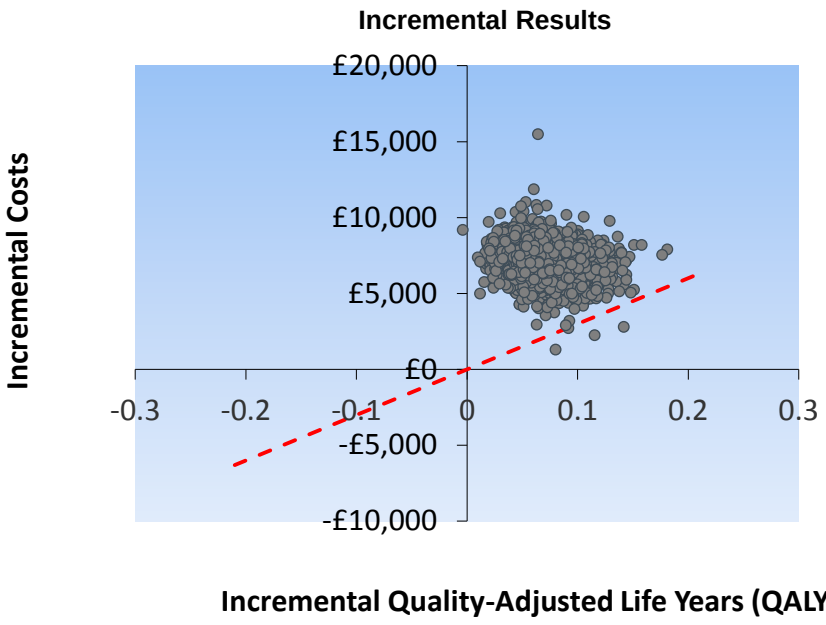
Figure 7.7.8.6: PSA: cost-effectiveness plane and CEAC for Vedolizumab versus conventional therapy for the mixed moderate patient population

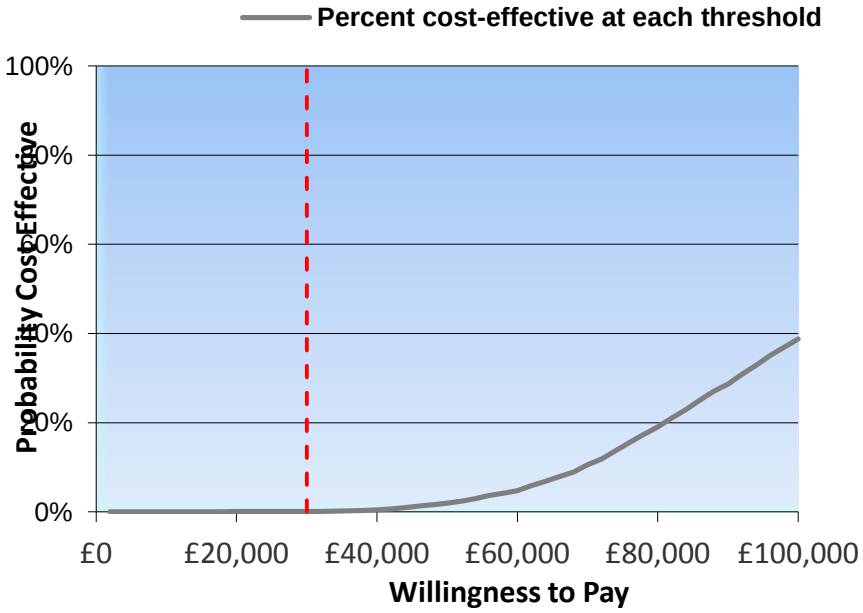




Anti-TNF Mixed Severe Population

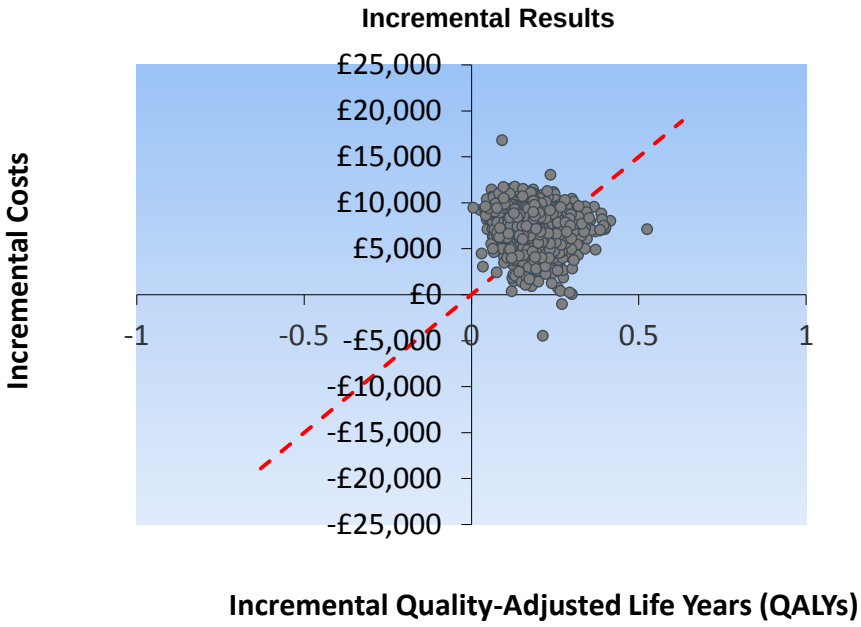
Figure 7.7.8.7: PSA: cost-effectiveness plane and CEAC for Vedolizumab versus conventional therapy for the mixed severe patient population





Moderate Anti-TNF-Naïve Population

Figure 7.7.8.8: PSA: cost-effectiveness plane and CEAC for Vedolizumab versus conventional therapy for the moderate Anti-TNF–Naïve patient population



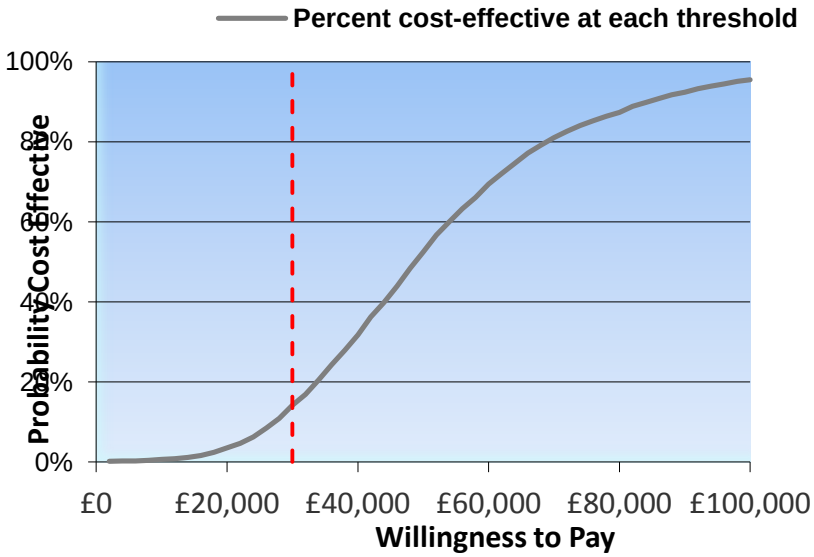
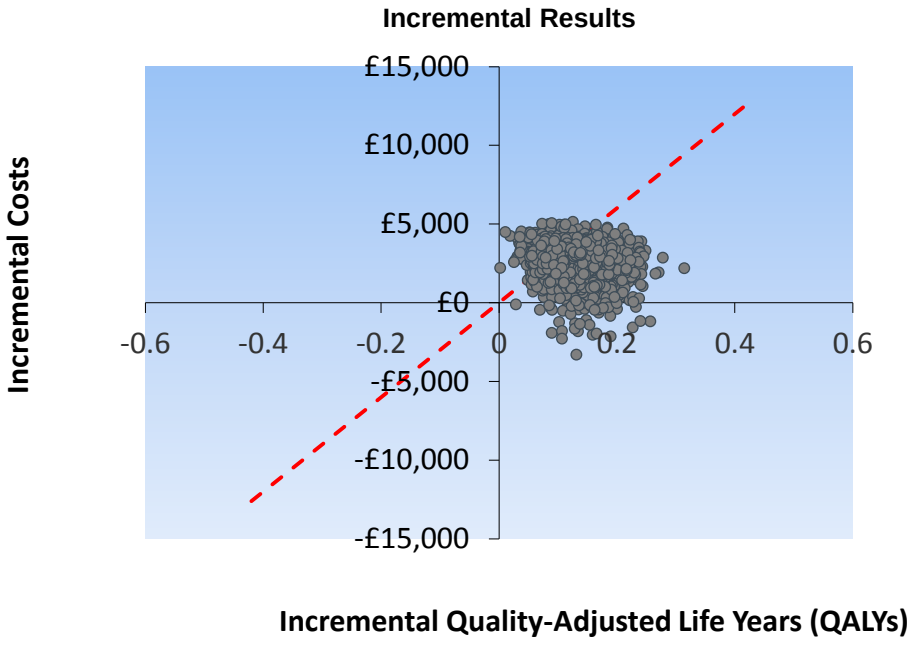


Figure 7.7.8.9: PSA: cost-effectiveness plane and CEAC for Vedolizumab versus Infliximab for the moderate Anti-TNF–Naïve patient population



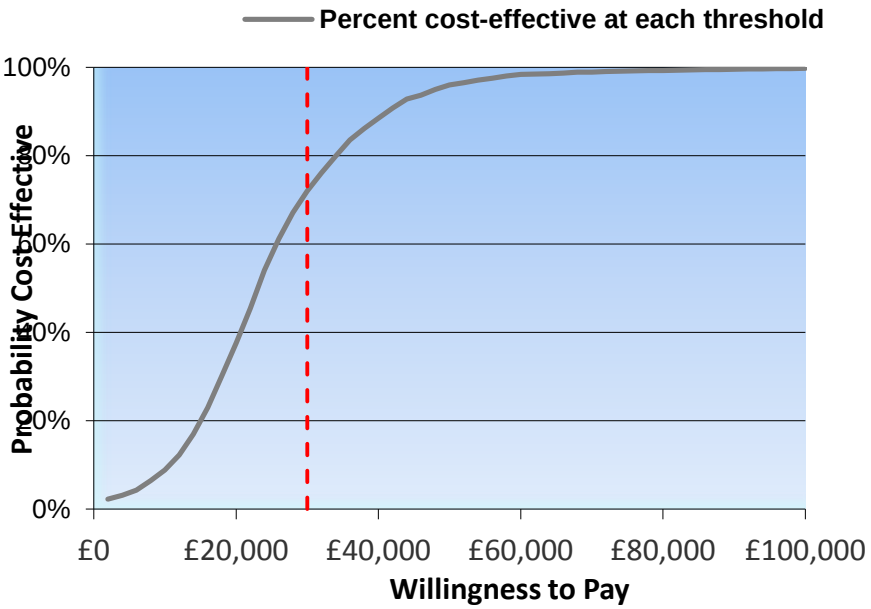
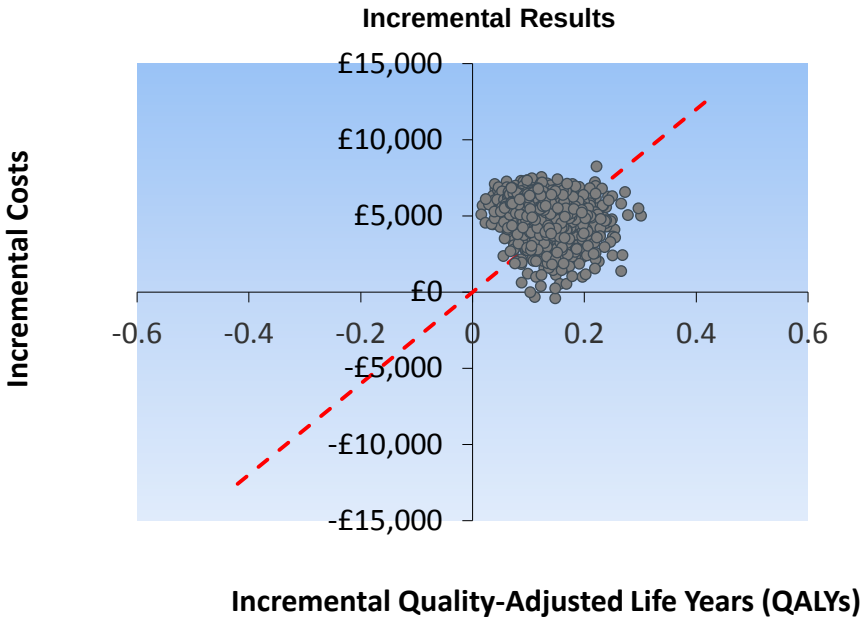
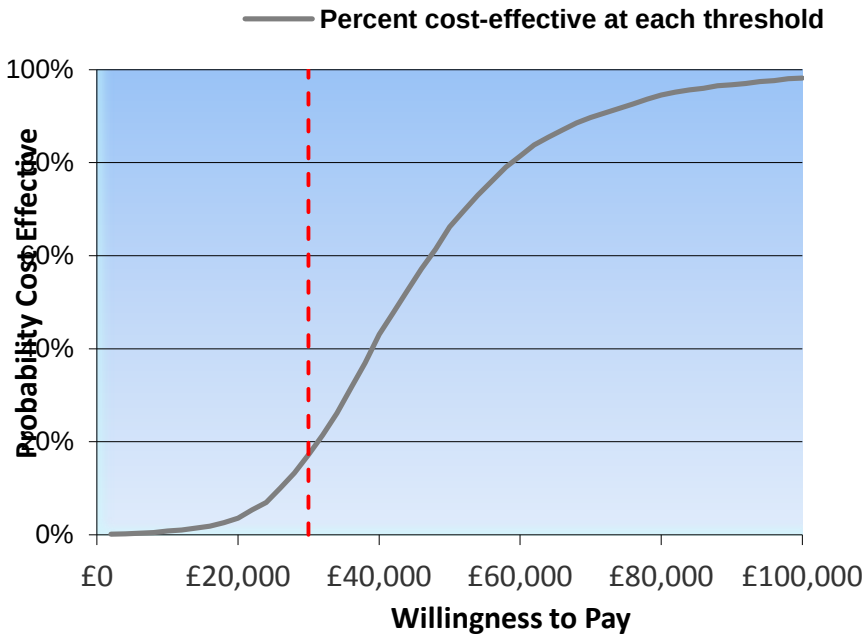


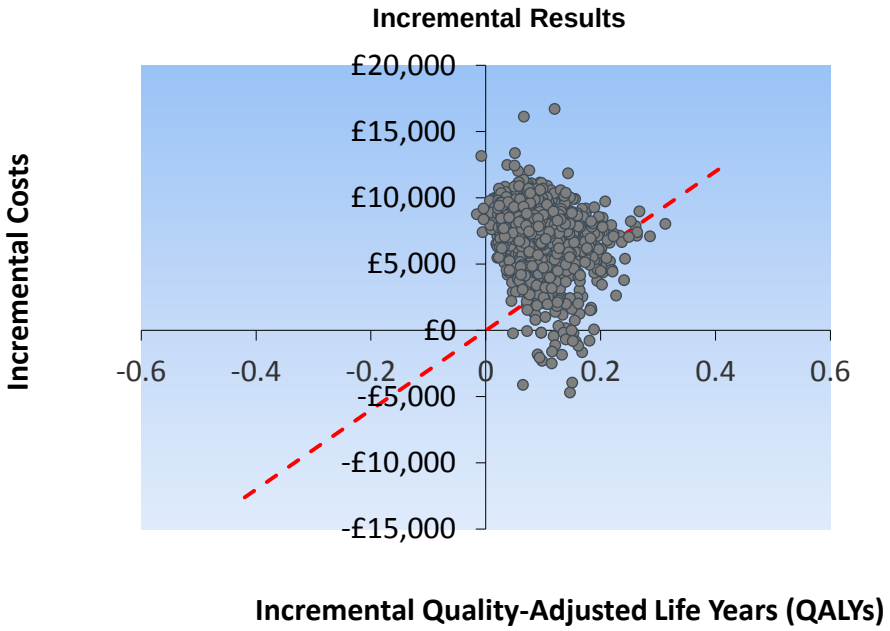
Figure 7.7.8.10: PSA: cost-effectiveness plane and CEAC for Vedolizumab versus Adalimumab for the moderate Anti-TNF–Naïve patient population





Severe Anti-TNF-Naïve Population

Figure 7.7.8.11: PSA: cost-effectiveness plane and CEAC for Vedolizumab versus conventional therapy for the severe Anti-TNF–Naïve patient population



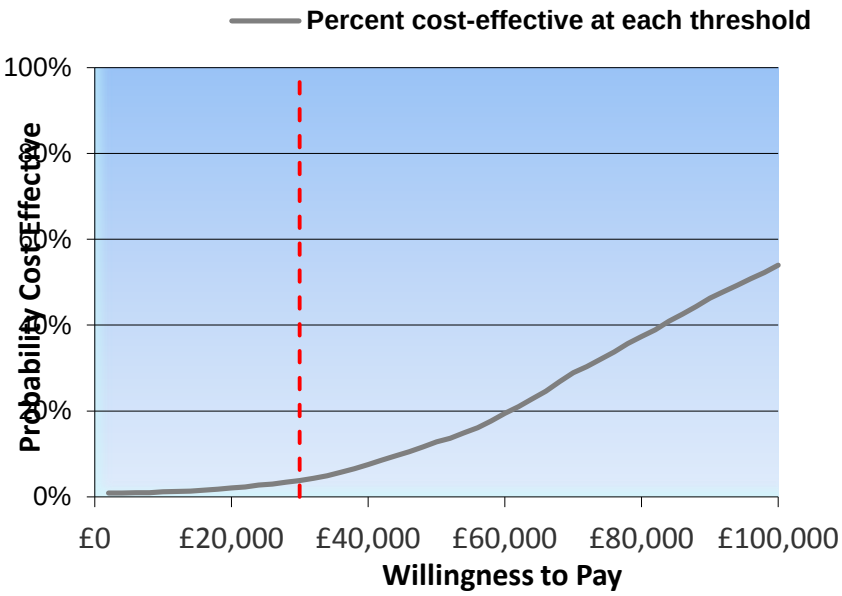
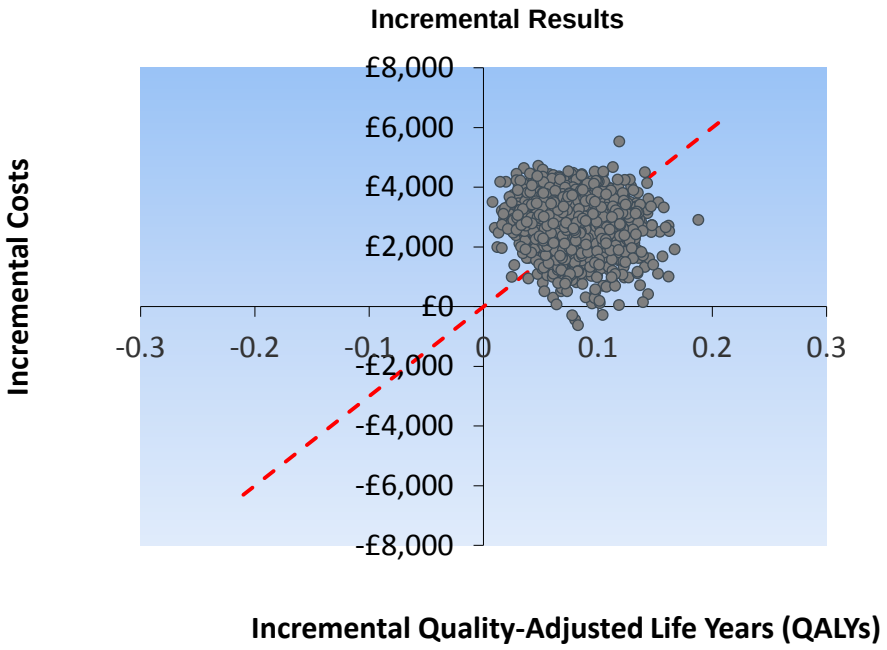


Figure 7.7.8.12: PSA: cost-effectiveness plane and CEAC for Vedolizumab versus Infliximab for the severe Anti-TNF–Naïve patient population



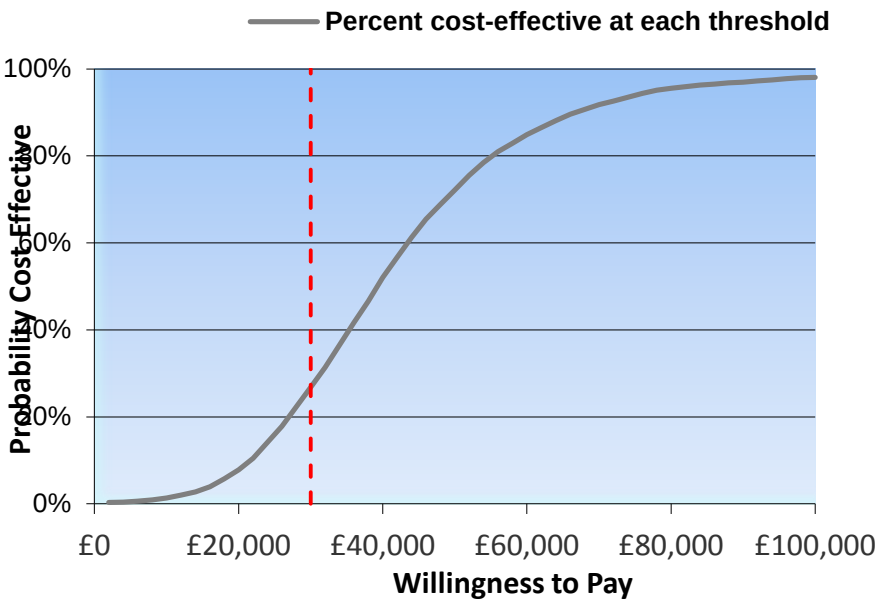
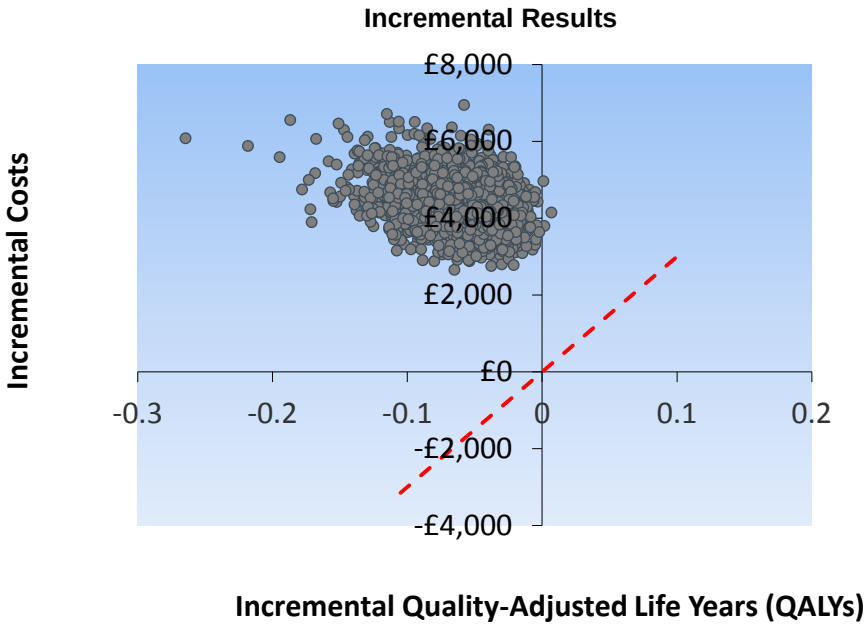
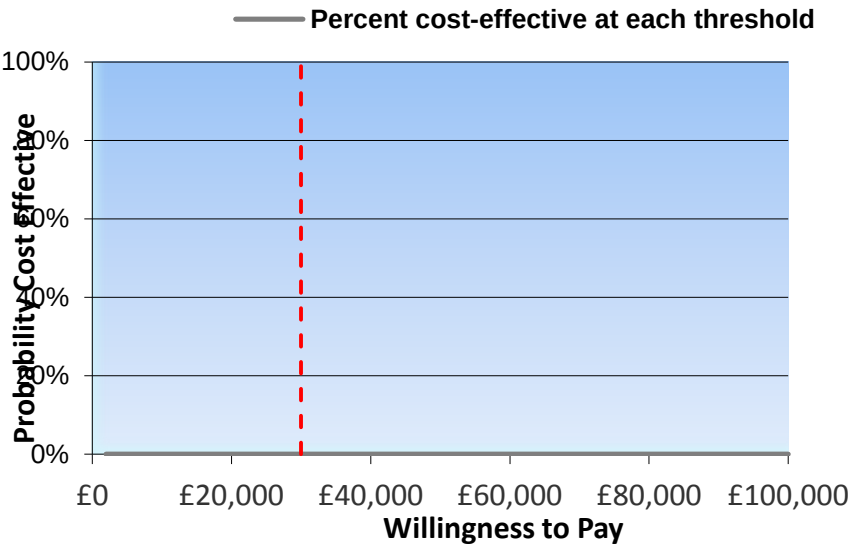


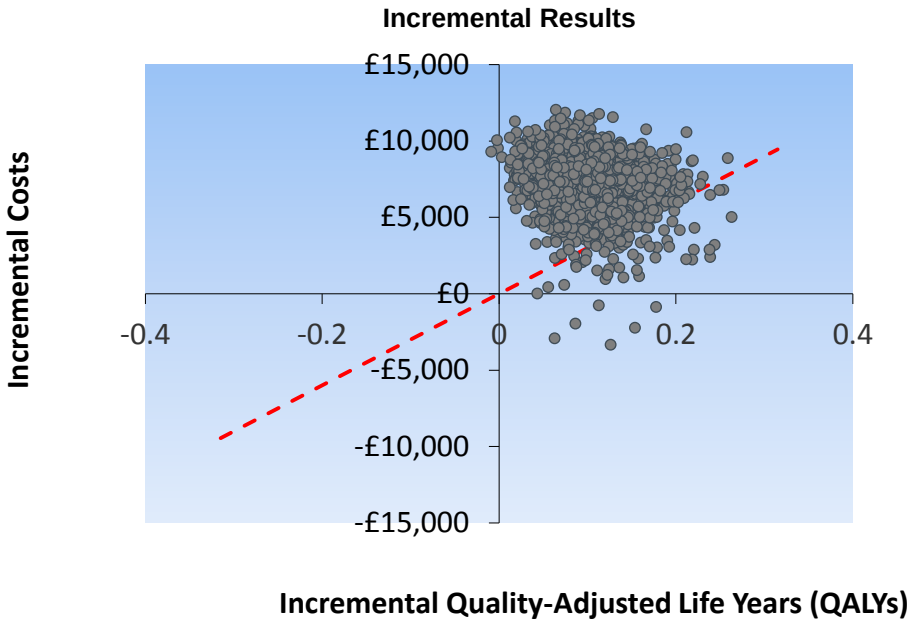
Figure 7.7.8.13: PSA: cost-effectiveness plane and CEAC for Vedolizumab versus Adalimumab for the severe Anti-TNF–Naïve patient population

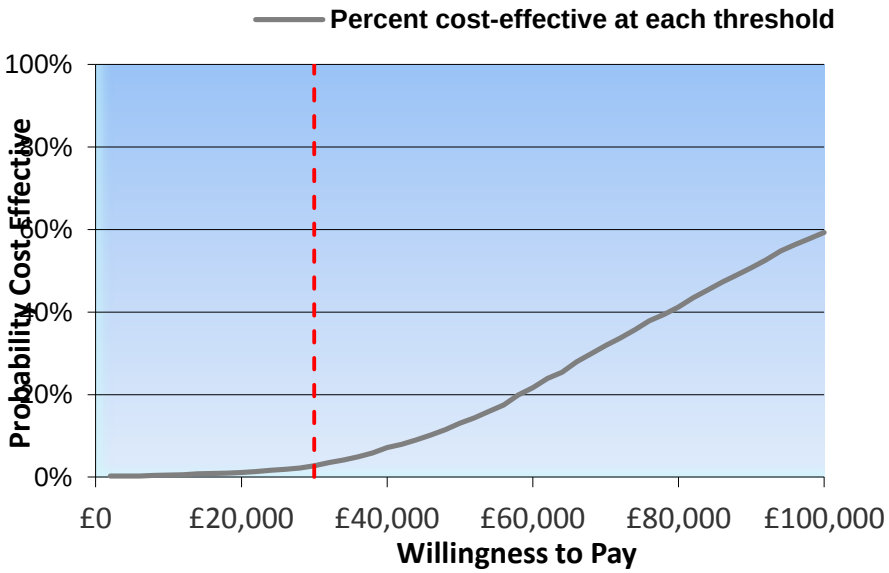




Moderate Anti-TNF-Failure Population

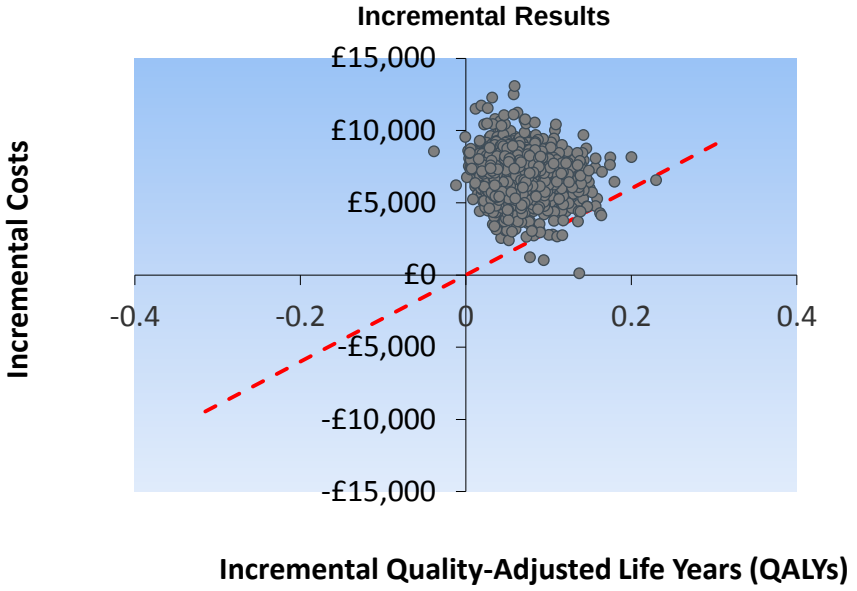
Figure 7.7.8.14: PSA: cost-effectiveness plane and CEAC for Vedolizumab versus conventional therapy for the moderate Anti-TNF-Failure patient population

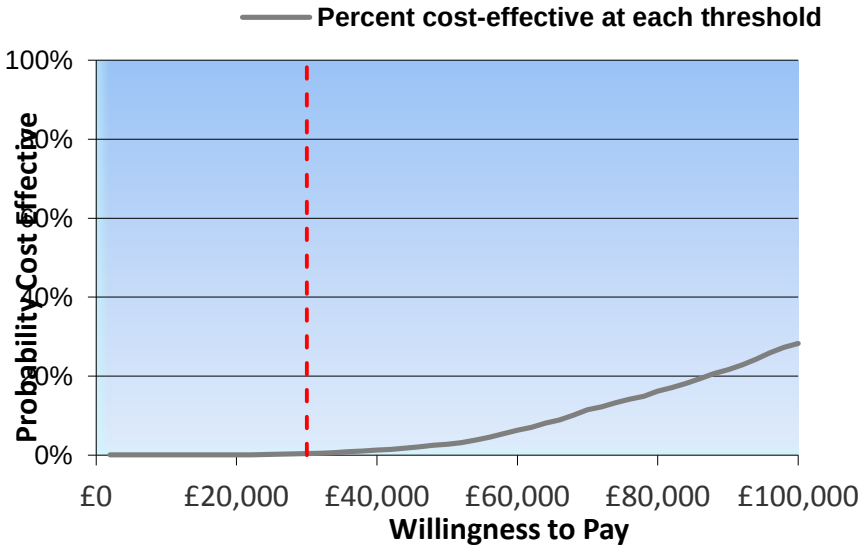




Severe Anti-TNF-Failure Population

Figure 7.7.8.15: PSA: cost-effectiveness plane and CEAC for Vedolizumab versus conventional therapy for the severe Anti-TNF failure patient population





7.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

Important variables in the model were altered in scenario analyses as presented below.

- The time horizon of the model was set to one year to reflect the duration of the clinical trial and to a lifetime (63 years) to reflect the potential effects of treatment over the course of a patient's lifetime.
- Whilst utilities from the clinical trial were used in the basecase model, there are different utilities reported in the literature. These alternative utility weights were applied in the model.
- The basecase model uses the 6-week continuation rule that reflects the design of the pivotal study. In separate analysis, a 10-week continuation rule was used. Section 7.2.8 for more information on the continuation rule.
- Finally, the assumption that patients remain on treatment for one year was altered: in this set of scenario analyses, the assumed duration of treatment with a Vedolizumab, Infliximab and Adalimumab was set to 3 years.

The following tables detail the results of the scenario analyses by population and comparator.

Mixed Population (ITT)

Table7.7.9.1: Scenario analysis – versus conventional therapy – mixed population (ITT)

Input(s)	Incremental Costs	Incremental QALYs	ICER
Time horizon			
1 year	£8,285	0.046	£180,640
Lifetime	£8,123	0.228	£35,703
Utility weight source			
Vedolizumab trial data	£7,639	0.126	£60,661
Buxton et all 2007	£7,639	0.203	£37,631
Vedolizumab response assessment			
Week 10	£8,077	0.231	£35,035
Week 14	£8,018	0.147	£54,443
Response criteria			
CDAI drop of 100 or more	£7,033	0.092	£76,664
Maximum time on treatment			
3 years	£11,199.86	0.197	£56,768

TNF-Naïve Population

Table 7.7.9.2: Scenario analysis – versus conventional therapy – TNF-Naïve population

Input(s)	Incremental Costs	Incremental QALYs	ICER
Time horizon			
1 year	£8,607	0.060	£144,036.37
Lifetime	£3,502	0.608	£5,759.72
Utility weight source			
Vedolizumab trial data	£5,580	0.272	£20,532.13
Buxton et all 2007	£5,580	0.438	£12,753.40
Vedolizumab response assessment			
Week 10	£6,089	0.467	£13,029.30
Week 14	£5,702	0.538	£10,606.33
Response criteria			
CDAI drop of 100 or more	£6,020	0.306	£19,656.36
Maximum time on treatment			
3 years	£11,639.17	0.324	£35,975.37

Table 7.7.9.3: Scenario analysis – versus Infliximab – TNF-Naïve population

Input(s)	Incremental Costs	Incremental QALYs	ICER
Time horizon			
1 year	-£914.94	-0.009	£107,574.95
Lifetime	-£671.73	-0.079	£8,457.60
Utility weight source			
Vedolizumab trial data	-£752.74	-0.031	£24,128.10
Buxton et all 2007	-£752.74	-0.052	£14,431.17
Vedolizumab response assessment			
Week 10	-£389.29	-0.067	£5,770.68
Week 14	-£389.29	-0.067	£5,770.68
Response criteria			
CDAI drop of 100 or more	£1,646.56	0.165	£9,952.01
Maximum time on treatment			
3 years	-£752.74	-0.031	£24,128.10

Table 7.7.9.4: Scenario analysis – versus Adalimumab – TNF-Naïve population

Input(s)	Incremental Costs	Incremental QALYs	ICER
Time horizon			
1 year	£3,192.32	0.008	£415,272.46
Lifetime	£3,265.53	0.031	£106,939.03
Utility weight source			
Vedolizumab trial data	£3,306.04	0.008	£398,195.18
Buxton et all 2007	£3,306.04	0.014	£241,268.41
Vedolizumab response assessment			
Week 10	£3,854.05	0.001	£4,308,680.85
Week 14	£3,722.56	0.001	£4,161,678.63
Response criteria			
CDAI drop of 100 or more	£3,705.23	-0.012	Dominant
Maximum time on treatment			
3 years	0.008	0.008	£398,195.18

TNF-Failure Population

Table 7.7.9.5: Scenario analysis – versus conventional therapy – TNF-Failure population

Input(s)	Incremental Costs	Incremental QALYs	ICER
Time horizon			
1 year	£8,266.44	0.030	£273,326.08
Lifetime	£8,189.60	0.151	£54,190.30
Utility weight source			
Vedolizumab trial data	£7,858.57	0.083	£94,440.82
Buxton et all 2007	£7,858.57	0.135	£58,427.92
Vedolizumab response assessment			
Week 10	£8,272.09	0.103	£80,541.65
Week 14	£8,138.55	0.094	£86,337.14
Response criteria			
CDAI drop of 100 or more	£7,155.43	0.065	£110,434.37
Maximum time on treatment			
3 years	£10,415.93	0.125	£83,043.80

Mixed Moderate Population

Table 7.7.9.6: Scenario analysis – versus conventional therapy – mixed moderate population

Input(s)	Incremental Costs	Incremental QALYs	ICER
Time horizon			
1 year	£8,912.63	0.065	£137,485.23
Lifetime	£3,867.59	0.608	£6,358.56
Utility weight source			
Vedolizumab trial data	£5,524.10	0.298	£18,531.03
Buxton et all 2007	£5,524.10	0.478	£11,563.56
Vedolizumab response assessment			
Week 10	£5,934.11	0.298	£19,906.43
Week 14	£0.30	0.298	£19,906.43
Response criteria			
CDAI drop of 100 or more	£5,524.10	0.298	£18,531.03
Maximum time on treatment			
3 years	£10,948.21	0.372	£29,420.70

Mixed Severe Population

Table 7.7.9.7: Scenario analysis – versus conventional therapy – mixed severe population

Input(s)	Incremental Costs	Incremental QALYs	ICER
Time horizon			
1 year	£7,681.90	0.032	£240,182.15
Lifetime	£7,457.60	0.191	£38,963.48
Utility weight source			
Vedolizumab trial data	£7,216.99	0.096	£75,433.26
Buxton et all 2007	£7,216.99	0.155	£46,640.35
Vedolizumab response assessment			
Week 10	£7,814.90	0.096	£81,682.76
Week 14	£7,814.90	0.096	£81,682.76
Response criteria			
CDAI drop of 100 or more	£7,216.99	0.096	£75,433.26
Maximum time on treatment			
3 years	£9,752.21	0.139	£70,286.85

Moderate TNF-Naïve Population

Table 7.7.9.8: Scenario analysis – versus conventional therapy – moderate TNF-Naïve population

Input(s)	Incremental Costs	Incremental QALYs	ICER
Time horizon			
1 year	£9,439.80	0.081	£117,145.54
Lifetime	£2,219.12	0.811	£2,735.91
Utility weight source			
Vedolizumab trial data	£4,902.64	0.384	£12,761.55
Buxton et all 2007	£4,902.64	0.616	£7,963.97
Vedolizumab response assessment			
Week 10	£5,235.48	0.384	£13,627.94
Week 14	£5,235.48	0.384	£13,627.94
Response criteria			
CDAI drop of 100 or more	£5,235.48	0.384	£13,627.94
Maximum time on treatment			
3 years	£12,568.79	0.480	£26,201.05

Table 7.7.9.9: Scenario analysis – versus Infliximab – moderate TNF-Naïve population

Input(s)	Incremental Costs	Incremental QALYs	ICER
Time horizon			
1 year	£3,856.27	0.055	£70,730.82
Lifetime	£2,438.84	0.319	£7,654.44
Utility weight source			
Vedolizumab trial data	£2,685.36	0.161	£16,710.83
Buxton et all 2007	£2,685.36	0.260	£10,344.56
Vedolizumab response assessment			
Week 10	£2,230.59	0.182	£12,276.60
Week 14	£2,044.90	0.214	£9,536.51
Response criteria			
CDAI drop of 100 or more	£2,182.94	0.131	£16,666.25
Maximum time on treatment			
3 years	£6,669.82	0.177	£37,751.16

Table 7.7.9.10: Scenario analysis – versus Adalimumab – moderate TNF-Naïve population

Input(s)	Incremental Costs	Incremental QALYs	ICER
Time horizon			
1 year	£6,327.58	0.054	£116,692.82
Lifetime	£4,910.15	0.318	£15,425.13
Utility weight source			
Vedolizumab trial data	£5,156.67	0.160	£32,148.86
Buxton et all 2007	£5,156.67	0.259	£19,881.44
Vedolizumab response assessment			
Week 10	£5,319.81	0.181	£29,326.64
Week 14	£4,794.72	0.214	£22,391.35
Response criteria			
CDAI drop of 100 or more	£4,654.24	0.131	£35,614.67
Maximum time on treatment			
3 years	£9,141.13	0.176	£51,825.62

Severe TNF-Naïve Population

Table 7.7.9.11: Scenario analysis – versus conventional therapy – severe TNF-Naïve population

Input(s)	Incremental Costs	Incremental QALYs	ICER
Time horizon			
1 year	£7,893.50	0.047	£167,375.50
Lifetime	£5,646.68	0.418	£13,513.99
Utility weight source			
Vedolizumab trial data	£6,305.70	0.189	£33,317.77
Buxton et all 2007	£6,305.70	0.306	£20,639.27
Vedolizumab response assessment			
Week 10	£6,859.07	0.189	£36,241.64
Week 14	£6,859.07	0.189	£36,241.64
Response criteria			
CDAI drop of 100 or more	£6,305.70	0.189	£33,317.77
Maximum time on treatment			
3 years	£10,584.13	0.230	£46,061.91

Table 7.7.9.12: Scenario analysis – versus Infliximab – severe TNF-Naïve population

Input(s)	Incremental Costs	Incremental QALYs	ICER
Time horizon			
1 year	£3,541.44	0.031	£112,531.46
Lifetime	£2,622.54	0.225	£11,656.71
Utility weight source			
Vedolizumab trial data	£2,815.69	0.105	£26,761.80
Buxton et all 2007	£2,815.69	0.170	£16,546.47
Vedolizumab response assessment			
Week 10	£2,186.37	0.122	£17,967.27
Week 14	£2,677.86	0.104	£25,706.07
Response criteria			
CDAI drop of 100 or more	£2,379.89	0.102	£23,248.75
Maximum time on treatment			
3 years	£5,601.91	0.109	£51,364.92

Table 7.7.9.13: Scenario analysis – versus Adalimumab – severe TNF-Naïve population

Input(s)	Incremental Costs	Incremental QALYs	ICER
Time horizon			
1 year	£3,601.05	-0.020	Dominant
Lifetime	£4,409.20	-0.104	Dominant
Utility weight source			
Vedolizumab trial data	£4,362.89	-0.068	Dominant
Buxton et all 2007	£4,362.89	-0.108	Dominant
Vedolizumab response assessment			
Week 10	£4,573.59	-0.060	Dominant
Week 14	£4,953.71	-0.074	Dominant
Response criteria			
CDAI drop of 100 or more	£4,281.76	-0.065	Dominant
Maximum time on treatment			
3 years	£4,362.89	-0.108	Dominant

Moderate TNF-Failure Population

Table 7.7.9.14: Scenario analysis – versus conventional therapy – moderate TNF-Failure population

Input(s)	Incremental Costs	Incremental QALYs	ICER
Time horizon			
1 year	£8,090.21	0.044	£184,904.80
Lifetime	£7,318.51	0.259	£28,259.89
Utility weight source			
Vedolizumab trial data	£7,174.24	0.137	£52,311.06
Buxton et all 2007	£7,174.24	0.221	£32,513.26
Vedolizumab response assessment			
Week 10	£7,708.28	0.137	£56,205.01
Week 14	£7,708.28	0.137	£56,205.01
Response criteria			
CDAI drop of 100 or more	£7,174.24	0.137	£52,311.06
Maximum time on treatment			
3 years	£7,174.24	0.137	£52,311.06

Severe TNF-Failure Population

Table 7.7.9.15: Scenario analysis – versus conventional therapy – severe TNF-Failure population

Input(s)	Incremental Costs	Incremental QALYs	ICER
Time horizon			
1 year	£7,486.61	0.022	£340,634.71
Lifetime	£7,566.06	0.109	£69,194.54
Utility weight source			
Vedolizumab trial data	£7,321.60	0.056	£130,035.27
Buxton et all 2007	£7,321.60	0.091	£80,268.26
Vedolizumab response assessment			
Week 10	£7,957.71	0.056	£141,332.88
Week 14	£7,957.71	0.056	£141,332.88
Response criteria			
CDAI drop of 100 or more	£7,321.60	0.056	£130,035.27
Maximum time on treatment			
3 years	£8,980.73	0.076	£117,894.05

7.7.10 What were the main findings of each of the sensitivity analyses?

The analyses reveal that the model is most sensitive to transition probabilities (particularly for the remission health state) as well as health state costs and utilities. For the comparison with surgery, the model is most sensitive to the surgery transition probabilities (for complications and post-surgical remission) and health state costs.

For almost all comparisons, the probabilistic sensitivity analysis found that Vedolizumab tends to be a dominant strategy (less costly and more effective) at all values of lambda. The exceptions to this general finding are in comparison with conventional therapy and in comparison with Adalimumab in the severe TNF-Naïve population sub group.

At an acceptability threshold of £30,000 per QALY, the probability of Vedolizumab being cost-effective is highest in the moderate anti-TNF naïve patient population sub group.

In scenario analyses, the model is found to be sensitive to the time horizon, with longer time horizons reducing the ICER. This suggests that if the effect of treatment with Vedolizumab is sustained over the longer term, it is likely to be a cost-effective strategy. It is important to note that, in the model, it is assumed that all patients

treated with a biologic will switch to conventional therapy after one year and face transition probabilities for conventional therapy. Thus, any sustained benefit of Vedolizumab treatment is assumed to derive only from the higher proportion of patients in better health states at the end of one year.

The model is sensitive to the utility weights that are applied; the cost-effectiveness of Vedolizumab is considerably improved based on the utility weights that are used. A CDAI drop of 100 or more also leads to a more improved cost-effectiveness of Vedolizumab in all the sub groups considered.

7.7.11 What are the key drivers of the cost-effectiveness results?

The model appears to be most sensitive to transition probabilities (in particular for remission), health state costs and utility values. The time horizon is an important variable in determining the cost-effectiveness of Vedolizumab. With a longer time-horizon, Vedolizumab is more cost-effective in all comparisons.

7.8 Validation

7.8.1	**Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.**

Several steps were taken in validating the model.

Clinical validity: For purposes of clinical validation, the model specification document was reviewed by clinical experts to ensure that the proposed model structures closely reflect real-world clinical practice and that all model assumptions are clinically valid. The experts agreed with the model structure and provided input on which adverse events to include in the model (see Section 7.3.5).

Face validity: The model was reviewed by two, independent, consultants with expertise in health economics.

Internal validity: Excel formulas, Visual Basic for Applications programming, and input data were verified for accuracy as part of quality-control procedures by a modeler not involved in the model development. The quality-control procedures were performed according to a prespecified test plan. In addition, a series of diagnostic tests were conducted to confirm that the model was correctly applying all formulas.

External validity: To ensure external validity, we compared the percentage of patients in each health state at 1 year with that observed based on the clinical trials as a means of external validation of the clinical results (see 7.7.1.1). We also compared the results to previous economic analyses (see Section 7.9.1).

7.9 Sub-group analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. This should be explored as part of the reference-case analysis by providing separate estimates of clinical and cost-effectiveness for each relevant subgroup of patients.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.10.

Types of sub-groups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Sub-groups based solely on differential treatment costs for individuals according to their social characteristics.
- Sub-groups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, when the costs of facilities available for providing the technology vary according to location).

7.9.1 Please specify whether analysis of sub-groups was undertaken and how these sub-groups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost-effectiveness because of known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 6.3.7.

As outlined in Section 7.2.1 the cost-effectiveness of Vedolizumab was assessed in comparison with Infliximab and Adalimumab only in patients that were TNF-Naïve (mixed, moderate and severe sub groups).

Sub-groups of patients defined by failure to TNF antagonist therapy were included in the scope of this appraisal. Patients randomized to the GEMINI II and III trials were stratified by TNF antagonist therapy and the outcomes data from the trial were analysed by these strata.

7.9.2	**Please clearly define the characteristics of patients in the subgroup.**

Patients that are TNF-Naïve have not received TNF antagonist therapy.

Patients that are TNF-failures have received and failed to respond to a TNF antagonist during induction treatment

7.9.3	**Please describe how the statistical analysis was undertaken.**

Please see Section 6.5.2 for a summary of the efficacy of Vedolizumab by prior TNF antagonist therapy outcomes.

Please see Section 6.7.6 for a summary of the indirect comparison of Vedolizumab with compartors in sub-groups defined by prior TNF antagonist therapy outcomes.

7.9.4	**What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 7.7.6 (Base-case analysis).**

As some comparators are not relevant for all sub-groups, results have been presented, above, by subgroup.

7.9.5	**Were any obvious sub-groups not considered? If so, which ones, and why were they not considered? Please refer to the sub-groups identified in the decision problem in section 5.**

No obvious sub-groups or sub-groups identified in the decision problem have been excluded from the analysis.

7.10 Interpretation of economic evidence

7.10.1	**Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?**

Comparisons with previous economic analyses are limited by the fact that there are differences in health states between this model and previous models. However, the results do not differ substantially from previous model.

When the model is set to a 1-year time horizon and using the utility weights presented by Dretzke and colleagues (2011), the model finds that there are 0.890 QALYs for conventional therapy and 0.910 QALYs for infliximab. These QALY estimates are similar to those presented by Dretzke and colleagues: 0.8119-0.8926 for conventional therapy and 0.8943-0.9245 for infliximab.

Using a lifetime time horizon, the model provides QALY estimates of 12.058 for conventional therapy, 12.621 for infliximab. These are lower than the estimates from Bodger and colleagues (2009): 14.209 for conventional therapy and 14.901 for infliximab. This is mainly due to the more favorable transition probabilities in the Bodger model. As noted by the Decision Support Unit, the cohort study from which these transition probabilities were derived was a much healthier population than the moderate-severe population eligible for biologic therapy. As such, it is not surprising to find higher lifetime QALYs from Bodger and colleagues (2009).

7.10.2	**Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 5?**

The economic evaluation presented here is relevant to all patients identified in the decision problem in Section 5.

7.10.3	**What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?**

The economic evaluation is based upon two large, international, well-controlled clinical trials that compared the use of Vedolizumab to the use of placebo plus conventional therapy. The use of conventional therapy in the clinical trial is similar to actual use in England and Wales. The trial stratified patients by prior treatment with TNF antagonists, allowing for the assessment of subgroups by prior treatment.

The mixed treatment comparison informed comparisons with Infliximab in the induction and maintenance phase and with adalimumab in the induction phase only. Vedolizumab did not show significant differences in the efficacy endpoints studied, when compared with other biologics in the induction setting. Results were consistent regardless of whether the week 6 or week 10 data for Vedolizumab were used in analyses. In addition, Vedolizumab did not show significant differences in efficacy results when compared with Infliximab in the maintenance setting. Rates of discontinuation due to adverse events were significantly better for Vedolizumab. The MTC was limited in its ability to inform comparisons with anti-TNF therapies in an anti-TNF experienced population or with surgery.

The model is similar to previous models published in the area (and presented to NICE) in terms of structure. The model does include the cost of treating adverse events as well as their impact on patients' quality of life. The model also incorporates mortality related to ulcerative colitis which has not been included in other models, to date. The costs used in the model are similar to other models in the area. Utilities in the model are based upon the EQ-5D data in the GEMINI 2 and 3 studies and are consistent with the reference case. Alternative utilities are explored in scenario analyses.

7.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

The analyses presented in the submission reflect the scope of the decision problem and do not appear to omit important analyses that could enhance the robustness or completeness of the results.

Section C – Implementation

8 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost-effectiveness. This will allow the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

8.1	**How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any sub-groups considered. Also present results for the subsequent 5 years.**

The incidence of IBD has risen dramatically in recent decades with a combined incidence now of over 400/100,000 (IBD, 2012). It is projected that in 2014, 11,642 Crohn's disease CD patients will be eligible for treatment with Vedolizumab in England and Wales. The total adult population for England and Wales is approximately 56,181,236 (ONS, 2014) and the estimated prevalence of CD is 0.20% (NICE, 2010). This meant a total of 112,362 people had Crohn's disease (CD). The proportion of moderate and severe CD patients is 20% (NICE, 2010) of the CD population and 51.11% (11,642) (Global assumption) of those are eligible for treatment biologics. Over the next 5 years, it is projected that the proportion of moderate to severe CD patients treated with biologics in England and Wales will rise steadily (Takeda, data on file, and 2013). With a projected year on year increase in the total population of England and Wales, and the projected prevalence rate remaining at 0.20% there would be a yearly increase in the number of CD patients eligible for treatment. A five year projection for the market authorized (eligible) patient population is presented below.

Table 8.1.1: 5 year projection of VDZ market authorized CD patients

Year	2014	2015	2016	2017	2018
Total population[a]	56,948,200	57,341,143	57,725,328	58,112,088	58,489,817
Prevalence rate (of total population)[b]	0.2%	0.2%	0.2%	0.2%	0.2%
Proportion of moderate to severe patients (biologic eligible in % of treated)[c]	20.00%	20.00%	20.00%	20.00%	20.00%
Proportion of patients treated with Biologic[d]	51.11%	51.67%	52.24%	52.81%	53.23%
Proportion of patients with moderate to severe UC	11,642	11,770	11,899	12,030	12,126

Source: a=ONS, 2014, b=NICE,2010, c=NICE,2010, d=global assumption

8.2 What assumption(s) were made about current treatment options and uptake of technologies?

In addition to Vedolizumab, it is assumed that the treatment options available to the eligible population are Adalimumab, and Infliximab. Takeda estimates that 92.3% of all patients (global assumption), including patients with mild disease, are treated with a biologic. It is therefore assumed the treatment rate is 100% in moderate and severe patient. 51.11% of the moderate to severe CD patient population fail conventional therapy and are therefore eligible for treatment in 2014 (Takeda, data on file, 2013). A projection of assumed yearly technologies uptake is presented in the table below.

Table 8.2.1: Projected uptake of Vedolizumab

Year	2014	2015	2016	2017	2018
Proportion of patients eligible for biologics uptake	0.6%	3.4%	9.7%	14.9%	17.0%

8.3 What assumption(s) were made about market share (when relevant)?

Market share proportion estimates are based on the latest market share or prescription share estimates derived from the Informa UK report (Informa UK, 2013). These estimates reflect the usage of available treatment options before the introduction of Vedolizumab (VDZ) in the population of patients with moderate to severe active CD who have had an inadequate response to conventional therapy and who are being treated with a biologic therapy.

Table 8.3.1: Current market share estimates

Comparator	2014	2015	2016	2017	2018
Adalimumab	40.2%	40.9%	41.1%	39.6%	38.1%
Infliximab	59.8%	59.1%	58.9%	60.4%	61.9%

The base-case analysis assumed Vedolizumab will take 40% of its market share from Adalimumab, and 60% from Infliximab. This assumption is based on the current usage of Adalimumab and Infliximab in 2014 The table below shows redistribution of the market share once Vedolizumab is introduced taking into consideration yearly growth in the moderate to severe CD patient population eligible for biologics into consideration.

Table 8.3.2: Market share estimates after introduction of VDZ

Drug	2014	2015	2016	2017	2018
Vedolizumab	0.6%	3.4%	9.7%	14.9%	17.0%
Adalimumab	40.0%	39.6%	37.3%	33.6%	31.3%
Infliximab	59.4%	57.0%	53.0%	51.5%	51.7%

8.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

In addition to the cost of treatment (drug acquisition cost), the budget impact analysis has taken into consideration the cost that will be incurred from administering Vedolizumab, the cost of surgery, resource use cost by disease severity, and cost accrued from the treatment of Vedolizumab related adverse events. Drug related adverse events taken into consideration in this budget impact analysis include; serious infections, tuberculosis, lymphoma, acute hypersensitivity reactions, and skin reactions.

8.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

The unit costs assumed in the calculations and the sources of these cost are presented in the table below.

Table 8.5.1: Drug acquisition cost

Treatment	Unit	Acquisition cost	Administration Cost (per administration)
Adalimumab	per 40 mg vial	£352.14[a]	£0.00[d]
Infliximab	per 100 mg vial	£419.62[a]	£308.00[e]
Vedolizumab	per 300 mg vial	[redacted]	£308.00[c]

Source: a = BNF, August 2014, b = Takeda, c = Assumed the cost of administering Vedolizumab was equal to the cost for Infliximab administration, d = Assumptions, e = PbR mandatory tariff 2013/14 FZ37F

Table 8.5.2: Breakdown of cost associated to drug related adverse events.

Adverse Event	Cost
Serious infection[a]	£1,470.00
Tuberculosis[b]	£2,272.00
Lymphoma[c]	£14,975.00
Acute hypersensitivity reactions[d]	£3,188.00
Skin reactions[e]	£1,363.00

Source: a= average of five different types of serious infections: sepsis, pneumonia, urinary tract infection, respiratory infection and bronchitis,
b=average of non-elective short-stay and long-stay tuberculosis,
c= Average of lymphoma costs from three NICE technological appraisals: TA65 (NICE, 2003), TA243 (NICE, 2012), and TA226 (NICE, 2011),
d=average of non-elective short-stay and long-stay pyrexia,
e=average of procedures associated with skin disorders.

Cost of surgery

The cost of surgery used in the model was £8,388. This estimate was obtained from published literature (Buchanan et al., 2011) and inflated using the Pay and Prices Index (Curtis, 2012).

Table 8.5.3: Resource use and cost

Resource Item	Unit Costs[a]	Annual Resource Units	
		Moderate to Severe (600 > CDAI > 220)	
Outpatient visits			
IBD related	£115.48	7.2	
Dietician	£93.00	2.6	
Stoma nurse	£43.24	0.2	
Laboratory	£2.95	0.5	
Radiology			
Plain x-ray	£30.26	2.6	
Barium enema	£118.67	0.0	
Barium follow through	£118.67	0.0	
Ultrasound of the abdomen	£51.27	0.0	
CT scan of abdomen/pelvis	£92.46	1.1	
MRI scan of abdomen/pelvis	£144.51	5.2	
WBC scan	£472.02	0.0	
DEXA scan	£67.14	0.0	
Fistulogram	£668.14	0.0	
Endoscopies			
Esophagogastroduodenoscopy	£726.44	1.0	
Sigmoidoscopy	£946.94	1.5	
Colonoscopy	£886.31	1.6	
Hospital admission (days)[b]	£402.35	14.4	
Total costs		£11,345.94	

CT = computed tomography; DEXA = dual-energy X-ray; IBD = irritable bowel disease; MRI = magnetic resonance imaging; WBC = white blood cell.
a = NHS Reference Costs schedule 2011-2012 (Department of Health, 2013).
a = Not relating to surgery.

Table 8.5.4: Postsurgical cost

Resource Item	Unit Cost	Postsurgical Complication			
		Wound Infection	Prolonged Ileus/Small Bowel Obstruction	Abdominal Abscess	Anastomotic Leak
Additional hospital days	£402.35	4	4	5	7
Outpatient visits	£115.48	1	0	0	0
Total cost		£1,724.87	£1,609.39	£2,011.73	£2,816.43

8.6 Were there any estimates of resource savings? If so, what were they?

Yes, there were estimates of resource savings in the budget impact analysis. At a cost of [redacted] per vial and an administration cost of £308, Vedolizumab in the base case analysis led to resource savings in the costs associated with the management of drug-related adverse events and the cost of surgery. In other scenario analysis carried out, resource saving were also seen in other disease related cost (disease monitoring and symptomatic treatment). Estimates for resource saving over the 5 years period in this analysis after Vedolizumab has been introduced are shown in the table below.

Table 8.6.1: Estimates of resource savings.

Type of Cost	2014	2015	2016	2017	2018
Drug related adverse events (AE's)	-£1,346	-£7,766	-£22,550	-£35,255	-£40,809
Surgery	-£21,937	-£126,543	-£367,438	-£574,452	-£664,958
Non-drug costs	-£127,636	-£736,279	-£2,137,899	-£3,342,386	-£3,868,987

8.7 What is the estimated annual budget impact for the NHS in England and Wales?

In the base case analysis, the introduction of Vedolizumab is likely to increase drug expenditure by £118,136 in the first year after launch and by £9,453,065 cumulatively over the 5 years considered in this analysis. A breakdown of the yearly budget impact is presented below.

Table 8.7.1: Base case estimated annual VDZ budget impact for the NHS in England and Wales.

Type of Cost	2014	2015	2016	2017	2018
Drug acquisition costs	£79,030	£455,890	£1,323,747	£2,069,543	£2,395,605
Drug administration	£62,390	£359,900	£1,045,025	£1,633,790	£1,891,198
Drug related AEs	-£1,346	-£7,766	-£22,550	-£35,255	-£40,809
Surgery	-£21,937	-£126,543	-£367,438	-£574,452	-£664,958
Total annual costs	£118,136	£681,481	£1,978,785	£3,093,627	£3,581,036
Cumulative costs	£118,136	799,617	£2,778,402	£5,872,029	£9,453,065

An alternative scenario was taken into consideration in which in addition to the drug acquisition and administration cost, and drug related adverse events cost, the cost of surgery and non-drug cost costs associated with disease monitoring and symptomatic treatment were also included. The budget impact analysis results show that the introduction of Vedolizumab is likely to reduce drug expenditure by £9,499 in the first year after launch and by £760,122 cumulatively over the 5 year period considered in this analysis. A yearly breakdown is presented below.

Table 8.7.2: Sensitivity analysis estimated annual VDZ budget impact for the NHS

Type of Cost	2014	2015	2016	2017	2018
Drug acquisition costs	£79,030	£455,890	£1,323,747	£2,069,543	£2,395,605
Drug administration cost	£62,390	£359,900	£1,045,025	£1,633,790	£1,891,198
Drug related AEs	-£1,346	-£7,766	-£22,550	-£35,255	-£40,809
Surgery	-£21,937	-£126,543	-£367,438	-£574,452	-£664,958
Non-drug cost	-£127,636	-£736,279	-£2,137,899	-£3,342,386	-£3,868,987
Total annual costs	-£9,499	-£54,798	-£159,114	-£248,759	-£287,952
Cumulative costs	-£9,499	-£64,297	-£223,412	-£472,171	-£760,122

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

This budget impact analysis, has not quantified the societal benefit that would come from indirect cost in the form of productivity gains, reduced rates of absenteeism, and reduce loss in caregiver time. CD as already mentioned is a chronic condition that affects the mucosa of the gastrointestinal tract, and its lesions can extend deep beyond the mucosal lining in a skip-like pattern (Baumgart and Sandborn, 2007). Its main symptoms range from mild to severe and include diarrhea, abdominal pain, weight loss, malaise, lethargy, anorexia, nausea, vomiting, and fever. These symptoms undoubtedly lead to indirect costs associated with absenteeism and productivity loss. Patients who benefit from the drug or working age are able to go back to work resulting in less absenteeism and productivity gains and caregiver time

is saved or better spent elsewhere. Also no equity issues are envisaged with the administering of Vedolizumab.

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