NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal (STA)

Vedolizumab (Entyvio ®) for the treatment of adults with moderate to severe active ulcerative colitis

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Abbreviations

Abbreviation	Term
5-ASAs	5-aminosalicylates
6-MP	6-mercaptopurine
ACT-1 and ACT-2	The Active Ulcerative Colitis Trials 1 and 2
AEs	adverse events
ADA	adalimumab
AZA	azathioprine
BECT	burden, epidemiology, costs, and treatment patterns
BMI	body mass index
BSG	British Society of Gastroenterology
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CI	confidence interval
DB	Double-blind
EOW	Every Other Week
EQ-5D	EuroQol-5 Dimensions
GOL	golimumab
HRQOL	health-related quality of life
HTA	Health technology assessment
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICER	Incremental cost-effectiveness ratio
IPAA	ileal pouch-anal anastomosis
IRR	Infusion-related reactions
ITT	intent-to-treat
IV	intravenous(ly)
JCV	JC virus; a neurotropic DNA polyomavirus
LOCF	last observation carried forward
LOCUS	Long-term Impacts of Colectomy Surgery among Ulcerative Colitis Patients
LOS	length of stay
MID	minimally important difference
MLN0002	VEDO, formerly LDP-02 and MLN02
MTX	methotrexate
N/A	not available
NICE	National Institute for Health and Care Excellence
NNT	number needed to treat
NR	not reported
OL	open-label
PC	Placebo-controlled
PK	pharmacokinetic(s)
PL	placebo
PML	progressive multifocal leukoencephalopath
PRO	Patient Reported Outcomes
Q4W	every 4 week dosing
Q8W	every 8 week dosing
QALY	quality-adjusted life-year
QOL	quality of life
RBC	red blood cell
RCT	Randomised controlled trial

RR	Relative risk
SAE(s)	serious adverse event(s)
SD	standard deviation
SE	standard error
SF-36	Medical Outcomes Study 36-item Short Form
SMR	standardised mortality ratio
SPC	summary of product characteristics
TEAE	treatment-emergent adverse events
TNF	tumour necrosis factor
TNF-α	tumour necrosis factor–alpha
UC	ulcerative colitis
VAS	visual analogue scale
VEDO	Vedolizumab
Wk(s)	Week(s)

Glossary

Term	Definition
Clinical Remission by Complete Mayo Score	A complete Mayo score of ≤ 2 points and no individual subscore > 1 Point
Clinical Remission by Partial Mayo Score	A partial Mayo score of ≤ 2 points and no individual subscore > 1 point
Clinical Response by Complete Mayo Score	A reduction in complete Mayo score of ≥ 3 points and ≥ 30% from baseline with an accompanying decrease in rectal bleeding subscore of ≥ 1 point or absolute rectal bleeding subscore of ≤ 1 point
Clinical Response by Partial Mayo Score	A reduction in partial Mayo score of ≥ 2 points and ≥ 25% from baseline with an accompanying decrease in rectal bleeding subscore of ≥ 1 point or absolute rectal bleeding subscore of ≤ 1 point
Combined VEDO Group	The Maintenance Intent-to-treat (ITT) VEDO groups (every 8 weeks [Q8W] and every 4 weeks [Q4W]) pooled with the Maintenance non-ITT VEDO group
Complete Mayo Score	A composite index of 4 disease activity variables (stool frequency, rectal bleeding, findings on sigmoidoscopy, and physician's global assessment), each scored on a scale from 0 to 3 (higher scores indicate greater disease activity)
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
Disease Worsening	An increase in partial Mayo score of ≥ 3 points from the Week 6 value on 2 consecutive visits (or an increase to 9 points on 2 consecutive visits if the Week 6 value > 6) and a partial Mayo score ≥ 5 points
Durable Clinical Remission	Clinical remission at Weeks 6 and 52
Durable Clinical Response	Clinical response at Weeks 6 and 52
Durable Mucosal Healing	A Mayo endoscopic subscore ≤ 1 at both Week 6 and Week 52
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 intravenously for 1 week • *Immunomodulators:* at least one 8-week regimen of azathioprine(≥ 1.5 mg/kg) or 6-mercaptopurine (≥ 0.75 mg/kg) (inadequate response to immunomodulators) • *Tumour necrosis factor alpha antagonists:* at least one 4-week induction regimen of a tumour necrosis factor alpha (TNF-α) antagonist such as infliximab 5 mg/kg IV, 2 doses at least 2 weeks apart
Induction Phase	The Induction Phase began at Week 0, included study drug dosing at Weeks 0 and 2, and concluded with induction-related assessments at Week 6
Induction Study	The placebo-controlled formal, planned induction efficacy analyses of the effects of VEDO administered at Weeks 0 and 2
Intolerance	• *Intolerance to corticosteroids*: including, but not limited to Cushing's syndrome, osteopenia/osteoporosis, hyperglycaemia, insomnia, infection • *Intolerance to immunomodulators*: including, but not limited to nausea/vomiting, abdominal pain, pancreatitis, liver function test abnormalities, lymphopenia, *TPMT* genetic mutation, infection • *Intolerance to* TNF-α *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 does not qualify)
Maintenance Phase	The Maintenance Phase began at Week 6, included study drug dosing at Week 6 and every 4 weeks thereafter, and concluded with Week 52 assessments
Maintenance Study	The placebo-controlled formal, planned maintenance efficacy analyses of VEDO administered as maintenance therapy
Mucosal Healing	Mayo endoscopic subscore of ≤ 1 point
Partial Mayo Score	A composite index of 3 disease activity variables (stool frequency, rectal bleeding, and physician's global assessment), each scored on a scale from 0 to 3 (higher scores indicate greater disease activity). Partial Mayo score is calculated analogously to the complete Mayo score but excludes the sigmoidoscopy subscore
Rescue Medication(s)	Any new medication or any increase in dose of a baseline medication required to treat new or unresolved UC symptoms (other than antidiarrheal for control of chronic diarrhoea)
Sustained Clinical Response	A clinical response at both Weeks 4 and 6 based on partial Mayo score (defined as reduction in partial Mayo score of ≥ 2 points and ≥ 25% from baseline with an accompanying decrease in rectal bleeding subscore of ≥ 1 point or absolute rectal bleeding subscore of ≤ 1 point)
Sustained Non-response	Failure to achieve a clinical response (as defined above) by Week 14 and a partial Mayo score ≥ 5 points
Treatment Failure	Disease worsening, need for rescue medications or surgical intervention for treatment of UC, or study drug-related adverse event leading to discontinuation from the study

Executive summary

Burden of Illness

UC is a chronic relapsing-remitting form of IBD (Burness & Keating 2013). Bloody diarrhoea is the hallmark clinical symptom but patients experience a range of debilitating symptoms like rectal urgency and tenesmus (ineffectual and painful straining at stool) (Kornbluth & Sachar 2010), abdominal pain, fever, malaise and weight loss (Reinisch et al. 2007; Danese et al. 2011), chronic fatigue and sleep disturbances (Jelsness-Jørgensen et al. 2011). Acute complications of UC include severe bleeding, toxic megacolon and peritonitis. (Danese et al. 2011). The onset of symptoms and diagnosis of UC usually occurs in young-middle aged working adults. Over two-thirds of patients describe interference with work and three-quarters describe interference with leisure activities (Dignass 2012). The unpredictable nature of relapse in ulcerative colitis and the significant symptom burden also has a negative effect on patients' psychological well-being and quality of life because patients find it hard to live a normal life and maintain work commitments (Irvine 2004).

Unmet Need

Current treatments, consisting of conventional therapies (e.g. 5-aminosalicylates (5-ASAs), corticosteroids and immunomodulators (thiopurines such as azathioprine [AZA] and 6-mercaptopurine [6-MP])) and TNFα antagonist's (infliximab, adalimumab and golimumab), have been and remain effective for many patients with ulcerative colitis. However there is real-world evidence and controlled trial evidence of patients who do not respond, lose their initial response or become refractory to both these types of treatment (Royal College of Physicians 2013; Sandborn et al. 2012; Rutgeerts 2005).

Patients who fail both conventional and TNFα antagonist therapy typically have no other medical therapeutic options available to them and up to 40% (Solberg et al. 2009) often progress to surgical options (EMEA 2014). In cases where the entire colon is removed, the surgeon may create an opening, or stoma, in the abdominal wall such that an external bag is attached to the stoma. This is called a permanent ileostomy. Stools pass through this opening and collect in the external bag. The patient must wear the pouch at all times (CCFA 2014). Many patients and their clinician are reluctant to consider surgery (Waljee 2011) due to the potential for serious post-surgery complications such as bleeding, faecal incontinence,

depression, sexual dysfunction, female infertility, pouchitis, pouch leakage, pelvic abscesses, pouch fistulae, small bowel obstruction and anastomotic stricture (Ochsenkühn & D'Haens 2011).

Along with limited efficacy, current treatment options are associated with significant safety concerns associated with chronic immunosuppression of the immune system associated with corticosteroids, immunomodulators and TNFα antagonists (McLean LP 2012; Janssen Biologics B.V 2013; AbbVie Ltd 2014; Merck Sharp & Dohme 2013).

From the patient's perspective, failure on treatment amounts to disease flares and complications of their disease that may require frequent hospitalisations, need for different treatment or surgeries and the associated treatment of post-surgical infections.

Place in Therapy

Vedolizumab (Entyvio®) is a new gut-selective targeted therapy without systemic immunosuppression that is indicated for 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 (TNFα) antagonist (Takeda Pharma A/S 2014).

Vedolizumab Clinical Evidence

The efficacy and safety of vedolizumab (VEDO) for the treatment of adult patients with moderately to severely active UC was demonstrated in a randomised, double-blind, placebo-controlled study evaluating efficacy endpoints at Week 6 and Week 52 (GEMINI I, (Feagan et al. 2013)). The study enrolled patients who had failed at least one conventional therapy and/or the TNFα antagonist (inadequate response, primary and secondary loss of response or intolerance to TNFα antagonist).

In GEMINI I, two cohorts of patients received VEDO at Week 0 and Week 2: cohort 1 in which 374 patients were randomised in a double-blind fashion (3:2) to receive VEDO 300 mg or placebo at Week 0 and Week 2 and cohort 2 (N=521) patients were treated with open-label VEDO 300 mg. To evaluate efficacy at Week 52, 373 patients from cohort 1 and 2 who were treated with VEDO and had achieved clinical response at Week 6 were randomised in a double-blind fashion (1:1:1) to one of the following regimens beginning at Week 6: VEDO 300 mg every eight weeks, VEDO 300 mg

every four weeks, or placebo every four weeks The results presented for week 52 here are for the VEDO 8 weekly dose versus placebo.

In the ITT population of GEMINI I study, compared with placebo, VEDO treatment resulted in significantly greater rates of clinical response, clinical remission, and mucosal healing at Week 6 and Week 52:

Week 6 (*VEDO 300mg or placebo week 0 and week 2 and assessment at Week 6*):

- Clinical response: VEDO, 47% versus placebo, 26%; P <0.0001.
- Clinical remission: VEDO, 17% versus placebo, 5%; P < 0.001.

Week 52 (*VEDO 300mg every 8 weeks [Q8W], or placebo for patients who achieved clinical response at Week 6*):

- Durable clinical response: VEDO Q8W:56.6% versus placebo, 23.8%; difference, 32.8%, P <0.001.
- Clinical remission: VEDO Q8W:41.8% versus placebo, 15.9%; difference, 25.9%, P = 0.001.
- Compared with placebo, VEDO maintenance treatment was associated with significantly higher rates of all secondary endpoints including durable clinical response (56.3% versus 23.8%, P <0.0001) and durable clinical remission (20.5% versus 8.7%, P = 0.008).

Approximately one-third of patients had failed prior TNFα antagonist therapy. The clinical remission and durable clinical response rates were greater for VEDO -treated patients than for placebo-treated patients regardless of prior TNF antagonist treatment status.

- **Anti-TNF Failure** (VEDO Q8W versus placebo, Week 52)
  - Clinical remission: VEDO 37.2% versus 5.3% for placebo at 52 weeks.
  - Durable clinical response: VEDO 46.5% versus 15.8% for placebo at 52 weeks.
- **Anti-TNF Naïve** (VEDO Q8W versus placebo, Week 52)
  - Clinical remission: VEDO 45.8% versus 5.3% for placebo at 52 weeks.
  - Durable clinical response: VEDO 46.5% versus 15.8% for placebo at 52 weeks.

Delayed Responder Analyses

- Exploratory analyses were conducted to asses delayed response among patients not responding at week 6 who remained in the study and received VEDO every four weeks.

- Clinical response using partial Mayo scores was achieved at Week 10 and Week 14 by greater proportions of VEDO patients (32% and 39%, respectively) compared with placebo patients (15% and 21%, respectively).

Impact on Health-related Quality of Life

- Exploratory analysis show clinically meaningful improvements were observed for VEDO groups, and the improvements were significantly greater as compared with the placebo group at Week 6 and Week 52 on EQ-5D and EQ-5D VAS scores, all subscales of IBDQ (bowel symptoms, systemic function, emotional function and social function) and all subscales of SF-36 including the Physical Component Summary (PCS) and Mental Component Summary (MCS).

Safety Outcomes

- The mechanism of action of vedolizumab is expected to result in a differentiated safety profile compared to systemically acting TNF-alpha antagonists; most importantly the lack of systemic immunosuppressive effects as VEDO does not inhibit immune response to an intramuscular antigenic challenge in humans and does not cross the blood-brain barrier. (Soler 2009)

- Further evidence re VEDO safety can be derived from 3-year interim results from an ongoing integrated safety analysis (Colombel 2013). This analysis which includes over 2700 IBD patients (including 1107 UC patients) have confirmed the safety profile of VEDO to be similar that observed in GEMINI I study and no new safety issues have been identified with long-term use. (Colombel 2013).

Relevant Comparators

The relevant comparators considered within this appraisal are also those identified in the final NICE scope.

Conventional Therapy	**Anti-Therapies**
E.g. (monotherapy or combination): • aminosalicylates • corticosteroids • thiopurines	• Infliximab • Adalimumab • Golimumab

Comparative Effectiveness versus Anti-TNF therapy

A mixed treatment comparison (MTC) were undertaken to calculate the relative treatment effect estimates of vedolizumab, infliximab, adalimumab and golimumab and to underpin the economic evaluation, based on anti-TNF failure and anti-TNF naive subgroups.

Few comparator studies provided data according to prior anti-TNF experience and many of those which did, only included anti-TNF–naïve patients; in particular, all infliximab and golimumab studies. Studies which did present data for more than one population presented data for anti-TNF–naïve and anti-TNF experienced patients.

- Unlike the anti-TNF failure population; anti-TNF experienced patients 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 studies. 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.

In general, notwithstanding study population and design differences, the results of the analysis demonstrates that vedolizumab has similar efficacy to anti-TNF therapies and lower rates of discontinuation due to adverse events (Takeda Data on File 2014).

Cost Effectiveness

Incremental cost-effectiveness estimates are derived for vedolizumab in each of the three settings (mixed population, TNF naïve and TNF failure) and compared with each alternative relevant for that patient sub-group.

In the mixed population, vedolizumab derives greater incremental costs and QALYs than conventional therapy and estimates an ICER of £33,297. Versus surgery, vedolizumab has lower costs and greater QALYs and hence dominates.

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 (£4,000 - £6,000 approx) or dominates.

In the TNF failure group, vedolizumab derives more QALYs than both surgery and conventional therapy, dominating the former (due to lower cost) and deriving an ICER of £64,999 against the latter.

Given these results, we would suggest that vedolizumab offers good value for money and would be a cost effective option for introduction to the NHS.

Indeed, the cost effectiveness model, when set to similar settings, produced comparable results for an anti-TNF–naive population consistent with the 10-year results presented by Tsai and colleagues (2008). Similarly, the NICE HTA submission for infliximab estimated similar results.

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 (VEDO) is a gut-selective immunosuppressive biologic which reduces gastrointestinal inflammation in UC, a chronic immunomodulatory mediated condition of the GI tract. It is a humanised monoclonal antibody that binds specifically to the α4β7 integrin, which is preferentially expressed on gut homing T helper lymphocytes. By binding to α4β7 on certain lymphocytes, VEDO inhibits adhesion of these cells to mucosal addressin cell adhesion molecule-1 (MAdCAM-1), but not to vascular cell adhesion molecule-1 (VCAM-1). MAdCAM-1 is mainly expressed on gut endothelial cells and plays a critical role in the homing of T lymphocytes to tissues within the gastrointestinal tract (Takeda Pharma A/S 2014).

VEDO does not bind to, or inhibit function of, the α4β1 and αEβ7 integrins. The inhibition of α4β7 integrin is a shared mechanism of action of both VEDO and natalizumab and has thus raised a question of whether or not VEDO may also increase the risk of PML. The gut-selective profile of VEDO is attributable to 2 distinct pharmacologic properties. VEDO binds solely to the α4β7 but not the α4β1 integrin, unlike natalizumab, which binds to both. As a result, the binding of VEDO is specific for α4β7 expressing cells including the gut-tropic subset of lymphocytes. The ability of natalizumab to bind to the α4β1 integrin broadens its mechanism of action to modulate the systemic immune system as the α4β1 integrin is more widely expressed by leukocytes than is the α4β7 integrin, and the α4β1 integrin mediates

pleiotropic activities that are not regulated by the α4β7 integrin. Review of the scientific evidence published to date in peer-reviewed scientific journals supports the concept that PML associated with natalizumab results from antagonising the α4β1 integrin and not the α4β7 integrin. The mechanism of action of VEDO represents a novel, selective intestinal-targeted approach relevant to the pathophysiology of UC. By virtue of this gut-selective mechanism of action, VEDO provides anti-inflammatory activity with the potential for avoiding systemic immunosuppression and many of the side effects which are associated with existing UC therapies. Hence, VEDO may offer a significant additional treatment option for the management of UC patients who have failed conventional or TNFα antagonist therapy (EMEA 2014).

Figure 1. Vedolizumab mechanism of action: blocks capture of pathogenic gut-homing lymphocytes

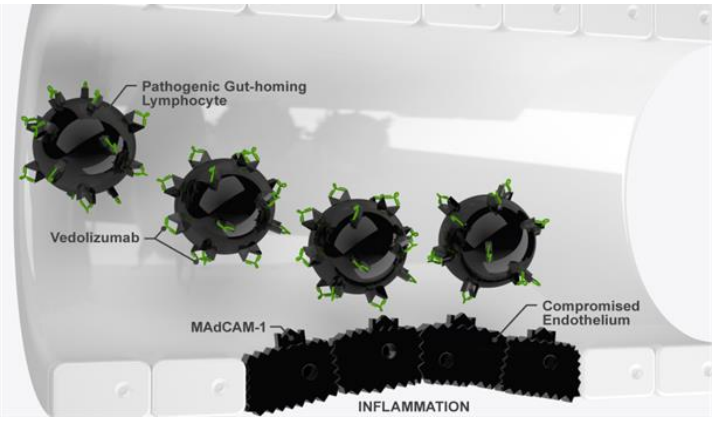
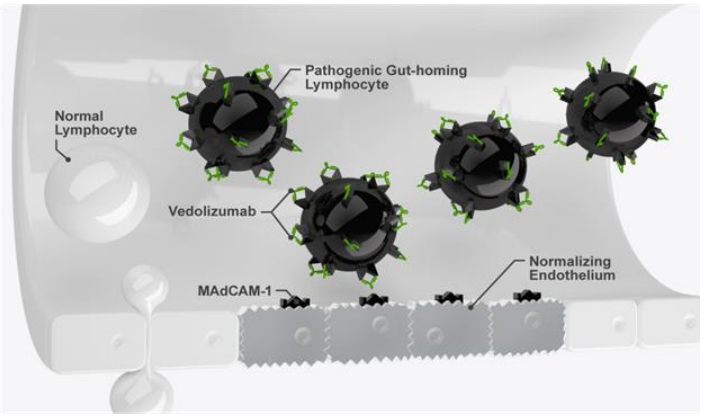


Figure 2. Vedolizumab mechanism of action: reduces inflammation by preventing selective migration of pathogenic gut-homing lymphocytes



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 granted marketing authorisation for the medicinal product Entyvio, 300 mg powder for concentrate for solution for infusion intended for the treatment of adult patients with moderately to severely active UC who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist. Marketing authorisation was also received at the same time for adult patients with moderately to severely active CD who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist.

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).**

- The GEMINI I study was conducted under a single protocol but analysed as 2 studies: the Induction Study (week 0-6) and the Maintenance Study (week 6-52).
- In the Induction study, two cohorts of patients, sequentially enrolled with identical eligibility criteria, were contained in the 6-week induction phase: Cohort 1 which included patients randomised and treated with double-blind study drug and Cohort 2 which included patients treated with open-label VEDO. Patients were enrolled in Cohort 2 to ensure that the sample size of induction responders randomised into the Maintenance Study provided sufficient power for the Maintenance Study primary efficacy analysis.
- The “enrichment design” of the study (week 6), allowing only responders to enter the double-blind maintenance phase, is acknowledged as it is commonly adopted in clinical trials conducted in IBD setting (EMEA 2014).

- 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; however, Takeda submitted supplemental analyses (reported in the Entyvio SmPC and in section 6 of this submission) which were accepted (EMEA 2014).
- 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-TNFα compound comparator arm was considered by EMA to represent a limit of the study in consideration of today's standard of care; however this may reflect UK clinical practices, where anti-TNF compounds are not standard of care (EMEA 2014).
- Primary and secondary objectives of both induction and maintenance studies are clearly stated and represent those commonly studied in the UC indication. However, in contrast to EMA guidelines the primary endpoint was the proportion of patients with clinical response at week 6 and not that with clinical remission. Pivotal studies for anti-TNFα (e.g. ACT-1 and ACT-2 infliximab studies) also use clinical response as primary outcomes rather than clinical remission (EMEA 2014).
- Although above deviations have been identified from EMA guidance, overall the study design of both phases is considered adequate (EMEA 2014).
- Evidence was also presented to CHMP for the proposal to wait until week 10 or week 14 before considering continuation of therapy in patients who fail to show a respond at week 6. In patients' who are non-responders to anti-TNFα therapy, the option to wait till week 10 or week 14 could be clinically relevant. These data are presented in section 6.3 and forms the basis of the recommendation in the Entyvio label regarding the Week 10 assessment.
- According to EMA, the safety profile of VEDO did not raise major objections and can be considered reassuring in UC. Adverse events AEs 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.
- Clinical studies showed reassuring data on systemic immunosuppression in terms of response to immunisation in healthy volunteers or opportunistic infections including PML and TB. However, the occurrence rate of these events with long-term exposure and in patients pre-treated with anti-TNFα

drugs and/or concomitant immunosuppressants is still not known. This lack of data is reflected in the product information and addressed in the RMP.

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

Entyvio is indicated for the treatment of adult patients with moderately to severely active UC who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist.

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.**

Estimated UK launch date for Entyvio (vedolizumab) is July 2014

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

Vedolizumab has recently been licenced in the United States of America (FDA), Europe (EMA) and Australia (TGA).

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 scheduled to go through a Single Technology appraisal for CD. The appraisal has been initiated with the manufacturer submission due August 2014.

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.**

Pharmaceutical formulation	Powder for concentrate for solution for infusion. White to off-white lyophilised cake or powder. Each pack contains 1 vial which contains 300mg of VEDO.
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 Frequency	The recommended dose regimen of vedolizumab is 300 mg administered by intravenous infusion at zero, two and six weeks and then every eight weeks thereafter. Continued therapy for patients with UC should be carefully reconsidered if no evidence of therapeutic benefit is observed by Week 10.
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	[redacted]
Anticipated average interval between courses of treatments	The treatment interruption period in clinical trials extended to one year. Efficacy was regained with no evident increase in adverse events or infusion-related reactions during retreatment with vedolizumab.
Anticipated number of repeat courses of treatments	Not applicable
Dose adjustments	Some patients who have experienced a decrease in response may benefit from an increase in dosing frequency to VEDO 300 mg every four weeks.

(Takeda Pharma A/S 2014)

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?

Before starting treatment with VEDO, patients must be screened for tuberculosis according to the local practice because treatment with VEDO is not to 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 VEDO. Caution should be exercised when considering the use of VEDO 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. VEDO is contraindicated in patients with active tuberculosis.

With respect to administration, 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 reactions. For all subsequent infusions, patients should be observed for approximately one hour following completion of the infusion.

These additional investigations and monitoring requirements are not dissimilar to current biologic therapy in UC.

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

The clinical evidence for VEDO has shown reassuring data on systemic immunosuppression in terms of response to immunisation in healthy volunteers or opportunistic infections including PML and TB. However, the occurrence rate of these events with long-term exposure and in patients pre-treated with anti TNF-alpha drugs and/or concomitant immunosuppressants is still not known.

As a result of the lack of data, the VEDO product information contains details on infections and infusion-related reactions. A regulatory requirement for VEDO includes the provision of a short pamphlet providing information to physicians on the identified and potential risks of treatment with VEDO and the need to monitor patients for emerging neurological signs/symptoms. 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 (EMEA 2014).

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 VEDO will be added-on to existing therapies in clinical practice. In the pivotal trial, patients were maintained on baseline medication including 5-ASAs, corticosteroids and immunomodulators (azathioprine or 6-mercaptopurine). Concomitant corticosteroid use was gradually reduced from week 6 for patients who achieved a clinical response, and treatment with VEDO was associated with significantly higher rates of corticosteroid-free remission at week 52 (see Section 6). Therefore, treatment with VEDO in practice is expected to lead to a reduction in concomitant corticosteroid use (EMEA 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.

Pathophysiology

UC is a form of IBD characterised by a widespread inflammation of the colonic mucosa that usually begins in the rectum and extends to involve any adjacent length of the colon (Burness & Keating 2013). UC can be categorised into four different types, depending on which part of the colon is affected (Crohn's and Colitis Foundation of America 2013):

- Ulcerative proctitis affects only the rectum. In 30% of all patients with UC, the disease begins as ulcerative proctitis. A milder form of UC, ulcerative proctitis is generally associated with fewer complications and a better outlook.
- Proctosigmoiditis affects the rectum and the sigmoid colon. Symptoms include bloody diarrhoea, cramps and tenesmus; active disease may result in mild, lower left abdominal pain.
- Left-sided colitis begins at the rectum and extends as far as the splenic flexure. Symptoms include loss of appetite, weight loss, diarrhoea, bleeding and severe left-sided abdominal pain.
- Pan-ulcerative (total) colitis affects the entire colon; symptoms include diarrhoea, severe abdominal cramps, pain and substantial weight loss.

The aetiology of UC remains unknown; however, a combination of genetic, environmental and immune system factors are believed to contribute to the abnormal immune response and inflammation involved in UC (Burness & Keating 2013; Crohn's and Colitis Foundation of America 2013).

Clinical Presentation

Due to rectal involvement in UC, bloody diarrhoea is the hallmark clinical symptom, and many patients experience rectal urgency and tenesmus (ineffectual and painful straining at stool) (Kornbluth & Sachar 2010). Extensive UC and left sided colitis may lead to abdominal pain, fever, malaise and weight loss (Reinisch et al. 2007; Danese

et al. 2011). Acute complications of UC include severe bleeding, toxic megacolon and peritonitis, while chronic complications include epithelial dysplasia and cancer (Danese et al. 2011). Most patients with UC experience periods of exacerbation and remission, which occur spontaneously or as a result of treatment or other illnesses (Kornbluth & Sachar 2010; Dignass et al. 2012).

The clinical course of UC usually consists of alternating patterns of disease exacerbation and inflammation, with periods of disease remission (Kornbluth & Sachar 2010; Burness & Keating 2013). These remissions can occur spontaneously but are most likely the result of response to therapy (Burness & Keating 2013). In a given year, 50% of patients with UC will experience a relapse of disease. In addition, between 20% and 30% of patients with pancolitis will ultimately require a colectomy (Mowat et al. 2011).

Assessment and Diagnosis

A diagnosis of UC is usually suspected on clinical grounds and confirmed by positive findings on a sigmoidoscopy, colonoscopy, or biopsy, as well as a stool examination that is negative for infectious disease (Kornbluth & Sachar 2010). In addition to these clinical and imaging tests, patient reports of stool frequency and consistency, urgency, rectal bleeding, abdominal pain, malaise, fever and weight loss must be considered during the diagnostic process (Mowat et al. 2011).

Table 1. Distinguishing Pathophysiology for UC (Porter 2013)

Characteristic	Ulcerative Colitis
Disease location	Confined to the colon
Rectosigmoid involvement	Rectosigmoid is invariably involved; colonic involvement is usually left-sided
Rectal bleeding	Gross rectal bleeding is always present
Fistula development	No fistulas
Perianal lesions	Significant perianal lesions never occur
Bowel wall	Bowel wall is affected symmetrically and uninterruptedly from rectum proximally
Endoscopic appearance	Inflammation is uniform and diffuse
Inflammation pattern	Inflammation is confined to mucosa except in severe cases
Epitheloid granulomas	Typical epithelioid granulomas do not occur

The British Society of Gastroenterology defines mildly active UC as less than 4 bowel movements daily. Moderately active UC is defined as more than 4 daily bowel

movements but where the patient is not systemically ill. Severe UC is potentially life threatening and is defined as an attack in which the patient has more than 6 bowel movements daily and is systemically ill as shown by tachycardia, fever and anaemia (Mowat et al. 2011).

Patient Burden

Living with the symptoms of active UC, including frequent urgent diarrhoea, abdominal pain and fatigue, profoundly diminishes the HRQoL of patients in a population that is typically young and active (Waljee et al. 2011). Over two-thirds of patients with UC describe interference of the disease with work and nearly three quarters describe interference with leisure activities (Dignass et al. 2012). Patients with UC report significantly more disease-related concerns, impaired social functioning and a reduced sense of well-being compared with age-matched disease-free controls (Waljee et al. 2011). The disease will often require lifelong treatment with the aim of treating active disease and maintaining a state of remission.

- ### Impact of Chronic Fatigue and Sleep Disturbances on HRQOL

Mitchell and colleagues (1988) noted that systemic symptoms, such as fatigue, were frequently reported in patients with IBD and rated as of the same importance as frequent bowel movements and abdominal pain (cited in (Jelsness-Jørgensen et al. 2011). Jelsness-Jorgensen and colleagues (2011) investigated the influence of chronic fatigue on both the generic and disease-specific HRQOL of patients with IBD (CD, n = 48; UC, n = 92) using the N-IBDQ and SF-36 (Jelsness-Jørgensen et al. 2011). In patients with UC, chronic fatigue was associated with all dimensions of the N-IBDQ and the total score, but the impact was the most pronounced in the dimension measuring emotional functioning and worries. For the SF-36, the largest associations were seen in the dimensions of role-physical and role-emotional for UC. The results showed that there were major differences in the SF-36 vitality dimension, whether taking chronic fatigue into account. This indicated that using a specific fatigue questionnaire when evaluating the impact of fatigue on HRQOL was important because the SF-36 vitality dimension alone might not be able to identify the most vulnerable patient groups.

Chronic sleep disturbances may modify the coping ability of patients and therefore affect the experience of symptoms, including abdominal pain and fatigue. Ranjbaran and colleagues (2007) conducted a cross-sectional survey using the IBD-Q and

PSQI (inactive IBD, n = 80; n= 24 with irritable bowel syndrome and healthy controls, n = 15) (Ranjbaran et al. 2007). In addition to measuring disease-related QOL, the IBD-Q also addresses psychosocial function, including degree of worry and anxiety and/or presence of depression. The survey respondents with IBD reported significantly prolonged sleep latency, frequent sleep fragmentation, higher rate of using sleeping pills, decreased daytime energy, increased tiredness and poor overall sleep quality compared with healthy controls, although the healthy control sample size was very small. Severity of abdominal pain (P = 0.04), cramps (P = 0.01), depression (P = 0.001) and irritability (P = 0.01) were significantly associated with poorer reported sleep quality in patients with IBD. The reported sleep quality was correlated with IBD disease severity score (r2 = 0.55, P = 0.02). These results showed that patients with IBD had significant sleep disturbances even when their disease was not active.

- **Impact of Pain on HRQOL in UC**

Inflammatory bowel disease is associated with abdominal pain, but pain can also occur throughout the body. Schirbel and colleagues (2010) conducted a cross-sectional study to evaluate the intensity, localisation and cofactors of pain in patients with IBD in connection with HRQOL and disease activity using the SIBDQ and the German Pain Questionnaire (CD, n = 179; UC, n = 155) (Schirbel 2010). For all patients with IBD, pain localisations were different between males and females, with females reporting arthralgia more frequently. A comparison of pain localisation in patients with UC revealed a higher pain frequency in the lower left abdomen (76.4%) compared with patients with CD (55.6%). HRQOL in patients with UC was not significantly reduced by abdominal or joint pain (P = 0.17 and 0.52, respectively). For patients with UC who had undergone surgery (8.0%), pain levels (P = 0.095) and HRQOL (P = 0.305) did not differ from those of patients with UC who had not undergone surgery. When separating patients with UC according to their disease activity index (Colitis Activity Index [CAI] < 4 = remission; CAI 4-9 = increased disease activity; CAI ≥ 10 = flare-up), pain intensity increased and HRQOL decreased with increased disease activity.

The table below presents results of the effect of UC on patient QOL in recent studies.

Table 2. Effect of Disease on Patient Quality of Life in UC

Study and Country	Study Description	Results
Casellas et al., 2012 Spain (Casellas et al. 2012)	Multicentre prospective, observational, cross-sectional study of patients who are in stable clinical remission and having mucosal healing (n = 67 with UC). Patients completed the IBDQ-36, EQ-5D and the Daily Fatigue Impact Scale. Complete restoration of health was set at an IBDQ-36 score of at least 209 points.	82% of patients with UC “normalised” their HRQOL (e.g., achieved an IBDQ-36 score of at least 209 points). Type of treatment was not related to normalisation of HRQOL. The lack of restoration of health was significantly related to fatigue and anxiety/depression.
Hoivik et al., 2012 IBSEN study[a] Norway (Hoivik et al. 2012)	Patients with UC for a population-based inception cohort had a 10-year follow-up visit (N = 196). Patients completed the SF-36 and Norwegian IBDQ-32. Follow-up patients were recruited between October 1, 1991 and December 31, 1993, and followed for 10 years. No patients received anti-TNF inhibitors. SF-36 scores were compared with scores from a general population sample.	The SF-36 scores at the 10-year disease duration were comparable to the general population except for lower scores in the General Health dimension. SF-36 scores were significantly lower in the presence of current symptoms, in patients who used corticosteroids and in patients who reported not working. Overall N-IBDQ scores were equivalent to patients in remission. Female gender, work status (not working), current symptoms and smoking had a negative impact on HRQOL (N-IBDQ).
Lesage et al., 2011 France (Lesage et al. 2011)	Patients were recruited by the Francois Aupetit Association or a gastroenterologist (N = 2,424 IBD responders; n = 741 for UC). The same questionnaire (RFIPC) was completed by a physician and close person to the patient (both named by the patient).	Pain was the most common symptom reported; for 11% of patients with UC, the pain had been extremely intense (VAS 9 or 10 on a 10-point scale). Half of the patients with UC stated that they felt tired, whereas only 23% were having a flare-up at the time of the questionnaire (as measured by the Multidimensional MFI-20 scale). Statistically significant effects of UC as measured by the RFIPC were: Feelings about my body

		Unable to have intercourse Development of intestinal cancer Premature death Manifestations affecting the body (i.e., have the impression of being dirty or smelling bad)
Reinisch et al., 2007 ACT-1 and -2 trials[a] Multicentre in Argentina, Australia, Canada, Europe, Israel, New Zealand and the US (Reinisch et al. 2007)	Prospective analysis of the ACT-1 and -2 UC trials regarding the impact of clinical response or remission on HRQOL using the SF-36 and IBDQ (N = 728).	At the baseline visit, the mean IBDQ score was 128. In comparison with the general US population (mean, 50; SD, 10), mean overall SF-36 scores in the combined ACT-1 and -2 patient population at baseline were ~1 SD lower (PCS, 39; MCS, 41). Patients with UC in clinical response (IBDQ mean change, 47) or remission (IBDQ mean change, 65) had significantly improved IBDQ and SF-36 scores at week 30 compared with non-responders (IBDQ mean change, 12; P < 0.001 for both IBDQ and SF-36). Patients in the responder group had mean PCS and MCS scores that approached the general US population; mean scores in the remission group showed even greater normalisation.

EQ-5D, EuroQol-5 Dimensions; HRQOL, health-related quality of life; IBDQ-32, Inflammatory Bowel Disease Questionnaire 32-item; IBDQ-36, Inflammatory Bowel Disease Questionnaire 36-item; MCS, Mental Component Summary; MFI-20, Multidimensional Fatigue Inventory; N-IBDQ, Norwegian Inflammatory Bowel Disease Questionnaire; PCS, Physical Component Summary; RFIPC, Rating Form of IBD Concerns; SF-36, Medical Outcomes Study 36-item Short Form; TNF, tumour necrosis factor; UC, ulcerative colitis; US, United States; VAS, visual analogue scale.

[a] IBSEN Study, Inflammatory Bowel in South Eastern Norway study designed to describe the natural course of IBD; ACT, Active Ulcerative Colitis Trials (multicentre).

Societal Burden

UC is a chronic disorder in which the onset of symptoms usually occurs in young-to-middle aged working adults and, therefore, can impact sick leave, unemployment and work disability.

Bernklev et al evaluated the impact of working status and disability pension on HRQOL in patients with IBD using the N-IBDQ and SF-36 from 1995-1999 (n=495 patients who were working or had been working during the 5-year period since diagnosis) (Bernklev et al. 2006). Forty-two patients (8.5%) were on disability pension compared with 8.8% in the background population (1997 data from the Norwegian population in Statistics Norway). A total of 44 patients with UC (13.2%) reported they had been unemployed at 5 years, which was greater than for patients with CD. Sick leave for all causes was reported in 47% of patients with UC. Sick leave related to IBD was reported by 18% of patients with UC. The length of sick leave was recorded as ≤4 weeks or >4 weeks for the previous 6 months. Most patients with IBD (75%) had been sick for less than 4 weeks, and 25% of patients contributed to a large number of the total sick leave days (>4 weeks). Both unemployment and disability reduced N-IBDQ and SF-36 scores, but the most pronounced (clinically significant) effect on HRQOL was in patients reporting IBD-related sick leave. Multiple regression analysis confirmed that IBD-related sick leave was the independent variable with the strongest association with the observed reduction in HRQOL scores.

No UK specific cost of illness studies that evaluated the annual mean cost of UC per patient were found, but Bassi and colleagues (2004) reviewed the 6-month costs in a cohort of IBD patients (Bassi et al. 2004). This retrospective study was conducted at a single centre in Northwest England. Mean 6-month costs per patient were £1,256 (95% CI, £988-£1,721) for UC (n = 307). Inpatient services (medical and/or surgical) were required by 67 (IBD) patients (14%) but accounted for 49% of total secondary care costs. Hospitalisation, disease severity grade and disease extent correlated positively with cost of illness, but costs were independent of age or sex. Disease relapse was associated with a two- to three-fold increase in costs for non-hospitalised IBD cases and a 20-fold increase in costs for hospitalised IBD patients. Survey data suggested that average 6-month patient costs were less than £30 per patient for primary care and median loss of earnings was £239 for UC.

Clinical Management of UC in the UK

There is no cure for UC. The aim of treatment is to relieve symptoms during a flare-up and to maintain remission thereafter. Management of mildly to moderately active colitis involves treatment with oral or topical aminosalicylates (sulfasalazine, mesalazine, balsalazide or olsalazine) or corticosteroids when aminosalicylates are contraindicated or not tolerated. Oral corticosteroids or oral immunosuppressants are added if the disease does not respond to treatment with aminosalicylates. Recommended conventional treatment options may vary according to the extent and location of colitis (NICE 2013; Mowat et al. 2011). Colectomy may be considered in the event of inadequate control of symptoms and/or poor quality of patient life on conventional treatment. Ultimate goal is to avoid surgery and to manage the symptoms and complications through pharmacologic therapy. Although ileostomy or ileopouch anal anastomosis is an option for some patients, these are reserved for patients with acute severe UC who are refractory to all medical treatments. This is because, while surgical options are linked with favourable clinical outcomes, there are risks IPAA; the worst being pouch failure, a complication defined as a condition leading to the necessity of a permanent diverting ileostomy, or pouch excision (Leowardi et al. 2010). The indication of colectomy and surgical therapy in UC is usually failure of medical therapy leading to chronic active disease or fulminant colitis (Burisch & Munkholm 2013). These morbidities, combined with the need for colectomy, can have substantial psychological and psychosocial consequences for the relatively young patients with UC.

TNF Antagonists

There are three TNF antagonists licenced in the UK for UC: infliximab, adalimumab and golimumab. NICE technology appraisal guidance 163 recommends infliximab for treating acute exacerbations of severely active UC when ciclosporin is contraindicated or inappropriate (NICE 2008a); however, NICE does not recommend infliximab for treating subacute manifestations of moderately to severely active UC (NICE 2008b). NICE was unable to appraise adalimumab for treating subacute manifestations of moderately to severely active UC because the manufacturer did not provide an evidence submission (NICE technology appraisal (NICE 2012). Therefore there are currently no biologics recommended by NICE for moderate to severe patients who have failed or are intolerant to conventional therapy or TNF antagonists.

Unmet Clinical and Therapeutic Need

Conventional therapies are the mainstay of drug therapy in the UK for mild-moderate disease and although not recommended by NICE (except infliximab for acute, severe hospitalised patients), TNF antagonists have been shown to be effective for both induction and remission of moderate to severe IBD. However, conventional therapy and TNF antagonists are associated with significant failure rates (87.2% failure to achieve remission on conventional therapy as reported in a multi-centre observational study which included the UK (van Assche 2014)), whilst with TNF antagonists, a considerable portion of patients with UC will not respond to induction therapy or will lose response over time (Allen 2012; McLean LP 2012). This, coupled with their potential for serious systemic AEs (e.g., serious infections, lupus-like reactions and hematologic malignancies) leaves a need for additional treatment modalities for moderate to severe UC (Clark et al. 2007; Curtis et al. 2007; Allen 2012; McLean LP 2012). Until now, a clinician's main choices prior to considering surgery would be dose escalation of TNF antagonists or switching to another TNF antagonists. Both options have an associated cost to patients (potentially increased risk of AEs) or to the healthcare systems (increase drug cost) and there is emerging evidence of lower response rates to subsequent TNF antagonists. Vedolizumab represents the first biologic integrin receptor antagonist with a new mode of action and tolerable safety profile for moderate-severe UC patients who have failed on conventional therapy and/or TNF antagonists in the UK.

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.**

Vedolizumab (VEDO) is indicated for UC and CD in patients who have failed or lost response to conventional therapy and anti-TNF antagonists. Therefore VEDO is an option in patients as a second line or third line treatment option following conventional therapy.

The summary below will present estimate for the number of patients who would be eligible for treatment with VEDO.

According to NICE Clinical Guidelines (CG166), UC has an incidence in the UK of approximately 10 per 100,000 people annually and a prevalence of approximately 240 per 100,000. Estimates for anti-TNF use in IBD are derived from the IBD audit which provides information on clinical practise 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. No specific data was available for adalimumab or golimumab.

Table 3. Estimated eligible patient population for Vedolizumab: UC

	Ulcerative Colitis		
	Estimate	Number	Source
Number of adult in England and Wales		56,948,200	ONS 2014
Number of adults with diagnosis	0.24%	136,676	UC: NICE 166 2013
Number with moderate-severe disease	52.33%	71,523	UC: Informa UK, 2013
Number eligible for biologic therapy	6.30%	4,506	Takeda Data on File, 2013

Using similarly sourced data for VEDO's simultaneous indication in CD (NICE Clinical Guidelines CG187), the table below estimates the number of patients eligible for treatment with VEDO in CD.

Table 4. Estimated eligible patient population for Vedolizumab: CD

	Crohn's Disease		
	Estimate	**Number**	Source
Number of adult in England and Wales		**56,948,200**	CD: ONS 2014
Number of adults with diagnosis	0.20%	**113,896**	NICE CG187 Costing Template 2010
Number with moderate-severe disease	20.00%	**22,779**	CD: NICE CG187 Costing Template 2010
Number eligible for biologic therapy	51.00%	**11,617**	Takeda Data on File, 2013

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.**

It has often been debated in the literature whether or not patients with UC are at greater risk of dying compared with the general population, and whether this increased mortality can be linked with a specific cause of death. To provide clarification around this debate, Jess and colleagues (2007) (Jess et al. 2007) conducted a meta-analysis of overall and cause-specific mortality in population-based cohort studies of patients with UC. The analysis included 10 studies of UC cohorts in the United States, Europe, the United Kingdom, Sweden, Denmark, New Zealand and Italy. Standardised mortality ratios from these cohorts were pooled using random effects analysis and revealed an overall SMR of 1.1 (95% CI, 0.9-1.2) for the entire UC population (P = 0.42) indicating little difference in risk of death between the patients with UC and the general population. Data for the UK in comparison to Europe is shown below. The figure for the UK is in line with that referenced by NICE: 0.8% (NICE 2013)

Table 5. Patient Characteristics and Standardised Mortality Ratios of Select Cohort Studies in UC

Country	Study Period	Number of Patients	Observed/Expected Deaths	SMR
United Kingdom	1972-1989	1,014	92/98.3	0.9
Europe	1991-2003	792	75/67.9	1.1

SMR, standardised mortality ratio.
Source: (Jess et al. 2007)

This analysis by Jess and colleagues also found that the mean percentage of patient deaths attributed to UC was 17%. The most common causes of death were colorectal cancer (37%) and surgical or postoperative complications including perforations and peritonitis (44%). The risk of death due to respiratory disease (pooled SMR, 1.6) was significantly increased in patients with UC (p<0.001). Notably, although the risk of dying from colorectal cancer was great among patients with UC (pooled SMR, 1.9; p=0.07), the overall risk of dying from cancer was similar to that of

the general population (SMR, 1.0; p=0.78). Although the overall mortality of patients with UC did not differ from the general background population, UC-related mortality accounted for a high percentage of UC deaths, and the patients with UC exhibited a greater risk of death from respiratory and gastrointestinal diseases (Jess et al. 2007).

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 subgroups were addressed.**

The tables below provide summary recommendations published in the NICE Clinical Guideline No. 166, June 2013, 'Ulcerative colitis: Management in adults, children and young people' and British Society of Gastroenterology.

The aim of drug treatment is to induce and maintain remission, with the optimal outcome of maintaining steroid-free remission, and reduce 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. Conventional pharmacologic treatments include 5-ASAs, corticosteroids and immunomodulators (thiopurines such as azathioprine and 6-mercaptopurine).

The Guidelines provide step-wise recommendations for mild-moderate disease and acute severe UC. In the case of the former conventional therapy is the mainstay of treatment either in topical or oral form. In the case of acute severe patients, IV corticosteroids, ciclosporin or surgery are treatment options. Only in specific cases where ciclosporin is not appropriate, can infliximab be used. There are currently no specific recommendations for patients with moderate-severe disease.

Table 6. NICE Clinical Guidelines on the Management of UC in Adults[a]

Inducing Remission: Mild to Moderate UC	Inducing Remission: Left-Sided and Extensive UC	Inducing Remission: Acute Severe Colitis	Maintenance of Remission
Step 1: Therapy • Offer a topical 5-ASA, alone, OR add an oral 5-ASA to supplement the regimen depending on patient preference • Consider an oral ASA alone, taking into account the person's preferences and explaining that this is not as effective as a topical ASA alone or combined treatment • In patients who cannot tolerate ASAs, or in whom ASAs are contraindicated; offer a topical corticosteroid or consider oral prednisolone, taking into account the person's preferences Step 2: Therapy • Consider adding oral prednisolone to aminosalicylic acid therapy to induce remission in people with mild to moderate UC if there is no improvement within 4 weeks of starting step 1 ASA therapy or if symptoms worsen despite treatment	Step 1 Therapy • Offer a high induction dose of an oral ASA • Consider adding a topical ASA or oral beclometasone dipropionate taking into account the person's preferences • Oral prednisolone should be used in patients with mild to moderate first presentation or inflammatory exacerbation of left-sided or extensive UC who cannot tolerate ASAs and in whom ASAs are contraindicated OR who have subacute UC	Step 1 Therapy • For patients admitted to the hospital with severe UC, offer intravenous corticosteroids to induce remission • Consider intravenous ciclosporin or surgery for patients who cannot tolerate or who decline intravenous corticosteroids or for whom treatment with intravenous corticosteroids is contraindicated Step 2 Therapy • Consider adding intravenous ciclosporin to intravenous corticosteroids or consider surgery for people: • Who have little or no improvement within 72 hours of starting intravenous corticosteroids or • Whose symptoms worsen at any time despite corticosteroid treatment • Take into account the person's preferences when choosing treatment	Mild to moderate UC • A topical ASA (daily or intermittent) or an oral ASA plus a topical ASA (daily or intermittent) or an oral ASA alone, explaining that this may not be as effective as combined treatment or an intermittent topical ASA alone • Left-sided and extensive UC • Offer a low maintenance dose of an oral ASA; when deciding which oral ASA to use, take into account the person's preferences, side effects and cost Acute severe colitis • Consider oral azathioprine or oral mercaptopurine • Consider oral ASAs in people who cannot tolerate or who decline azathioprine and/or mercaptopurine, or in whom azathioprine and/or mercaptopurine are contraindicated

• Consider adding oral tacrolimus to oral prednisolone to induce remission in patients if there is inadequate response to oral prednisolone after 2-4 weeks • No specific recommendations on biologics are included with the exception of referring reader to NICE guidance on infliximab for acute UC (NICE HTA #140)		• For guidance on infliximab for treating acute severe UC in people for whom ciclosporin is contraindicated or clinically inappropriate, refer to infliximab for acute exacerbations of UC (NICE technology appraisal guidance 163)	

5-ASA, 5-aminosalicylic acid; HTA, health technology assessment; NICE, National Institute for Health and Care Excellence; UC, ulcerative colitis.
[a] Guidelines for paediatric patients are discussed in the guideline but not presented in this submission.
Source: (NICE 2013)

Table 7. Summary of British Society of Gastroenterology: UC Treatment Guidelines

Disease Extent/Severity	Recommendations
Active, left-sided or extensive disease	• Oral mesalazine 2.4-4.8 g daily or balsalazide 6.75 g (delivering 2.4 g mesalazine) daily is effective first-line therapy for mild or moderately active disease • Topical mesalazine combined with oral mesalazine >2 g/day is more effective than oral therapy alone for both left-sided (EL 1b, RG B) and extensive colitis (EL 1b, RG A). • Once-daily dosing with mesalazine is at least as effective as twice or three times daily regimens. • Prednisolone 20-40 mg daily is appropriate for those patients with moderately active disease in whom mesalazine in appropriate dose and route has been unsuccessful. • Prednisolone should be reduced gradually according to severity and patient response, generally over 8 weeks. More rapid reduction is associated with early relapse.
Active distal disease	• In mild to moderate disease, topical mesalazine 1-2 g daily (in appropriate form for extent of disease) may be effective alone. • Topical corticosteroids are less effective than topical mesalazine and should be reserved as second-line therapy for patients who are unresponsive to topical mesalazine. • Patients who have failed to improve on a combination of oral mesalazine with either topical mesalazine or topical corticosteroids should be treated with oral prednisolone 40 mg daily. • Topical agents may be used as adjunctive therapy in this situation (EL 1b, RG A). • In the management of proximal faecal loading associated with distal colitis, non-stimulant osmotic laxatives, such as a PEG-based preparation, are often helpful. • Refractory proctitis should prompt exclusion of alternative pathology, consideration of drug compliance, change of formulation, associated irritable bowel and further escalation of therapy.
Severe disease	• Infliximab: The patient with severe colitis refractory to maximal oral treatment with prednisone, oral aminosalicylic acids, and topical medications may be treated with infliximab 5 mg / kg if urgent hospitalisation is not necessary. • Infliximab may also be effective in avoiding colectomy in patients failing intravenous steroids but its long-term efficacy is unknown. • Consideration of colectomy or intravenous ciclosporin 2 mg/kg per day if there is no improvement during the first 3 days. • Intravenous ciclosporin alone may be as effective as methylprednisolone, but potential side effects mean that it is rarely an appropriate single first-line therapy. • IV corticosteroids (hydrocortisone 400 mg per day or methylprednisolone 60 mg per day). • Following induction of remission, oral ciclosporin for 3-6 months is appropriate. • Continuation of 5-ASAs once oral intake resumes, although these have not been studied in severe

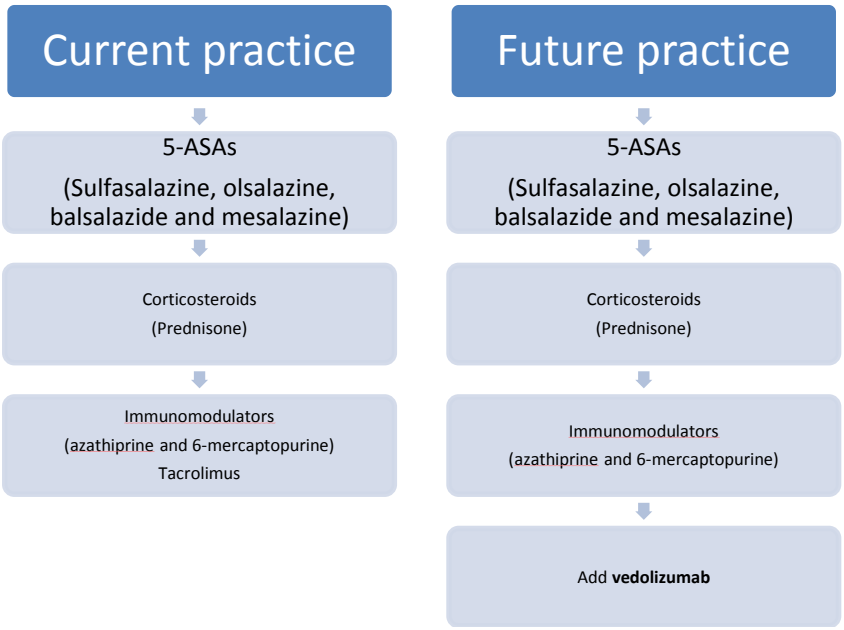
	disease. • Topical therapy (corticosteroids or mesalazine) if tolerated and retained, although there have been limited studies in acute severe disease. • IV antibiotics only if infection is considered, or immediately before surgery.
Maintenance of remission	Steroids are ineffective at maintaining remission. • Oral mesalazine 1.2-2.4 g daily or balsalazide 4.5 g daily should be considered as first-line therapy. • Topical mesalazine 1 g daily may be used in patients with distal disease with/without oral mesalazine, but patients are less likely to be compliant. • Long-term treatment with steroids is unacceptable. If steroids cannot be withdrawn, surgery should be considered. • Azathioprine 2-2.5 mg/kg per day or mercaptopurine 0.75-1.5 mg/kg per day is effective at maintaining remission in UC. These are the first-line agents of choice in steroid dependent UC. • Azathioprine is significantly more effective than mesalazine at inducing clinical and endoscopic remission in the treatment of steroid-dependent UC. • Methotrexate may be considered in the treatment of patients who do not respond to or are intolerant of thiopurines.

5-ASA, 5-aminosalicylic acid; IV, intravenous; UC, ulcerative colitis.
Source: (Mowat et al. 2011)

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 steroid-free remission, reducing ulcerative colitising 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. According to the NICE clinical guidelines, treatment for patients with mild to moderate disease should be initiated with aminosalicylates and or corticosteroids as part of 'Step 1 therapy', whilst Step 2 therapy includes the addition of tacrolimus in patients who have not responded to oral prednisone (NICE 2013). For patients who fail conventional therapy or who cannot tolerate these types of drugs, there are currently no treatment recommendations. This is where VEDO is expected to fit in the clinical pathway. As the first biologic treatment with proven efficacy and good safety and tolerability profile, VEDO will be an option for patients for whom current treatment is no longer effective or cannot be tolerated.

Figure 3. Suggested Place in Therapy for Vedolizumab in Moderate to Severe UC



With a unique licence to existing biologic treatment, vedolizumab can also be a treatment option for patients who have not responded to or cannot tolerate existing anti-TNF treatments (infliximab, adalimumab or golimumab), thus addressing an unmet need for this subpopulation of patients.

Despite the lack of NICE recommendation for anti-TNF therapy patients with moderate to severe patients, clinical practice would suggest that 56% of patients are treated with anti-TNF therapy for acute severe UC and up to 39% for chronic refractory UC (Royal College of Physicians 2013). The report also notes that in the follow-up phase 7% of patients stop infliximab treatment for reason of loss of or poor response and AEs; 15% stop taking adalimumab, however the reasons for this are not reported.

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

Current acceptable therapy for moderate to severe UC is conventional treatment with corticosteroids and immunomodulators (NICE 2013). Anti-TNF drugs have recently become available with infliximab being the first licenced biologic for UC and golimumab being the most recent addition to the armamentarium of UC treatment. Whilst these treatments are effective for many patients there are many limitations. The evidence presented below will show that a large percentage of patients experience a significant failure rate on conventional therapy and TNF antagonists, highlighting the need for alternate treatments with proven efficacy, tolerable safety profile and with a unique mode of action.
In the UK patients with UC are disadvantaged as there is currently no alternative treatment option for patients with moderate to severe (non-systemic) disease failing conventional treatment.

Issues relating to current clinical practice

A number of key issues related to current clinical management of UC are described here:

- Failure of conventional therapy
- Challenges of surgical intervention
- Difficulties associated with anti-TNF drugs
- Uncertainties regarding best practice

2.6.1 Failure on conventional therapy

According to the observational, multicentre cross-sectional UC CARES study (van Assche 2014), which includes patients from the UK, 63.2% of patients receive thiopurines, 75.2% aminosalicylates, 23.6% corticosteroids, 8.8% gastrointestinal drugs and 3.6% 'other' immunosuppressants. The study revealed high levels of treatment failures: 87.2% failed to achieve disease control (i.e. maintaining remission status) and 46.8% were not satisfied with their current UC treatment.

Aminosalicylates (sulfasalazine, mesalamine, olsalazine and balsalazide) are considered first-line therapy for mild to moderate UC and they are not effective in severe IBD (McLean LP 2012). Aminosalicylates are associated with approximately a 50% remission rate in UC; therefore, escalation to other modalities is often needed (McLean LP 2012).

The thiopurine immunosuppressants 6-MP and azathioprine are often used for maintenance therapy in patients not responding to aminosalicylates (McLean LP 2012). Thiopurines cannot be used for induction therapy due to their very slow onset of action and potentially serious AEs: toxic hepatitis, pancreatitis, opportunistic infections, and a four-fold increased risk of lymphoma.

Corticosteroids effectively reduce remission in UC, with response rates between 45% and 90% in UC (McLean LP 2012). However, approximately a third of patients do not respond to steroids. Among those who do respond, one third develop steroid dependence and up to one third of patients develop steroid refractory disease, considered to be treatment failure. Chronic corticosteroid use causes hypertension, glucose intolerance, glaucoma, cataracts, poor wound healing, opportunistic infections and osteoporosis (Dignass et al. 2012). Other agents used in refractory patients are cyclosporine and methotrexate, both of which have poor safety profiles (McLean LP 2012).

2.6.2 Challenges associated with surgical intervention in UC

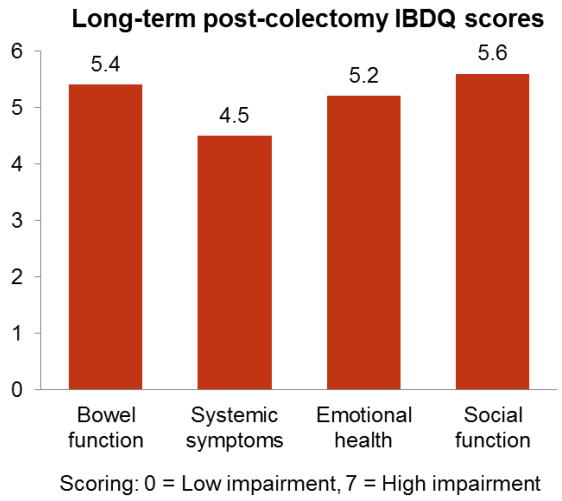
When all medical treatment options have been exhausted, patients with intractable or badly controlled UC may undergo colectomy (removal of a section of the affected part of the colon). Although there is an overall trend of decreasing rates of colectomy, about 40% of patients with UC will eventually require surgery (Solberg et al. 2009). However, surgery is usually a last resort for clinicians and patients due to the

potential for serious sequelae: bleeding, faecal incontinence, depression, sexual dysfunction, female infertility, pouchitis, pouch leakage, pelvic abscesses, pouch fistulae, small bowel obstruction and anastomotic stricture (Ochsenkühn & D'Haens 2011).

- In a study by Leowardi and colleagues (2010), 37 of 294 patients (12.6%) who underwent IPAA experienced pouch failure, while 15 patients (5.1%) had their pouch excised and 22 (7.5%) had a diverting ileostomy (Leowardi et al. 2010). The median time between operation and pouch failure was 4.5 years. In a Kaplan-Meier analysis, the pouch failure rate was 7.7%, 11.3% and 15.5% at 5, 10, and 15 years, respectively (Leowardi et al. 2010).
- Retrospective analyses have shown that within 1 month following closure of ileostomy, 27% of patients develop at least one complication, with pouchitis being the most common type of complication (reports of >1 in 4 of all patients with IPAA) and global pouch failure rate of 5%. Further, more than half of patients with IPAA had between 5 and 10 bowel movements per day, and soiling or seepage at night was reported by 15% to 25%. Around one third of patients reported an ongoing need for continuous or occasional IBD-related medication (Ochsenkühn & D'Haens 2011)
- A recent meta-analysis of seven studies indicated that IPAA increased the rate of infertility from 15% to 48%. Further, an online survey of 424 patients revealed that two thirds of women reported difficulty conceiving post-surgery and 31% said their sexual life was worse after surgery compared with before surgery (Ochsenkühn & D'Haens 2011).
- IPAA-induced pouch failure and ileostomy can dramatically and negatively impact HRQOL.
    - Using the GIQLI, Leowardi and colleagues (2010) noted that the median score of patients with a functioning pouch (n = 182) was significantly higher (i.e. better QOL) than those who required ileostomy (n = 15) (108 vs. 94; P = 0.05). Patients with an ileostomy also scored significantly lower on both physical function (17 vs. 11; P = 0.003) and social function (14 vs. 12; P = 0.02) compared with patients with a functioning pouch.
    - Based on the results of 424 patients across three countries (Australia, Canada, UK), the Long-term Impacts of Colectomy Surgery among Ulcerative Colitis Patients (LOCUS) study using the IBDQ instrument

showed high degrees of impairment and impact on the patient's QOL (Brown et al. 2013).

- Specifically, patients reported inferior sense of body image, increased dietary limitations, impaired sexual functioning (particularly in women), reduced fertility in both men and women and the need for ongoing bowel-related medication.
- In comparison to the general population, there was a reduced mean health-status utility (preference) score on the EQ-5D.
- One third of patients with moderate to severe UC report decreased work productivity post colectomy.
- Among patients currently working and who reported being less productive post-surgery, 6.8% reported time missed from work due to health issues in the previous month.



2.6.3 Failure on Anti-TNF therapies

Despite their efficacy compared with conventional treatments, between 20% and 40% of patients with IBD will not respond to induction therapy with TNF antagonists (i.e., primary non-response/failure) or will lose response to TNF antagonists over time (i.e., secondary non-response/failure) (Allez et al. 2010; Yanai & Hanauer 2011; Allen 2012; McLean LP 2012).

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 2010). 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 (see 2.6.3.1) (Wu et al. 2008; Gisbert & Panés 2009; Molnár et al. 2012; Pariente et al. 2012).

Evidence from the key pivotal studies for TNF antagonists is summarised in the table below. In each study, eligible patients had active disease and had inadequate response or failure to tolerate >1 types of conventional therapy (including 5-aminosalicylates (5-ASAs), corticosteroids, immunosuppressives (azathioprine or 6-mercaptopurine). In general, between 35% and 49% of patients with refractory UC who had not responded to conventional therapy failed to demonstrate an initial response to one of the three currently available TNF antagonists; 50%–56% did not show a clinical response at week 54.

VEDO is the first biologic therapy to be studied in patients who were primary non-responders to TNF therapy (Feagan et al. 2013). All pivotal studies of anti-TNF drugs included only patients who were naïve to treatment with a biologic agent (see table below) with the exception of the ULTRA2 adalimumab study (Sandborn 2013a), which included patients who may have experienced prior TNF antagonists. However, in ULTRA2, prior anti-TNF agents other than adalimumab was permitted provided that the patient had discontinued its use due to a loss of response or intolerance to the agent for longer than 8 weeks, i.e. ULTRA2 excluded patients with primary non response or treatment failure.

Table 8. Response and Remission Rates With TNF Antagonists

Treatment	Time Point	Response Rate*	Remission Rate†
Infliximab (Remicade) (Rutgeerts 2005; Janssen Biologics B.V 2013)			
5 mg/kg at Weeks 0, 2, 6 and every 8 weeks thereafter	Week 8	65%-69%	34%-39%
	Week 30	47%-52%	26%-34%
	Week 54	45%	35%
	Weeks 8 and 30 (sustained)	41%-49%	15%-23%
	Weeks 8, 30 and 54 (sustained)	39%	20%
10 mg/kg at Weeks 0, 2, 6 and every 8 weeks thereafter	Week 8	62%-69%	28%-32%
	Week 30	51%-60%	36%-37%
	Week 54	44%	34%
	Weeks 8 and 30 (sustained)	46%-53%	23%-26%
	Weeks 8, 30 and 54 (sustained)	37%	20%
Adalimumab (Humira) (Reinisch et al. 2011; Sandborn et al. 2012; AbbVie Ltd 2014)			
160 mg at Week 0 and 80 mg at Week 2 followed by 40 mg every other week	Week 8	---	16.5%-18.5%
	Weeks 8 and 52 (sustained)	---	8.5%

Golimumab (Simponi) (Sandborn 2013; Sandborn et al. 2014; Merck Sharp & Dohme 2013)			
200 mg at week 0 and 100 mg at week 2 then 100 mg every 4 weeks	Week 6	52%	19%
	Week 54	51%	---
	Weeks 30 and 54 (sustained)	---	29%
100mg or every 4 week (responders to induction therapy)	Week 54	49.7%	---
	Weeks 30 and 54 (sustained)	---	27.8%
*** Clinical response was defined as a decrease from baseline in Mayo score by ≥30% and ≥3 points, accompanied by a decrease in the rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1.** **† Clinical remission was defined as a Mayo score ≤2 points with no individual score >1.**			

2.6.3.1 Dose escalation or TNF cycling

In patients who are intolerant to or lose response to anti-TNFα therapies, current clinical practice suggests that patients cycle through the available anti-TNFα treatments trialling successive anti-TNFα therapies where adequate response to the prior treatment was not observed (IBD Audit 2014). This practice is potentially flawed, because a patient who fails one anti-TNFα is more likely to fail subsequent trials of drugs with the same mechanism of action. Therefore, TNF-cycling may have limited utility from the patient's perspective. Further, there is a lack of empirical evidence characterising the nature and outcomes associated with TNF cycling.

Information regarding cycling and dose escalation comes from four sources, two of which were initiated by Takeda:

- Systematic literature review.
- UK survey of current expert clinical opinion on treatment patterns, outcomes and unmet medical need in people with UC treated with biologic therapy.
- UK IBD audit.
- US audit.

Literature review (Takeda, data on file 2014)

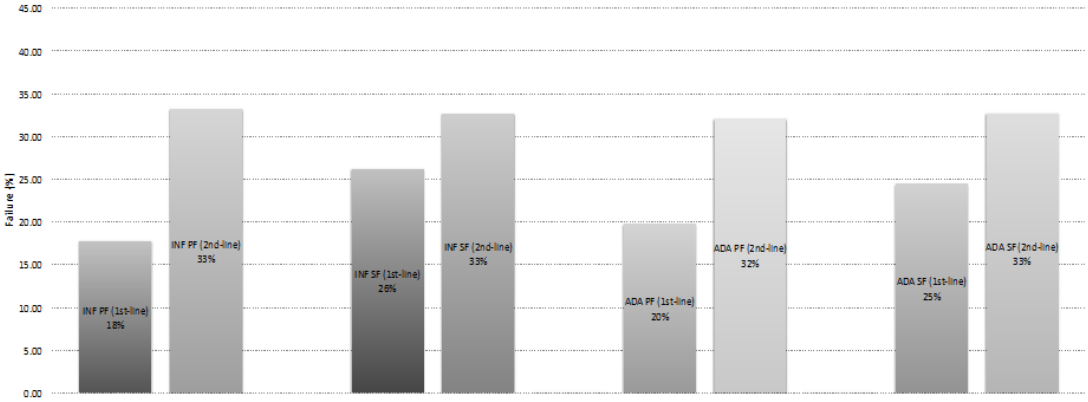
- The majority of the studies reviewed assessed infliximab as first-line therapy.
- Rate of failure with first-line anti-TNF therapy was due to primary failure and loss of response (LOR), and resulted in dose escalation or switching to subsequent line of therapy.
- Definitive conclusions around differences in the rates of failure between first-line and second-line therapy were difficult to achieve given the wide range in reported values and heterogeneity between studies:

- Rate of primary failure ranged from 19% to 58.3% with first-line infliximab therapy, and to 52.4% for second-line therapy.
- Loss of response (secondary failure) ranged from 16.7% to 22.2% with first-line infliximab therapy (Gies 2010) and to 43.3% with second-line adalimumab therapy (higher than first-line infliximab therapy).
- Rate of dose escalation and switching with first-line infliximab therapy ranged from 18.9% to 40%, and switching of anti-TNFα therapy was associated with a range from 7.7% to 16.7%.
- Rate of dose escalation ranged from 35% to 46.2% with second-line adalimumab therapy.

UK expert survey

- To inform gaps in the published literature identified in the systematic review, and to cross-validate the findings of the systematic literature review, a cross-sectional survey elicited expert clinical opinion among gastroenterologists practising in a secondary care setting in the UK.
    - Failure rate (primary and secondary) with a second-line biologic was consistently higher that the rate of failure with first-line biologic (Figure 4).
    - Primary and secondary failure rates were higher with infliximab compared with adalimumab when used as either a first-line or second-line therapy (Figure 4).
    - The results of the systematic literature review and clinician surveys were complementary and indicate there is a need for other treatment options, especially after first-line anti-TNFα failure, to improve the management and outcomes for people with CD. The practice of TNF cycling may be a direct consequence of the limited number of treatment options currently available.

Figure 4. First- Versus Second-line Treatment Failure in UC Patients



US database analysis

- Data available from a US claims database study (2006–2010) for patients experiencing treatment change or discontinuation during a 12-month post-index period reveal high rates of failure (see Table below) (Rubin DT, Mody R, Wang E 2012)
- The label indication and dosing regimens are the same in the US and in the UK; therefore this study provides some indication of clinical practice with respect to dose escalation (referred to as upward titration) as well as switching to other treatments.
- As many as one in two patients undergo dose escalation (augmentation) in a 12-month period.

Table 9. Patients experiencing treatment change or discontinuity over a 12-month post-index period (US claims database study 2006-2010)

Treatment change over 12 months[4]	5-ASA (n = 13,783)	CS (n = 5,455)	IM (n = 473)	Adalimumab (n = 38)	Infliximab (n = 128)
Discontinuation or interruption (%)	50.5	N/A	0.0	0.0	13.3
Upward titration (%)	20.4	36.8	7.8	5.3	28.9
Augmentation (%)	20.9	41.1	59.4	55.3	33.6
Switch (%)	5.8	N/A	8.5	10.5	9.4

(Rubin DT, Mody R, Wang E 2012)

2.6.3.2 Safety Concerns with Anti-TNF Therapy

- The currently available biologics indicated for UC are associated with broad systemic immunosuppressive effects. TNF antagonists are associated with a number of serious systemic AEs including serious infections, lupus-like reactions, psoriaform eruption and hematologic malignancies (Clark et al. 2007; Curtis et al. 2007; McLean LP 2012).

- Although the systematic reviews confirming efficacy of the class as induction and maintenance treatment have not identified an increased risk of serious AEs with TNF antagonists, the study size and duration were generally insufficient to allow an adequate assessment of serious AEs associated with long-term use (Behm BW & Bickston SJ 2009; Dretzke et al. 2011).
- Additionally, a meta-analysis exploring the risk of serious infection and malignancy associated with TNF antagonist therapy in rheumatoid arthritis found an increased risk of serious infection and a dose-dependent increased risk of malignancy with TNF antagonists (Bongartz et al. 2006).
- The failure rate for patients receiving TNF therapy, coupled with the potential for serious systemic AEs, suggests a need for additional treatment modalities with a new mode of action for the treatment of moderate to severe IBD.

2.6.4 Uncertainty regarding best clinical practice

The UK IBD audit may also provide evidence that the NICE CGs for UC are not necessarily translated into clinical practice despite the guidelines being recently published. The audit shows that TNF antagonists are being used following failure of conventional therapy in patients with acute disease and in chronic refractory patients; adalimumab appears to be used as a second TNF agent after treatment with infliximab (Royal College of Physicians 2013).

2.6.4.1 UK IBD Audit (Royal College of Physicians 2013)

- The first full national audit report of the biological therapy (which included patients newly started on biological therapies between 12 September 2011 and 28 February 2013 (n=141 with UC) provides a picture of efficacy, safety and appropriate use of infliximab and adalimumab in the UK.
- It recorded information on initial anti-TNF treatment as well as follow-up treatment.
- At the time of the decision to start biologic therapy, between 95% and 100% of patients had left-sided or extensive disease and at least 94% had no IBD related surgery.
- In patients for whom data are available on previous treatments (n=112 infliximab and n=18 adalimumab), 40% of patients receiving infliximab and 67% of patients receiving adalimumab had discontinued previous treatment (50%-82% had received prior immunosuppressant, 17%-22% had received 5-ASA and up to 27% had received prednisolone). The reason for discontinuing

previous treatment included lack of response (20%–30%), loss of response (8%–17%), and intolerance to treatment (35%–45%).

- Initial dose of infliximab was 5mg/kg (the recommended induction dose), while for adalimumab most patients (89%) received a higher induction dose of 160mg or 180mg. Most patients received concomitant medication including conventional therapies. In the follow-up phase, 15% of patients had stopped treatment with infliximab and 15% had stopped treatment with adalimumab. Reasons for discontinuing infliximab included loss of response (3%), poor response (23%) and AEs (23%). No reasons for discontinuing treatment with adalimumab are provided. 91% of patients received 40mg every other week as their maintenance dose.

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

The relevant main comparator is standard of care, comprising 5-ASAs, corticosteroids and immunomodulators. This reflects the baseline therapies in the GEMINI I trial (Feagan et al. 2013) and is supported by current NICE clinical practice guidelines and UK IBD patient audit data. In the GEMINI I trial, patients received VEDO or placebo in addition to 5-ASAs, corticosteroids and immunomodulators, therefore the placebo arm of the GEMINI I trial represents standard of care and is the main comparator presented in this submission.

In addition, supplementary comparisons with adalimumab, infliximab and golimumab are presented because these treatments are regulatory approved with the same indication as VEDO (see Table 10.) At present, NICE only recommend infliximab for acute severe patient, but UK IBD audit data demonstrate the use of both infliximab and adalimumab for patients who have failed on conventional therapy. As a recently approved treatment, no data are available on golimumab through the UK IBD audit (2013) (Royal College of Physicians 2013).

Table 10. Summary of the UK label Indication for the Biologics in UC

Biologic	Licenced Indication	NICE Recommendation
Infliximab	Remicade is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.	TA 163 (2008): NICE recommends Infliximab as an option for the treatment of acute exacerbations of severely active UC only in patients in whom ciclosporin is contraindicated or clinically inappropriate. TA140 (2008): Infliximab is not recommended for the treatment of subacute manifestations of moderately to severely active UC.
Adalimumab	Humira is indicated for treatment of moderately to severely active UC in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.	TA262 (2012): NICE is unable to recommend the use in the NHS of adalimumab for the treatment of moderate to severe UC because no evidence submission was received from the manufacturer or sponsor of the technology.
Golimumab	Simponi is indicated for treatment of moderately to severely active UC in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.	In progress as part of Multiple Technology Appraisal
Vedolizumab	Entyvio is indicated for the treatment of adult patients with moderately to severely active UC who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist.	**In progress**

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

In the combined studies of UC and CD 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. (Takeda Pharma A/S 2014)

Infusion-related reactions were reported in 4% of patients receiving VEDO. Most infusion-related reactions occurred within the first 2 hours. Of those patients who had infusion-related reactions, those dosed with VEDO 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 VEDO 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 VEDO, in order to minimise risk of recurrence. (Takeda Pharma A/S 2014)

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

VEDO treatment should be initiated and supervised by specialist healthcare professionals experienced in the diagnosis and treatment of UC. VEDO 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 VEDO will be a secondary care delivered product.

Monitoring requirements

The following monitoring requirements are specified in the Summary of Product Characteristics for vedolizumab:

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 VEDO, 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 VEDO for any new onset or worsening of neurological signs and symptoms for PML, and should consider neurological referral if they occur**.**

Staff usage and costs

Other than the routine monitoring outlined above, no additional resource use is anticipated.

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

There is no need for additional infrastructure to be put in place for VEDO as the NHS currently uses biologic therapy to treat UC.

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 licensed;
- 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

4.1.1	**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.**

Vedolizumab (VEDO) is the first integrin receptor antagonists indicated for the treatment of moderate to severe UC patients. It binds specifically to the α4β7 integrin, which is preferentially expressed on gut homing T helper lymphocytes, and modulates inflammation at the site of UC lesions (Takeda Pharma A/S 2014). 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 (Janssen Biologics B.V 2013; AbbVie Ltd 2014; Merck Sharp & Dohme 2013). The benefit with VEDO is that because it is gut-specific action, the chance of extra-intestinal effects is very low.

The unique and different mechanism of action of VEDO translates into a significant step forward in the management of IBD. Current existing therapies whilst effective are associated with concerns on safety and limited efficacy. Conventional therapies, which are the main type of pharmacological treatment in the UK, are associated with poor effectiveness in real world data with up to 87.2% of patients failing to achieve disease control and almost half expressing dissatisfaction with their conventional therapy (van Assche 2014).

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/failure) or will lose response to TNF antagonists over time (i.e., secondary non-response/failure) (Allez et al. 2010; Yanai & Hanauer 2011; McLean LP 2012; Allen 2012). In general, between 35%- 49% of patients with refractory UC who have not responded to conventional therapy may fail to demonstrate an initial response to one of the three currently available TNF antagonists and 50%-56% did not show a clinical response at week 54 (see table 8). Strategies used to overcome issues of loss of response include dose escalation or augmentation of anti-TNF therapy or switching treatment. Internationally, rates of

dose escalation and switching with first-line infliximab therapy ranged from 39% to 42% and 17% to 53%, respectively, while rate of dose escalation ranged from 35% to 46% with second-line adalimumab therapy (Takeda Data on File, 2014). Therefore, new agents with novel mechanisms of action that have good efficacy and tolerability are needed to improve management of UC.

VEDO has a different MOA from the anti-TNF drugs, which has implications for tolerability. Avoiding adverse events specifically associated with anti-TNF drugs may help reduce costs associated with these drugs.

VEDO is effective when directly compared with placebo at achieving clinical remission (41.8% versus 15.9%) and durable clinical response (56.6% versus 23.8%), at 52 weeks, in UC patients who have failed conventional therapy(Feagan et al. 2013).

The benefits of VEDO in UC are the ability to induce clinical response, remission and mucosal healing in patients who have failed prior TNF antagonist therapy as well as those with no prior TNF antagonist exposure. Therefore VEDO is clinically effective in all patients who have failed conventional therapy independent of whether they have failed anti-TNFs or not. This evidence from the GEMINI I study supports the licence indication for use in patients who have failed/intolerant to anti-TNF therapy, making VEDO the only licensed treatment in this subgroup of patients.

In UC, VEDO has shown a similar rate of adverse events compared with placebo. The rate of adverse events (80%) was similar in patients treated with VEDO or placebo and discontinuation rates due to AEs are 6% for VEDO versus 11% for placebo. Infection rates for VEDO vs. placebo are 1.9% vs. 2.9% (Feagan et al. 2013).

Takeda UK considers VEDO innovative defined by its unique mechanism of action and published data outcomes for efficacy and safety in its potential to make a significant and substantial impact on health-related benefits and address current unmet need.

4.1.2	**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.**

UC has a clinically meaningful, negative impact of HRQoL, which can be at least partly reversed by treatment. This featured in the QALY calculation as presented in section 7. Additionally, successful management of UC symptoms and prolongation of remission may have societal benefits that are less straightforward to calculate but that may increase the value of VEDO for the treatment of moderate to severe UC.

Although there are very limited 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 UC symptoms demonstrated in GEMINI I (see section 6.3).

Employment

Several studies have shown that UC (or undifferentiated IBD) has a direct impact on employment status and opportunities in Europe (including the UK) (Büsch et al. 2014; Brown et al. 2013; Reinisch et al. 2007). This can be expected to have a range of personal, social and business implications, from impaired QoL to indirect economic burden (e.g. (Bernklev et al. 2006).

- A recent systematic review of 30 non-interventional and 17 interventional studies of IBD overall or CD or UC specifically, revealed low but variable employment rates compared to otherwise healthy age- and sex-matched controls: up to half those of a non-IBD cohort (Büsch et al. 2014). Additionally, the authors observed that 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.
    - It is worth noting that employment rates were similar between patients with IBD and age- and sex-matched people with other chronic conditions. Takeda believes that any opportunity to reduce the burden of chronic diseases to the UK health and general economy is to be valued.

- The LOCUS study of 424 patients with UC undergoing colectomy in Australia, Canada and the UK revealed that a third of patients with moderate to severe disease experienced reduced work productivity following surgery (Brown et al. 2013). Another study of patients undergoing colectomy for UC in Sweden reported the mean number of work days lost annually increased dramatically from 40 days before to 141 in the year after surgery (Neovius et al. 2013).Therefore, options to delay the time to surgery, such as VEDO, can bring a clear value to patients, healthcare systems and employers.

- Reinisch et al (2007) reported that clinical response and remission induced by infliximab not only improved QoL but resulted in a return to employment in 20% compared with 8% not in remission ($P<0.05$) (Reinisch et al. 2007). There was also a statistically significant difference in the percentage of patients not requiring disability compensation (58.8% of those in remission compared with 20% of those not in remission, $P<0.05$).

- In the UK, a small study of 54 adult patients with UC revealed that 31% of participants were absent from work for a total of more than 6 months in the previous year due to their disease (Dorrian et al. 2009). According to Bassi et al, in the early 2000s, the median 6-month loss of earnings for a patient with IBD in the UK was £299 (Bassi et al. 2004).

- In a 2013 editorial by Dr Tine Jess, the need to help patients with UC stay in the workplace was highlighted in the context of increased financial burden on disability pension provision (Jess 2013) . Although the specific situation under discussion referred to Scandinavian countries, there is an opportunity in England and Wales to reduce costs associated with workplace absenteeism, disability and early retirement by improving the management of UC and associated patient wellbeing (Reinisch et al. 2007).

Birth outcomes and fertility

- An extensive study of published data revealed that conventional treatments (5-ASA, immunosuppressants) were associated with an increased risk of adverse birth outcomes: low birth weight, pre-term births, still birth and/or congenital abnormalities (Nørgård 2011). There was also an indication that newly-diagnosed UC itself could increase the risk of pre-term birth, possibly related to symptoms during pregnancy.

- Female infertility may be a negative consequence of surgery, whereas male fertility appears to be largely unaffected by IBD drugs. On the other hand, in women, well-controlled IBD appears to have no effect on fertility (O'Connor et al. 2010).

Impact on carers

- Two studies in southern Europe (Greece and Portugal) reveal that carers of patients with IBD (CD or UC) experience high levels of emotional and physical distress (Magro et al. 2009; Argyriou et al. 2014). 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).

- In the context of this submission for reimbursement, the independent study by the Portuguese Group of Studies of IBD (Magro et al. 2009) reported that both patients and their carers considered that information about new drugs and contact time with the physicians would have the greatest impact on improving care.

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

The evidence for benefits of VEDO with respect to improvement in HRQoL is presented in section 6.

5 Statement of the decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	Adults with moderately to severely active UC (excluding those with acute severe UC that is a medical emergency and requires inpatient treatment) who are intolerant of, or whose disease has had an inadequate response or loss of response to conventional therapy (immunosuppressants and/or corticosteroids) or a TNF-alpha inhibitor.	Adult patients with moderately to severely active UC who are intolerant of, or whose disease has had an inadequate response or loss of response to conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist. This population is in line with the VEDO label and the pivotal study, GEMINI I	
Intervention	Vedolizumab	Vedolizumab	
Comparator(s)	Established clinical management without VEDO, which may include a combination of aminosalicylates (sulfasalazine, mesalazine, balsalazide or olsalazine), corticosteroids (beclometasone, budesonide, hydrocortisone or prednisolone), thiopurines (mercaptopurine or azathioprine), calcineurin inhibitors (tacrolimus or ciclosporin), TNF-alpha inhibitors (infliximab, adalimumab or golimumab) and surgical intervention	The comparators addressed in the submission include conventional therapy, as defined in the GEMINI I study and those used in UK clinical practice based on the UK IBD audit; and TNF-alpha antagonists licensed in the UK for UC (infliximab, adalimumab and golimumab).	**Surgical intervention is not included** as a comparator but rather as an outcome to avoid in UC. Surgery is generally reserved for patients with severe disease not amenable to medical management, those intolerant to medical therapies, or those with certain disease-related complications (McLean 2012; Ford 2013). In the GEMINI study (Feagan 2013), only patients with an additional eligibility criterion was documentation of unsuccessful previous drug treatment (i.e., lack of response or unacceptable

			adverse events) with one or more glucocorticoids, immunosuppressive medications (i.e., azathioprine and 6-mercaptopurine), or TNF antagonists. Patients were also excluded if there was an anticipated requirement for major surgery. Therefore we do not consider surgery to be a relevant comparator as there is a difference in the patient population who would be considered eligible for VEDO compared with surgical intervention. A further reason for exclusion of surgery as a comparator is the availability of comparable evidence to VEDO. Similarly to other appraisal in UC, surgery could not pragmatically be compared with drug therapy.

Outcomes	The outcome measures to be considered include: • mortality • measures of disease activity • rates of and duration of response, relapse and remission • rates of hospitalisation • rates of surgical intervention • time to surgical intervention • adverse effects of treatment (including leakage and infections following surgery) • Health-related quality of life.	The outcome measures to be considered are in line with the final scope.	
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 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. The availability of any patient access schemes for the comparator technologies should be taken into account.	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 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. The base is in line with the NICE reference case.	

Subgroups to be considered	If evidence allows following subgroups will be considered: • People who have been previously treated with one or more TNF-alpha inhibitors and people who have not received prior TNF-alpha inhibitor therapy	Analyses in various pre-specified subgroups of GEMINI I patient population will be presented including • anti-TNF naïve population • anti-TNF failure population • mixed population (includes both anti-TNF naïve and anti-TNF failure patients, representing the ITT population of the GEMINI I trials)	

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.**

The clinical evidence on VEDO was derived through a systematic review performed to inform a mixed treatment comparison of the efficacy and safety of VEDO and the TNF antagonists. In this section, we describe the strategies used to retrieve the relevant VEDO clinical data from published and unpublished data. In section 6.7 we present results relating to the TNF antagonists.

The objective of the systematic review was to collate the published randomised controlled trials (RCTs) data assessing the efficacy and safety of biological therapies prescribed for the treatment of UC. In terms of PICOS (participants, interventions, comparisons, outcomes, and study design), the patient group of interest is those with moderate to severe UC, and the intervention of interest is VEDO; comparators are the available biologics, and outcomes are key efficacy and safety outcomes.

The systematic review was conducted in line with Cochrane methodology and following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) recommendations, according to the protocol developed in April 2013. In May 2013, the protocol was amended to also capture the published clinical data assessing the efficacy and safety of surgery and ciclosporin for the treatment of UC. An updated protocol was developed in February 2014 and was then used to conduct an update of the systematic review for the purpose of this appraisal.

The search strategy 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

For the update of the review, the same databases were searched.

Internet and Other Sources

For the original review, the website 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 Organisation's International Clinical Trials Registry Platform Search Portal (http://apps.who.int/trialsearch/)

Although searching of United European Gastroenterology (UEG) Week was included in the protocol; it was not possible due to technical difficulties with the website which were not addressed by the UEG within our timeline.

Bibliographic reference lists of identified systematic reviews and meta-analyses were reviewed for relevant publications.

For full details of the search strategy, search terms, data extraction and date span for the biologics literature search are presented in section 10.2, Appendix 4

As mentioned above, in this section 6.1, we describe the strategies used to retrieve the relevant clinical data from published and unpublished data for VEDO in UC and the results of the search with respect to VEDO. The results for the remaining comparators will be presented in section 6.7 as part of the indirect comparison section.

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.**

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 independently by two 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 two 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.

Inclusion and Exclusion Criteria

The tables below present the inclusion and exclusion criteria for level 1 and level 2 screenings, respectively.

Table 11. List of Criteria for the Inclusion and Exclusion of Studies During the Level 1 Screening Process

Criteria	Included	Excluded
Study design	• Randomised, controlled, prospective clinical trials • Nonrandomised, controlled clinical trials • Long-term follow-up studies (e.g., open-label follow-up of randomised 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 UC (both treatment naïve and treatment experienced)	• Patients who do not have UC
Interventions	• Biologics search: • VEDO • Infliximab (Remicade) • Adalimumab (Humira) • Golimumab (Simponi)[b] • Additional search: • Surgery (of any type)[c] • Ciclosporin[d]	• Studies that do not investigate one of the biologics of interest in at least one of the arms
Outcomes	• None	• None: the studies will not be excluded on the basis of outcomes at the level 1 screening process

UC, ulcerative colitis.

a Systematic reviews and meta-analyses will be used for identification of primary studies.

b Golimumab was not included as part of the initial screening in the original review, but was added for the update.

c Terms for surgery included in the searches: colectomy, proctocolectomy, colonic pouch, ileostomy, ileal pouch anastomosis, ileoanal pouch anal anastomosis, IPAA, Koch pouch, continent ileostomy, Brooke ileostomy, ilcorectal anastomosis, ileorectal anastomosis.

d At the time of the original review, ciclosporin was also considered relevant and was included in the update searches to ensure that the update is comparable with the original review, but it was not included as part of the initial screening.

Table 12. List of Criteria for the Inclusion and Exclusion of Studies During the Level 2 Screening Process

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 level 1 criteria with the addition of systematic reviews and meta-analyses: • 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 UC (both treatment naïve and treatment experienced)	• Patients who do not have UC
Intervention	• Same as the level 1 criteria: • Biologics search: • VEDO • Infliximab (Remicade) • Adalimumab (Humira) • Golimumab (Simponi)b • Additional search: • Surgery • Ciclosporin	• Same as the level 1 criteria: • Studies that do not investigate one of the biologics of interest in at least one of the arms
Outcomes[a]	• Clinical response (with timing and definition) • Sustained clinical response (with timing and definition) • Durable clinical response (with timing and definition) • Clinical remission (with timing and definition) • Durable clinical remission (with timing and definition) • Mucosal healing (with timing and definition) • Safety outcomes (AEs, SAEs, specific AEs of interest) • Quality of life outcomes, including IBDQ • Surgery • Hospitalisations • Change in Mayo score from baseline • Mean Mayo at baseline and each subsequent visit • Additional surgery search: • Surgical outcomes • Surgical complications	• None • For IBD articles, exclude if IBD results not broken down into CD and UC

AE, adverse event; CD, Crohn's disease; IBD, irritable bowel disease; IBDQ, Inflammatory Bowel Disease Questionnaire; SAE, serious adverse event; UC, ulcerative colitis.

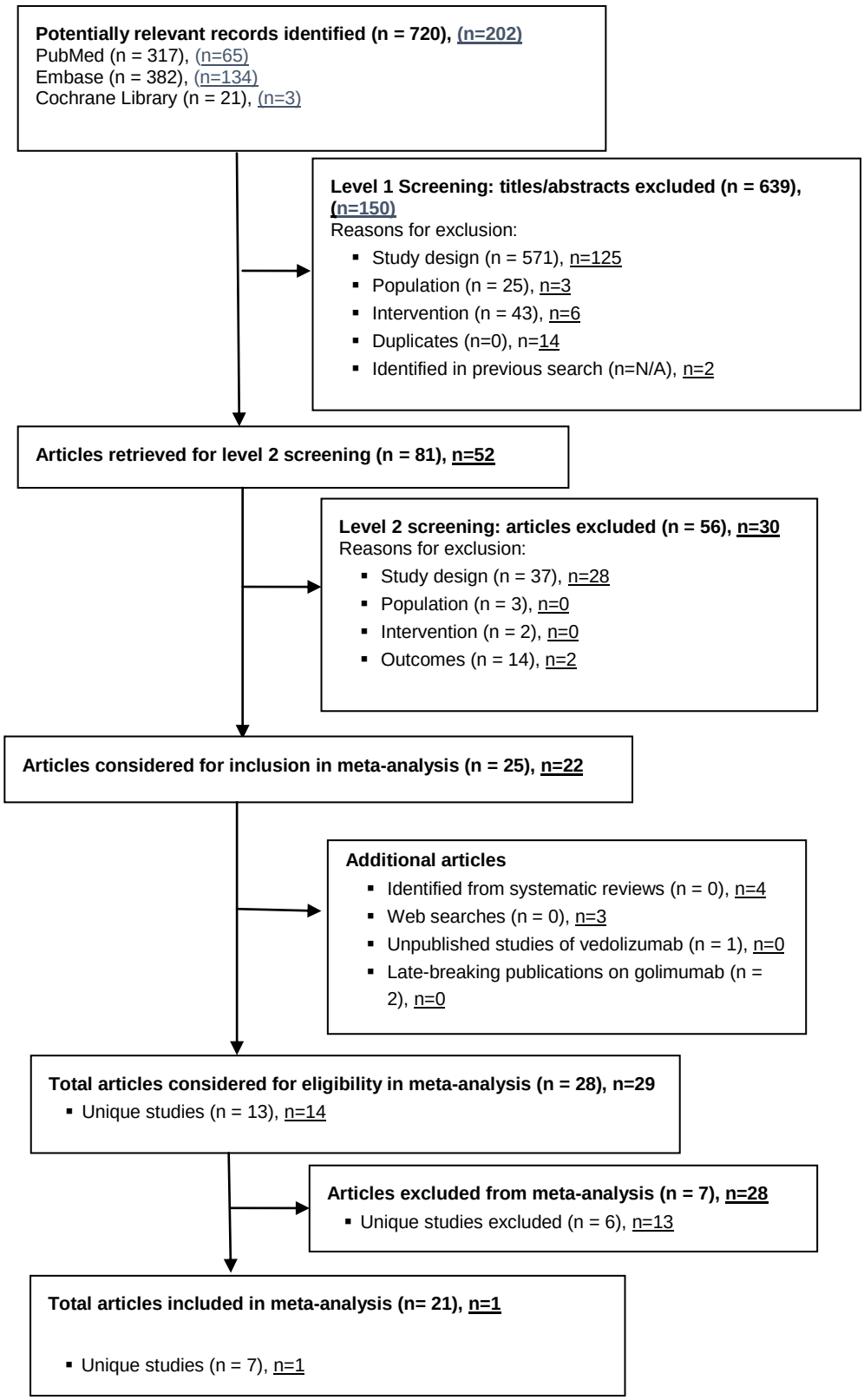
a Outcomes to be included were finalised following RTI Health Solutions' review of the clinical study reports. As definitions of response, remission, and mucosal healing, along with the timings of outcome measurement, may differ between studies, heterogeneity of reporting was considered during data extraction.

b Golimumab was not included as part of the initial screening in the original review, but was added for the update.

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. For VEDO, one phase III RCTs was identified (GEMINI I), the results of which are published in Feagan et al (2013).

Figure 5. Biologics Search PRISMA Diagram: Identification and Selection of Sources (original, updated search)



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.**

As mentioned above, one randomised controlled trial, GEMINI I was found, the results of which are published inFeagan et al. (2013). The core information in this submission is from GEMINI I Clinical Study Report and the main publication (Feagan et al, 2013).

Trial	Reports/Publication
Main Comparator: Placebo + standard care	
GEMINI I	**Clinical Study Report** – A Phase 3, Randomized, Placebo-Controlled, Blinded, Multicentre Study of the Induction and Maintenance of Clinical Response and Remission by VEDO (MLN0002) in Patients with Moderate to Severe Ulcerative Colitis **Main publication** – Feagan, B. G., Rutgeerts, P., Sands, B. E., Hanauer, S., Colombel, J. F., Sandborn, W. J., Van Assche, G., Axler, J., Kim, H. J., Danese, S., Fox, I., Milch, C., Sankoh, S., Wyant, T., Xu, J., and Parikh, A. VEDO as induction and maintenance therapy for ulcerative colitis. New England Journal of Medicine 2013; 369 (8): 699-710

Complete list of relevant RCTs

6.2.4	**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.**

GEMINI I compared VEDO with placebo. In this study, patients were permitted to take mesalamine, up to 30 mg of prednisone (or equivalent) daily, or immunosuppressive agents at stable doses. Permitted glucocorticoid doses remained unaltered until Week 6, then were tapered according to a defined regimen for patients with a clinical response to VEDO. Permitted immunosuppressants were maintained at stable doses throughout the induction and maintenance periods, except for US study sites, where these agents were discontinued after induction.

Therefore for the purpose of the submission, the placebo arm of GEMINI I is representative of conventional therapy.
A separate systematic search and indirect comparison for anti-TNFs are described in section 6.7. The results of the search revealed that none of the biologics have head-to-head trial data with another biologic.

All systematically-identified published clinical trials considered biologic therapy compared 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 this comparison are provided in section 6.7

Table 13. List of relevant RCTs

Trial No/Name	**C13006/ GEMINI I**
Intervention and Comparator	VEDO IV (300mg) Placebo
Population	GEMINI I enrolled adult (aged 18 to 80 years) patients with moderately to severely active UC, defined as a Mayo Clinic score of 6 to 12 (range, 0 to 12, with higher scores indicating more active disease), with a sigmoidoscopy subscore of at least 2 and disease that extended ≥15 cm from the anal verge. Additional inclusion criteria were documented unsuccessful prior therapy (i.e., lack of response or unacceptable AEs) with 1 or more glucocorticoids, immunosuppressive medications (i.e., azathioprine, 6-MP), or TNF antagonists. Patients were permitted to take mesalamine, up to 30 mg of prednisone (or equivalent) daily, or immunosuppressive agents at stable doses.
Primary Reference	Feagan, B. G., P. Rutgeerts et al., (2013)."Vedolizumab as induction and maintenance therapy for ulcerative colitis." N Engl J Med 369(8):699-710. & GEMINI I Clinical Study Report, September 2012

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.**

The relevant main comparator is standard of care, comprising 5-ASAs, corticosteroids and immunomodulators. This reflects the baseline therapies in the GEMINI I trial (Feagan et al. 2013). In the GEMINI I trial, patients received VEDO or placebo in addition to 5-ASAs, corticosteroids and immunomodulators, therefore the placebo arm of the GEMINI I trial represents standard of care and is the main comparator presented in this submission.

The systematic search did not identify any head-to-head trial data with VEDO and other relevant comparator's identified in the decision problem. All systematically-identified published clinical trials considered biologic therapy compared with conventional therapy plus a placebo biologic. Further information on the approach to comparing VEDO with other biologics are presented in section 6.7.

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 VEDO RCT has been excluded.

List of relevant non-RCTs

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.**

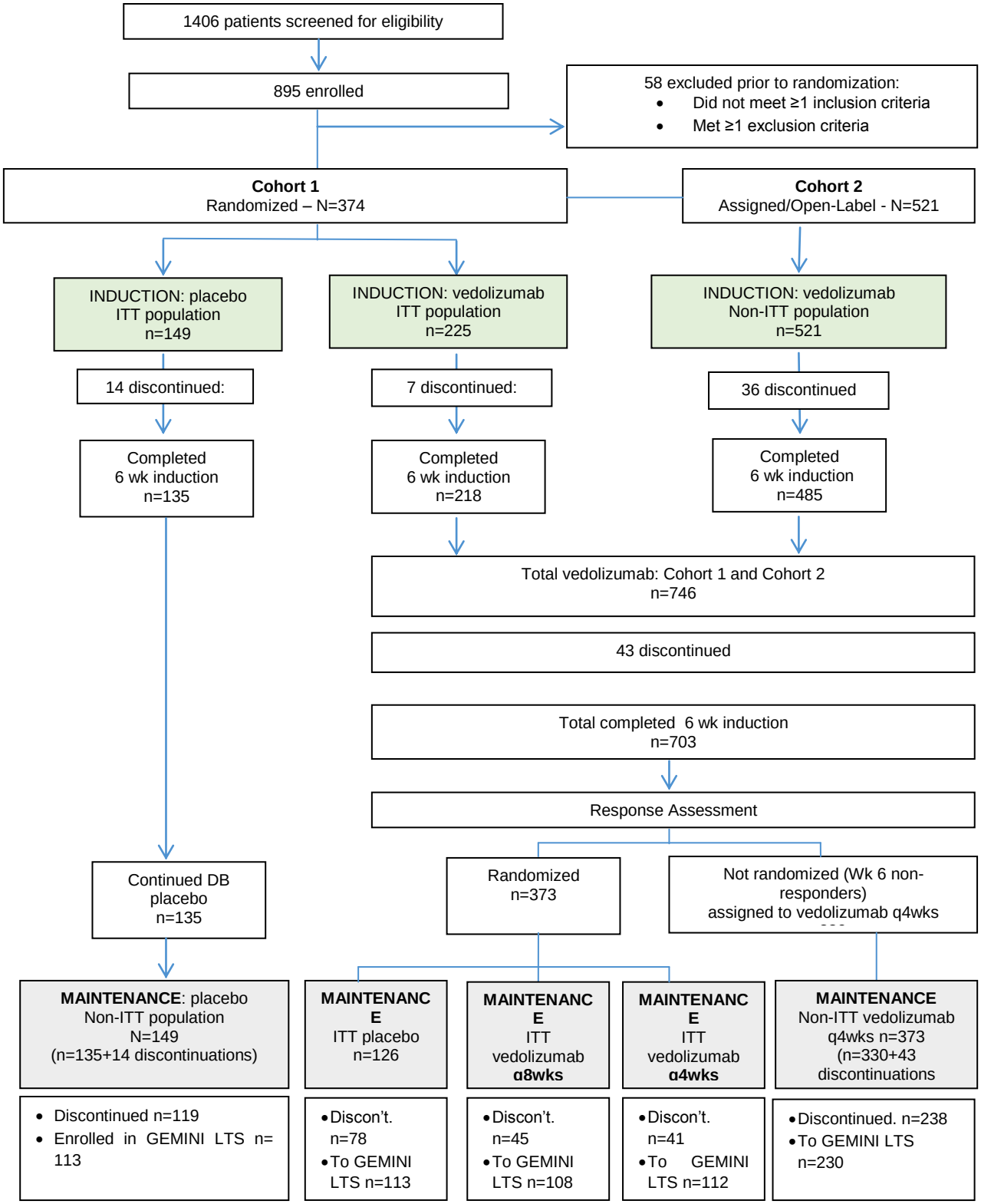
No relevant non-RCTs were identified however results from a long term safety study of vedolizumab in patients with CD and UC are presented in section 6.9

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.**

GEMINI I was a Phase III, multicentre, randomised, double-blind, placebo-controlled study that consisted of separate induction and maintenance trials, as described in this section. Figure 6 below provides an overview of the treatment phases, the study drug randomisation, and the treatment assignments in GEMINI I.

Figure 6. GEMINI I Treatment Phases, Randomisation, and Treatment Assignments (Feagan et al. 2013; Takeda Data on File 2012)



Methods

6.3.2	**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.**

GEMINI I Locations

GEMINI I was conducted at 211 medical centres, in 34 countries from 2008 to 2012. Participating countries included Australia (13 centres), Austria (4 centres), Belgium (6 centres), Bulgaria (1 centre), Canada (16 centres), Czech Republic (6 centres), Denmark (3 centres), Estonia (2 centres), France (5 centres), Germany (7 centres), Greece (3 centres), Hong Kong (1 centre), Hungary (5 centres), Iceland (2 centres), India (13 centres), Ireland (1 centre), Israel (2 centres), Italy (6 centres), Latvia (1 centre), Malaysia (4 centres), New Zealand (2 centres), Netherlands (2 centres), Norway (4 centres), Poland (7 centres), Russia (7 centres), Singapore (1 centre), South Africa (7 centres), South Korea (7 centres), Spain (2 centres), Switzerland (2 centres), Taiwan (2 centres), Turkey (2 centres), United Kingdom (2 centres) and the United States (63 centres).

GEMINI I Screening Procedures

In addition to demographic data collection, the following assessments were performed prior to randomisation: physical and neurologic examinations, blood tests, stool analysis for enteric pathogens and faecal calprotectin, chest radiography, TB test and symptom questionnaires for PML. Eligible patients were scheduled for a study visit immediately prior to randomisation, when the sigmoidoscopy was performed and baseline Mayo Clinic scores and scores on the IBDQ (range, 0 to 224, with higher scores indicating a better quality of life) were determined.

GEMINI I Randomisation and Dosing

For the induction study, 374 patients were randomised (3:2) to receive double-blind VEDO 300 mg IV or placebo on Days 1 and 15 (cohort 1). Randomisation was stratified by: (1) concomitant use or non-use of glucocorticoids and (2) by concomitant use or non-use of immunosuppressive agents or prior use or non-use of TNF antagonists. The proportion of patients with prior TNF antagonist exposure was limited to 50%. In order to fulfil sample size requirements for the

maintenance trial, an additional 521 patients were assigned to open-label VEDO on Days 1 and 15 (cohort 2).

The maintenance study included patients from both induction cohorts who had a clinical response to VEDO at Week 6. Patients were randomised (1:1:1) to VEDO every 8 weeks, VEDO every 4 weeks, or placebo for up to 52 weeks. Randomisation was stratified by: (1) cohort, (2) concomitant use or non-use of glucocorticoids, and (3) concomitant use or non-use of immunosuppressive agents or prior use or non-use of TNF antagonists. Patients in the induction study not having a clinical response at Week 6 continued to receive their assigned study drug (VEDO or placebo) every 4 weeks and were followed through Week 52.

Randomisation was performed centrally using a computer-generated randomisation schedule.

Blinding Procedures

Placebo infusions consisted of 250mL of normal saline (0.9% sodium chloride). During the induction phase, placebo infusions were administered at Weeks 0 and 2 to the Cohort 1 patients randomised to the double-blind group. During the maintenance phase, placebo infusions were administered to patients randomised to the placebo group every 4 weeks from Week 6 to Week 50. In order to maintain blinding, placebo infusions were administered to patients randomised to the VEDO-every-8-weeks dosing regimen at visits at which they did not receive VEDO (i.e., Weeks 10, 18, 26, 34, 42, and 50). Placebo infusions were also administered every 4 weeks in the maintenance phase placebo treatment group, who had been randomised to placebo treatment during the induction phase and continued on placebo treatment during the maintenance phase.

Study Visits

Study visits were performed at Weeks 2, 4 and 6 during induction therapy and every 4 weeks thereafter until Week 52. A each study visit, a partial Mayo Clinic score was calculated (i.e., Mayo Clinic score minus the sigmoidoscopy subscore; range, 0 to 9, with higher scores indicating more active disease), AEs were noted and neurologic-symptom questionnaires were administered, for which positive responses to objective testing prompted further evaluation. Blood draws for serum chemical and hematologic testing were performed every 8 weeks and blood samples for anti-VEDO antibody testing were obtained every 12 weeks. Faecal calprotectin concentrations and IBDQ scores were obtained at Weeks 6, 30, and 52.

Sigmoidoscopy was performed at baseline and Weeks 6 and 52. Serum VEDO concentrations were assessed at Weeks 0, 2, 4, and 6 and approximately every 8 weeks

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.**

GEMINI I enrolled adult (aged 18 to 80 years) patients with moderately to severely active UC, defined as a Mayo Clinic score of 6 to 12 (range, 0 to 12, with higher scores indicating more active disease), with a sigmoidoscopy subscore of at least 2, and disease that extended ≥15 cm from the anal verge. Additional inclusion criteria were documented unsuccessful prior therapy (i.e., lack of response or unacceptable AEs) with 1 or more glucocorticoids, immunosuppressive medications (i.e., azathioprine, 6-MP), or TNF antagonists:

Each patient had to demonstrated, over the previous 5-year period, an inadequate response to, loss of response to, or intolerance of at least 1 of the following agents as defined below:

Immunomodulators

- Signs and symptoms of persistently active disease despite a history of at least one 8-week regimen of oral azathioprine (≥ 1.5 mg/kg) or 6-mercaptopurine (≥ 0.75 mg/kg) OR
- History of intolerance of at least 1 immunomodulator (including but not limited to nausea/vomiting, abdominal pain, pancreatitis, liver function test abnormalities, lymphopenia, TPMT genetic mutation, infection)

TNF antagonists

- Signs and symptoms of persistently active disease despite a history of at least one 4-week induction regimen of infliximab 5 mg/kg IV,2 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, infection)

Corticosteroids

- Signs and symptoms of persistently active disease despite a history of at least one 4-week induction regimen that included a dose equivalent to prednisone 30 mg daily orally for 2 weeks or IV for 1 week, OR

- Two failed attempts to taper corticosteroids to below a dose equivalent to prednisone 10 mg daily orally on 2 separate occasions, OR

- History of intolerance of corticosteroids (including, but not limited to, Cushing's syndrome, osteopenia/osteoporosis, hyperglycaemia, insomnia, and infection).

Patients were permitted to take mesalamine, up to 30 mg of prednisone (or equivalent) daily, or immunosuppressive agents at stable doses. Mesalamine or glucocorticoid rectal therapy was discontinued 2 weeks prior to screening. Permitted aminosalicylates were continued at stable doses throughout the induction and maintenance periods. Permitted glucocorticoid doses remained unaltered until Week 6, then were tapered according to a defined regimen for patients with a clinical response to VEDO. Permitted immunosuppressants were maintained at stable doses throughout the induction and maintenance periods, except for US study sites, where these agents were discontinued after induction.

Patients were excluded for TNF antagonist therapy within 60 days prior to enrolment, for ciclosporin, thalidomide, or investigational agents within 30 days prior to enrolment, or for prior treatment with VEDO, natalizumab, efalizumab, or rituximab. Additional exclusion criteria were toxic megacolon, abdominal abscess, symptomatic colonic stricture, stoma, a history of colectomy, an increased risk of infectious complications (e.g., recent pyogenic infection, enteric pathogens detected on stool analysis, active or latent TB, immunodeficiency, HBV, HCV, or recent live vaccination), clinically meaningful laboratory abnormalities, pregnancy or lactation, unstable or uncontrolled medical disorders, anticipated need for major surgery, colonic dysplasia or adenomas, and malignant neoplasms.

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.**

Baseline demographics and disease characteristics were comparable among the VEDO (N=225) and placebo (N=149) groups in Cohort 1. Among all study patients, approximately half had used TNF antagonists prior to study enrolment, with 41% having failed prior TNF antagonist therapy. Patients had a mean age of 40.3 years, a mean disease duration of 6.9 years, and a mean baseline Mayo score of 8.6. Details on baseline characteristics in both Cohorts are shown below.

Table 14. Demographic and Baseline Patient Characteristics (GEMINI I Induction Phase) *(Feagan et al. 2013; Takeda Data on File 2012)

Characteristic	Placebo (N=149)	VEDO			Total (N=895)
		Cohort 1 (N=225)†	Cohort 2 (N=521)	Combined (N=746)	
Age, years	41.2±12.5	40.1±13.1	40.1±13.3	40.1±13.2	40.3±13.1
Male gender, n (%)	92(61.7)	132(58.7)	301(57.8)	433(58.0)	525(58.7)
White race, n (%) ‡	115(77.2)	183(81.3)	436(83.7)	619(83.0)	734(82.0)
Body weight, kg	72.4±17.6	72.4±17.1	74.2±19.3	73.6±18.7	73.4±18.5
Current smoker, n (%)	11(7.4)	12(5.3)	32(6.1)	44(5.9)	55(6.1)
Duration of disease, years	7.1±7.2	6.1±5.1	7.2±6.6	6.8±6.2	6.9±6.4
Mayo Clinic Score§	8.6±1.7	8.5±1.8	8.6±1.8	8.6±1.8	8.6±1.8
Partial Mayo Clinic Score^	6.1±1.5	6.0±1.6	6.0±1.6	6.0±1.6	6.0±1.6
IBDQ score ǁ	126±34	125±35	121±32	122±33	122±33
Faecal calprotectin, µg/g**					
• **Median**	1006	1112	782	868	899
• **Interquartile range**	333-2943	449-2931	331-1594	344-1915	341-2127
Site of disease, n (%)					
• **Rectum and sigmoid colon only**	22(14.8)	25(11.1)	69(13.2)	94(12.6)	116(13.0)
• **Left side of colon**	59(39.6)	92(40.9)	188(36.1)	280(37.5)	339(37.9)
• **Proximal to the splenic flexure**	18(12.1)	25(11.1)	66(12.7)	91(12.2)	109(12.2)
• **All of the colon**	50(33.6)	83(36.9)	198(38.0)	281(37.7)	331(37.0)
Concomitant medications for UC, n (%)					
• **Glucocorticoids only**	58(38.9)	79(35.1)	195(37.4)	274(36.7)	332(37.1)
• **Immunosuppressants only††**	18(12.1)	28(12.4)	113(21.7)	141(18.9)	159(17.8)
• **Glucocorticoids+immunosuppressants**	26(17.4)	47(20.9)	76(14.6)	123(16.5)	149(16.6)
• **No glucocorticoids or immunosuppressant's**	47(31.5)	71(31.6)	137(26.3)	208(27.9)	255(28.5)
Prednisone-equivalent dose, mg					
• **Median**	20	20	20	20	20
• **Interquartile range**	10-30	10-25	10-30	10-25	10-25
Prior anti-TNF therapy, n (%)	73(49.0)	95(42.2)	263(50.5)	358(48.0)	367(41.0)
Prior failure of anti-TNF therapy, n (%)					
• **≥1 failure**	63(42.3)	82(36.4)	222(42.6)	304(40.8)	367(41.0)
• **Inadequate response**	29(46.0)	44(53.7)	103(46.4)	147(48.4)	176(48.0)
	26(41.3)	32(39.0)	83(37.4)	115(37.8)	141(38.4)

• **Loss of response‡‡** • **Unacceptable adverse events**	8(12.7)	6(7.3)	36(16.2)	42(13.8)	50(13.6)
Haemoglobin concentration, g/L	123±19.6	125±19.6	124.9±119.5	125.0±19.5	124.8±19.5
White cell count, x109/L	8.7±3.3	8.2±3.1	8.6±3.2	8.5±3.2	8.5±3.2

*** Plus/minus values are means±SD.**
† P values for the comparison in Cohort 1 between the placebo group and the VEDO group are all >0.05.
‡ Race was self-reported.
§ Mayo Clinic score range from 0 to 12, with higher scores indicating more active disease.
^ The partial Mayo Clinic score consists of Mayo Clinic score minus the sigmoidoscopy subscore; range, 0 to 9, with higher scores indicating more active disease.
‖ Scores on the Irritable Bowel Disease Questionnaire (IBDQ) range from 0 to 224, with higher scores indicating a better quality of life.
****Data on faecal calprotectin were available for 857 patients: 139 receiving placebo, 213 receiving VEDO in Cohort 1, 505 receiving VEDO in Cohort 2, and 718 receiving VEDO in the combined cohorts.**
††Immunosuppressants included azathioprine and mercaptopurine.
‡‡Loss of response indicates that the patient had a response initially but subsequently did not have a response.

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 posthoc 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.**

Induction Efficacy Endpoints

For the induction study, the primary endpoint was the effect of VEDO on clinical response (defined as a reduction in complete Mayo score of ≥3 points and ≥30% from baseline, along with a decrease in rectal bleeding subscore of ≥1 points or an absolute rectal bleeding subscore of ≤1 point) at Week 6.

Secondary endpoints included clinical remission (defined as complete Mayo score of ≤2 points and no individual subscore >1 point) and mucosal healing (defined as an endoscopic subscore of ≤1 point) at Week 6.

Exploratory outcomes included correlation of partial Mayo scores with complete Mayo scores and analysis of the endpoints in the following patient subgroups: patients with previous exposure to TNF antagonists, those failing TNF antagonists, and those on concomitant therapies.

Maintenance Efficacy Endpoints

For the maintenance study, the primary endpoint was clinical remission at Week 52. This was the differences in proportions of patients with clinical remission (defined as a complete Mayo score of ≤2 points and no individual subscore >1 point) at Week 52 in the VEDO-every-4-weeks group versus placebo group and VEDO-every-8-weeks versus placebo group.

Secondary endpoints included durability of clinical response (response at Weeks 6 and 52) and clinical remission (remission at Weeks 6 and 52), mucosal healing at Week 52 (Mayo endoscopic subscore of ≤1 point), and glucocorticoid-free remission at Week 52 (clinical remission at Week 52 and no concomitant corticosteroid use).

Exploratory outcomes included the effect of VEDO on time to disease worsening, reduction of oral corticosteroids, and reduction in faecal calprotectin, analysis of the endpoints in patient subgroups with previous exposure and/or failure to TNF antagonists and those on concomitant therapies, and identification of covariates that may affect VEDO pharmacokinetics and pharmacodynamics.

Safety Assessment (Induction and Maintenance)

In the induction phase, safety analyses included all safety data collected from baseline (Week 0) through Week 6 (until the first maintenance dose was given) for all patients in Cohorts 1 and 2 who received study medication. In the maintenance phase, safety analyses were cumulative and included all safety data collected from baseline (Week 0) through the end of the study for all patients in the safety population, including those who withdrew prematurely during the induction phase.

Safety assessments were based on the incidence, severity, and type of AE, PML symptom checklist, plasma JC virus DNA testing, vital signs, stool samples, electrocardiogram (ECG) results, and laboratory results, including standard haematology, clinical chemistry, coagulation, and urinalysis. Adverse event coding was completed using the Medical Dictionary for Regulatory Activities (MedDRA), version 14.0. Blood samples for human anti-human antibody (HAHA) assessments were performed to assess the potential immunogenicity of VEDO. Blood samples were also drawn for pharmacokinetic (PK) and pharmacodynamics (PD) assessment.

HRQOL Assessment (Induction and Maintenance)

For both the induction and maintenance phases, resource utilisation was evaluated by analysing the effect of VEDO on the time to major UC-related events (i.e., hospitalisations, colectomies, and UC-related procedures) and on HRQOL at Weeks 6 and 52. Change in HRQOL over time was evaluated with the IBDQ, SF-36 and the EQ-5D questionnaire.

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.**

Overall, analyses were performed according to the intent-to-treat (ITT) principle. The Cochran-Mantel-Haenszel chi-square test was used to analyse the primary endpoint of clinical response in the induction study. Patients who withdrew prematurely were considered treatment failures. More detail on the statistical analyses used is described below:

It was expected that 35% of patients who received placebo and 53% of those who received study drug would have a response during the induction phase. In the maintenance phase, the corresponding estimates of remission rates at Week 52 for the most effective VEDO regimen were 30% and 50%. The planned enrolment of 375 patients in the induction phase and 372 patients in the maintenance phase provided at least 90% power to detect differences with an alpha error of 5%.

Primary Efficacy Endpoint Statistical Analysis (Induction)

In the induction phase, the primary comparison was tested using the Cochran-Mantel-Haenszel (CMH) chi-square test at a 5% significance level, with stratification according to the randomisation stratification factors (concomitant use of oral corticosteroids and previous

exposure to TNF antagonists or concomitant immunomodulator [i.e., 6-MP or azathioprine] use). The CMH chi-square p-value and the risk difference, along with its 95% confidence interval were calculated. In addition, the relative risk and the 95% two-sided confidence interval were performed.

Secondary Efficacy Endpoint Statistical Analyses (Induction)

The proportion-based secondary endpoints were analysed in the same manner as the primary endpoint. The remaining secondary endpoints were tested in a non-hierarchical manner without adjustments for multiplicity. The Type I error rate in the multiple dose comparisons in each secondary endpoint was controlled through the closed sequential method. To further maintain the overall Type I error rate at 5%, the secondary assessments were performed sequentially. The first secondary endpoint was to be tested only if the primary comparison was significant and the second secondary endpoint was to be tested only if the first secondary endpoint was significant for VEDO.

Exploratory Efficacy Statistical Analyses (Induction)

For the proportion-based exploratory analyses, the proportions and absolute treatment differences were provided along with their corresponding 95% two-sided confidence intervals. For continuous variables, the changes from baseline (Week 0) over time were summarised. A logistic regression model with clinical response and clinical remission as the response variable and treatment group, baseline (Week 0) Mayo score, stratification factors (concomitant use of corticosteroids [yes/no]; previous exposure to TNF antagonists or concomitant use of immunomodulators [yes/no]), and geographic region as independent variables was fit using the ITT population.

Primary Efficacy Endpoint Statistical Analyses (Maintenance)

For the 2 comparisons of the primary endpoint of clinical remission at 52 weeks, the Hochberg method was applied to control the overall Type I error rate at a 5% significance level. For both assessments of the primary endpoint, the CMH chi-square test was used to compare the 2 treatment groups at the 5% level of significance with stratification according to the randomisation stratification factors (i.e., enrolment in Cohort 1 or 2 in the induction phase, concomitant use of oral corticosteroids, and previous exposure to TNF antagonists or concomitant immunomodulator [i.e., 6-MP or azathioprine] use). The CMH chi-square p-value and the absolute treatment difference along with its 95% two-sided confidence interval were calculated. In addition, the relative risks were performed along with the 95% two-sided confidence interval estimate.

Secondary Efficacy Endpoint Statistical Analyses (Maintenance)

The proportion-based secondary endpoints were analysed in the same manner as the primary endpoint. The remaining secondary endpoints were tested in a non-hierarchical manner without adjustments for multiplicity. To maintain the overall Type I error rate at 5% for the 2 dose regimen comparisons for each key secondary endpoint, the Hochberg method was used. To further maintain the overall Type I error rate at 5%, the key secondary assessments were also performed sequentially. The first secondary endpoint was to be tested only if 1 or both of the primary comparisons were significant and the next key secondary endpoint was to be tested only if the previous secondary endpoint was significant for at least 1 dose.

Exploratory Efficacy Statistical Analyses (Maintenance)

For the proportion-based exploratory analyses, the proportions and absolute treatment differences were calculated along with their corresponding 95% two-sided confidence intervals. For continuous variables, the changes from baseline (Week 0) over time were summarised. Clinical remission and durable clinical response were analysed for the ITT population using a logistic regression model with treatment group, baseline (Week 0) Mayo score, randomisation stratification factors (Induction Phase Cohort 1 or Cohort 2; concomitant use of corticosteroids [yes/no]; previous exposure to TNF antagonists or concomitant use of immunomodulators [yes/no]), and geographic region as independent variables.

Safety Statistical Analyses

Safety evaluations were based on the incidence, severity, and type of AEs and clinically significant changes or abnormalities in the patient's physical or neurological examinations, vital signs, ECG, and laboratory results. Descriptive statistics were performed. The AEs were coded using MedDRA version 14.0 according to the primary system organ class (SOC), high level term, and preferred term. Descriptive statistics were calculated. Other safety data, including HAHA assessments, neutralizing HAHA assessments, serum JC virus assessments, neurologist's evaluation, and PML checklist results were listed.

HRQOL Analysis Methods

For the induction phase, changes in the IBDQ, SF-36, and EQ-5D scores were assessed at Week 6. The mean changes from baseline (Week 0) in IBDQ, SF-36, and EQ-5D scores were calculated by treatment arm along with 95% two-sided confidence intervals for the differences in mean changes from baseline (Week 0) based on an analysis of covariance (ANCOVA) model.

For the maintenance phase, mean changes from baseline (Week 0) in IBDQ, SF-36 and EQ-5D scores were calculated by treatment arm along with 95% two-sided confidence intervals for the differences in mean changes from baseline (Week 0) based on an ANCOVA model.

Time to UC-related hospitalisation, time to colectomy, and time to UC-related procedure were analysed using the Kaplan-Meier method. The 95% confidence intervals around the median were performed. Time to major UC-related events (defined as the combination of hospitalisations, colectomies, and UC-related procedures) was assessed using the Wei, Lin, and Weissfeld method. To apply the Wei, Lin and Weissfeld method, a separate test statistic (log-rank test) first needed to be computed for each type of event using Cox proportional hazard models adjusting for concomitant medications in use at baseline (Week 0), prior exposure to TNF antagonists, geographic region and Mayo score at baseline (Week 0).

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

In the induction phase and maintenance phase, pre-specified exploratory subgroup analyses included analysis of the key endpoints in the subgroup of patients with previous exposure to TNF-alpha antagonist therapy and in the subgroup of patients defined as having failed TNF-alpha antagonist therapy; and in the subgroups of patients on concomitant therapies

Participant flow

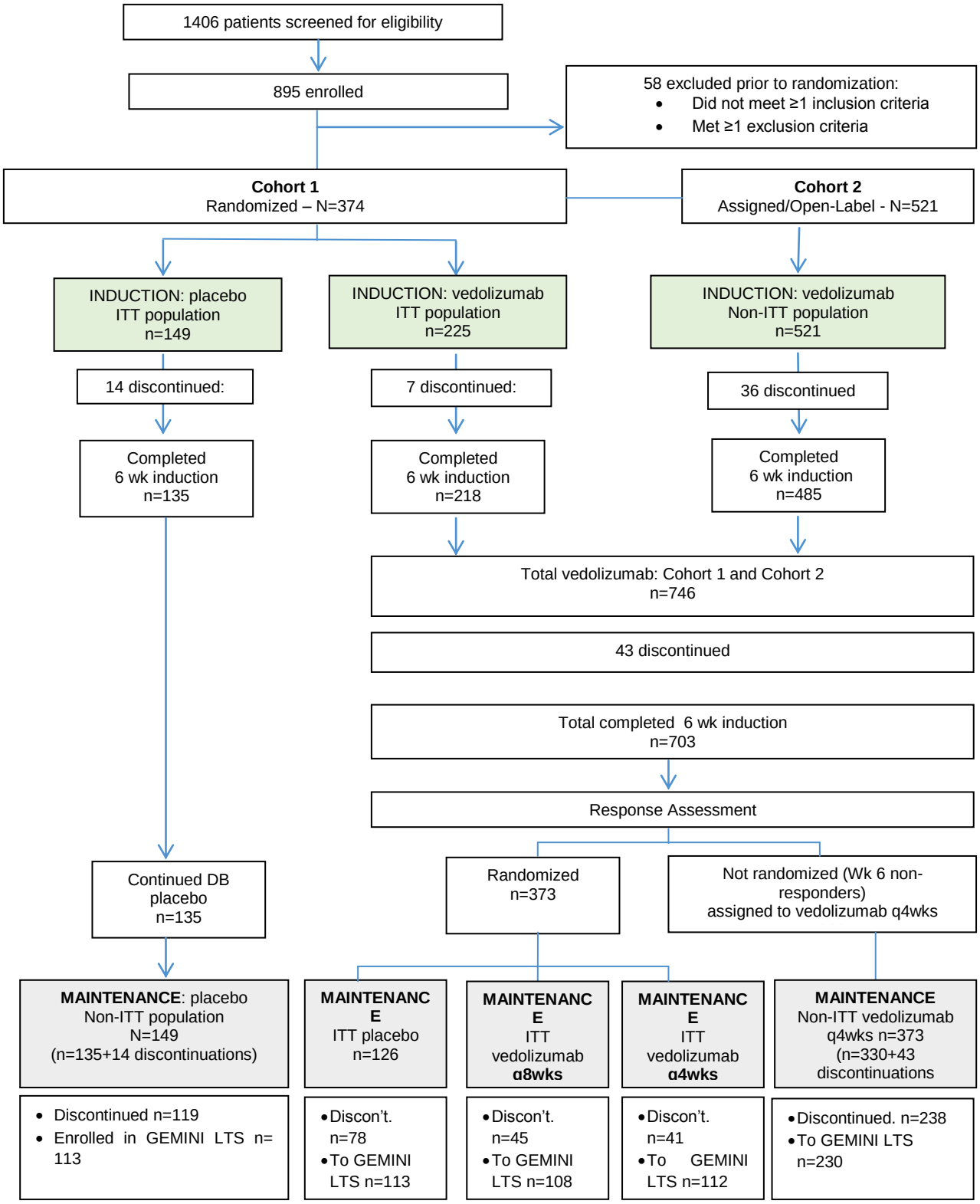
6.3.8	**Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should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

Figure 7 shows the overall GEMINI I trial design, indicating the Induction Phase and the Maintenance Phase treatment periods. After the Week 52 assessments, patients meeting protocol-defined criteria were eligible to enrol in Study C13008 (Long-term Safety, see section 6.9 for further information) to receive open-label VEDO treatment. Patients who withdrew early (prior to Week 52) due to sustained non response, disease worsening or the need for rescue medications may also have been also eligible for Study C13008.

Patients who did not enrol into Study C13008 were to complete a final on-study safety assessment at Week 66 (or Final Safety visit 16 weeks after the last dose) in the Maintenance Phase of GEMINI I.

In addition, after the end of the study, all patients who did not enrol in Study C13008 were to participate in a follow-up period in which they were contacted by telephone every 6 months for 2 years. . The follow-up questionnaire administered at each time point collected information on events such as infections resulting in hospitalisation (at 6 months only), pregnancy, colorectal dysplasia, cancer, IBD-related surgeries and the development of PML.

Figure 7. GEMINI I Consort Diagram (Feagan et al. 2013; Takeda Data on File 2012)



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 15. Quality assessment results for RCTs

Trial no. (acronym)	GEMINI I
Was randomisation carried out appropriately?	Yes, see question 6.3.2
Was the concealment of treatment allocation adequate?	Yes, see question 6.3.2
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes, see question 6.3.4
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes, see question 6.3.2
Were there any unexpected imbalances in drop-outs between groups?	No, see question 6.3.8
Is there any evidence to suggest that the authors measured more outcomes than they reported?	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 No data were imputed for missing values in the VEDO pharmacokinetic or pharmacodynamics data sets.

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 both as 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.

Induction Dosing

A total of 57 patients (6%) discontinued with no notable differences between treatment groups (see table below). In the ITT population, 9% of placebo patients discontinued for any reason, compared with 3% of VEDO patients. A total of 4 placebo-treated patients (3%) and no VEDO-treated patients (0%) discontinued due to AEs. Reasons for the 57 discontinuation included AEs

(11 patients), protocol violations (8 patients), lack of efficacy (21 patients), withdrawal of consent (15 patients), and lost to follow up (2 patients).

Table 16. GEMINI I Patient Disposition (Induction Phase)

	Induction Phase ITT[a]		Non-ITT		
	Placebo	VEDO Cohort 1	VEDO Cohort 2[b]	VEDO Combined	TOTAL
Randomised/assigned	149	225	521	746	895
Study Populations, n (%)					
• **Safety[c]**	149(100)	225(100)	521(100)	746(100)	895(100)
• **Intent-to-Treat[d]**	149(100)	225(100)	---	225(30)	374(42)
• **Per-Protocol[e]**	138(93)	215(96)	---	215(29)	353(39)
Completed Induction Phase, n(%)[f]	135(91)	218(97)	485(93)	703(94)	838(94)
Discontinued	14(9)	7(3)	36(7)	43(6)	57(6)
Adverse event	4(3)	0	7(1)	7(<1)	11(1)
Protocol violation(s)	1(<1)	1(<1)	6(1)	7(<1)	8(<1)
Lack of efficacy	5(3)	2(<1)	14(3)	16(2)	21(2)
Study terminated by sponsor	0	0	0	0	0
Withdrawal of consent	3(2)	4(2)	8(2)	12(2)	15(2)
Lost to follow-up	1(<1)	0	1(<1)	1(<1)	2(<1)
Other	0	0	0	0	0

a All patients enrolled in Cohort 1 who were randomised to blinded induction treatment with VEDO or placebo.
b All patients enrolled in Cohort 2 who received open-label VEDO induction treatment.
c Safety population consisted of all patients who received any amount of study drug during the induction phase based on what they actually received.
d The ITT population consisted of all randomised patients who received any amount of blinded study drug during the induction phase based on what they were randomised to receive.
e The Per-Protocol population consisted of all patients without any major protocol deviations.
f These patients completed dosing at Weeks 0 and 2 and completed the predose assessments at Week 6.

Maintenance Dosing

In the ITT population, a larger proportion of placebo-treated patients discontinued study treatment than did VEDO-treated patients (62% placebo vs. 37% and 33% VEDO in the every 8 week and every 4 week groups, respectively) (see table below). The common reason for discontinuation across the full ITT population was lack of efficacy, which occurred in 48%, 25%, and 25% in the placebo, every 8 week VEDO, and every 4 week VEDO groups, respectively. Discontinuations due to AEs were twice as frequent in the placebo group (12% vs. 6% and 5% in the two VEDO groups, respectively). The majority of patients in the ITT population continued to the long-term safety trial (GEMINI LTS/13008).

Table 17. GEMINI I Patient Disposition (Maintenance Phase), (Feagan et al. 2013)

	Maintenance Study ITT[a] (Responders to VEDO induction, randomised to maintenance at Wk 6)			Non-ITT		Combined	
	Placebo n=126	**VEDO every 8 wks n=122**	**VEDO every 4 wks n=125**	**Placebo[b] (from Wk 0) n=149**	**VEDO every 4 wks (Wk 6 non responders) n=373**	**Placebo n=275**	**VEDO n=620**
Completed induction, n (%)	126(100)	122(100)	125(100)	135(91)	330(88)	261(95)	577(93)
Randomised, n (%)	126(100)	122(100)	125(100)	149(100)	373(100)	275(100)	620(100)
Randomised but not dosed	0	0	0	0	0	0	0
Safety population[d], n (%)	126(100)	122(100)	125(100)	149(100	373(100)	275(100)	620(100)
Maintenance phase ITT population[a], n (%)	126(100	122(100)	125(100)	---	---	126(46)	247(40)
Maintenance Phase Per-Protocol population[e]	121(96)	117(96)	121(97)	---	---	121(44)	238(38)
Completed Maintenance[f]	48(38)	77(63)	84(67)	30(20)	135(36)	78(28)	296(48)
Discontinued[g]	78(62)	45(37)	41(33)	119(80)	238(64)	197(72)	324(52)
Adverse event	15(12)	7(6)	6(5)	16(11)	23(6)	31(11)	36(6)
Protocol violations(s)	0	0	0	2(1)	9(2)	2(<1)	9(1)
Lack of efficacy	61(48)	31(25)	33(26)	88(59)	171(46)	149(54)	235(38)
Study terminated by sponsor	0	0	0	0	0	0	0
Withdrawal of consent	2(2)	5(4)	2(2)	9(6)	32(9)	11(4)	39(6)
Lost to follow-up	0	2(2)	0	4(3)	3(<1)	4(1)	5(<1)
Other	0	0	0	0	0	0	0
Enrolled into C13008 (GEMINI LTS)	113(90)	108(89)	112(90)	112(75)	230(62)	225(82)	450(73)

a The maintenance phase ITT population consisted of all patients randomised at Week 6 (i.e., patients who received VEDO during the induction phase and were classified as responders at Week 6) who received any amount of blinded study drug during the maintenance phase, based on what they were randomised to receive.

b Patients who received placebo during the induction phase and continued to receive placebo during the maintenance phase.
c Patients who received VEDO in the induction phase but did not achieve clinical response at Week 6 and continued to receive VEDO every 4 weeks during the maintenance phase.
d The safety population consisted of all patients who received any amount of study drug at any time in the study (i.e., Week 0 through Week 50), based on what they actually received.
e The maintenance phase Per-Protocol population consisted of all maintenance phase ITT patients without any major protocol deviations.
f Completed study was defined as patients who completed the Week 52 analyses.
g Included patients who discontinued at any time during the study, even before Week 6.

GEMINI I Efficacy Results

Induction Treatment

As shown in the table below, compared with placebo, patients treated with VEDO had significantly greater rates of clinical response, clinical remission, and mucosal healing at 6 weeks (Feagan, 2013). Efficacy was generally similar between subgroups based on patient demographics and disease severity. Of the patients who received open-label VEDO, 231 had a clinical response (44.3%), 100 had clinical remission (19.2%) and 191 had mucosal healing (36.7%).

Table 18. GEMINI I Efficacy Endpoints at Week 6 in Induction Study (Feagan 2013)

Study Endpoint	VEDO (n=225)	Placebo (n=149)	Percentage Difference (95% CI)†	p value
Clinical Response* (%)	47.1	25.5	21.7 (11.6 to 31.7)	<0.001
Clinical Remission (%)	16.9	5.4	11.5 (4.7 to 18.3)	0.001
Mucosal Healing (%)	40.9	24.8	16.1 (6.4 to 25.9)	0.001

CI=confidence interval
***Primary endpoint**
†Percentage differences were adjusted for two stratification factors: concomitant use or non-use of glucocorticoids, and concomitant use or non-use of immunosuppressive agents or prior use or non-use of TNF antagonists.

Subgroups Including Anti-TNF Failure

Clinical response rates were higher with VEDO compared to placebo in both patients with prior TNF antagonist failure and those with no prior TNF antagonist exposure (Takeda Data on File 2012; Feagan et al. 2013). In the patients with prior TNF antagonist failure, VEDO was also associated with higher clinical remission and mucosal healing rates compared to placebo, but the 95% confidence intervals for the difference between VEDO and placebo included zero (Takeda Data on File 2012). VEDO treatment benefits were also demonstrated in patients with prior immunomodulator failure and corticosteroid failure. Of the induction study patients receiving VEDO who did not have a response by Week 6, a total of 102 (102/322 patients, 31.7%) had a clinical response at Week 10 (an additional 4 weeks of treatment/1 additional infusion), and 126 (126/322 patients, 39.1%) had a clinical response at Week 14 (an additional 8 weeks of treatment/2 additional infusions).

The exploratory analyses comparing partial and complete Mayo scores found high agreement between the partial and complete scores in all 374 patients in the ITT population, with Pearson correlation coefficients of 0.95 (95% CI: 0.94 to 0.96) at baseline and 0.98 (95% CI: 0.97 to 0.98) at Week 6 (Takeda Data on File 2012). Clinical response by partial Mayo score showed substantial agreement (0.78, 95% CI: 0.70 to 0.86) with clinical response by complete Mayo score in the VEDO-treated patients and almost perfect agreement (0.82, 95% CI: 0.76 to 0.88) in the entire population. Additionally, clinical response based on partial Mayo score at Weeks 2, 4, and 6 all favoured VEDO compared to placebo.

Maintenance Treatment

A total of 373 met response criteria at Week 6 and were enrolled into the maintenance treatment study and randomised to receive VEDO every 8 weeks (n=122), VEDO every 4 weeks (n=125), or placebo (n=126) (Feagan, 2012; Feagan, 2013). As shown in table below patients receiving VEDO maintenance either every 4 weeks or every 8 weeks were significantly more likely to achieve clinical remission at Week 52 compared to placebo-treated patients. Compared to placebo, VEDO maintenance treatment was associated with significantly higher rates of durable clinical response, durable clinical remission, mucosal healing, and glucocorticoid-free remission. There were no clear differences found between VEDO every 8 or every 4 weeks.

Table 19. GEMINI I Efficacy Endpoints In Maintenance Study (Feagan, 2013)

Study Endpoint	VEDO Every 8 Wks (n=122)	VEDO Every 4 Wks (n=125)	Placebo (n=126)	Between Group Percentage Difference*			
				Every 8 Wk vs. Placebo (95% CI)	p value	Every 4 Wk vs. Placebo (95% CI)	p value
Clinical Remission at Wk 52 (%)	41.8	44.8	15.9	26.1 (14.9 to 37.2)	<0.001	29.1 (17.9 to 40.4)	<0.001
Durable Clinical Response (%)	56.6	52.0	23.8	32.8 (20.8 to 44.7)	<0.001	28.5 (16.7 to 40.3)	<0.001
Durable Clinical Remission (%)	20.5	24.0	8.7	11.8 (3.1 to 20.5)	0.008	15.3 (6.2 to 24.4)	0.001
Mucosal Healing at Wk 52 (%)	51.6	56.0	19.8	32.0 (20.3 to 43.8)	<0.001	36.3 (24.4 to 48.3)	<0.001
Glucocorticoid-free Remission at Wk 52 (%) †	31.4	45.2	13.9	17.6 (3.9 to 31.3)	0.01	31.4 (16.6 to 46.2)	<0.001

CI=confidence interval; Wk(s)=week(s)
*** Between-group differences in percentage points were adjusted for three stratification factors: cohort, concomitant use or non-use of glucocorticoids, and concomitant use or non-use of immunosuppressive agents or prior use or non-use of TNF antagonists.**
† Glucocorticoid-free remission was analysed in patients on oral glucocorticoids at baseline: VEDO every 8 wks, n=70; VEDO every 4 wks, n=73; placebo, n=72.

The efficacy of VEDO maintenance treatment was not substantively affected by concomitant use of glucocorticoids or immunosuppressants. The clinical remission and durable clinical response rates were greater for VEDO-treated patients than for placebo-treated patients regardless of prior TNF antagonist treatment status.

Table 20. Results at Week 52 by Prior TNF Antagonist Status (GEMINI I) (Feagan et al. 2013)

Study Endpoint	**Patients With Prior TNF Antagonist Failure***				
	VEDO Every 8 Wks (n=43)	VEDO Every 4 Wks (n=40)	Placebo (n=38)	Between Group Difference (95% CI)‡	
				Every 8 Wks vs. Placebo	Every 4 Wks vs. Placebo
Clinical Remission (%)	37.2	35.0	5.3	31.9 (10.3 to 51.4)	29.7 (7.4 to 49.4)
Durable Clinical Response (%)	46.5	42.5	15.8	30.7 (11.8 to 49.6)	26.7 (7.5 to 45.9)
	Patients **Without** TNF Antagonist Exposure†				
	VEDO Every 8 Wks (n=72)	VEDO Every 4 Wks (n=73)	Placebo (n=79)	Between Group Difference (95% CI)	
				Every 8 Wks vs. Placebo	Every 4 Wks vs. Placebo
Clinical Remission (%)	45.8	47.9	19.0	26.8 (12.4 to 41.2)	29.0 (14.6 to 43.3)
Durable Clinical Response (%)	65.3	56.2	26.6	38.7 (24.0 to 53.4)	29.6 (14.6 to 44.6)

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

In patients with a successful response to induction therapy, the partial Mayo scores remained substantially lower than baseline throughout Week 52 in the VEDO-treated patients, whereas an increase in the partial Mayo scores was observed starting in Week 22 in the placebo-treated patients (Feagan et al. 2013). The median corticosteroid dose declined in the maintenance study in both VEDO groups, compared to a rise in corticosteroid use after Week 26 was observed in the placebo group.

Time to disease worsening and time to treatment failure were not estimable among the study groups because of the large percentage of patients for whom events were censored at Week 52 (Takeda Data on File 2012).

VEDO-treated patients had greater improvements in faecal calprotectin concentration compared to placebo-treated patients (Feagan et al. 2013; Takeda Data on File 2012). The percentage of patients with faecal calprotectin concentrations >500 mcg/g at Week 52 was 36% for placebo, 15% for VEDO every 8 weeks, and 21% for VEDO every 4 weeks.

Delayed responder analysis (Takeda Data on File 2012)

For patients who had failed to demonstrate response at Week 6, there was the clinical question of whether further treatment could lead to induction either by allowing more time or additional VEDO dosing. Exploratory analyses were conducted on the two phases of the GEMINI I trial and allowed for an analysis of delayed response among patients not responding at week 6.

As described above, during the induction phase of GEMINI I, patients randomised (cohort 1) or assigned (cohort 2) to VEDO were administered two intravenous infusion of VEDO 300 mg (at weeks 0 and 2). Induction VEDO was administered in a blinded fashion in cohort 1, whereas for cohort 2 it was open label administration. At week 6 (randomisation into the maintenance phase) patients not meeting the clinical response criteria were assigned VEDO 300 mg every 4 weeks for 46 weeks, whereas those demonstrating a response from Cohort 1 and 2 were randomised to placebo or VEDO every 4 or 8 weeks. Patients without a response at week 6 and who subsequently received the 4-week dosing were included in the posthoc 'delayed responder' analysis. Patient data were analysed at weeks 10 and 14 versus the placebo group.

Among week 6 non-responders, clinical response using partial Mayo scores was achieved at Week 10 and Week 14 by greater proportions of vedolizumab patients (32% and 39%, respectively) compared with placebo patients (15% and 21%, respectively).

Table 21. Clinical response by Partial Mayo scores in patients who did not achieve clinical response at week 6 - Delayed response population

Clinical response	***Placebo (N=82)***		***VEDO q4w (N=322) (combined Cohort 1 and 2)***	
	n	% (95% CI)	N	% (95% CI)
Week 10	12	14.6 (7.0, 22.3)	102	31.7 (26.6, 36.8)
Week 14	17	20.7 (12.0, 29.5)	126	39.1 (33.8, 44.5)

Additional Post-Hoc Analyses for Section 7 (Takeda Data on File 2012)

Further analyses were conducted on clinical response and clinical remission at week 10 in the cohort 1 population and in the combined cohort 1 and 2 patient population (referred to as the safety population as it is all patients treated with vedolizumab regardless of their subsequent treatment in the maintenance phase).

These post-hoc analyses are based on all patients regardless of induction response and were specifically conducted to support the cost-effectiveness analysis presented in section 7.

Table 22. Clinical response and remission by Partial Mayo scores for patients at Week 10 (Cohort 1 and Safety Population) - Overall

	Placebo	VEDO
Cohort 1	**N=149**	**N=225**
Number (%) achieving clinical response	48 (32.2)	122 (54.2)
95% CI	(24.7, 39.7)	(47.7, 60.7)
Number (%) achieving clinical remission	26 (17.4)	87 (38.7)
95% CI	(11.4, 23.5)	(32.3, 45.0)
Safety Population (Cohort 1 and Cohort 2)*	**N=149**	**N=746**
Number (%) achieving clinical response	48 (32.2)	422 (56.6)
95% CI	(24.7, 39.7)	(53.0, 60.1)
Number (%) achieving clinical remission	26 (17.4)	283 (37.9)
95% CI	(11.4, 23.5)	(34.5, 41.4)

Table 23. Clinical response and remission by Partial Mayo scores for patients at Week 10 (Cohort 1 and Safety Population) - Anti-TNF Failure Subgroup

	Placebo	VEDO
Cohort 1	N=149	N=225
Number of Failure Patients	**63**	**82**
Number (%) achieving clinical response	18 (28.6)	30 (36.6)
95% CI	(17.4, 39.7)	(26.2, 47.0)
Number (%) achieving clinical remission	10 (15.9)	19 (23.2)
95% CI	(6.8, 24.9)	(14.0, 32.3)
Safety Population (Cohort 1 and Cohort 2)*	**N=149**	**N=746**
Number of Failure Patients	63	304
Number (%) achieving clinical response	18 (28.6)	136 (44.7)
95% CI	17.4, 39.7	39.1, 50.3
Number (%) achieving clinical remission	10 (15.9)	93 (30.6)
95% CI	6.8, 24.9	25.4, 35.8

Table 24. Clinical response and remission by Partial Mayo scores for patients at Week 10 (Cohort 1 and Safety Population) - Anti-TNF Naive Subgroup

	Placebo	VEDO
Cohort 1	**N=149**	**N=225**
Number of Anti-TNF Naive Patients	71	128
Number (%) achieving clinical response	25 (35.2)	83 (64.8)
95% CI	24.1, 46.3	56.6, 73.1
Number (%) achieving clinical remission	12 (16.9)	63 (49.2)
95% CI	(8.2, 25.6)	40.6, 57.9
Safety Population (Cohort 1 and Cohort 2)	**N=149**	**N=746**
Number of Anti-TNF Naive Patients	71	383
Number (%) achieving clinical response	25 (35.2)	247 (64.5)
95% CI	24.1, 46.3	59.7, 69.3
Number (%) achieving clinical remission	12 (16.9)	165 (43.1)
95% CI	(8.2, 25.6)	(38.1, 48.0)

Patient Reported Outcomes in GEMINI I

Improvements in HRQOL assessments favoured VEDO, with statistically significant and clinically meaningful improvements seen for IBDQ total and domain scores; the SF-36 Physical Component Summary (PCS) and Mental Component Summary (MCS) as well as the scale scores; and the EQ-5D (overall and visual analog scale [VAS] scores) (**see table below**).

<u>Induction</u>

At Week 6 of induction treatment, patients with UC treated with VEDO had statistically significantly greater improvements in HRQOL outcomes than patients treated with placebo as assessed by the total IBDQ total score, with the changes considered to be clinically meaningful improvements based on the minimally important differences (MIDs). VEDO induction treatment was associated with statistically significantly greater improvements than placebo treatment in the SF-36 summary scores at Week 6. Patients receiving VEDO also had significant improvements in the EQ-5D and EQ-5D VAS scores compared to placebo, with the changes considered to be clinically meaningful improvements.

Table 25. Changes in HRQOL From Baseline at Week 6 of UC Induction Therapy (GEMINI I)

IBDQ Total Score[a]	**n=144**	**n=219**
• **Baseline mean**	126.8	124.5
• **Week 6 mean**	137.2	153.7
• **Adjusted mean change from baseline (95% CI)[b]**	10.9 (5.5 to 16.3)	28.9 (24.5 to 33.2)
• **Difference in adjusted change from baseline vs. placebo, mean (95% CI)[c]**		18.0[d] (11.0 to 24.9)
SF-36 Physical Component Summary[a]	**n=144**	**n=219**
• **Baseline mean**	40.8	41.3
• **Week 6 mean**	42.3	45.4
• **Adjusted mean change from baseline (95% CI)[b]**	1.4 (0.3 to 2.5)	4.1 (3.2 to 5.0)
• **Difference in adjusted change from baseline vs. placebo, mean (95% CI)[c]**		2.7[d] (1.3 to 4.1)
SF-36 Mental Component Summary[a]	**n=144**	**n=219**
• **Baseline mean**	39.1	39.1
• **Week 6 mean**	39.0	43.5
• **Adjusted mean change from baseline (95% CI)[b]**	–0.0 (–1.6 to 1.5)	4.4 (3.1 to 5.6)
• **Difference in adjusted change from baseline vs. placebo, mean (95% CI)[c]**		4.4[d] (2.5 to 6.4)
EQ-5D Score[a]	**n=144**	**n=219**
• **Baseline mean**	7.4	7.4
• **Week 6 mean**	7.4	6.9
• **Adjusted mean change from baseline (95% CI)[b]**	–0.0 (–0.3 to 0.2)	–0.5 (–0.7 to –0.4)
• **Difference in adjusted change from baseline vs. placebo, mean (95% CI)[c]**		–0.5[d] (–0.7 to –0.2)
EQ-5D VAS Score[a]	**n=142**	**n=217**
• **Baseline mean**	56.4	54.6
• **Week 6 mean**	56.6	65.3
• **Adjusted mean change from baseline (95% CI)[b]**	0.8 (–2.2 to 3.8)	10.4 (7.9 to 12.8)
• **Difference in adjusted change from baseline vs. placebo, mean (95% CI)[c]**		9.6[d] (5.8 to 13.5)

Abbreviations: CI, confidence interval; EQ, EuroQol; HRQOL, 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 HRQOL; lower EQ-5D scores indicate improvements in HRQOL.
[b] Mean changes were adjusted for individual baseline measurements.
[c] Difference = adjusted mean change for VEDO – adjusted mean change for placebo.
[d] Statistically significant result.

Maintenance

Compared to placebo, VEDO every 4 weeks and every 8 weeks resulted in significantly greater improvements in HRQOL as measured by the IBDQ score from baseline to both Week 30 and Week 52, with the differences considered clinically meaningful based on the MIDs. In a posthoc analysis evaluating the Week 52 last observation carried forward (LOCF) data, both VEDO treatment groups achieved substantial improvements in the total IBDQ score compared to the placebo group. By Week 52, patients in both VEDO treatment groups had higher scores than the placebo group on the SF-36 physical component score, mental component score, and all SF-36 scales. For the posthoc analysis evaluating LOCF data at Week 52, the improvements in the SF-36 physical and mental component summaries were considered clinically significant for both VEDO regimens. In this analysis, the VEDO groups had greater improvements than the placebo group except for the VEDO every 4 weeks group on the LOCF Week 52 physical component summary score (the 95% CI included 0). Both VEDO regimens were associated with improvements in HRQOL as assessed by the EQ-5D by Week 52. Although no improvements over placebo were seen with VEDO treatment in the EQ-5D score at Week 30, greater improvements were seen in the EQ-5D VAS score at this time point for patients receiving VEDO every 4 weeks.

Table 26. Patient Reported Outcomes in UC (GEMINI I): Changes From Baseline by Study Visit in the Maintenance Phase (Takeda Data on File 2012)

Endpoint	Placebo	VEDO Every 4 Weeks	VEDO Every 8 Weeks	Endpoint	Placebo	VEDO Every 4 Weeks	VEDO Every 8 Weeks
IBDQ[a] Results							
Week 30 IBDQ	n=98	n=110	n=99				
• **Baseline mean**	123.0	122.7	127.9				
• **Week 30 mean**	159.7	170.6	178.9				
• **Adjusted mean change from baseline (95% CI)[b]**	35.8 (28.4 to 43.3)	46.9 (39.9 to 53.9)	52.9 (45.6 to 60.3)				
• **Difference in adjusted change from baseline vs. placebo, mean (95% CI)[c]**		11.0 (0.8 to 21.2)	17.1 (6.6 to 27.6)				
Week 52 IBDQ	n=58	n=86	n=77	**LOCF Week 52 IBDQ[e]**	n=126	n=124	n=121
• **Baseline mean**	125.8	122.8	130.7	• Baseline mean	122.2	123.7	124.5
• **Week 52 mean**	159.0	183.6	186.8	• Week 52 mean	150.2	172.5	172.4
• **Adjusted mean change from baseline (95% CI)[b]**	32.8 (24.6 to 41.0)	58.5 (51.8 to 65.3)	58.9 (51.8 to 66.0)	• Adjusted mean change from baseline (95% CI)[b]	27.3 (20.8 to 33.9)	49.0 (42.4 to 55.5)	48.4 (41.8 to 55.1)
• **Difference in adjusted change from baseline vs. placebo, mean (95% CI)[c]**		25.7[d] (15.1 to 36.3)	26.1[d] (15.2 to 36.9)	• Difference in adjusted change from baseline vs. placebo, mean (95% CI)[c]		21.6[d] (12.4 to 30.9)	21.1[d] (11.8 to 30.4)
SF-36[a] Results				**EQ-5D[a] Results**			
Week 30 Physical Component Summary	n=99	n=109	n=99	**Week 30 EQ-5D Score**	n=99	n=109	n=98
• **Baseline mean**	39.9	40.7	40.6	• Baseline mean	7.4	7.5	7.4
• **Adjusted mean change from baseline (95% CI)[b]**	6.2 (4.8 to 7.6)	7.5 (6.2 to 8.9)	7.2 (5.8 to 8.6)	• Adjusted mean change from baseline (95% CI)[b]	–0.9 (–1.2 to –0.6)	–0.9 (–1.2 to –0.7)	–1.2 (–1.5 to –0.9)

Endpoint	Placebo	VEDO Every 4 Weeks	VEDO Every 8 Weeks	Endpoint	Placebo	VEDO Every 4 Weeks	VEDO Every 8 Weeks
SF-36[a] Results (cont.)				**EQ-5D[a] Results (cont.)**			
Week 30 Physical Component Summary	n=99	n=109	n=99	**Week 30 EQ-5D Score**	n=99	n=109	n=98
• **Difference in adjusted change from baseline vs. placebo, mean (95% CI)[c]**		1.3 (–0.6 to 3.2)	1.0 (–1.0 to 3.0)	• Difference in adjusted change from baseline vs. placebo, mean (95% CI)[c]		–0.0 (–0.4 to 0.4)	–0.3 (–0.7 to 0.1)
Week 52 Physical Component Summary	n=58	n=86	n=77	**Week 52 EQ-5D Score**	n=58	n=86	n=76
• **Baseline mean**	40.2	40.2	41.4	• Baseline mean	7.3	7.5	7.2
• **Adjusted mean change from baseline (95% CI)[b]**	4.8 (2.9 to 6.6)	8.5 (6.9 to 10.0)	9.5 (7.9 to 11.1)	• Adjusted mean change from baseline (95% CI)[b]	–0.6 (–1.0 to –0.3)	–1.2 (–1.5 to –0.9)	–1.2 (–1.5 to –0.9)
• **Difference in adjusted change from baseline vs. placebo, mean (95% CI)[c]**		3.7[d] (1.3 to 6.1)	4.7[d] (2.3 to 7.2)	• Difference in adjusted change from baseline vs. placebo, mean (95% CI)[c]		–0.6 (–1.1 to –0.1)	–0.6 (–1.1 to –0.1)
Week 52 LOCF Physical Component Summary[e]	n=126	n=123	n=121	**Week 52 LOCF EQ-5D Score[e]**	n=126	n=123	n=121
• **Baseline mean**	39.7	41.1	40.0	• Baseline mean	7.5	7.4	7.5
• **Adjusted mean change from baseline (95% CI)[b]**	4.5 (3.2 to 5.8)	7.3 (6.0 to 8.6)	7.9 (6.6 to 9.2)	• Adjusted mean change from baseline (95% CI)[b]	–0.6 (–0.9 to –0.4)	–1.1 (–1.4 to –0.9)	–1.1 (–1.3 to –0.8)
• **Difference in adjusted change from baseline vs. placebo, mean (95% CI)[c]**		2.8[d] (1.0 to 4.6)	3.3[d] (1.5 to 5.2)	• Difference in adjusted change from baseline vs. placebo, mean (95% CI)[c]		–0.5 (–0.8 to –0.1)	–0.4 (–0.8 to –0.1)

Week 30 Mental Component Summary	**n=99**	**n=109**	**n=99**	**Week 30 EQ-5D VAS Score**	**n=99**	**n=109**	**n=99**
• **Baseline mean**	38.3	37.6	40.1	• Baseline mean	54.6	58.0	52.6
• **Adjusted mean change from baseline (95% CI)[b]**	5.9 (3.8 to 7.9)	8.4 (6.4 to 10.3)	10.2 (8.2 to 12.3)	• Adjusted mean change from baseline (95% CI)[b]	13.4 (9.8 to 17.1)	18.8 (15.3 to 22.3)	19.8 (16.1 to 23.4)
• **Difference in adjusted change from baseline vs. placebo, mean (95% CI)[c]**		2.5 (–0.3 to 5.4)	4.4 (1.5 to 7.3)	• Difference in adjusted change from baseline vs. placebo, mean (95% CI)[c]		5.4 (0.3 to 10.4)	6.3 (1.1 to 11.5)
Week 52 Mental Component Summary	n=58	n=86	n=77	**Week 52 EQ-5D VAS Score**	n=58	n=85	n=76
• **Baseline mean**	39.9	38.2	41.0	• Baseline mean	57.8	51.9	61.6
• **Adjusted mean change from baseline (95% CI)[b]**	3.6 (1.2 to 6.1)	9.6 (7.6 to 11.6)	10.3 (8.2 to 12.4)	• Adjusted mean change from baseline (95% CI)[b]	11.2 (6.8 to 15.6)	22.2 (18.5 to 25.8)	23.7 (19.9 to 27.6)
• **Difference in adjusted change from baseline vs. placebo, mean (95% CI)[c]**		6.0[d] (2.9 to 9.2)	6.6[d] (3.4 to 9.8)	• Difference in adjusted change from baseline vs. placebo, mean (95% CI)[c]		11.0[d] (5.2 to 16.7)	12.5[d] (6.7 to 18.4)
Week 52 LOCF Mental Component Summary[e]	n=126	n=123	n=121	**Week 52 LOCF EQ-5D VAS Score[e]**	n=125	n=123	n=121
• **Baseline mean**	38.5	37.9	39.2	• Baseline mean	54.6	53.6	56.6
• **Adjusted mean change from baseline (95% CI)[b]**	3.9 (2.2 to 5.7)	8.7 (7.0 to 10.5)	8.7 (6.9 to 10.5)	• Adjusted mean change from baseline (95% CI)[b]	9.7 (6.4 to 13.0)	19.4 (16.1 to 22.7)	19.0 (15.6 to 22.3)
• **Difference in adjusted change from baseline vs. placebo, mean (95% CI)[c]**		4.8[d] (2.3 to 7.2)	4.7[d] (2.3 to 7.2)	• Difference in adjusted change from baseline vs. placebo, mean (95% CI)[c]		9.7[d] (5.0 to 14.4)	9.3[d] (4.6 to 14.0)

Abbreviations: CI, confidence interval; EQ, EuroQol; IBDQ, Inflammatory Bowel Disease Questionnaire; LOCF, last observation carried forward; SF-36, Short Form-36; VAS, visual analog scale.
[a] Higher IBDQ, SF-36, and EQ-5D VAS scores indicate less severe disease; lower EQ-5D scores indicate less severe disease.
[b] Mean changes were adjusted for individual baseline measurements.
[c] Difference = adjusted mean change for VEDO – adjusted mean change for placebo.
[d] Statistically significant result.
[e] Posthoc analysis.

Pharmacokinetics and Immunogenicity

Mean steady state concentrations were 11.2±7.2 mcg/mL and 38.3±24.4 mcg/mL for VEDO every 8 weeks and every 4 weeks, respectively (Feagan, 2013). Both regimens achieved more than 95% saturation of the α4β7 integrin on peripheral-blood lymphocytes. Blood samples were available in 620 VEDO-treated patients, of which 23 (3.7%) had samples that were positive for anti-VEDO antibodies at any time, and 6 (1.0%) had samples that were persistently positive (i.e., ≥2 consecutive positive samples) through Week 52.

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 four 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.**

A systematic review and mixed treatment comparison (MTC) were undertaken to calculate the relative treatment effect estimates of efficacy and safety among VEDO and other biologic therapies indicated for the treatment of moderate to severe UC, using indirect comparisons.

The biologic interventions of interest for this review were as follows:

- VEDO (Entyvio)
- Infliximab (Remicade)
- Adalimumab (Humira)
- Golimumab (Simponi)

The objective of the systematic review was to collate the published randomised controlled trials (RCTs) data assessing the efficacy and safety of biological therapies prescribed for the treatment of UC. In terms of PICOS (participants, interventions, comparisons, outcomes, and study design), the patient group of interest is those with

moderate to severe UC, and the intervention of interest is VEDO; comparators are the available biologics, and outcomes are key efficacy and safety outcomes.

The systematic review was conducted in line with Cochrane methodology and following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) recommendations, according to the protocol developed in April 2013. In May 2013, the protocol was amended to also capture the published clinical data assessing the efficacy and safety of surgery and ciclosporin for the treatment of UC, because it was thought that these might be considered relevant comparators to VEDO in the treatment pathway for moderate to severe UC. An updated protocol was developed in February 2014 and was then used to conduct an update of the systematic review.

Full details of the search strategies, inclusion and exclusion criteria have been previously presented in section 6.1 as the same systematic search was used to identify clinical evidence on VEDO and relevant comparators within this appraisal. Further information on the extract search terms can be found in Appendix 10.2 and in the accompanying report for the MTC (Takeda Data on File 2014).

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.**

Biologics and Surgery/Ciclosporin Search Strategy

Please see section 6.1 and 6.2 and associated appendix 10.2 for information on the search strategy and the complete search terms.

Biologics Search Results

The original search and the updated search flow diagram of studies included at each stage for the biologics have been previously presented (see figure 5). A total of 22 articles of which 8 were unique studies were considered relevant for inclusion in the mixed treatment comparison. Reasons for exclusion for the remaining articles are provided in the appendix 10.2. Please also see Appendix 5 for information on the quality assessment of the biologic studies identified for inclusion in the MTC.

Surgery/Ciclosporin Search Results

In view of the submission length, full details for the search on surgery and ciclosporin and complete results are provided in an accompanying report (Takeda Data on File 2014) however, below we provide a summary of the results found in the surgery systematic review.

For the original review, the 9 articles and 1 conference abstract each represented a unique study. Six of the studies evaluated surgery methods: 5 studies on ileal pouch-anal anastomosis (IPAA); 1 study evaluated total colectomy. Five of the studies evaluated ciclosporin

During the conduct of the review, it became clear that cyclosporine is not a relevant comparator to VEDO in the chronic setting, because it is largely used in hospitalised patients with an acute exacerbation. Furthermore, none of the surgery or ciclosporin studies were suitable for meta-analysis for the following reasons:

- Variation in study design; studies were not comparable
- Lack of a common comparator to connect the network; surgery studies tended to compare one approach to another without a placebo arm
- Differing outcomes in each study
- Small sample sizes

For the update, the one abstract represented one unique study. This study (Hicks et al., 2013) evaluated IPAA and was not suitable for meta-analysis due to a lack of a common comparator with the network.

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.**

As mentioned above, a total of 22 articles of which 8 were unique studies were considered relevant for inclusion in the mixed treatment comparison. Reasons for exclusion for the remaining articles are provided in the section 6.2

Table 27. Summary of the trials used to conduct the indirect comparison: Induction Study Characteristics

Trial Name or NCT Code	Methodology	Primary Endpoint Time (Weeks)	Study Duration (Weeks)	Treatment, Dose, and Sample Size (ITT)	Patient Characteristics[a]	Key Outcomes Measured
GEMINI I CSR13006, 4 Sept 2012	DB Pb-RCT Central randomisation; stratified by 1) concomitant oral CS use and 2) prior anti-TNF or concomitant IM	6	6	VEDO (IV) 300 mg at Weeks 0 and 2 n = 225 Placebo n = 149	Adults with moderate to severely active UC with inadequate response to, loss of response to, or intolerance of ≥ 1 of IM or anti-TNF % anti-TNF–naïve: 51-58 Mean age: 40.1-41.2 % male: 59-62	Clinical response (primary endpoint) Clinical remission Mucosal healing Serious AEs Discontinuation due to AEs
ULTRA-1 NCT00385736 Reinisch et al., 2011 [[p. 780]]	DB Pb-RCT Central randomisation	8	8	Adalimumab (SC) 160/80: 160 mg at week 0, 80 mg at week 2, 40 mg at weeks 4 and 6 n = 130 Adalimumab (SC) 80/40: 80 mg at week 0, 40 mg at weeks 2, 4 and 6 n = 130 Placebo n = 130	Ambulatory adults with moderate to severely active UC despite concurrent and stable treatment with oral CSs and/or IMs % anti-TNF–naïve: 100 Mean age: NR (median, 36.5-40 years) % male: 60.0-63.8	Clinical remission (primary endpoint) Clinical response Mucosal healing Serious AEs Discontinuation due to AEs

Trial Name or NCT Code	Methodology	Primary Endpoint Time (Weeks)	Study Duration (Weeks)	Treatment, Dose, and Sample Size (ITT)	Patient Characteristics[a]	Key Outcomes Measured
ULTRA-2 Sandborn et al., 2012 [[p. 257]]	DB Pb-RCT Central randomisation and stratification by prior infliximab or other anti-TNF exposure	8	52	Adalimumab (SC) 160 mg at week 0, 80 mg at week 2 and then 40 mg eow beginning at week 4 n = 258 Placebo n = 260	Adults with moderate to severely active UC for ≥ 3 months despite concurrent therapy with steroids and/or AZA or 6-MP % anti-TNF–naïve: 58.9-60.9 Mean age: 39.6-41.3 years % male: 57.3-61.8	Clinical remission (primary endpoint) Clinical response Mucosal healing
ACT-1 Rutgeerts et al., 2005 [[p. 2462]]	DB Pb-RCT Central randomisation; stratified by investigational site and CS-refractory UC	8	54	Infliximab (IV), 5 mg per kilogram of body weight at weeks 0, 2, and 6 n = 121 Infliximab (IV), 10 mg per kilogram of body weight at weeks 0, 2, and 6 n = 122 Placebo n = 121	Adults with moderate to severely active UC despite concurrent treatment with CS ± AZA or 6-MP[b] % anti-TNF–naïve: 100 Mean age: 41.4-42.4 years % male: 59-64.5	Clinical response (primary endpoint) Clinical remission

Trial Name or NCT Code	Methodology	Primary Endpoint Time (Weeks)	Study Duration (Weeks)	Treatment, Dose, and Sample Size (ITT)	Patient Characteristics[a]	Key Outcomes Measured
ACT-2 Rutgeerts et al., 2005 [[p. 2462]]	DB Pb-RCT Central randomisation; stratified by investigational site and CS-refractory UC	8	30	Infliximab (IV) 5 mg/kg at weeks 0, 2, and 6 Infliximab (IV) 10 mg/kg at weeks 0, 2, and 6 Placebo	Adults with moderate to severely active UC despite concurrent treatment with CS ± AZA or 6-MP and 5-aminosalicylate-containing medications[c] % anti-TNF–naïve: 100 Mean age: 39.3-40.5 years % male: 56.7-62.8	Clinical response (primary endpoint) Clinical remission Mucosal healing
PURSUIT-SC Sanborn et al., 2014 [[p. 96]]	DB Pb-RCT Central randomisation; in phase 2, stratified by investigational site; after phase 2, permuted block randomisation scheme	6	6	Golimumab (SC) 400 mg at week 0 and 200 mg at week 2 n = 331 Golimumab (SC) 200 mg at week 0 and 100 mg at week 2 n = 331 Golimumab (SC) 100 mg at week 0 and 50 mg at week 2 n = 72 Placebo n = 331	Adults with moderate to severely active UC; no minimum disease duration; and inadequate response to, or intolerance of ≥ 1 of conventional therapies; or were CS-dependent % anti-TNF–naïve: 100 Mean age: 39-40.9 years % male: 52.9-60.7	Clinical response (primary endpoint) Clinical remission Mucosal healing Serious AEs Discontinuation due to AEs

Trial Name or NCT Code	Methodology	Primary Endpoint Time (Weeks)	Study Duration (Weeks)	Treatment, Dose, and Sample Size (ITT)	Patient Characteristics[a]	Key Outcomes Measured
Suzuki (2014) (Suzuki et al. 2014) [[p. 283]]	DB Pb-RCT Randomisation was based on a centrally designed randomisation table	8	52	Adalimumab (SC) 160 mg at week 0, 80 mg at week 2, and then 40 mg eow beginning at week 4 n = 90 Adalimumab (SC) 80 mg at week 0, 40 mg at week 2, and then 40 mg eow beginning at week 4 n = 87 Placebo n = 96	Japanese patients age ≥ 15 years with biopsy-confirmed, moderately to severely active UC despite concurrent treatment with stable doses of oral corticosteroids and/or immunomodulators % anti-TNF–naïve: 100 Mean age: 41.3-44.4 years % male: 57.5-67.8	Clinical response Clinical remission Mucosal healing Serious AEs Discontinuation due to AEs

6-MP, 6-mercaptopurine; AZA, azathioprine; CS, corticosteroid; DB, double blind; eow, every other week; IM, immunomodulator; ITT, intention-to-treat; IV, intravenous; NR, not reported; Pb-RCT, placebo-controlled, randomised trial; SC, subcutaneous; UC, ulcerative colitis.
Notes: Clinical remission = A Mayo score of 2 points or lower and no individual subscore above 1.
Clinical response = A decrease from baseline in the total Mayo score by at least 3 points and at least 30% with an accompanying decrease in rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1.
Mucosal healing was defined as a Mayo endoscopy subscore of 0 or 1.
[a] A range of values indicates across treatment groups (e.g., mean age).
[b] In ACT-1, concurrent therapy was not required of patients who had no response to corticosteroids within 18 months prior to enrolment or no response to azathioprine or mercaptopurine within 5 years prior to enrolment, or patients who could not tolerate corticosteroids, azathioprine, or mercaptopurine. Rutgeerts et al., 2005 [[p. 2462]]
[c] In ACT-2, concurrent therapy was not required of patients who had no response to corticosteroids or 5-aminosalicylate-containing medications within 18 months prior to enrolment or no response to azathioprine or mercaptopurine within 5 years prior to enrolment, or patients who could not tolerate corticosteroids, azathioprine, mercaptopurine, or 5-aminosalicylate-containing medications. Rutgeerts et al., 2005 [[p. 2462]]
[d] Conventional therapies are oral mesalamine, oral CSs, AZA, and 6-MP.

Table 28. Maintenance Study Characteristics

Trial Name or NCT Code	Methodology	Primary Endpoint Time (Weeks)	Study Duration (Weeks)	Treatment, Dose, and Sample Size	Patient Characteristics[a]	Key Outcomes Measured
GEMINI I CSR13006, 4 Sept 2012	DB RCT Central randomisation; stratified by 1) concomitant oral CS use and 2) prior anti-TNF or concomitant IM Responders to 6 weeks of VEDO induction were randomised to maintenance therapy	52	66	VEDO (IV) 300 mg every 4 weeks from week 6 to week 50 n = 125 (ITT) VEDO (IV) 300 mg every 8 weeks from week 6 to week 50 n = 122 (ITT) n = Placebo n = 126 (ITT)	Adults with moderate to severely active UC with inadequate response to, loss of response to, or intolerance of ≥ 1 of IM or anti-TNF % anti-TNF–naïve: 58-63 (ITT) Mean age: 38.6-41 years (ITT) % male: 54-57 (ITT)	Clinical remission (primary endpoint) Durable clinical response (clinical response at both 6 and 52 weeks) Clinical response at 52 weeks CSF remission Mucosal healing Serious AEs Discontinuation due to AEs
ULTRA-2 Sandborn et al., 2012 [[p. 257]]; Sandborn et al., 2011d [[pS4]]	DB RCT Central randomisation and stratification by prior infliximab or other anti-TNF exposure Patients were randomised to an induction plus maintenance regimen at baseline[b]	52	52	Adalimumab (SC) 160 mg at week 0, 80 mg at week 2 and then 40 mg eow beginning at week 4 to through week 52 n = NR (248 treated) Placebo n = NR (246 treated)	Adults with moderate to severely active UC for ≥ 3 months despite concurrent therapy with steroids and/or AZA or 6-MP % anti-TNF–naïve: 58.9-60.5 Mean age: NR % male: NR	Clinical remission (primary endpoint) Durable clinical response (clinical response at both weeks 8 and 52) Clinical response at week 52 Mucosal healing Discontinuations due to AEs

Trial Name or NCT Code	Methodology	Primary Endpoint Time (Weeks)	Study Duration (Weeks)	Treatment, Dose, and Sample Size	Patient Characteristics[a]	Key Outcomes Measured
ACT-1 Rutgeerts et al., 2005 [[p. 2462]]	DB RCT Central randomisation; stratified by investigational site and CS-refractory UC Patients were randomised to an induction plus maintenance regimen at baseline[b]	8	54	Infliximab (IV), 5 mg per kilogram of body weight every 8 weeks through week 46 n = 121 Infliximab (IV), 10 mg per kilogram of body weight every 8 weeks through week 46 n = 122 Placebo n = 121	Adults with moderate to severely active UC despite concurrent treatment with CS ± AZA or 6-MP[b] % anti-TNF–naïve: 100 Mean age: 41.4-42.4 years % male: 59-64.5	Clinical remission Durable clinical response (clinical response at both weeks 8 and 30) Clinical response at week 54 Discontinuation due to AEs CSF remission Mucosal healing
PURSUIT-M Sandborn et al., 2014 [[p. 85]]	DB RCT Adaptive randomisation based on investigational site, clinical remission status, and CS use at PURSUIT-M baseline, and induction therapy Responders to 6-weeks of induction golimumab were randomised at maintenance baseline visit	54	54	Golimumab (SC) 50 mg every 4 weeks through to 52 weeks n = 154 Golimumab (SC) 100 mg every 4 weeks through to 52 weeks n = 154 Placebo n = 156	Adults with moderate to severely active UC; no minimum disease duration; and inadequate response to, or intolerance of ≥ 1 of conventional therapies[d]; or were CS-dependent % anti-TNF–naïve: 100 Mean age: 39.1-41.4 years % male: 48.1-57.8	Durable clinical response (maintained from induction response to week 54) (primary endpoint) Clinical response at week 54 Clinical remission Serious AEs Discontinuation due to AEs

Trial Name or NCT Code	Methodology	Primary Endpoint Time (Weeks)	Study Duration (Weeks)	Treatment, Dose, and Sample Size	Patient Characteristics[a]	Key Outcomes Measured
Suzuki (2014) Suzuki et al., 2014 [[p. 283]]	DB RCT Randomisation was based on a centrally designed randomisation table Patients were randomised to an induction plus maintenance regimen at baseline[b]	52	52	Adalimumab (SC) 160 mg at week 0, 80 mg at week 2, or 80 mg at week 0, 40 mg at week 2; and then 40 mg eow beginning at week 4 n = NR (177 treated) Placebo n = NR (96 treated)	Japanese patients aged ≥ 15 years with biopsy-confirmed, moderately to severely active UC despite concurrent treatment with stable doses of oral corticosteroids and/or immunomodulators[b] % anti-TNF–naïve: 100 Mean age: NR % male: NR	Clinical response at week 52 Clinical remission Mucosal healing

Discussion of the trials used in the MTC

It can be seen from the tables presented above there are some differences in patient populations between studies. The main patient characteristic that might affect outcomes is prior anti-TNF exposure. Patients who have previously received treatment with anti-TNFs may be a more difficult to treat population than those that are anti-TNF–naïve; it is, therefore, important to compare similar populations. For this reason, where data were available, we conducted analyses of anti-TNF–naïve and anti-TNF–experienced/failure subpopulations separately; the reasoning behind these analyses is described further below.

In the vedolizumab trials, patients who had failed previous anti-TNF therapy were analysed as an important subgroup. The label will include the anti-TNF failure population defined as patients with inadequate response, loss of response or intolerance to anti-TNF.

Few comparator studies provided data according to prior anti-TNF experience and many of those which did, only included anti-TNF–naïve patients; in particular, all infliximab and golimumab studies. Studies which did present data for more than one population presented data for anti-TNF–naïve and anti-TNF experienced patients. Unlike the anti-TNF failure population; anti-TNF experienced patients 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 studies. 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. The table below shows the definitions of the anti-TNF–experienced/failure subpopulations.

Table 29. Definition of Anti-TNF–Experienced/Failure Population

Trial	Biologic Studied	Anti-TNF–Experienced/Failure Subpopulation	Subpopulation Definition
GEMINI I	Vedolizumab 300 mg, Q4W, Q8W	Failure	Patients with prior TNF antagonist failure
ULTRA-2	Adalimumab 160 mg/80 mg, 40 mg eow	Experienced	Patients with prior anti-TNF experience Previous use of anti-TNF agents other than adalimumab was permitted if the patient had discontinued its use due to a loss of response or intolerance to the agent for longer than 8 weeks

Only robust studies of similar design have been included. However the clinical trials varied in terms of study design and patient populations; (i.e., heterogeneity between trials).

Two maintenance studies had a study design in which all patients were randomized based on response criteria following induction therapy (GEMINI I and PURSUIT M). In comparison, in ULTRA-2, ACT-1, and Suzuki (2014), patients were randomized to induction and maintenance regimens at baseline.

The analyses presented in question 6.7.6 include ULTRA-2, ACT-, and Suzuki (2014), to allow the inclusion of adalimumab and infliximab in the comparisons. If ULTRA-2, ACT-1, and Suzuki (2014) are excluded, only vedolizumab and golimumab are included in the analysis of anti-TNF–naïve patients, and no MTC of anti-TNF experienced patients is possible. The different study design may have implications for the results: in ULTRA-2, ACT 1, and Suzuki (2014), patients who had not responded after induction were maintained on the same treatment and contribute to the efficacy data at the end of maintenance, whereas in GEMINI-I and PURSUIT-M only patients who responded to induction therapy were included in the maintenance analysis, and were re-randomized to either active treatment or placebo at the start of maintenance.

In addition, duration of studies varied slightly; in the induction studies, the time point for the primary efficacy analyses was either 6 weeks (GEMINI I and PURSUIT-SC) or 8 weeks (ULTRA-1, ULTRA-2, ACT-1, ACT-2, Suzuki [2014]). The MTC included only the primary endpoint data since this is how the treatments are labelled. The

results should therefore be interpreted as being for the complete treatment regimens instead of purely by treatment. Since we only had data for 6 and 8 weeks, it was not possible to try to take into account the effect of time.

In the maintenance studies, the time point for primary efficacy analyses was either 52 weeks (GEMINI I, ULTRA-2, Suzuki [2014]) or 54 weeks (ACT-1, PURSUIT-M). In maintenance studies, this time difference was not considered likely to affect results; no studies relied on data from an earlier time point (e.g., 26 weeks), when previous therapy may still affect results.

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 5. The table below highlights the data that has been extracted from the 8 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 and having SAEs 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 30. Summary of data available for the analyses that are presented in Appendix 5

Study Population (Study Phase)	Clinical Response	Clinical Remission	Discontinuation due to AEs	Serious Adverse Events (SAEs)
ITT (Induction)	√	√	√	√
ITT (Maintenance)		√	√	√
TNF Naïve (Induction)	√	√	√	
TNF Naïve (Maintenance)		√	√	
TNF Experienced/Failure (Induction)	√	√		
TNF Experienced/Failure (Maintenance)		√		

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 & Ades 2004). However, instead of the models being run directly from within WinBUGS or OpenBUGS (Lunn et al. 2000), the R package R2WinBUGS (Sturtz et al. 2005) was used to run OpenBUGS. The data were therefore 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.

- 3 chains
- Burnin of 20,000 iterations
- Total of 60,000 iterations
- Thin rate of 50

Bayesian Fixed Effects MTC

The Bayesian fixed effects model was run for all of the subpopulation MTCs (i.e., anti-TNF–naïve or experienced alone) and some of the whole population networks that contained a sufficient number of closed loops to be able to estimate the random effect.

The full fixed model is shown below

$$r_{jk} \sim Binomial(p_{jk}, n_{jk})$$
$$logit(P_{jk}) = \mu_j + d_{XY} I(k = Y)$$

The remaining contrasts (functional parameters) can be expressed in terms of these basic parameters (example for three treatments).

$$d_{BC} = d_{AC} - d_{AB}$$
$$d_{BD} = d_{AD} - d_{AB}$$
$$d_{CD} = d_{AD} - d_{AC}$$

with

$$d_{AA} = 0$$

The code used to run the Bayesian fixed effects MTCs is displayed in Appendix 14.

Bayesian Random Effects MTC

Bayesian random effects MTCs were only conducted on networks where closed loops existed. However, the results did not appear to be reliable; the resulting credible intervals appeared inflated, with none of the active treatments showing improvement over placebo. Welton and colleagues warn about use of informative or weekly informative priors where there is insufficient information in the network to reliably estimate the random error (Welton et al. 2012).

The full model is shown below

$$r_{jk} \sim Binomial(p_{jk}, n_{jk})$$
$$logit(P_{jk}) = \mu_j + \delta_{jXY} I(k = Y)$$
$$\delta_{jXY} = N(d_{XY}, \sigma_{XY}{}^2)$$

The remaining contrasts (functional parameters) can be expressed in terms of these basic parameters:

$$d_{BC} = d_{AC} - d_{AB}$$
$$d_{BD} = d_{AD} - d_{AB}$$
$$d_{CD} = d_{AD} - d_{AC}$$

with

$$d_{AA} = 0$$

The code used to run the random effects MTCs is displayed in Appendix 14.

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 SAEs 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), (Dias et al. 2012). The WinBUGS code used to run this model is provided in Appendix 14.

6.7.6 Please present the results of the analysis.

The primary analysis presented here is the subgroup analyses 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. Undertaking the subgroup analyses ensured that similar patient populations were compared, but also reduced the size of the networks analysed. Data for the analysis of the entire study

population are also presented for completeness. The results should be interpreted with consideration for the different populations included in the various studies as discussed above.

In terms of the anti-TNF experienced population, limited data were available. While 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 by definition may have responded to prior anti-TNF therapy). Despite this difference, vedolizumab did not demonstrate significant differences in efficacy to adalimumab in this population.

Summary of the MTC results

- In anti-TNF naïve patients, vedolizumab and infliximab had constantly higher odds ratios for the efficacy endpoints compared with adalimumab and golimumab; although the only significant differences were for comparisons between infliximab and vedolizumab compared to adalimumab. In the maintenance treatment of anti-TNF–naïve patients, vedolizumab Q8W was significantly better than golimumab and infliximab 5 mg in terms of durable clinical response, and both vedolizumab regimens were significantly better than adalimumab 40 mg eow in terms of durable clinical response and mucosal healing. In both induction and maintenance treatment of anti-TNF–naïve patients, vedolizumab was found to result in lower rates of discontinuation due to AEs than some comparators (induction: adalimumab; maintenance: vedolizumab Q4W versus adalimumab, golimumab, and infliximab).
- In the failed/experienced patient population the only comparison that could be made for vedolizumab was with adalimumab which was for anti-TNF-experienced patients (compared to GEMINI I which looked at ant-TNF-failed patients). In the induction phase, vedolizumab had directionally better efficacy for response, remission but none of the differences were significant compared to adalimumab and only response for vedolizumab was significantly better than placebo. In the maintenance phase the only data available for adalimumab was for non-re-randomized patients so a further assumption was needed i.e. patients that responded at 12 months must have also responded

at end of induction. All of the vedolizumab results were significantly better compared to placebo.

Anti-TNF naïve sub-population: *Induction*

Table 31. Summary of MTC: Induction Anti-TNF–Naïve Subpopulation: Odds Ratio vs. VEDO (95% CI)

Outcome Measured	Placebo	Adalimumab 80 mg/ 40 mg	Adalimumab 160 mg/ 80 mg	Golimumab 200 mg/ 100 mg	Golimumab 400 mg/ 200 mg	Infliximab 5 mg/kg	Infliximab 10 mg/kg
Clinical response	2.62 (1.69, 4.2)	1.88 (1.09, 3.40)	1.48 (0.90, 2.50)	1.04 (0.58, 1.80)	0.91 (0.51, 1.6)	0.64 (0.36, 1.2)	0.69 (0.39, 1.3)
Clinical remission	3.67 (1.67, 9.1)	3.00 (1.15, 8.30)	2.09 (0.88, 5.7)	1.05 (0.39, 3.1)	1.11 (0.4, 3.1)	0.72 (0.29, 1.9)	0.97 (0.39, 2.6)
Discontinuation due to AEs	0 (0,0.18)	0 (0, 0.28)	0 (0, 0.16)	0 (0, 1.51)	0 (0, 1.63)	NA	NA

Table 32. Summary of MTC: Maintenance Anti-TNF–Naïve Subpopulation: Odds Ratio vs. VEDO Q4W (95% CrI)

Outcome Measured	Placebo	Adalimumab 40 mg eow	Golimumab 50 mg	Golimumab 100 mg	Infliximab 5 mg/kg	Infliximab 10 mg/kg
Clinical remission	3.83 (1.94, 8.98)	2.28 (0.88, 6.18)	2.26 (0.96, 5.71)	2.16 (0.92, 5.38)	3.16 (1.05, 8.88)	2.46 (0.86, 7.15)
Discontinuation due to AEs	-2.54 (0, 0.54)	-3.36 (0, 0.3)	-2.34 (0, 0.87)	-2.94 (0, 0.43)	-2.44 (0, 0.78)	-2.54 (0, 0.68)

Table 33. Summary of MTC: Maintenance Anti-TNF–Naïve Subpopulation: Odds Ratio vs. VEDO Q8W (95% CrI)

Outcome Measured	Placebo	Adalimumab 40 mg eow	Golimumab 50 mg	Golimumab 100 mg	Infliximab 5 mg/kg	Infliximab 10 mg/kg
Clinical remission	3.67 (1.85, 7.88)	2.14 (0.81, 5.82)	2.1 (0.9, 5.32)	2.01 (0.82, 4.97)	2.93 (1.03, 8.46)	2.3 (0.78, 6.69)
Discontinuation due to AEs	-1.17 (0.06, 1.13)	-1.97 (0.02, 0.67)	-0.96 (0.06, 1.97)	-1.55 (0.03, 0.99)	-1.07 (0.05, 1.69)	-1.14 (0.05, 1.48)

Table 34. Summary of MTC: Induction Anti-TNF–Experienced/Failure Subpopulation: Odds Ratio vs. VEDO (95% CrI)

Outcome Measured	Placebo	Adalimumab 160mg/80mg
Clinical response	2.5 (1.2, 5.5)	1.7 (0.7, 4.4)
Clinical remission	-3.7 (0.9, 28)	2.7 (0.4, 24)

Table 35. Summary of MTC: Maintenance Anti-TNF–Experienced/Failure Subpopulation: Odds Ratio vs. VEDO Q4W (95% CrI)

Outcome Measured	Placebo	Adalimumab 40mg eow
Clinical remission	11 (2.62, 76.0)	3.06 (0.34, 31.0)

Table 36. Summary of MTC: Maintenance Anti-TNF–Experienced/Failure Subpopulation: Odds Ratio vs. VEDO Q8W (95% CrI)

Outcome Measured	Placebo	Adalimumab 40mg eow
Clinical remission	12 (3.14, 78)	34 (0.4, 33)

Table 37. Summary of MTC: Induction ITT population: Odds Ratio vs. VEDO (95% CrI)

Outcome Measured	Placebo	Adalimumab 80 mg/ 40 mg	Adalimumab 160 mg/ 80 mg	Golimumab 200 mg/ 100 mg	Golimumab 400 mg/ 200 mg	Infliximab 5 mg/kg	Infliximab 10 mg/kg
Clinical response	2.6 (1.68, 4.1)	1.82 (1.01, 3.4)	1.48 (0.89, 2.5)	1.02 (0.58, 1.8)	0.9 (0.51, 1.6)	0.64 (0.34, 1.2)	0.68 (0.39, 1.2)
Clinical remission	3.67 (1.67, 9.1)	3 (1.15, 8.3)	2.09 (0.88, 5.7)	1.05 (0.39, 3.1)	1.11 (0.4, 3.1)	0.72 (0.29, 1.9)	0.97 (0.39, 2.6)
Discontinuation due to AEs	0 (0, 0.18)	0 (0, 0.28)	0 (0, 0.16)	0 (0, 1.51)	0 (0, 1.63)	NR	NR
Serious Adverse Events	1.35 (0.09, 0.9)	2.23 (0.17, 3.31)	1.82 (0.15, 2.26)	2.01 (0.18, 2.8)	1.82 (0.14, 2.12)	NR	NR

Table 38. Summary of MTC: Maintenance ITT population: Odds Ratio vs. VEDO Q4W (95% CrI)

Outcome Measured	Placebo	Adalimumab 40 mg eow	Golimumab 50mg	Golimumab 100mg	Infliximab 5 mg	Infliximab 10 mg
Clinical remission	4.33 (2.46, 8.02)	1.71 (0.76, 3.96)	2.51 (1.16, 5.51)	2.35 (1.1, 5.33)	3.49 (1.41, 8.73)	2.73 (1.06, 6.9)
Discontinuation due to AEs	0.4 (0.1, 0.9)	0.4 (0.1, 1.1)	0.4 (0.1, 1.7)	0.2 (0.1, 0.8)	0.4 (0.1, 1.5)	0.4 (0.1, 1.2)
Serious Adverse Events	0.5 (0.33, 1.1)	0.46 (0.19, 1.11)	0.45 (0.14, 1.44)	0.25 (0.08, 0.72)	0.63 (0.24, 1.72)	0.56 (0.21, 1.53)

Table 39. Summary of MTC: Maintenance ITT Population: Odds Ratio vs. VEDO Q8W (95% CrI)

Outcome Measured	Placebo	Adalimumab 40 mg eow	Golimumab 50mg	Golimumab 100mg	Infliximab 5 mg	Infliximab 10 mg
Clinical remission	3.78 (2.04, 7.19)	1.5 (0.64, 3.51)	2.2 (0.99, 4.92)	2.08 (0.96, 4.71)	3.06 (1.21, 7.91)	2.35 (0.9, 6.11)
Discontinuation due to AEs	0.4 (0.2, 1.1)	0.5 (0.2, 1.4)	0.5 (0.1, 2.2)	0.3 (0.1, 1)	0.5 (0.1, 1.7)	0.4 (0.1, 1.6)
Serious Adverse Events	0.47 (0.19, 1)	0.43 (0.16, 1.03)	0.42 (0.13, 1.36)	0.23 (0.07, 0.67)	0.59 (0.21, 1.52)	0.52 (0.19, 1.34

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.**

Based on clinical considerations and data availability, we explored the impact of the following list of covariates on the outcomes of interest using meta-regression analyses.

- Proportion of Anti-TNF naïve patients
- Proportion of males
- Mean age
- Week (primary endpoint) (for induction)

For UC there was no baseline severity information available. Baseline Mayo or partial Mayo scores were recorded differently by study. Some use mean, whilst others used median or proportion of patients in different categories. The covariates used in the analysis were included as fixed effects in the MTC models. Treatment was also included and was grouped according to treatment name (ignoring dose etc.) to help reduce the number of parameters in the model. We recorded the test for statistical significance for each covariate in each model. This type of technique assumes that all the important variables are included in the analysis. If this assumption does not hold and there is significant variation in the network, then this can produce misleading results by falsely indicating significance which was due to unknown factors. The networks used in this study were considered to be too small to perform this type of analysis.

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.**

The ULTRA-2, Suzuki (2014), and ACT-1 studies of adalimumab and infliximab, respectively had a different design to the GEMINI-I and PURSUIT-M studies. They have been included in the MTC to allow comparison with adalimumab and infliximab that would not otherwise be possible; sensitivity

analyses without these three studies have been conducted and are presented in below. In those studies that did not re-randomise, the percentage of responders at the end of induction and the end of maintenance was used as a proxy of durable response in the re-randomised studies.

Maintenance MTC results excluding ACT-1, ULTRA-2, and Suzuki (2014):

Table 40. Summary of MTC: Maintenance Anti-TNF–Naïve Subpopulation: Odds Ratio vs. VEDO Q4W (95% CrI)

Outcome Measured	Placebo	Golimumab 50 mg	Golimumab 100 mg
Clinical remission	4 (1.9, 8.8)	2.3 (1, 5.7)	2.2 (0.9, 5.3)
Discontinuation due to AEs	0.1 (0, 0.5)	0.1 (0, 0.8)	0 (0, 0.4)

Table 41. Summary of MTC: Maintenance Anti-TNF–Naïve Subpopulation: Odds Ratio vs. VEDO Q8W (95% CrI)

Outcome Measured	Placebo	Golimumab 50 mg	Golimumab 100 mg
Clinical remission	3.7 (1.8, 7.8)	2.1 (0.9, 5.2)	2 (0.9, 5.1)
Discontinuation due to AEs	0.3 (0.1, 1.1)	0.4 (0.1, 1.9)	0.2 (0, 1)

Anti-TNF Experienced/Failure Patients Maintenance

Analysis at this time point in the anti-TNF–experienced/failure subpopulation was not possible, when excluding ACT-1 and ULTRA-2, because data were available only for VEDO.

Table 42. Summary of MTC: Maintenance All Patients: Odds Ratio vs. VEDO Q4W (95% CrI)

Outcome Measured	Placebo	Golimumab 50 mg	Golimumab 100 mg
Clinical remission	4.3 (2.4, 8)	2.5 (1.2, 5.4)	2.4 (1.1, 5.3)
Discontinuation due to AEs	0.4 (0.1, 0.9)	0.4 (0.1, 1.9)	0.2 (0.1, 0.8)
Serious Adverse Events	0.5 (0.2, 1.1)	0.4 (0.1, 1.4)	0.2 (0.1, 0.7)

Table 43. Summary of MTC: Maintenance All patients: Odds Ratio vs. VEDO Q8W (95% CrI)

Outcome Measured	Placebo	Golimumab 50 mg	Golimumab 100 mg
Clinical remission	3.8 (2.2, 7.2)	2.2 (1, 4.7)	2.1 (1, 4.6)
Discontinuation due to AEs	0.4 (0.2, 1.1)	0.5 (0.1, 2.1)	0.3 (0.1, 1)
Serious Adverse Events	0.5 (0.2, 1)	0.4 (0.1, 1.3)	0.2 (0.1, 0.7)

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

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.

Meta-regression analyses were conducted to try to explain some of the between study heterogeneity. However, due to the number of studies included the resulting models with the covariates were underpowered and so non-significant results have little meaning.

Heterogeneity checks on placebo response rates were also performed to investigate the similarity of patient populations between trials; unless otherwise stated, patient populations were found to be consistent.

The design of the studies for the maintenance phase differed across studies with some studies following the same patients throughout both phases and others re-randomizing responders. This meant that the available network of evidence was very limited for the maintenance phase. We did try and expand the network using different assumptions as sensitivity analyses by using the number of responders at end of induction and end of maintenance for the studies that followed the same patients. However , this made the assumption that patients that responded at end of maintenance also all responded at end of induction and it may not fully address carry-over effects from the induction phase (although end of maintenance was only considered at around 52 weeks).

All the treatments were directly connected to placebo and no closed loops existed that were formed by more than one trial, no tests could be performed to look at consistency/inconsistency in the network.

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.**

Not applicable as there were 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 was a secondary outcome of the GEMINI I study so no separate search was undertaken for safety.

Three further key sources of evidence on the safety profile of VEDO will be presented in this section in addition to results from GEMINI I.

- 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 VEDO in patients with UC and CD will be presented (Colombel, B. E. Sands, et al. 2013a).
- Results from a pooled safety analysis of two phase 3 GEMINI studies VEDO randomised placebo-controlled in IBD (UC and CD). (Colombel et al. 2012)
- Results from an integrated safety analysis of six VEDO randomised placebo-controlled in IBD (UC and CD) (Colombel, B. E. Sands, et al. 2013b).

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.**

(a) GEMINI I Safety Summary

Table 44. Adverse Events Occurring in ≥5% of Patients Receiving VEDO (GEMINI I Safety Population)* (Feagan, 2013)

Event	Placebo N=275 n (%)	VEDO (N=620) n (%)
• **Headache**	28 (10.2)	80 (12.9)
• **Ulcerative colitis**	58 (21.1)	97 (15.6)
• **Nasopharyngitis**	26 (9.5)	80 (12.9)
• **Upper respiratory tract infection**	21 (7.6)	52 (8.4)
• **Arthralgia**	25 (9.1)	56 (9.0)
• **Nausea**	19 (6.9)	38 (6.1)
• **Abdominal pain**	10 (3.6)	35 (5.6)
• **Anaemia**	16 (5.8)	35 (5.6)
• **Fatigue**	10 (3.6)	33 (5.3)
• **Cough**	13 (4.7)	36 (5.8)
• **Any serious adverse event**	37 (13.5)	77 (12.4)
• **Any serious infection†**	8 (2.9)	12 (1.9)
• **Any cancer**	3 (1.1)‡	1 (0.2)§

*** Adverse events were classified according to the MedDRA SOC categorisation and preferred terms. Patients with >1 event in a category were counted only once if the start and stop dates of the multiple events overlapped or if the start and stop dates were the same; if the start and stop dates of the multiple events did not overlap, they were counted as separate events.**
The safety population was defined as all patients who received at least one dose of the study drug.
The VEDO group includes patients who received maintenance therapy with VEDO (patients who had a response to VEDO as induction therapy and who were assigned to VEDO every 4 weeks or every 8 weeks during the trial of maintenance therapy and patients who did not have a response to VEDO as induction therapy).
The placebo group includes patients who did not receive maintenance therapy with VEDO (patients assigned to placebo during the trial of induction therapy and patients who had a response to VEDO during that trial and who were assigned to placebo in the trial of maintenance therapy).
† A serious infection was defined as a serious adverse event of infection according to the MedDRA, version 15, criteria.
‡ Colon cancer, transitional-cell carcinoma, and squamous-cell carcinoma of the skin occurred in 1 patient each in the placebo group.
§ Colon cancer occurred in 1 patient in the VEDO group.

(b) GEMINI Long-Term Safety Trial: UC and CD Patients Receiving VEDO (C13008)

This Phase III, open-label, multicentre, long-term safety study is ongoing and evaluating VEDO in patients with UC and CD (Colombel, B. Sands, et al. 2013a). The objective of this study is to collect and characterise important clinical safety events resulting from chronic VEDO 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 VEDO every 4 weeks for up to a maximum of 7 years (or until VEDO 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 VEDO trials and who tolerated VEDO treatment in the opinion of the investigator, or who had moderate to severe CD or UC that had not previously received VEDO. Therapeutic doses of conventional therapies for CD or UC 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 UC and 37.7 years (SD 12.52) for those with CD. VEDO exposure was ≥6, ≥12, and ≥24 months for 1534, 1149, and 502 patients, respectively.

The safety profile of VEDO in long-term extension study was similar to that observed in the prior 12-month Phase III trials. Drug-related AEs were similar between UC and CD patients with the most common AEs being headache 6%, nasopharyngitis 4%, nausea 4%, arthralgia 4%, upper respiratory infection 3%, and fatigue 3%.

Table 45. GEMINI Long term study - 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 • **Serious infection** • **Drug related** • **Leading to discontinuation**	127 (18%) 30 (4%) 15 (2%) 23 (3%)	285 (25%) 74 (7%) 51 (5%) 65 (6%)
Death	3 (<1)*	3 (<1)†

AE, adverse event; CD, Crohn's disease; SAE, serious adverse event; UC, ulcerative colitis
*** Respiratory failure, acute stroke, pulmonary embolism**
† 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 UC or CD most commonly reported (5% each). Malignancies were observed in <1% of patients (two cases of colon cancer and two malignant melanomas).

(c) Vedolizumab Pooled Safety Analyses

Data were pooled from 2 phase 3, randomized, placebo-controlled, double-blind studies (GEMINI I] and GEMINI 2 (CD patients))(Colombel et al. 2012) . 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.

This analysis concluded that patients receiving VEDO had higher rates of overall AEs and SAEs vs. placebo; however, the overall incidence of AEs adjusted for patient-years was higher for placebo vs. VEDO groups. Data from this integrated safety analysis support the safety of VEDO for the treatment of moderately to severely active UC or CD.

The incidence of AEs occurring in ≥10% of patients is shown in the table below:

Table 46. Incidence of AEs in >10% of patients: Pooled Analysis of two Phase 3 Gemini studies

Preferred Term	ITT-Placebo* (n=279)		Non-ITT Placebo† (n=297)		Vedolizumab (n=1434)	
	Pts n (%)	Events (per 100 P-Y)	Pts n (%)	Events (per 100 P-Y)	Pts n (%)	Events (per 100 P-Y)
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

A second integrated analysis of pooled safety data from six randomised placebo-controlled trials of VEDO in UC and CD has been presented recently (Colombel, B. E. Sands, et al. 2013b). 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.

The baseline characteristics across the studies are shown below. In general, 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 2700 patients with UC or CD have received ≥1 infusion of VEDO and the median duration of VEDO exposure was approximately 1 year.

Table 47. Baseline Characteristics for the Majority of Patients Included in the Integrated Safety Population

Baseline Characteristic	C13006 UC (N=895)	C13007 CD (N=1115)	C13011 CD (N=416)	C13008 Direct Enrolment UC and CD (N=421)
Age, mean (SD), y	40 (13)	36 (12)	38 (13)	39 (14)
Sex, n (%)				
• **Male**	525 (59)	520 (47)	180 (43)	206 (49)
• **Female**	370 (41)	595 (53)	236 (57)	215 (51)
Disease Duration, n (%)				
• **<1 year**	64 (7)	69 (6)	23 (6)	25 (6)
• **1 year**	228 (25)	201 (18)	53 (13)	75 (18)
• **3 to <7 year**	279 (31)	285 (26)	104 (25)	106 (25)
• **≥ 7 year**	322 (36)	560 (50)	236 (57)	215 (51)
Failure of prior anti-TNF therapy, n (%)	367 (41)	645 (58)	312 (75)	287 (68)

C13006: GEMINI I (Feagan et al. 2012); C13007: GEMINI 2 (Talley et al. 2011)(Sandborn et al. 2013); C13011: GEMINI 3 (Sands et al. 2014)

Summary results

Across the integrated safety population, VEDO demonstrated a tolerable safety profile for the treatment of adults with moderately to severely active CD or UC

• The most common AEs and SAEs observed in the 52-week induction and maintenance studies were the same as those reported in the long-term integrated safety population

• The incidence rate of serious infections of interest was low with VEDO

• Consistent with the purported mechanism of action, there were no cases of PML reported in the context of substantial exposure

Table 48. Most common adverse events (Integrated Safety Analysis)

	UC (N=1107)		CD (N=1723)		UC and CD (N=2830)	
AE, Preferred term	n	No. of patients with event/1000 px-years	n	No. of patients with event/1000 px-years	n	No. of patients with event/1000 px-years
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]
SAE						
• **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 VEDO 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 in the VEDO Integrated Safety Population

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

Progressive Multifocal Leukoencephalopathy (PML) Monitoring During VEDO Clinical Trials

- Dedicated risk assessment and minimisation plan in all studies since 2007 using stepwise algorithm-based approach. As of June 2013, no PML cases have been reported in any of the >2700 patients treated with VEDO during the entire development program, including approximately 900 patients with ≥24 months exposure. 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 VEDO carried similar risk.

Malignancies Reported for VEDO in the Integrated Safety Population

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

In summary, safety and tolerability of VEDO 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 VEDO for ≥2 years.

Across the integrated safety population, VEDO demonstrated a tolerable safety profile for the treatment of adults with moderately to severely active CD or UC. The most common AEs and SAEs observed in the 52-week induction and maintenance studies were the same as those reported in the long-term integrated safety population. The incidence rate of serious infections of interest was low with VEDO and consistent with the mechanism of action, there were no cases of PML reported in the context of substantial exposure.

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

VEDO has been studied in three placebo-controlled clinical trials in patients with UC (GEMINI I) or CD (GEMINI II and III). In two controlled studies (GEMINI I and II) involving 1,434 patients receiving VEDO 300 mg at Week 0, Week 2 and then every eight weeks or every four weeks for up to 52 weeks, and 297 patients receiving placebo for up to 52 weeks, AEs were reported in 84% of VEDO-treated patients and 78% of placebo-treated patients. Over 52 weeks, 19% of VEDO-treated patients experienced SAEs compared with 13% of placebo-treated patients. Similar rates of AEs were seen in the every eight week and every four week dosing groups in the Phase 3 clinical trials. The proportion of patients who discontinued treatment due to AEs was 9% for VEDO-treated patients and 10% for placebo-treated patients. In the combined studies of GEMINI I and II the AEs that occurred in ≥5% were nausea, nasopharyngitis, upper respiratory tract infection, arthralgia, pyrexia, fatigue,

headache and cough. Infusion-related reactions were reported in 4% of patients receiving VEDO.

In summary, the EMA view was that the safety profile of VEDO did not raise major objections and can be considered reassuring in both UC and CD indications, although differences between these two pathologies have been reported (with higher incidence of AEs in CD).

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.**

VEDO is the first gut selective biologic therapy which has proven efficacy in moderate to severe UC in patients who have failed treatment or are intolerant to conventional therapy including patients who are naïve to TNF therapy and in patients who have previously failed anti-TNF therapy.

Remission and Response

In the ITT population of GEMINI I study, compared with placebo, VEDO induction treatment resulted in significantly greater rates of clinical response, clinical remission, and mucosal healing at Week 52:

- Durable clinical response: VEDO, 56.6% versus placebo, 23.8%; difference, 32.8%, P <0.001.
- Clinical remission: VEDO, 41.8% versus placebo, 15.9%; difference, 25.9%, P = 0.001.
- Compared with placebo, VEDO maintenance treatment was associated with significantly higher rates of all secondary endpoints including durable clinical response (56.3% versus 23.8%, P <0.0001) and durable clinical remission (20.5% versus 8.7%, P = 0.008).

Efficacy in anti-TNF Failure

In GEMINI I, VEDO was shown to be effective when directly compared with placebo in patients who had previously failed anti-TNF therapy.

- Clinical remission: 37.2% versus 5.3% for placebo at 52 weeks.

- Durable clinical response: 46.5% versus 15.8% for placebo at 52 weeks. Currently VEDO is the only biologic treatment indicated for patients with UC who have failed anti-TNF therapy.

Mucosal Healing

In the maintenance phase of the GEMINI I study, 31.8% more patients receiving VEDO had improvement in mucosal healing. This was considered clinically meaningful.

Glucocorticosteriod-free Remission

Corticosteroids are an effective option in the treatment of UC but associated AEs make it a less desirable option. For patients receiving concomitant corticosteroids in GEMINI I (approximately 58% of the ITT population), the protocol specified a corticosteroid tapering regimen. Following successful tapering, patients could reintroduce corticosteroids to manage symptoms if required. Corticosteroid-free clinical remission at week 52 was statistically significantly better in the VEDO groups compared with placebo (51.6% vs. 19.8%, respectively; P <0.01). Also, the median prednisone dose was lower in patients treated with VEDO. Thus, not only did VEDO treatment allow reduced exposure to the risks of corticosteroids, but the treatment benefit was preserved in these patients.

Health-related QoL Improvements

In GEMINI I, VEDO improved overall health-related QOL in patients with UC compared with placebo, as assessed by IBDQ, EQ-5D VAS and SF-36 scores.

- Improvement of 21.1% in IBDQ (disease specific outcome measure) overall score as well as various lifestyle domains including: emotional and social function, and bowel system functioning.
- Improvements of 12.5% in EQ-5D VAS (general well-being outcome measure) were reported by patients on VEDO compared with patients on placebo.
- Statistically significant improvements in HRQOL were reported with the SF-36 measure: improvements of 3.3% in physical functioning and 4.7% in mental functioning were reported by patients receiving VEDO.

- Additionally, improved SF-36 outcomes may relate to physical improvements and reduction in pain, enabling greater involvement in everyday activities.

In general, these results met pre-specified criteria for minimally important differences and, therefore, represent clinically meaningful improvements.

Safety Profile

The mechanism of action for VEDO is expected to result in a differentiated safety profile compared with systemically-acting biologic agents for UC and CD (Soler 2009). Studies in healthy volunteers have shown no evidence that VEDO affects immune surveillance of the CNS (Soler 2009; Fedyk E 2011; Fedyk 2012; Milch 2013). To date, there have been no reported cases of PML in patients receiving VEDO for IBD; however, the drug will continue to be evaluated in a long-term safety trial to confirm its long-term safety profile.
In GEMINI I study, VEDO was well tolerated and an acceptable safety profile and has shown a similar rate of adverse events compared to placebo.

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

Induction and maintenance data from GEMINI I provide substantial evidence for efficacy of VEDO in inducing and maintaining clinical response and remission in patients with moderately to severely active UC.

- The magnitudes of treatment effects on multiple endpoints were clinically meaningful and highly statistically significant.
- In induction, P values were less than 0.001 for the primary endpoint of clinical response and the secondary endpoint of clinical remission.
- In maintenance, for both VEDO dosing regimen groups P values were less than 0.001 for the primary endpoint of clinical remission and the secondary endpoints of durable clinical response and mucosal healing, and, for the Q4W group, durable clinical remission and corticosteroid-free remission.

There was strong evidence of consistency of effects in the study:

- Positive efficacy results for VEDO across multiple secondary and exploratory efficacy endpoints, including quality of life measures, biomarkers of inflammation and healthcare resource utilization.
- Efficacy in different subgroups of patients according to demographic factors, disease severity, disease activity and failure of previous treatments for UC.
- For the ITT induction population, no site contributed >5% of patients and for the ITT maintenance population, no site contributed >4% of patients, making it unlikely that any single site contributed disproportionately to the observed treatment benefit.

Regarding safety, VEDO was well-tolerated in this 52-week study and there were no clinically meaningful, drug-related differences in adverse event frequencies between the ITT VEDO and placebo groups.

GEMINI I was a placebo-controlled trial, which could be considered a limitation. However, it must be recognised that conventional therapies were concomitantly administered to patients: 5-ASAs, corticosteroids, immunomodulators, antibiotics, probiotics and antidiarrheal. This reflects standard clinical practice in the UK, and VEDO is expected to be used as an add-on to existing conventional therapy. Therefore this design feature may reflect clinical practice more than being a limitation of the study.

A further potential limitation is the choice of primary endpoint in the induction phase: proportion of patients with clinical response at week 6, not clinical remission as recommended by EMA guidelines. However, this approach to study design is similar to that of other pivotal studies with anti-TNFα agents, where clinical response is used as the primary endpoint. Further, as a long term condition, the aim of treatment is remission, and the GEMINI I study includes clinical remission as the primary endpoint in the maintenance study.

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.**

UC is a relapsing, remitting, inflammatory disease of the colonic mucosa which manifests with symptoms of bloody diarrhoea, abdominal pain, faecal urgency and incontinence. Systemic features such as fever, weight loss, malaise and fatigue are indicators of more extensive disease.

Current treatments which include conventional therapies and anti-TNF agents have been effective for many patients with UC but have numerous limitations for patients with moderate to severe disease, with 9%–35% of UC patients requiring colectomy within 5 years of initial diagnosis. Colectomy with ileal pouch anal anastomosis (the standard surgical therapy) has many limitations and is associated with its own set of complications, including high stool frequency, female infertility and pouchitis. The limitations of current therapies for UC indicate that there is a significant need for safer and more effective therapies. VEDO has been developed to fulfil this important unmet medical need.

Primary and secondary objectives of both induction and maintenance studies are common to those of other pivotal studies of biologics in the UC indication. The exploratory endpoint, data on sustained response/remission (partial Mayo score) at every visit (from week 6 to week 52) reflects the importance of maintenance of remission during 52 weeks. The grading for the assessment of rectal bleeding, in the definition of clinical remission, including a rectal bleeding subscore of 0 (absence of bleeding) or 1 (minimal bleeding) is common to clinical trials with other comparators.

In the placebo arm of the GEMINI I study patients continued to receive conventional therapies, whilst the comparator arm consisted of conventional therapy plus VEDO. This design reflects the anticipated use of VEDO in clinical practise.

The inclusion of patients who have failed treatment with anti-TNFs reflects current clinical practise (Royal College of Physicians 2013). In the GEMINI I induction study, approximately 40% of patients had a history of failure on a TNFα antagonist. In the maintenance study a reasonable difference was reported in the non-ITT every four week treatment group (e.g. Week 6 non-responders) in which a higher proportion of

patients who had prior TNFα antagonist failure was recorded (49%, compared with 30%, 35% and 32% in the ITT placebo, VEDO every eight weeks and VEDO every four weeks groups, respectively). Taken together, the reported characteristics reflect those of the target population of moderate to severe UC patients in the UK.

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 SPC?**

The EMA-approved dosing schedule does not differentiate between induction and maintenance, which reflects standard clinical practice. However, the SmPC contains a stopping rule if there is no response after 3 doses in patients with UC. This 'test of response' differs from the evaluation of induction in GEMINI I after two doses. The 3-dose stopping rule is a pragmatic solution that offers more patients an opportunity to respond to VEDO and helps some patients achieve remission at 10 weeks who do not meet response criteria at week 6.

In order to understand the external validity of the GEMINI I study, we approached a small group of 5 UK gastro-enterologists for their comment on the implications of the study design and results of GEMINI I to routine clinical practice.

In general the clinical experts agreed that the GEMINI I did reflect clinical practice as it recruited patients who had failed on conventional therapy (including thiopurines like azathiopurine and 6-mercaptopurine) and/or failed anti-TNF treatment. This is most likely where vedolizumab will be used, therefore the results from the trial are clinically relevant. In terms of assessing response, the experts commented on the use of 'clinical' parameters rather than use of Mayo scores which they felt was not routinely used in clinical practice. However the use of this measurement in the GEMINI I trial was supported and they said that clinical practice needed to change to include either the use of complete Mayo or partial Mayo scores to assess patients' response.

The clinical experts were also asked to specifically comment on the assessment of response at week 10 as recommended by the Entyvio label. They recognised the difference in the trial design versus the label and felt that assessment of response at week 10 would be pragmatic, particularly with the availability of the delayed responder data (see section 6.3).

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 UC as well as studies of costs, resource use and utility values for UC. The results in this section are focussed on the cost-effectiveness analyses that were identified. Additional information on studies that assessed utility values in UC 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 UC is provided in Sections 7.5.3.

Original Search, April 2013

The following electronic databases were searched on April 15, 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 15, 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 UC (e.g., “Colitis, Ulcerative”[MeSH], “ulcerative colitis”)

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 VEDO, infliximab, and adalimumab

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. **Error! Reference source not found.** presents the MEDLINE search strategy. This search strategy was adapted to search other electronic databases, and the specific search strategies are presented in **Error! Reference source not found.** to **Error! Reference source not found.**.

Inclusion and Exclusion Criteria

The selection of studies was guided by a prespecified inclusion and exclusion criteria. Table 49 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 49. 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 with UC (both treatment naïve and treatment experienced)	Patients who do not have UC
Interventions (applied to economic evaluations only)[c]	VEDO Infliximab (Remicade) Adalimumab (Humira)	Economic evaluations that do not investigate one of the interventions of interest in at least one of the arms

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.

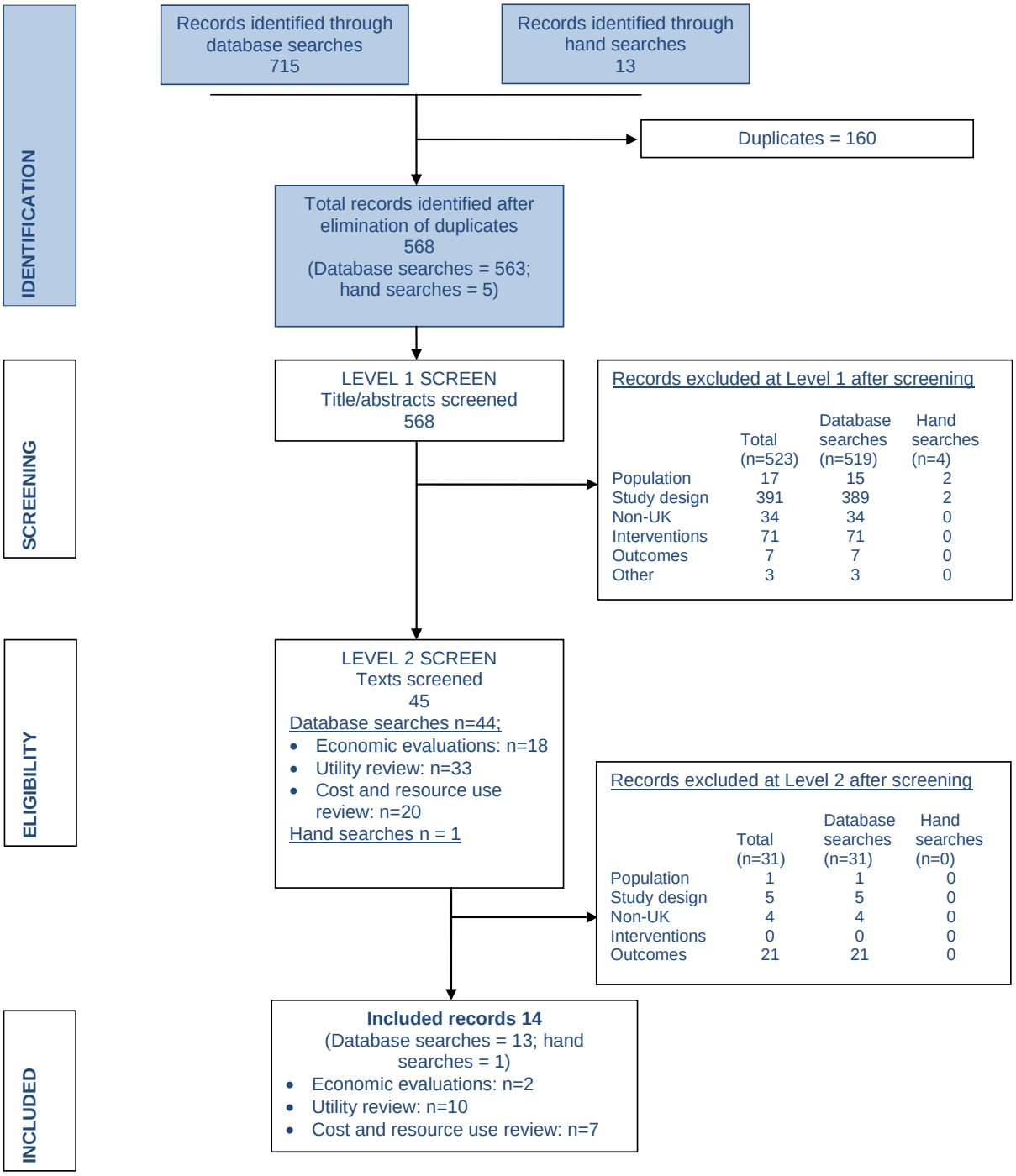
Full texts of studies selected at level 1 were reviewed by one researcher to determine eligibility at level 2 screening. Any uncertainties about inclusion were checked by a second researcher. A random selection (10%) of studies was checked by a second researcher. No discrepancies were identified by this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

All extracted data were checked against the original sources.

In the original search, a total of 568 unique records were identified (563 from the database search and 5 additional records from hand-searching the one systematic

review that was identified from the database search). 45 records were retained after the level 1 screen and 14 were retained after the level 2 screen. 2 of the identified papers were cost-effectiveness analyses relevant to the UK and the remaining papers concerned the costs and / or utility values associated with UC (Figure 8).

Figure 8. 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.

Source: Adapted from Moher et al., 2009.

Second Literature Search

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 UC (both treatment naive and treatment experienced)
- Intervention: VEDO
- Comparators: adalimumab, infliximab, golimumab 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 present, 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 will be excluded electronically if they are 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 13/03/14)
- MEDLINE (R) In-Process Citations and Daily Updates (Ovid SP) (searched 13/03/14)
- EMBASE (Ovid SP) (searched 13/03/14)
- 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:

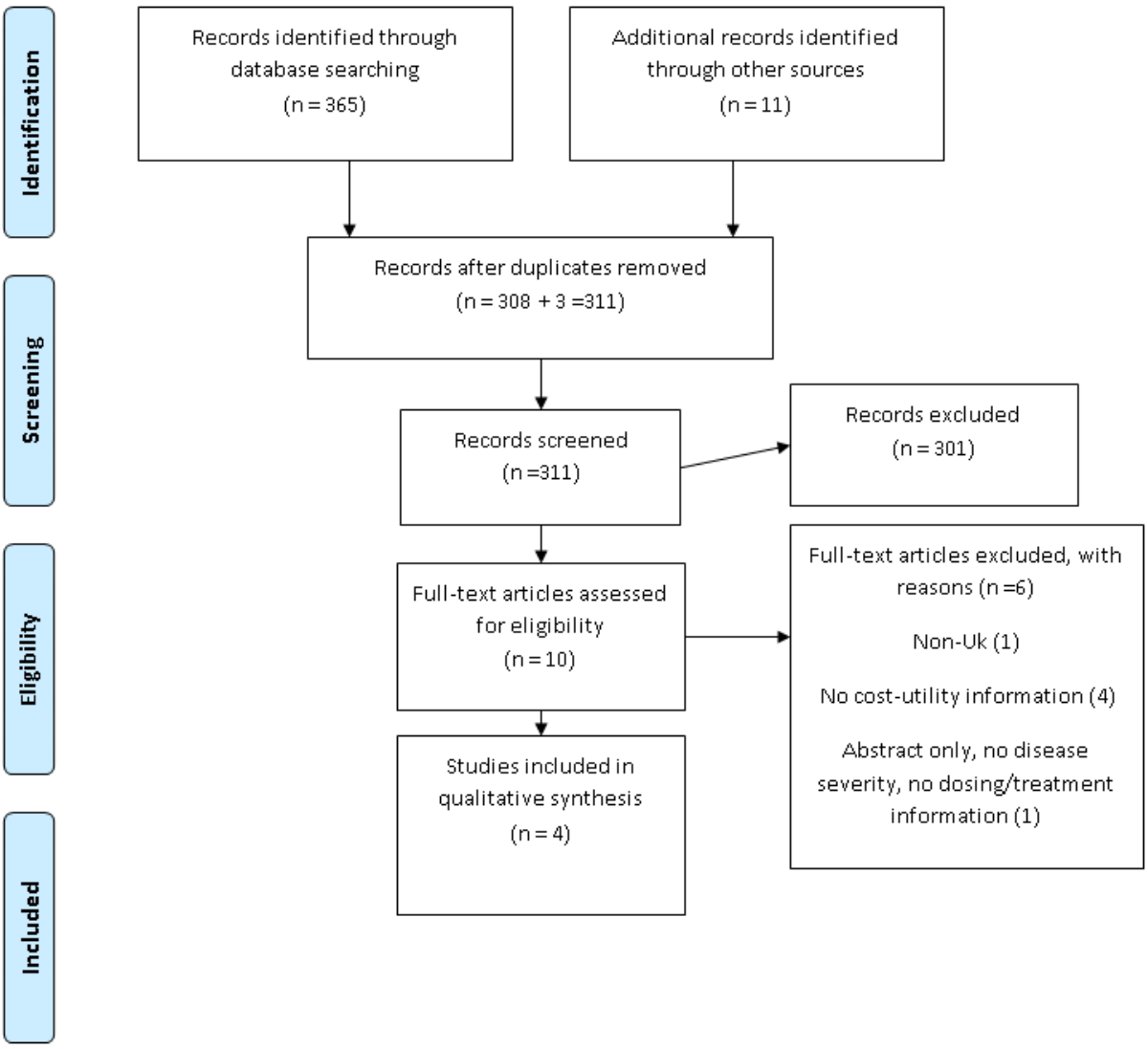
- NICE Website
- Cost effectiveness analysis registry
- International Society for Pharmacoeconomics and Outcomes Research: Research Digest, at http://www.ispor.org/research_study_digest/research_index.asp
- European Crohn's and Colitis Organisation, at https://www.ecco-ibd.eu/
- Digestive Disease Week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

- American College of Gastroenterology.

The search yielded a total of 376 records. Of these 65 were duplicates leaving 311 titles eligible for screening (Figure 9). A hand search of other resources, to identify any papers that may not have shown up in the database search, yielded 3 relevant titles. A total of 311 papers were therefore eligible for screening.

Of the 311 eligible papers, 301 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, 6 of the 10 articles were excluded (1 was non-UK, 4 had no cost-utility information or resource use data and 1 was an abstract only, and was excluded because the information available did not meet the inclusion criteria). None of the studies are included in this submission as none of them were UK-based cost-effectiveness analyses.

Figure 9. PRISMA Diagram for Study Inclusion and Exclusion for the Second Search of Economic Evaluations, Utility Studies and Cost and Resource Use Studies, March 2014



Description of identified studies

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.**

A summary of the two UK-based cost-effectiveness analyses are provided in Table 50.

Table 50. Summary of Economic Analyses Identified in the Literature Searches

First Author (Year)	Publication Type, Country, Cost Year	Methods	Patient Population (Average Age)	Results			
				Interventions	Cost	Outcome[a]	ICER[b]
Puneka r (2010)	Full article, UK, 2006-2007	A decision-analytic model; perspective = NHS and PSS; time horizon = 1 (base case) Health events: remission, active UC, surgical remission, and surgical complications The baseline risk of colectomy was estimated via a meta-analysis of the placebo arms of the infliximab and ciclosporin trials. Relative risk of colectomy on different treatments from a network meta-analysis between trials (for infliximab using studies by Jarnerot et al. [2005] and Sands et al. [2001]; for ciclosporin,	Acute, severe UC patients not responding to 72 hours of IV steroid therapy	**Cost effectiveness over 1 year**	Total costs (£)	Total QALYs	ICER (£ per QALY) (vs. surgery)
				Surgery	17,067	0.58	—
				Ciclosporin	18,122	0.70	9,032
				Standard care	18,524	0.68	Dominated
				Infliximab	19,847	0.80	18,388

First Author (Year)	Publication Type, Country, Cost Year	Methods	Patient Population (Average Age)	Results			
				Interventions	Cost	Outcome[a]	ICER[b]
		D'Haens et al. [2001] and Lichtiger et al. [1994]). Rate of surgical complications was derived from the UK IBD Audit (Leiper et al., 2006). Health state preferences obtained from a UC patient survey carried out in Cardiff Hospital using the EQ-5D and valued using UK tariffs. Resource use estimates based on expert opinion; unit costs from relevant national sources Costs and outcomes were discounted at 3.5%. One-way and probabilistic sensitivity analyses were performed to estimate the uncertainty around the results.					
Tsai (2008)	Full article, UK, 2006-2007	A Markov model; cycle = 8 weeks (cycle 1), 6 weeks (cycle 2), 8 weeks thereafter; perspective = NHS and PSS; time horizon = 10 years Health states: remission (Mayo score 0-2), mild (Mayo score 3-5) and moderate-severe (Mayo score 6-12), surgery, post-surgery remission and post-surgery complications, temporary discontinuers, and death. Health-state preferences obtained from a	Moderate-severe UC patients (age: NR) Responders only	Cost-effectiveness results at 10 years	Mean costs (£)	Mean QALYs	ICER (£ per QALY)
				Standard care	45,798	3.838	—
				Infliximab SMT	66,460	4.591	27,424
			Moderate-severe UC patients (age: NR) Remission	Cost-effectiveness results at 10 years	Mean costs (£)	Mean QALYs	ICER (£ per QALY)
				Standard care	46,529	3.767	—

First Author (Year)	Publication Type, Country, Cost Year	Methods	Patient Population (Average Age)	Results			
				Interventions	Cost	Outcome[a]	ICER[b]
		UC patient survey carried out in Cardiff Hospital using the EQ-5D and valued using UK tariffs. Utilities associated with temporally discontinuers and post-surgery complications were obtained from literature (Arseneau et al., 2006). Resource use for pre-surgery health states was based on a panel of 6 gastroenterologists. The cost of hospitalisation was based on the ACT trials. Cost of surgery was calculated as a weighted average of ileostomies (71%) and IPAAs (29%). Costs and outcomes were discounted at 3.5%. One-way sensitivity analysis and probabilistic sensitivity analysis were conducted to estimate the uncertainty around the results.	only	Infliximab SMT	53,874	4.154	19,696

EQ-5D, EuroQol 5 Dimensions; IBD, inflammatory bowel disease; ICER, incremental cost-effectiveness ratio; IPAA, ileal pouch anal anastomosis; IV, intravenous; NHS, National Health Service; NR, not reported; PSS, Personal Social Services; QALY, quality-adjusted life-year; SMT, scheduled maintenance treatment; UC, ulcerative colitis; UK, United Kingdom.

[a] Outcomes will be extracted for the general population and for any subgroups of interest.

[b] Results will include total expected costs and QALYs for each intervention, incremental costs and QALYs, and ICERs (where reported).

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 51. Quality Assessment of Economic Analyses Identified in the Literature Searches

	Study identification ***Include author, title, reference, year of publication***	**Tsai, H. H., Punekar, Y. S., Morris, J., & Fortun, P. (2008).** A model of the long-term cost effectiveness of scheduled maintenance treatment with infliximab for moderate-to-severe ulcerative colitis. Alimentary Pharmacology & Therapeutics, 28(10), 1230–9.		**Punekar, Y. S., & Hawkins, N. (2010).** Cost-effectiveness of infliximab for the treatment of acute exacerbations of ulcerative colitis. *The European Journal of Health Economics : HEPAC : Health Economics in Prevention and Care*, *11*(1), 67–76.	
	Section 1: Applicability (relevance to specific guideline review question(s) and the NICE reference case[a])	Yes/ Partly/ No /Unclear /NA	Comments	Yes/ Partly/ No /Unclear /NA	Comments
1.1	Is the study population appropriate for the guideline?	Yes	Patients suffering from moderate-severe chronic UC	Yes	Patients with 'moderate-to-severe' UC
1.2	Are the interventions and services appropriate for the guideline?	Yes	Relevant for guidelines	Yes	Relevant for guidelines
1.3	Is the healthcare system in which the study was conducted sufficiently similar to the current UK NHS context?	Yes	N/A	Yes	N/A
1.4	Are costs measured from the NHS and personal social services (PSS) perspective?	Yes	UK NHS perspective	Yes	UK NHS perspective

	Study identification ***Include author, title, reference, year of publication***	**Tsai, H. H., Punekar, Y. S., Morris, J., & Fortun, P. (2008).** A model of the long-term cost effectiveness of scheduled maintenance treatment with infliximab for moderate-to-severe ulcerative colitis. Alimentary Pharmacology & Therapeutics, 28(10), 1230–9.		**Punekar, Y. S., & Hawkins, N. (2010).** Cost-effectiveness of infliximab for the treatment of acute exacerbations of ulcerative colitis. *The European Journal of Health Economics : HEPAC : Health Economics in Prevention and Care*, *11*(1), 67–76.	
1.6	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 outcomes were both discounted at 3.5%
1.7	Is the value of health effects expressed in terms of quality-adjusted life years (QALYs)?	Yes	N/A	Yes	N/A
1.8	Are changes in health-related quality of life (HRQoL) reported directly from patients and/or carers?	yes	N/A	Yes	N/A
1.9	Is the valuation of changes in HRQoL (utilities) obtained from a representative sample of the general public?	Yes	N/A	Yes	N/A
1.10	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)	Yes/ Partly/ No /Unclear /NA	Comments	Yes/ Partly/ No /Unclear /NA	Comments
2.1	Does the model structure adequately reflect the nature of the health condition under evaluation?	Yes	Reflects health condition	Yes	Reflects UC patients.
2.2	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	No	1 year time frame, and extrapolation to 10 year time frame justified.	No	1 year time frame, with sensitivity analysis for longer term analysis.

	Study identification ***Include author, title, reference, year of publication***	**Tsai, H. H., Punekar, Y. S., Morris, J., & Fortun, P. (2008).** A model of the long-term cost effectiveness of scheduled maintenance treatment with infliximab for moderate-to-severe ulcerative colitis. Alimentary Pharmacology & Therapeutics, 28(10), 1230–9.		**Punekar, Y. S., & Hawkins, N. (2010).** Cost-effectiveness of infliximab for the treatment of acute exacerbations of ulcerative colitis. *The European Journal of Health Economics : HEPAC : Health Economics in Prevention and Care*, *11*(1), 67–76.	
2.3	Are all important and relevant health outcomes included?	Yes	Includes adverse events; post-surgery remission and complications.	partly	Adverse effects of treatment alternatives were excluded from the analysis.
2.4	Are the estimates of baseline health outcomes from the best available source?	Yes	N/A	Yes	N/A
2.5	Are the estimates of relative treatment effects from the best available source?	Yes	Pooled from clinical ACT I and ACT II trials	Yes	Meta analyses was conducted to estimate values.
2.6	Are all important and relevant costs included?	Yes	N/A	yes	N/A
2.7	Are the estimates of resource use from the best available source?	Yes	Resource use for pre surgery health states were estimated by a panel of UK gastroenterologists.	Partly	longer term surgical complications such as pouchitis and pouch failure were not considered. These complications are likely to incur costs
2.8	Are the unit costs of resources from the best available source?	Yes	NHS national schedule of reference cost database 2006-2007	yes	NHS national schedule of reference cost database 2006-2007.
2.9	Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	ICER is calculated and reported	Yes	ICER is calculated and reported

	Study identification ***Include author, title, reference, year of publication***	**Tsai, H. H., Punekar, Y. S., Morris, J., & Fortun, P. (2008).** A model of the long-term cost effectiveness of scheduled maintenance treatment with infliximab for moderate-to-severe ulcerative colitis. Alimentary Pharmacology & Therapeutics, 28(10), 1230–9.		**Punekar, Y. S., & Hawkins, N. (2010).** Cost-effectiveness of infliximab for the treatment of acute exacerbations of ulcerative colitis. *The European Journal of Health Economics : HEPAC : Health Economics in Prevention and Care*, *11*(1), 67–76.	
2.10	Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Yes	Deterministic and PSA carried out	partly	Some variables were not subjected to PSA.
2.11	Is there no potential conflict of interest?	Yes	No conflict of interest declared.	yes	No conflict of interest declared
2.12	Overall assessment: Minor limitations/ Potentially serious limitations/ Very serious limitations	Minor limitations	Timeframe is limited due to lack of long term follow up data.	Minor limitations	additional sensitivity analysis may be required.

7.2 De novo analysis

Patients

7.2.1 What patient group(s) is (are) included in the economic evaluation? Do they reflect the licensed 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) SPC/IFU and included in the trials.

The patient population included in the model reflects the licensed population for VEDO. Specifically, the model includes patients with moderately to severely active UC (i.e. a Mayo score of 6 or greater) who have had an inadequate response with, lost response to, or are intolerant to either a conventional therapy or anti-TNFs.

As well as assessing the cost-effectiveness of VEDO in the overall patient population included in the GEMINI I trial, analyses are conducted for two subgroups: for patients that are naïve to anti-TNFs and for patients that are anti-TNF failures. Thus, the three groups considered in the model are:

- Mixed population (includes both anti-TNF–naive and anti-TNF–failure patients, representing the intention to treat [ITT] population of the GEMINI I trial).
- Anti-TNF–naive population. In the GEMINI I trial, 51.8% of patients were anti-TNF naive.
- Anti-TNF–failure population (both primary failure [no response] and secondary failure [loss of response after initially responding]). According to the GEMINI I trial, 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)

Clinical trials for infliximab and golimumab were conducted in an anti-TNF–naive population only. Adalimumab has clinical data in both an anti-TNF–naive and an experienced (secondary failure) population. However, a higher percentage of the adalimumab trial population (approximately 60%) was anti-TNF naive than was observed in the GEMINI I trial (51.8%). Additionally, the failure population in adalimumab clinical trials was not comparable to the VEDO trial as it only included secondary failure patients (primary failure patients were excluded). Given the lack of data for infliximab and golimumab and the lack of comparable data for adalimumab, we only compare VEDO to the 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 and surgery.

Model structure

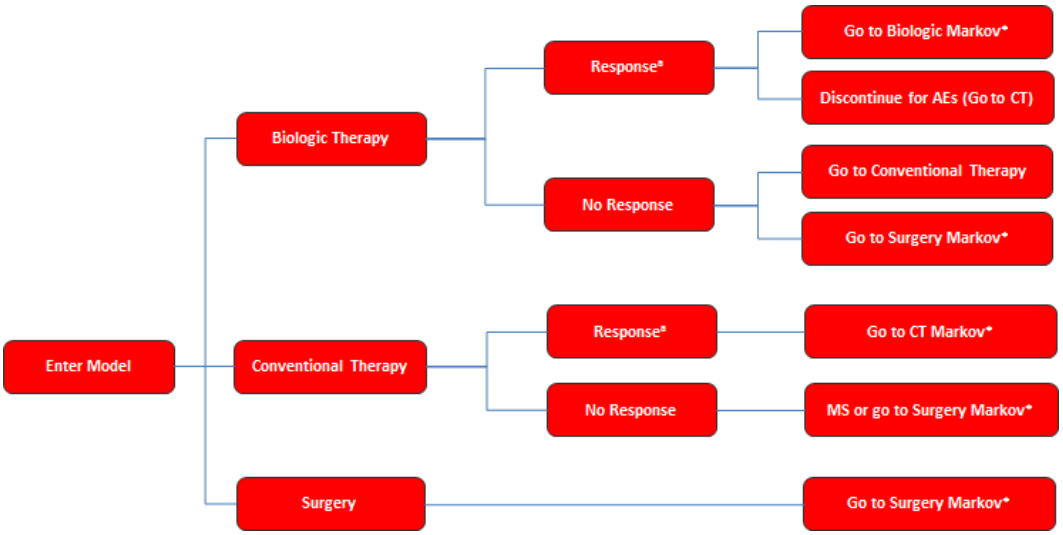
7.2.2	Please provide a diagrammatical representation of the model you have chosen.

To estimate the cost-effectiveness of VEDO in an active moderate to severe UC population, we took a modelling approach similar to that taken by the infliximab NICE submission for sub-acute manifestations of UC (NICE, 2007) as well as that presented in a recent publication by Tsai and colleagues (2008). We adapt this model structure to include a decision tree for the induction phase and a Markov structure for the maintenance phase to most closely reflect the clinical trials. These phases are outlined below.

Induction Phase

The induction phase of the model is intended to represent the induction phase of the clinical trials. During this phase, patients initiate treatment with one of the defined treatments (VEDO, infliximab, adalimumab, golimumab, conventional therapy, or surgery). These patients enter the model through a decision tree based on treatment and treatment response (Figure 10).

Figure 10. Decision-Tree Schematics for UC Induction Phase



AE, adverse event; CT, conventional therapy; MS, moderate-severe.
[a] Response is defined as a drop in Mayo score of 3 points or more. This includes patients who also achieve remission, as remission is a subset of response. Remission is defined as a Mayo score less than 3.

The Markov structures can be seen in Figure 11 below. The structures for biologic therapies and conventional therapies are similar, with differences arising in transition probabilities. The surgery Markov is a subset of the Markov for biologics and conventional therapy. Patients who begin the model on a biologic therapy are monitored for response to the drug at the end of a 6-week induction phase. Response is defined as drop in the Mayo score of 3 points or more. This is not the same as remission, which is defined as achieving a Mayo score of less than 3 (moderate to severe is considered a score of between 6 and 12). A patient could respond to treatment without being in remission. The duration of the induction period was chosen to mirror the VEDO clinical trial. Those 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 (Figure 11). Patients who fail to respond during the induction phase or who discontinue due to adverse events switch to conventional therapy and then remain on conventional therapy for the remainder of the model or until they transition to surgery.

Patients who enter the induction phase on conventional therapy may respond to treatment. Responders in the induction phase then enter the Markov model for conventional therapy in one of the three Mayo-based health states (Figure 11). The Markov structure for conventional therapy is similar to that for biologic therapy, with differences arising in the transition probabilities. Patients who fail to respond are assumed to remain in the moderate-severe disease health state for the remainder of the model time horizon or until they transition to surgery. Regardless of response or lack thereof, patients on conventional therapy remain on conventional therapy for the remainder of the model time horizon or until they transition to surgery.

Patients who enter the model with surgery immediately move to the surgery portion of the Markov structure (Figure 11).

The 6-week duration of the induction phase was chosen to be consistent with the VEDO clinical trial. 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. Table 52 presents the induction schedules for each of the biologic therapies.

Table 52. Induction Schedules for Biologic Therapies

Treatment	Measurement of Response	Label Indication

Treatment	Measurement of Response	Label Indication
Adalimumab	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 8, treatment should not be continued
Infliximab	Week 8 (after doses at weeks 0, 2, and 6)	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
VEDO	Induction response measured prior to week 6 dose (after doses at weeks 0 and 2)	Induction: weeks 0, 2, and 6 Maintenance: starts at week 14, every 8 weeks thereafter. If no response at week 10, treatment should not be continued
Golimumab	Week 6 (after doses at weeks 0 and 2)	Induction: weeks 0 and 2 Maintenance: every 4 weeks thereafter If no response at week 12-14, treatment should not be continued

For the model, induction efficacy data as reported from the clinical trials are used. For infliximab and adalimumab, this means that patients received their week 6 dose prior to assessment at week 8. For VEDO and golimumab, this meant that patients received only their week 0 and week 2 doses before assessment. For the base-case analysis, it is assumed that all VEDO patients receive their week 0 and week 2 dose before assessment at week 6. We then consider a scenario in which assessment is conducted at week 10. In this scenario, we assumed that all VEDO patients receive their week 6 dose before assessment.

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

- VEDO: 300 mg at weeks 0 and 2
- Infliximab: 5 mg/kg at weeks 0, 2, and 6
- Adalimumab: 160 mg at week 0, 80 mg at week 2, 40 mg at weeks 4 and 6
- Golimumab: 200 mg at week 0, 100 mg at week 2

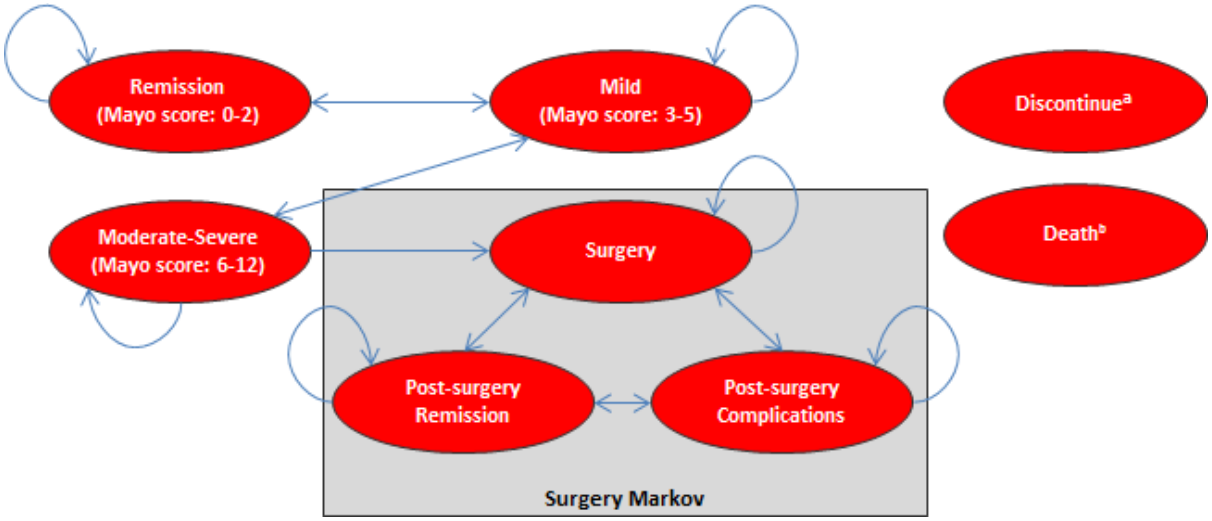
These dosing assumptions are consistent with the trial-based doses from which the efficacy data were obtained.

Maintenance Phase

Patients on biologic therapy who respond to therapy enter the biologic Markov model for maintenance treatment. The underlying Markov model structure was adapted from a recently published UK economic analysis in UC (Tsai et al., 2008). The modelled health states are defined according to Mayo scores (Figure 11):

- Remission (Mayo = 0-2), which is equivalent to full response
- Mild (Mayo = 3-5)
- Moderate-Severe (Mayo = 6-12)
- Surgery
- Post surgery Remission
- Post surgery Complications
- Death

Figure 11. Markov Model Schematics for UC 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 or until the patients require surgery.

[b] Patients may transition to death from any health state during any cycle.

In the Markov model, patients on treatment (biologic or conventional therapy) may transition among each of the three disease severity health states (remission, mild, moderate-severe). The probability of transition to each health state depends on the patient's current health state as well as the current treatment. Patients in moderate-severe disease may also transition to surgery.

The probability of surgery is dependent on the patient's current health state. We assumed patients on treatment only transition to surgery from the moderate-severe health state. Thus, the probability of a patient requiring surgery is indirectly dependent upon the drug they are receiving, as the probability of entering the moderate-severe health state is dependent upon what drug the patient receives.

Patients who transition to surgery discontinue their current treatment for the remainder of their lifetime. Following surgery, these patients may subsequently experience postsurgical complications, require additional surgeries, or remain in postsurgical remission.

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. A proportion of these patients in moderate-severe disease will require surgery. The rest will switch to conventional therapy.

The Markov model is similar to that presented in Tsai and colleagues (2008) with the exception of temporary discontinuation. We do not include temporary discontinuation in the model due to lack of available data for all comparators. We assumed that the clinical trials capture any temporary discontinuation, and as such, the efficacy data within the model already reflect the effects of any such temporary discontinuations. As a result, any adjustments for temporary discontinuation could be captured in the drug costs.

Patients may experience death from any health state in the model. We consider a general age- and sex-specific mortality risk that increases with time. We then apply a health-state mortality risk multiplier to UC patients for time spent in each health state. The mortality inputs are described in more detail in Section 7.3.2.

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. The model makes comparisons with conventional therapy, biologics and surgery on the basis of prior therapies received.

The severity of the disease as measured by the Mayo score is the primary source for the health states as this is related to disease severity, quality of life and costs (Reinisch et al. 2007, Buchanan et al. 2011). This disease severity index was routinely measured within the trial, helped to determine entry to the maintenance phase of the GEMINI I 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.

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, adalimumab and golimumab) in patients that are anti-TNF naïve. These therapies represent the likely treatments that will be displaced by VEDO and the therapies that patients may have received before being considered for treatment with VEDO.

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 3 or more points of the Mayo score). This reflects the decision rule that was used in the GEMINI I clinical trial.

To model the maintenance period a Markov model is used. Three health states in the Markov model are based upon the Mayo score. The Mayo score is a measure of disease severity, consisting of four items: stool frequency, rectal bleeding, endoscopic assessment of disease severity, and a physician global assessment of disease severity. A partial Mayo score can be calculated if an endoscopy has not been conducted. Within the GEMINI I study, complete Mayo scores were assessed at baseline, week 6 (the end of the induction period) and at week 52. Partial Mayo scores were assessed every 4 weeks during the maintenance phase of the trial. The model has health states for remission (a Mayo score of 0 to 2), mild disease (a Mayo score

of 3 to 5) and moderate to severe disease (a Mayo score of 6 or more). These represent increasing severity of disease.

In addition to Mayo score, the model includes surgery and postsurgical health states: postsurgical remission and postsurgical complications. In the model, surgery is defined as a composite of two surgical procedures: 40% of patients are assumed to undergo proctocolectomy with ileostomy and 60% are assumed to undergo subtotal proctocolectomy with pouch formation +/− loop ileostomy. This is in line with the study by Buchanan et al., 2011. Surgery is usually seen as a last resort and can result in complications such as postoperative bleeding, faecal incontinence, depression, sexual dysfunction, female infertility, pouchitis, pouch leakage, pelvic abscesses, pouch fistulae, small bowel obstruction, and anastomotic stricture (Ochsenkühn & D'Haens 2011). See Section 2.6 for more information. Within the model, patients in the postsurgical complications health state have higher costs and lower utilities than patients without complications.

The model allows for patients to switch from one treatment to another: as indicated by the "Discontinue" health state shown in Figure 11. Within the model, patients treated with VEDO 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). Patients can transition to and from more severe health states: the model is not a progressive model as might be seen with cancer, for example, where patients would typically progress to more severe health states with periods of remission. In addition to Mayo scores, the model captures patients moving to surgery and then to postsurgical health states, often seen as a last resort for patients with UC.

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 53. Key Features of Analysis

Factor	Chosen Values	Justification
Time Horizon	10 years	In line with model by Tsai et al. (2008) and with previous models submitted to NICE.
Cycle Length	Induction (decision tree): 6 weeks Maintenance (Markov model): 8 weeks	6 weeks was the induction period of the GEMINI I trial. Mayo scores are likely to be relatively stable over an 8 week period
Half-cycle correction	Not applied	
Were health effects measured in QALYs; if not, what was used?	QALYs were used, as measured by the EQ-5D within the GEMINI I study	Most closely matches the NICE 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

Technology

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?**

The comparators included in the model are summarised below. The dosing of each comparator represents the recommendations of the European Medicines Agency. The surgical interventions are based upon the study by Buchanan et al, 2011.

Table 54. Treatment Regimens for Comparators of UC Treatment

Comparator	Regimens Considered in the Model
VEDO	300 mg intravenous infusions at weeks 0, 2, and 6, and every 8 weeks thereafter
Adalimumab	160 mg over 1-2 days at week 0, 80 mg at week 2, and 40 mg on alternate weeks
Infliximab	5 mg/kg intravenous infusions at weeks 0, 2, and 6, and every 8 weeks thereafter
Golimumab	200 mg at week 0, 100 mg at week 2, and 50 mg every 4 weeks thereafter
Conventional therapy (antibiotic)	A user-defined combination of azathioprine, 6-mercaptoprurine, methotrexate, 5-aminosalicylate, sulfasalazine, oral mesalamine, prednisolone or budesonide, and antibiotics
Surgical intervention	Patients undergo surgery and are admitted as an inpatient. We assumed that 40% of surgery patients undergo proctocolectomy with ileostomy and 60% undergo subtotal proctocolectomy with pouch formation +/− loop ileostomy (Buchanan et al., 2011)

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) SPC/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 VEDO states: "Continued therapy for patients with UC should be carefully reconsidered if no evidence of therapeutic benefit is observed by Week 10 (see section 5.1)." The GEMINI I clinical trial was designed with an induction period of 6 weeks and patients enrolled in the maintenance phase of the trial based at that time point. The response at week 6 and enrolment in the maintenance phase was based upon the complete Mayo score at that point. Patients that did not respond in the induction period continued to receive their original treatment: either VEDO 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 I trial, there is a treatment continuation rule at week 6 for VEDO. 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 10 (see Table 22 to Table 24 for data from the GEMINI I study).

The different biologic treatments considered in the model have different continuation rules in their licensed indications: week 14 for infliximab, week 8 for adalimumab and week 12-14 for golimumab. Given the variety of assessment time points, 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 10-week continuation rule, the patients that responded at week 10 were assumed to all be responders at week 6 (i.e. the proportion of patients that responded at week 10 was actually applied at week 6 within the model). However, it was also assumed in this scenario analysis that the VEDO-treated patients that received three doses before response assessment at week 10 (at baseline, week 2 and week 6).

Implementing the continuation rule requires a physician visit (for the partial Mayo score) and an endoscopy (for the complete Mayo score). 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 UC.

The use of the Mayo score is common in UC patients and predicts disease severity, quality of life and costs. The Mayo 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 10-week continuation rule limits the number of doses of VEDO 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 10-week rule, patients would receive three doses, at weeks 0, 2 and 6. Within the GEMINI I trial, 47.1% of patients responded at week 6 (106 patients of 225 randomised to VEDO), and amongst the non-responders at week 6, an additional 23 patients responded at week 10 for an overall response rate of 57.3% at week 10 (129 patients of 225

randomised to VEDO). Therefore, approximately 40-50% of patients would receive 2 or 3 doses of VEDO, depending upon the different decision rule adopted.

Please see Section 7.7.9 for results of the cost-effectiveness of VEDO using a scenario of a 10-week continuation rule.

7.3 Clinical parameters and variables

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

Population Baseline Characteristics

The model cohort's characteristics in terms of patient age, sex, and weight are included in the model. Age and sex are used to estimate general mortality risk, while weight is used to estimate weight-based drug dosing. The model estimates for age, sex, and weight are based on the mean distributions from pooled patient population of trials included in the mixed-treatment comparison (MTC) (Table 55) (see Section 6.7).

Table 55. Patient Characteristics

Parameter	Estimate
Age (years)	40.36
Percentage male	58%
Weight (kg)	76.29

Source: Pooled data from UC clinical trials in MTC. This MTC included the following articles: CSR C13006 (2013); Rutgeerts et al. (2005); Reinisch et al. (2011); Sandborn et al. (2012); Sandborn et al. (2014).

Treatment efficacy data used in the model includes response and remission data for the induction phase as well as the probability of staying in remission or mild disease during the maintenance phase.

The definitions of response and remission are as follows:

- Response: a decrease in Mayo score of 3 or more (30% or more) from baseline
- Remission: a Mayo score of 2 or less and no individual subscore of more than 1

The modelled health states described in Section 7.2.2 are defined using the following clinical characteristics:

- Remission: a Mayo score of 2 or less and no individual subscore of more than 1
- Mild: a Mayo score of 3-5
- Moderate-severe: a Mayo score of greater than 5 (6-12)
- Surgery: patients who require a surgical intervention to resolve UC
- Post surgery remission: patients who have previously had a surgery and are not currently experiencing complications from surgery
- Post surgery complications: patients who have previously had a surgery and are experiencing complications from surgery such as wound infection, bowel obstruction, intra-abdominal abscess, or anastomotic leak.

The following subsections outline the approach to estimating these data for each treatment.

Response and Remission

Data from the GEMINI I study was used to inform the comparison with conventional therapy, as patients that received placebo in the trial were permitted to receive conventional therapy. Data from the trial was used to inform the response and remission inputs for the model for the induction and maintenance phase. The results of the GEMINI I clinical trial were used to estimate the response and remission percentages for each treatment.

To conduct indirect comparisons against other biologics (infliximab, adalimumab and golimumab), an indirect comparison approach is necessary, because none of the biologics have head-to-head trial data with another biologic. An indirect comparison was conducted using 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 for naive, experienced, and overall populations. We use these odds ratios to derive probabilities relative to a common comparator (conventional therapy). Specifically, we make use of the formula for 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.

Table 56 and 0 present the odds ratios and the calculated probability estimates of response and remission during the induction and maintenance phases using the MTC approach.

Table 56. Probability of Achieving Response/Remission for Naive Patients During the Induction Period Based on Network Meta-analysis

	Response		Remission	
Treatment	Odds Ratio	Probability	Odds Ratio	Probability
VEDO[a]	3.17	62.4%	4.42	30.2%
Infliximab[b]	4.11	68.2%	5.12	33.4%
Adalimumab[c]	1.89	49.6%	1.82	15.1%
Golimumab[d]	2.54	57.0%	3.54	25.8%
Conventional therapy[a-e]	1.00	34.3%	1.00	8.9%

Studies included in the network meta-analysis include: a CSR C13006 (2012); b Rutgeerts et al. (2005); c Reinisch et al. (2011); Sandborn et al. (2012); Suzuki et al., 2014; d Sandborn et al. (2014).

Table 57. Probability of Achieving Response/Remission for Naive Patients During the Maintenance Period Based on Network Meta-analysis

	Response		Remission	
Treatment	Odds Ratio	Probability	Odds Ratio	Probability
VEDO[a]	5.27	80.6%	3.63	57.5%
Infliximab[b]	1.66	56.7%	1.24	31.7%
Adalimumab[c]	1.33	51.1%	1.97	42.4%
Golimumab[d]	1.94	60.4%	1.71	39.0%
Conventional therapy[a-d]	1.00	44.0%	1.00	27.2%

Studies included in the network meta-analysis include: [a] CSR C13006 (2012); [b] Rutgeerts et al. (2005); [c] Sandborn et al. (2012); Suzuki et al., 2014; [d] Sandborn et al. (2014).

Table 58 presents the proportion of patients in response and remission for each treatment at the end of the induction phase (6 weeks) and at the end of a year. The data for the mixed population and the anti-TNF–failure population are from the GEMINI I trial. Data for the anti-TNF naive population are based on the mixed treatment comparison (see Section 6.7).

Table 58. 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	25.5%	5.4%	23.8%	15.9%
VEDO	47.1%	16.9%	56.6%	41.8%
Naive population				
Conventional therapy	34.3%	8.9%	44.0%	27.2%
VEDO	62.4%	30.3%	80.6%	57.5%
Infliximab	68.2%	33.4%	56.7%	31.7%
Adalimumab	49.6%	15.1%	51.1%	42.4%
Golimumab	57.1%	25.8%	60.4%	39.0%
Failure population				
Conventional therapy	20.6%	3.2%	15.8%	5.3%
VEDO	39.0%	9.8%	46.5%	37.2%

[a] Mixed population refers to a combination of anti-TNF–naive patients and anti-TNF–failure patients. For VEDO, this is the intention to treat population of the clinical trial.

Patients may respond to treatment without transitioning out of the moderate-severe health state. We do not have data on the proportion of responders in moderate-severe disease for all therapies. To estimate the percentage of patients who responded but remained in the moderate-severe health state during the induction phase, we used patient-level data from the VEDO trial. Specifically, we pooled all patients who responded in the VEDO trial and calculated the proportion of responders with a Mayo score falling within each health state (remission, mild, and moderate-severe). 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. These can be seen in Table 59.

Table 59. Percentage of Moderate-Severe Responders

Treatment	Mixed	Naive	Failure
All treatments	13.2%	10.1%	20.9%

Source: Calculated from pooled patient-level trial data from CSR C13006. Due to lack of data for all comparators, we apply the same percentages to all treatments (conventional therapy and all biologics). The observed proportion of GEMINI I responders who remained in moderate-severe disease were as follows: 19 of 144 for the mixed population; 9 of 89 for the anti-TNF–naive population; 9 of 43 for the failure population.

Discontinuation

Within the model discontinuation of treatment can be due to a lack of response by the end of the induction phase or due to adverse events. In addition, it is assumed in the model that treatment with a biologic (VEDO, infliximab, adalimumab or golimumab) is limited to one year and all patients on therapy at week 54 of the model switch to conventional therapy.

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 discontinuations in induction and maintenance phase were obtained from the published phase 3 clinical trial data (Table 60).

Table 60. Probability of Discontinuation

Treatment	Mixed	Naive	Failure
Induction			
VEDO	0.00%	0.00%	0.00%
Infliximab	—	0.00%	—
Adalimumab	—	5.00%	—
Golimumab	—	0.30%	—
Maintenance			
VEDO	5.74%	4.17%	9.30%
Infliximab	—	8.26%	—
Adalimumab	—	12.43%	—
Golimumab	—	5.19%	—

Source: Probability of discontinuation was estimated from the studies included in the mixed-treatment comparison. However, not all of these studies included discontinuation data. The trials from which these data were obtained include GEMINI I; Rutgeerts et al. (2005); Reinisch et al. (2011); Sandborn et al. (2012); Sandborn et al. (2014); Suzuki et al., 2014.

Adverse Events

Adverse events for inclusion in the economic model were selected based on clinical expert opinion (see Section 7.3.5). The corresponding treatment-specific adverse-event rates for the selected events were obtained from each relevant clinical trial. Because not all adverse events were reported in all trials, these values could not be estimated in a network meta-analysis. As such, we obtained the number of patients with each event among the ITT populations of the induction and maintenance trials for each treatment. We then estimated the probability of experiencing the event based on the total ITT population. Table 61 presents the included adverse events and the corresponding probability of occurrence for each treatment.

Table 61. Probability of Adverse Events, by Treatment

Adverse Event	VEDO[a]	Infliximab[b]	Adalimumab[c]	Golimumab[d]	Conventional Therapy[e]
Serious infection	1.15%	2.48%	0.83%	1.37%	1.98%
Tuberculosis	0.00%	0.00%	0.00%	0.00%	0.08%
Lymphoma	0.00%	0.00%	0.00%	0.00%	0.00%
Acute hypersensitivity reactions	0.00%	1.65%	0.00%	0.30%	0.29%
Skin Reactions	0.29%	11.57%	0.00%	5.03%	3.20%

Adverse event probabilities were obtained from the same studies included in the meta-analysis. However, not all of these studies reported adverse events. The data presented above were obtained from [a] Final Clinical Study Report, GEMINI I; [b] Rutgeerts et al. (2005); [c] Reinisch et al. (2011), Sandborn et al. (2012); [d] Sandborn et al. (2014). [e] Pooled placebo data from the trials listed above (a-d).

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 each health state at the end of induction and at the end of 1 year were used. We used linear programming 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.

We assumed that the transition probabilities beyond the first year on treatment are the same as those estimated for the first year on treatment, excluding initial induction.

Table 62. Transition Probabilities: Mixed Population

From/To	Remission	Mild	Moderate-Severe	Surgery

From/To	Remission	Mild	Moderate-Severe	Surgery
VEDO				
Remission	0.974	0.026	0.000	0.000
Mild	0.089	0.595	0.316	0.000
Moderate-severe	0.000	0.121	0.871	0.008
Conventional therapy				
Remission	0.915	0.085	0.000	0.000
Mild	0.030	0.546	0.424	0.000
Moderate-severe	0.000	0.020	0.972	0.008

Source: Estimated based on response and remission data from the VEDO clinical trial (CSR C13006, 2012).

Table 63. Transition Probabilities: Naive Population

From/To	Remission	Mild	Moderate-Severe	Surgery
VEDO				
Remission	0.927	0.073	0.000	0.000
Mild	0.200	0.619	0.181	0.000
Moderate-severe	0.000	0.281	0.711	0.008
Infliximab				
Remission	0.920	0.080	0.000	0.000
Mild	0.027	0.678	0.295	0.000
Moderate-severe	0.000	0.159	0.834	0.008
Adalimumab				
Remission	0.980	0.020	0.000	0.000
Mild	0.152	0.559	0.289	0.000
Moderate-severe	0.000	0.077	0.870	0.008
Golimumab				
Remission	0.947	0.053	0.000	0.000
Mild	0.055	0.622	0.323	0.000
Moderate-severe	0.000	0.179	0.813	0.008
Conventional therapy				
Remission	0.937	0.063	0.000	0.000
Mild	0.063	0.552	0.385	0.000
Moderate-severe	0.000	0.104	0.888	0.008

Source: Estimated based on response and remission data from the MTC.

Table 64. Transition Probabilities: Failure Population

From/To	Remission	Mild	Moderate-Severe	Surgery
VEDO				
Remission	0.988	0.012	0.000	0.000

From/To	Remission	Mild	Moderate-Severe	Surgery
Mild	0.120	0.567	0.314	0.000
Moderate-severe	0.000	0.070	0.923	0.008
Conventional therapy				
Remission	0.837	0.163	0.000	0.000
Mild	0.000	0.593	0.407	0.000
Moderate-severe	0.000	0.028	0.964	0.008

Source: Estimated based on response and remission data from the VEDO clinical trial (CSR C13006, 2012).

Surgery

The transition probabilities above are used to estimate the proportion of patients, receiving a biologic or conventional therapy, in each “Mayo health state,” reflecting the proportion of patients with different severity of disease over time. Once patients transition to surgery, they discontinue therapy and enter the surgery section of the Markov model. For the comparison with surgery as the first treatment for UC, the following transition probabilities are also applied.

Previously published models in UC have not explicitly presented the transition probabilities from surgery and the post surgery health states. Due to the limited availability of data and a lack of placebo-controlled data (which prevented inclusion in the MTC), we derived these probabilities from a targeted review of the available published literature (Table 65).

Table 65. Transition Probabilities for Surgery and Post surgery

Health State	Surgery[a]	Post surgery Remission[a]	Post surgery Complications[a]
Surgery	0.050[b]	0.450[c]	0.500[e]
Post surgery remission	0.050[b]	0.777[c]	0.173[f]
Post surgery complications	0.050[b]	0.245[d]	0.705[c]

[a] Probabilities presented above do not include the mortality risk. As such, each of these probabilities is multiplied by (1 – p($mort_{hs,y}$)), where p($mort_{hs,y}$) represents the probability of mortality for health state *hs* in year *y*.

[b] Loftus (2008) presents a 6-month probability of 0.153. We convert this probability to an 8-week probability using the formula 1 − (1 − 0.153)^(56/180) and assume this probability for the duration of the model.

[c] Values are the result of subtracting the other two transition probabilities from 1.

[d] Xie et al. (2009) present an annual probability of 0.84. We convert this to an 8-week probability using the formula 1 − (1 − 0.84)^(56/365).

[e] Loftus (2008) (citing Mahadevan et al., 2002) presents a monthly probability of 0.31. We convert this to an 8-week probability using the formula 1 − (1 − 0.31)^(8/(30/7)).

[f] Loftus (2008). The value is the sum of the 6-month probabilities of late complications in the total column of Table 4, which gives a value of 0.457. We convert this to an 8-week probability using the formula 1 − (1 − 0.457)^(56/180).

Mortality

Previous cost-effectiveness analyses did not incorporate 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 from 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. Table 66 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 66. UK Annual Mortality Rates (per 1,000 Population)

	Annual Mortality Rate (per 1,000)	
Age (Years)	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, we estimate an initial annual mortality rate of 0.0015, which translates to a 6-week probability of 0.000174. Assuming an exponential function and fitting the curve to the data above, we estimate the per-cycle (8-week) mortality change factor to be 1.01385.

We then adjust mortality based on the patient's 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 67. 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).

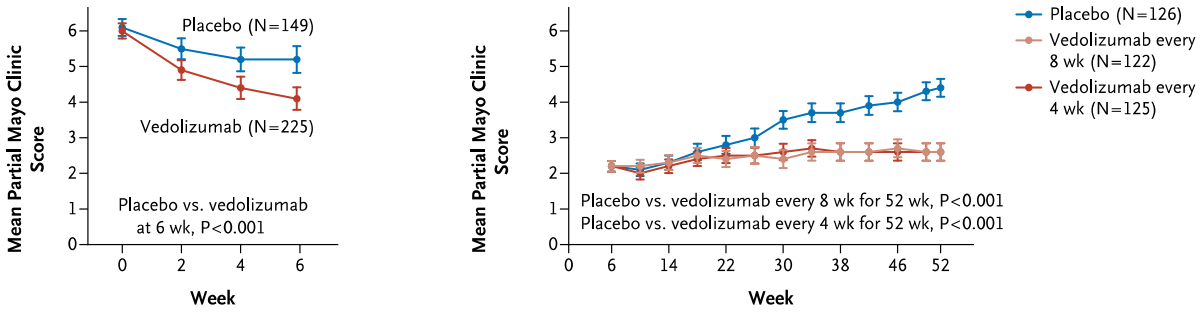
[c] Jess et al. (2007). Due to lack of available data, we assumed the same risk for patients in surgery and post surgery health states.

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).

We have not formally assessed whether transition probabilities should vary with time. However, examining graphs of the mean partial Mayo scores over the course of the trial, a constant transition probability seems reasonable (Feagan et al, 2013). Figure 1a from that paper, reproduced below (Figure 12) does not suggests non-linearity in partial Mayo scores over the course of the trial.

Figure 12. Exploratory Outcomes in the GEMINI I Trial: Partial Mayo Scores by Treatment and Study Visit



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 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).

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.

[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.

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 only used for validation purposes and not to estimate any input parameter values other than the selection of adverse events.

The Questionnaire is provided in Appendix 16, Section 10.16.

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.**

Table 68 provides a list of all of the variables used in the model, their base-case values, calculated 95% confidence interval (where appropriate) for use in the one-way sensitivity analysis and the distribution used in the probabilistic sensitivity analysis.

Table 68. List of All Variables in the Model, Base-Case Values, Values in One-Way Sensitivity Analysis and Distribution in the Probabilistic Sensitivity Analysis

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)	40.36	32.69	48.82	Gamma	20%	96.04	0.42
Percent male		Percent male (95% CI)			N		
Percent male	57.80%	56.32%	59.28%	Beta	4277	2472	1805
Weight (in kg)		Average weight (+/- 5%)			% in tails		
Weight	76.29	61.80	92.29	Gamma	20%	96.04	0.79

Parameter	Base Case Value	One-Way Sensitivity Analysis		Probabilistic Sensitivity Analysis			
		Lower Bound	Upper Bound	Distribution	N / Calc.	Alpha	Beta
Efficacy							
Efficacy - Induction Period							
Mixed Population (ITT)							
Conventional therapy (trial-based, 10-week data)		Conventional therapy efficacy - induction period (95% CI)			N		
Remission	17.45%	11.81%	23.92%	Beta	149	26	123
Response	32.21%	24.98%	39.91%	Beta	149	48	101
Vedolizumab (trial-based 10-week data)		Vedolizumab efficacy - induction period (95% CI)			N		
Remission	37.94%	31.72%	44.36%	Beta	746	283	463
Response	56.57%	50.06%	62.97%	Beta	746	422	324
TNF-Naive Population							
Conventional therapy (trial-based, 10-week data)		Conventional therapy efficacy - induction period (95% CI)			N		
Remission	16.90%	9.18%	26.38%	Beta	71	12	59
Response	35.21%	24.61%	46.60%	Beta	71	25	46
Vedolizumab (trial-based 10-week data)		Vedolizumab efficacy - induction period (95% CI)			N		

Parameter	Base Case Value	One-Way Sensitivity Analysis		Probabilistic Sensitivity Analysis			
		Lower Bound	Upper Bound	Distribution	N / Calc.	Alpha	Beta
Remission	43.08%	39.55%	46.65%	Beta	383	165	218
Response	64.49%	61.02%	67.88%	Beta	383	247	136
Conventional therapy (MTC-based 6-week data)		Conventional therapy efficacy - induction period (95% CI)			N		
Remission	8.93%	3.65%	16.24%	Beta	76	5	71
Response	34.29%	24.12%	45.25%	Beta	76	20	56
Vedolizumab (MTC-based 6-week data)		Vedolizumab efficacy - induction period (95% CI)			N		
Remission	30.25%	27.00%	33.59%	Beta	130	30	100
Response	62.35%	58.85%	65.80%	Beta	130	69	61
Infliximab (MTC-based data)		Infliximab efficacy -initial response period (95% CI)			N		
Remission	33.41%	27.62%	39.47%	Beta	242	81	161
Response	68.18%	62.19%	73.89%	Beta	242	165	77
Adalimumab (MTC-based data)		Adalimumab efficacy -initial response period (95% CI)			N		
Remission	15.14%	11.68%	18.96%	Beta	370	56	314
Response	49.60%	44.51%	54.68%	Beta	370	184	186

Parameter	Base Case Value	One-Way Sensitivity Analysis		Probabilistic Sensitivity Analysis			
		Lower Bound	Upper Bound	Distribution	N / Calc.	Alpha	Beta
Golimumab (MTC-based data)		Golimumab efficacy -initial response period (95% CI)			N		
Remission	25.78%	20.62%	31.28%	Beta	257	66	191
Response	57.05%	50.96%	63.03%	Beta	257	147	110
TNF-Failure Population							
Conventional therapy (trial-based, 10-week data)		Conventional therapy efficacy - induction period (95% CI)			N		
Remission	15.87%	8.02%	25.78%	Beta	63	10	53
Response	28.57%	18.20%	40.23%	Beta	63	18	45
Vedolizumab (trial-based 10-week data)		Vedolizumab efficacy - induction period (95% CI)			N		
Remission	30.59%	27.34%	33.94%	Beta	304	93	211
Response	44.74%	41.19%	48.31%	Beta	304	136	168
Transition probabilities (post-induction)							
Mixed Population (ITT)							
Vedolizumab							
Remission to:		VDZ transition probabilities: remission (95% CI)			N		
Remission	0.974	0.940	0.994	Dirichlet	122	119	120

Parameter	Base Case Value	One-Way Sensitivity Analysis		Probabilistic Sensitivity Analysis			
		Lower Bound	Upper Bound	Distribution	N / Calc.	Alpha	Beta
Mild	0.026	0.060	0.006	Dirichlet	122	3	4
Moderate-to-severe	0.000	0.000	0.000	Dirichlet	122	0	0
Surgery	0.000	0.000	0.000	Dirichlet	122	0	0
Mild to:		VDZ transition probabilities: mild (95% CI)					
Remission	0.089	0.108	0.070	Dirichlet	122	11	9
Mild	0.595	0.507	0.680	Dirichlet	122	73	73
Moderate-to-severe	0.316	0.385	0.250	Dirichlet	122	39	34
Surgery	0.000	0.000	0.000	Dirichlet	122	0	0
Moderate-to-severe to:		VDZ transition probabilities: moderate-severe (95% CI)					
Remission	0.000	0.000	0.000	Dirichlet	122	0	0
Mild	0.121	0.070	0.184	Dirichlet	122	15	16
Moderate-to-severe	0.871	0.922	0.809	Dirichlet	122	106	105
Surgery	0.008	0.008	0.007	Dirichlet	122	1	2
Conventional therapy							
Remission to:		CT transition probabilities: remission (95% CI)			N		
Remission	0.915	0.860	0.957	Dirichlet	126	115	146
Mild	0.085	0.140	0.043	Dirichlet	126	11	15
Moderate-to-severe	0.000	0.000	0.000	Dirichlet	126	0	0
Surgery	0.000	0.000	0.000	Dirichlet	126	0	0

Parameter	Base Case Value	One-Way Sensitivity Analysis		Probabilistic Sensitivity Analysis			
		Lower Bound	Upper Bound	Distribution	N / Calc.	Alpha	Beta
Mild to:		CT transition probabilities: mild (95% CI)					
Remission	0.030	0.036	0.024	Dirichlet	126	4	3
Mild	0.546	0.459	0.632	Dirichlet	126	69	65
Moderate-to-severe	0.424	0.505	0.344	Dirichlet	126	53	63
Surgery	0.000	0.000	0.000	Dirichlet	126	0	0
Moderate-to-severe to:		CT transition probabilities: moderate-severe (95% CI)					
Remission	0.000	0.000	0.000	Dirichlet	126	0	0
Mild	0.020	0.003	0.051	Dirichlet	126	3	4
Moderate-to-severe	0.972	0.989	0.942	Dirichlet	126	122	114
Surgery	0.008	0.008	0.007	Dirichlet	126	1	2
Surgery							
Surgery to:		Surgery transition probabilities (95% CI)			N		
Surgery	0.050	0.025	0.083	Dirichlet	215	11	14
Post-surgery remission	0.450	0.462	0.434	Dirichlet	215	97	104
Post-surgery complications	0.500	0.513	0.482	Dirichlet	215	107	110
Post-surgery remission to:							
Surgery	0.050	0.025	0.083	Dirichlet	215	11	10
Post-surgery remission	0.777	0.797	0.750	Dirichlet	215	167	169
Post-surgery complications	0.173	0.178	0.167	Dirichlet	215	37	44

Parameter	Base Case Value	One-Way Sensitivity Analysis		Probabilistic Sensitivity Analysis			
		Lower Bound	Upper Bound	Distribution	N / Calc.	Alpha	Beta
Post-surgery complications to:							
Surgery	0.050	0.025	0.083	Dirichlet	215	11	10
Post-surgery remission	0.245	0.252	0.237	Dirichlet	100	25	18
Post-surgery complications	0.705	0.723	0.680	Dirichlet	215	151	169
TNF-Naive Population							
Vedolizumab (trial-based data)		VDZ transition probabilities: remission (95% CI)			N		
Remission to:	0.961	0.960	0.906	Dirichlet	72	69	68
Remission	0.039	0.040	0.094	Dirichlet	72	3	0
Mild	0.000	0.000	0.000	Dirichlet	72	0	0
Moderate-to-severe	0.000	0.000	0.000	Dirichlet	72	0	0
Surgery							
Mild to:		VDZ transition probabilities: mild (95% CI)					
Remission	0.087	0.086	0.114	Dirichlet	72	6	9
Mild	0.625	0.592	0.512	Dirichlet	72	45	38
Moderate-to-severe	0.287	0.322	0.375	Dirichlet	72	21	21
Surgery	0.000	0.000	0.000	Dirichlet	72	0	0
Moderate-to-severe to:		VDZ transition probabilities: moderate-severe (95% CI)					
Remission	0.000	0.000	0.000	Dirichlet	72	0	0
Mild	0.175	0.150	0.097	Dirichlet	72	13	11

Parameter	Base Case Value	One-Way Sensitivity Analysis		Probabilistic Sensitivity Analysis			
		Lower Bound	Upper Bound	Distribution	N / Calc.	Alpha	Beta
Moderate-to-severe	0.817	0.839	0.895	Dirichlet	72	59	62
Surgery	0.008	0.011	0.008	Dirichlet	72	1	0
Conventional therapy (trial-based data)							
Remission to:		CT transition probabilities: remission (95% CI)			N		
Remission	0.922	0.854	0.970	Dirichlet	79	73	83
Mild	0.078	0.146	0.030	Dirichlet	79	6	6
Moderate-to-severe	0.000	0.000	0.000	Dirichlet	79	0	0
Surgery	0.000	0.000	0.000	Dirichlet	79	0	0
Mild to:		CT transition probabilities: mild (95% CI)					
Remission	0.030	0.037	0.022	Dirichlet	79	2	4
Mild	0.557	0.448	0.665	Dirichlet	79	44	53
Moderate-to-severe	0.413	0.516	0.313	Dirichlet	79	33	31
Surgery	0.000	0.000	0.000	Dirichlet	79	0	0
Moderate-to-severe to:		CT transition probabilities: moderate-severe (95% CI)					
Remission	0.000	0.000	0.000	Dirichlet	79	0	0
Mild	0.014	0.001	0.050	Dirichlet	79	1	1
Moderate-to-severe	0.978	0.992	0.943	Dirichlet	79	77	62
Surgery	0.008	0.008	0.007	Dirichlet	79	1	0

Parameter	Base Case Value	One-Way Sensitivity Analysis		Probabilistic Sensitivity Analysis			
		Lower Bound	Upper Bound	Distribution	N / Calc.	Alpha	Beta
Vedolizumab (MTC-based data)							
Remission to:		VDZ transition probabilities: remission (95% CI)			N		
Remission	0.927	0.857	0.975	Dirichlet	72	67	54
Mild	0.073	0.143	0.025	Dirichlet	72	5	3
Moderate-to-severe	0.000	0.000	0.000	Dirichlet	72	0	0
Surgery	0.000	0.000	0.000	Dirichlet	72	0	0
Mild to:		VDZ transition probabilities: mild (95% CI)					
Remission	0.200	0.260	0.143	Dirichlet	72	14	12
Mild	0.619	0.504	0.727	Dirichlet	72	45	47
Moderate-to-severe	0.181	0.236	0.130	Dirichlet	72	13	12
Surgery	0.000	0.000	0.000	Dirichlet	72	0	0
Moderate-to-severe to:		VDZ transition probabilities: moderate-severe (95% CI)					
Remission	0.000	0.000	0.000	Dirichlet	72	0	0
Mild	0.281	0.184	0.389	Dirichlet	72	20	18
Moderate-to-severe	0.711	0.807	0.604	Dirichlet	72	51	57
Surgery	0.008	0.009	0.007	Dirichlet	72	1	0
Conventional therapy (MTC-based data)							

Parameter	Base Case Value	One-Way Sensitivity Analysis		Probabilistic Sensitivity Analysis			
		Lower Bound	Upper Bound	Distribution	N / Calc.	Alpha	Beta
Remission to:		CT transition probabilities: remission (95% CI)			N		
Remission	0.920	0.852	0.969	Dirichlet	79	73	91
Mild	0.080	0.148	0.031	Dirichlet	79	6	9
Moderate-to-severe	0.000	0.000	0.000	Dirichlet	79	0	0
Surgery	0.000	0.000	0.000	Dirichlet	79	0	0
Mild to:		CT transition probabilities: mild (95% CI)					
Remission	0.027	0.036	0.019	Dirichlet	79	2	1
Mild	0.678	0.572	0.776	Dirichlet	79	54	58
Moderate-to-severe	0.295	0.393	0.206	Dirichlet	79	23	21
Surgery	0.000	0.000	0.000	Dirichlet	79	0	0
Moderate-to-severe to:		CT transition probabilities: moderate-severe (95% CI)					
Remission	0.000	0.000	0.000	Dirichlet	79	0	0
Mild	0.159	0.087	0.246	Dirichlet	79	13	11
Moderate-to-severe	0.834	0.904	0.747	Dirichlet	79	66	62
Surgery	0.008	0.008	0.007	Dirichlet	79	1	2
Infliximab							
Remission to:		IFX transition probabilities: remission (95% CI)			N		

Parameter	Base Case Value	One-Way Sensitivity Analysis		Probabilistic Sensitivity Analysis			
		Lower Bound	Upper Bound	Distribution	N / Calc.	Alpha	Beta
Remission	0.920	0.854	0.968	Dirichlet	84	77	70
Mild	0.080	0.146	0.032	Dirichlet	84	7	10
Moderate-to-severe	0.000	0.000	0.000	Dirichlet	84	0	0
Surgery	0.000	0.000	0.000	Dirichlet	84	0	0
Mild to:		IFX transition probabilities: mild (95% CI)					
Remission	0.027	0.035	0.019	Dirichlet	84	2	2
Mild	0.678	0.575	0.773	Dirichlet	84	57	51
Moderate-to-severe	0.295	0.390	0.208	Dirichlet	84	25	21
Surgery	0.000	0.000	0.000	Dirichlet	84	0	0
Moderate-to-severe to:		IFX transition probabilities: moderate-severe (95% CI)					
Remission	0.000	0.000	0.000	Dirichlet	84	0	0
Mild	0.159	0.089	0.244	Dirichlet	84	13	14
Moderate-to-severe	0.834	0.902	0.749	Dirichlet	84	70	73
Surgery	0.008	0.008	0.007	Dirichlet	84	1	1
Adalimumab							
Remission to:		ADA transition probabilities: remission (95% CI)			N		
Remission	0.980	0.955	0.995	Dirichlet	171	168	153
Mild	0.020	0.045	0.005	Dirichlet	171	3	3

Parameter	Base Case Value	One-Way Sensitivity Analysis		Probabilistic Sensitivity Analysis			
		Lower Bound	Upper Bound	Distribution	N / Calc.	Alpha	Beta
Moderate-to-severe	0.000	0.000	0.000	Dirichlet	171	0	0
Surgery	0.000	0.000	0.000	Dirichlet	171	0	0
Mild to:		ADA transition probabilities: mild (95% CI)					
Remission	0.152	0.178	0.127	Dirichlet	171	26	29
Mild	0.559	0.484	0.632	Dirichlet	171	96	113
Moderate-to-severe	0.289	0.338	0.241	Dirichlet	171	49	45
Surgery	0.000	0.000	0.000	Dirichlet	171	0	0
Moderate-to-severe to:		ADA transition probabilities: moderate-severe (95% CI)					
Remission	0.000	0.000	0.000	Dirichlet	171	0	0
Mild	0.077	0.042	0.122	Dirichlet	171	13	15
Moderate-to-severe	0.915	0.950	0.871	Dirichlet	171	156	167
Surgery	0.008	0.008	0.007	Dirichlet	171	1	1
Golimumab							
Remission to:		GOL transition probabilities: remission (95% CI)			N		
Remission	0.947	0.907	0.977	Dirichlet	153	145	149
Mild	0.053	0.093	0.023	Dirichlet	153	8	7
Moderate-to-severe	0.000	0.000	0.000	Dirichlet	153	0	0
Surgery	0.000	0.000	0.000	Dirichlet	153	0	0

Parameter	Base Case Value	One-Way Sensitivity Analysis		Probabilistic Sensitivity Analysis			
		Lower Bound	Upper Bound	Distribution	N / Calc.	Alpha	Beta
Mild to:		GOL transition probabilities: mild (95% CI)					
Remission	0.055	0.066	0.044	Dirichlet	153	8	10
Mild	0.622	0.544	0.697	Dirichlet	153	95	87
Moderate-to-severe	0.323	0.390	0.259	Dirichlet	153	49	59
Surgery	0.000	0.000	0.000	Dirichlet	153	0	0
Moderate-to-severe to:		GOL transition probabilities: moderate-severe (95% CI)					
Remission	0.000	0.000	0.000	Dirichlet	153	0	0
Mild	0.179	0.123	0.244	Dirichlet	153	27	20
Moderate-to-severe	0.813	0.869	0.749	Dirichlet	153	124	105
Surgery	0.008	0.008	0.007	Dirichlet	153	1	0
Surgery							
Surgery to:		Surgery transition probabilities (95% CI)			N		
Surgery	0.050	0.025	0.083	Dirichlet	215	11	14
Post-surgery remission	0.450	0.462	0.434	Dirichlet	215	97	104
Post-surgery complications	0.500	0.513	0.482	Dirichlet	215	107	110
Post-surgery remission to:							
Surgery	0.050	0.025	0.083	Dirichlet	215	11	10
Post-surgery remission	0.777	0.797	0.750	Dirichlet	215	167	169

Parameter	Base Case Value	One-Way Sensitivity Analysis		Probabilistic Sensitivity Analysis			
		Lower Bound	Upper Bound	Distribution	N / Calc.	Alpha	Beta
Post-surgery complications	0.173	0.178	0.167	Dirichlet	215	37	44
Post-surgery complications to:							
Surgery	0.050	0.025	0.083	Dirichlet	215	11	10
Post-surgery remission	0.245	0.252	0.237	Dirichlet	100	25	18
Post-surgery complications	0.705	0.723	0.680	Dirichlet	215	151	169
TNF-Failure Population							
Vedolizumab (trial-based data)							
Remission to:		VDZ transition probabilities: remission (95% CI)			N		
Remission	0.988	0.941	1.000	Dirichlet	43	42	44
Mild	0.012	0.059	0.000	Dirichlet	43	1	0
Moderate-to-severe	0.000	0.000	0.000	Dirichlet	43	0	0
Surgery	0.000	0.000	0.000	Dirichlet	43	0	0
Mild to:		VDZ transition probabilities: mild (95% CI)					
Remission	0.120	0.161	0.080	Dirichlet	43	5	6
Mild	0.567	0.418	0.709	Dirichlet	43	24	29
Moderate-to-severe	0.314	0.421	0.210	Dirichlet	43	13	13
Surgery	0.000	0.000	0.000	Dirichlet	43	0	0
Moderate-to-severe to:		VDZ transition probabilities: moderate-					

Parameter	Base Case Value	One-Way Sensitivity Analysis		Probabilistic Sensitivity Analysis			
		Lower Bound	Upper Bound	Distribution	N / Calc.	Alpha	Beta
		severe (95% CI)					
Remission	0.000	0.000	0.000	Dirichlet	43	0	0
Mild	0.070	0.015	0.161	Dirichlet	43	3	1
Moderate-to-severe	0.923	0.977	0.832	Dirichlet	43	40	43
Surgery	0.008	0.008	0.007	Dirichlet	43	0	0
Conventional therapy (trial-based data)							
Remission to:		CT transition probabilities: remission (95% CI)			N		
Remission	0.837	0.705	0.935	Dirichlet	38	32	24
Mild	0.163	0.295	0.065	Dirichlet	38	6	3
Moderate-to-severe	0.000	0.000	0.000	Dirichlet	38	0	0
Surgery	0.000	0.000	0.000	Dirichlet	38	0	0
Mild to:		CT transition probabilities: mild (95% CI)					
Remission	0.000	0.000	0.000	Dirichlet	38	0	0
Mild	0.593	0.435	0.742	Dirichlet	38	23	19
Moderate-to-severe	0.407	0.565	0.258	Dirichlet	38	15	25
Surgery	0.000	0.000	0.000	Dirichlet	38	0	0
Moderate-to-severe to:		CT transition probabilities: moderate-severe (95% CI)					

Parameter	Base Case Value	One-Way Sensitivity Analysis		Probabilistic Sensitivity Analysis			
		Lower Bound	Upper Bound	Distribution	N / Calc.	Alpha	Beta
Remission	0.000	0.000	0.000	Dirichlet	38	0	0
Mild	0.028	0.001	0.098	Dirichlet	38	1	2
Moderate-to-severe	0.965	0.991	0.895	Dirichlet	38	37	32
Surgery	0.008	0.008	0.007	Dirichlet	38	0	0
Surgery							
Surgery to:		Surgery transition probabilities (95% CI)			N		
Surgery	0.050	0.025	0.083	Dirichlet	215	11	11
Post-surgery remission	0.450	0.462	0.434	Dirichlet	215	97	83
Post-surgery complications	0.500	0.513	0.482	Dirichlet	215	107	92
Post-surgery remission to:							
Surgery	0.050	0.025	0.083	Dirichlet	215	11	9
Post-surgery remission	0.777	0.797	0.750	Dirichlet	215	167	168
Post-surgery complications	0.173	0.178	0.167	Dirichlet	215	37	42
Post-surgery complications to:							
Surgery	0.050	0.025	0.083	Dirichlet	215	11	9
Post-surgery remission	0.245	0.252	0.237	Dirichlet	100	25	26
Post-surgery complications	0.705	0.723	0.680	Dirichlet	215	151	163

Parameter	Base Case Value	One-Way Sensitivity Analysis		Probabilistic Sensitivity Analysis			
		Lower Bound	Upper Bound	Distribution	N / Calc.	Alpha	Beta
Other Efficacy Parameters							
Probability of surgery		Probability of surgery (95% CI)			N		
Induction	0.58%	0.45%	0.72%	Beta	11,535	67	11,468
Maintenance	0.77%	0.62%	0.94%	Beta	11,535	89	11,446
Percentage of responders in moderate-severe		Percentage of responders in moderate-severe (95% CI)			N		
Percentage	13.19%	8.19%	19.16%	Beta	144	19	125
Mortality relative risks		Relative risk of all-cause mortality (+/- 20%)			% in tails		
Remission	1	0.81	1.21	Gamma	20%	96.04	0.010
Mild	1	0.81	1.21	Gamma	20%	96.04	0.010
Moderate-Severe	1.9	1.54	2.30	Gamma	20%	96.04	0.020
Surgery	1.3	1.05	1.57	Gamma	20%	96.04	0.014
Post-surgery remission	1.3	1.05	1.57	Gamma	20%	96.04	0.014
Post-surgery complications	1.3	1.05	1.57	Gamma	20%	96.04	0.014

Parameter	Base Case Value	One-Way Sensitivity Analysis		Probabilistic Sensitivity Analysis			
		Lower Bound	Upper Bound	Distribution	N / Calc.	Alpha	Beta
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)	£924.00						
Cost of administration per cycle (maintenance phase)	£308.00						
Infliximab							
Vedolizumab (Induction phase)	[redacted]						
Vedolizumab per cycle (maintenance phase)	[redacted]						
Cost of administration (induction phase)	£924.00						
Cost of administration per cycle (maintenance phase)	£308.00						
Adalimumab							
Vedolizumab (Induction phase)	[redacted]						

Parameter	Base Case Value	One-Way Sensitivity Analysis		Probabilistic Sensitivity Analysis			
		Lower Bound	Upper Bound	Distribution	N / Calc.	Alpha	Beta
Vedolizumab per cycle (maintenance phase)	[redacted]						
Cost of administration (induction phase)	£0.00						
Cost of administration per cycle (maintenance phase)	£0.00						
Golimumab							
Vedolizumab (Induction phase)	[redacted]						
Vedolizumab per cycle (maintenance phase)	[redacted]						
Cost of administration (induction phase)	£0.00						
Cost of administration per cycle (maintenance phase)	£0.00						
Conventional Therapy	% Use	Cost per day					
Balsalazide	13.4%	£0.94					
Mesalazine	13.4%	£1.47					
Olsalazine	13.4%	£0.71					
Sulfasalazine	13.4%	£0.24					
Budesonide	0.8%	£2.25					
Prednisolone	35.8%	£5.14					
Azathioprine	39.0%	£0.23					

Parameter	Base Case Value	One-Way Sensitivity Analysis		Probabilistic Sensitivity Analysis			
		Lower Bound	Upper Bound	Distribution	N / Calc.	Alpha	Beta
Mercaptopurine	15.4%	£7.70					
Methotrexate	8.9%	£0.80					
Weighted average cost per cycle		**£204.80**					
Cost per cycle for patients treated with biologic		**£102.40**					
Health State Costs		Health state costs (-/+ 20%)			% in tails		
Remission	£236.52	£191.59	£286.11	Gamma	20%	96.04	2.46
Mild	£424.02	£343.48	£512.93	Gamma	20%	96.04	4.42
Moderate-to-Severe	£957.77	£775.83	£1,158.59	Gamma	20%	96.04	9.97
Surgery	£13,577.27	£10,998.14	£16,424.00	Gamma	20%	96.04	141.37
Post-surgery remission	£467.65	£378.81	£565.70	Gamma	20%	96.04	4.87
Post-surgery complications	£1,913.24	£1,549.80	£2,314.39	Gamma	20%	96.04	19.92
Health state utilities		Health state utilities (+/- 20%)			N		
Remission	0.860	0.786	0.920	Beta	100	86	14
Mild	0.800	0.717	0.872	Beta	100	80	20
Moderate-to-Severe	0.680	0.586	0.767	Beta	100	68	32
Surgery	0.420	0.325	0.518	Beta	100	42	58
Post-surgery remission	0.600	0.503	0.693	Beta	100	60	40

Parameter	Base Case Value	One-Way Sensitivity Analysis		Probabilistic Sensitivity Analysis			
		Lower Bound	Upper Bound	Distribution	N / Calc.	Alpha	Beta
Post-surgery complications	0.420	0.325	0.518	Beta	100	42	58
Adverse Events							
Adverse Events: Incidence							
Vedolizumab		AE incidence - Vedolizumab (95% CI)			N		
Serious Infection	1.15%	0.32%	2.51%	Beta	347	4	343
Tuberculosis	0.00%	0.00%	0.00%	Beta	0	0	0
Lymphoma	0.00%	0.00%	0.00%	Beta	122	0	122
Acute hypersensitivity reaction	0.00%	0.00%	0.00%	Beta	122	0	122
Skin reactions	0.29%	0.01%	1.06%	Beta	347	1	346
Infliximab		AE incidence - Infliximab (95% CI)					
Serious Infection	2.48%	0.52%	5.89%	Beta	121	3	118
Tuberculosis	0.00%	0.00%	0.00%	Beta	121	0	121
Lymphoma	0.00%	0.00%	0.00%	Beta	121	0	121
Acute hypersensitivity reaction	1.65%	0.20%	4.56%	Beta	121	2	119
Skin reactions	11.57%	6.53%	17.81%	Beta	121	14	107
Adalimumab		AE incidence - Adalimumab (95% CI)					
Serious Infection	0.83%	0.23%	1.82%	Beta	480	4	476
Tuberculosis	0.00%	0.00%	0.00%	Beta	480	0	480
Lymphoma	0.00%	0.00%	0.00%	Beta	480	0	480
Acute hypersensitivity reaction	0.00%	0.00%	0.00%	Beta	0	0	0

Parameter	Base Case Value	One-Way Sensitivity Analysis		Probabilistic Sensitivity Analysis			
		Lower Bound	Upper Bound	Distribution	N / Calc.	Alpha	Beta
Skin reactions	0.00%	0.00%	0.00%	Beta	0	0	0
Golimumab		AE incidence - Golimumab (95% CI)					
Serious Infection	1.37%	0.55%	2.55%	Beta	510	7	503
Tuberculosis	0.00%	0.00%	0.00%	Beta	485	0	485
Lymphoma	0.00%	0.00%	0.00%	Beta	179	0	179
Acute hypersensitivity reaction	0.30%	0.01%	1.11%	Beta	331	1	330
Skin reactions	5.03%	2.34%	8.66%	Beta	179	9	170
Conventional therapy		AE incidence - Conventional therapy (95% CI)					
Serious Infection	1.98%	1.35%	2.73%	Beta	1564	31	1533
Tuberculosis	0.08%	0.00%	0.30%	Beta	1213	1	1212
Lymphoma	0.00%	0.00%	0.00%	Beta	1085	0	1085
Acute hypersensitivity reaction	0.29%	0.03%	0.79%	Beta	700	2	698
Skin reactions	3.20%	2.06%	4.57%	Beta	751	24	727
Cost per adverse event		Cost per adverse event (+/- 20%)			% in tails		
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

Parameter	Base Case Value	One-Way Sensitivity Analysis		Probabilistic Sensitivity Analysis			
		Lower Bound	Upper Bound	Distribution	N / Calc.	Alpha	Beta
Adverse event disutilities		Adverse event disutilities (+/- 20%)			N		
Serious Infection	0.520	0.422	0.617	Beta	100	52	48
Tuberculosis	0.550	0.452	0.646	Beta	100	55	45
Lymphoma	0.195	0.124	0.278	Beta	100	19.5	80.5
Acute hypersensitivity reaction	0.110	0.057	0.178	Beta	100	11	89
Skin reactions	0.030	0.006	0.071	Beta	100	3	97
Proportion Discontinuing due to AEs							
Vedolizumab		Vedolizumab discontinuation rate (95% CI)			N		
Induction	0.00%	0.00%	0.00%	Beta	225	0	225
Maintenance	5.74%	2.36%	10.48%	Beta	122	7	115
Infliximab		Infliximab discontinuation rate (95% CI)					
Induction	0.00%	0.00%	0.00%	Beta	242	0	242
Maintenance	0.00%	0.00%	0.00%	Beta	84	0	84
Adalimumab		Adalimumab discontinuation rate (95% CI)					
Induction	0.00%	0.00%	0.00%	Beta	370	0	370
Maintenance	5.74%	2.78%	9.67%	Beta	171	10	161

Parameter	Base Case Value	One-Way Sensitivity Analysis		Probabilistic Sensitivity Analysis			
		Lower Bound	Upper Bound	Distribution	N / Calc.	Alpha	Beta
Golimumab		Golimumab discontinuation rate (95% CI)					
Induction	0.00%	0.00%	0.00%	Beta	257	0	257
Maintenance	0.00%	0.00%	0.00%	Beta	153	0	153
Conventional therapy		Conventional therapy discontinuation rate (95% CI)					
Induction	0.00%	0.00%	0.00%	Beta	149	0	149
Maintenance	0.00%	0.00%	0.00%	Beta	126	0	126

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 to ten years in the base-case. It is assumed that all patients receiving biologics (VEDO, infliximab, adalimumab or golimumab) have one year of treatment and then switch to a conventional therapy. They are subject to the transition probabilities for conventional therapy after one year. Thus, it is assumed that for each original comparator (with the exception of surgery), the transition probabilities are the same after one year (as are costs).

Within the model, more patients are in remission after treatment with VEDO 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.

The transition probabilities for patients that receive surgery in the model are constant over the course of the model.

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).
- 1 year of treatment is assumed for all biologic treatments. We test this assumption in scenario analyses.
- In scenario analysis where the duration of treatment is more than one year, we assumed the transition probabilities beyond the first year on treatment are the same as those estimated for the first year on treatment, excluding initial induction.

- After discontinuation of treatment, a patient switches to conventional therapy and faces the costs and clinical effects observed for conventional therapy.
- In scenarios where time on treatment is more than one year for the biologics, patients who respond to treatment during the induction phase continue on treatment for at least 1 year. After 1 year, patients who are in mild disease or remission continue on treatment. Patients entering the moderate-severe disease state after 1 year on treatment will discontinue treatment and switch to conventional therapy.
- The cost of surgery as a comparator is assumed to be the same as the cost of surgery as a health state in the biologic and conventional therapy Markov models. Specifically, we assumed the same costs as presented by Buchanan et al, 2011. Ideally the cost of surgery as a comparator should be based on the type of surgical procedure for which the efficacy data are used in the model. However, the Reference Cost schedule does not provide this level of detail, and only provides national costs by the broad category of inflammatory bowel disease–related surgery.
- Patients may discontinue biologic treatment due to intolerability to adverse events at any time during the first year on treatment. We assumed that adverse events leading to discontinuation would present during the first year on treatment as observed in the clinical trials. In scenario analyses where the duration of treatment is more than 1 year we assumed that any patients who tolerate treatment through 1 year would continue to tolerate treatment for the remainder of their time on treatment.
- 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 costs due to a 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 probably overestimating the costs somewhat.

7.4 Measurement and valuation of health effects

Patient experience

7.4.1	**Please outline the aspects of the condition that most affect patients' quality of life.**

Living with the symptoms of active UC, including frequent urgent diarrhoea, abdominal pain and fatigue, profoundly diminishes the HRQoL of patients in a population that is typically young and active (Waljee et al. 2011). Over two-thirds of patients with UC describe interference of the disease with work and nearly three quarters describe interference with leisure activities (Dignass et al. 2012). Patients with UC report significantly more disease-related concerns, impaired social functioning and a reduced sense of well-being compared with age-matched disease-free controls (Waljee et al. 2011). The disease will often require lifelong treatment with the aim of treating active disease and maintaining a state of remission.

A full assessment of the impact of chronic fatigue, sleep disturbance and pain are described in greater detail in section 2 of this document with top line details provided here. Mitchell and colleagues (1988) noted that systemic symptoms, such as fatigue, were frequently reported in patients with IBD and rated as of the same importance as frequent bowel movements and abdominal pain (cited in (Jelsness-Jørgensen et al. 2011). Jelsness-Jorgensen and colleagues (2011) investigated the influence of chronic fatigue on both the generic and disease-specific HRQOL of patients with IBD.

Chronic sleep disturbances may modify the coping ability of patients and therefore affect the experience of symptoms, including abdominal pain and fatigue. Ranjbaran and colleagues (2007) conducted a cross-sectional survey using the IBD-Q and PSQI. In addition to measuring disease-related QOL, the IBD-Q also addresses psychosocial function, including degree of worry and anxiety and/or presence of depression.

Inflammatory bowel disease is associated with abdominal pain, but pain can also occur throughout the body. Schirbel and colleagues (2010) conducted a cross-sectional study to evaluate the intensity, localisation and cofactors of pain in patients with IBD in connection with HRQOL and disease activity using the SIBDQ and the German Pain Questionnaire (CD, n =

179; UC, n = 155) (Schirbel 2010). For all patients with IBD, pain localisations were different between males and females, with females reporting arthralgia more frequently. A comparison of pain localisation in patients with UC revealed a higher pain frequency in the lower left abdomen (76.4%) compared with patients with CD (55.6%).

7.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition.

When all medical treatment options have been exhausted, patients with intractable or badly controlled UC may undergo colectomy (removal of a section of the affected part of the colon).

Although there is an overall trend of decreasing rates of colectomy, about 40% of patients with UC will eventually require surgery (Solberg et al. 2009). However, surgery is usually a last resort for clinicians and patients due to the potential for serious sequelae: bleeding, faecal incontinence, depression, sexual dysfunction, female infertility, pouchitis, pouch leakage, pelvic abscesses, pouch fistulae, small bowel obstruction and anastomotic stricture (Ochsenkühn & D'Haens 2011).

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 I trial using the IBDQ, SF-36 and EQ-5D instruments. 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). Results of the HRQL assessment are provided in Table 28, above. 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).

In a posthoc analysis, using data from the maintenance phase of the GEMINI I trial, patients were categorised as being in remission (Mayo 0-2), mild disease (Mayo 3-5) or moderate to severe disease (Mayo 6-12) regardless of study visit or treatment received. The mean utility values observed by health state were used in the base-case of the model (Table 69).

Table 69. EQ-5D Scores in the Maintenance Phase of the GEMINI I Study by Mayo Score

	Remission (Mayo 0-2) Mean (SD)	Mild (Mayo 3-5) Mean (SD)	Moderate to Severe (Mayo 6-12) Mean (SD)
Overall Population	0.86 (0.188)	0.80 (0.184)	0.68 (0.224)
Moderate Health State at Baseline	0.86 (0.192)	0.81 (0.179)	0.71 (0.200)
Severe Health State at Baseline	0.85 (0.188)	0.86 (0.183)	0.86 (0.242)

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 UC. 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 70 summarises the results of the literature search for utility studies. And Table 71 summarises the compliance of the studies with the NICE reference case.

Table 70. 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 activity, and 24% with moderate/severe	Observational, cross-sectional study used a patient questionnaire to collect EQ-5D scores Clinical assessment of the patients disease severity was measured using the partial Mayo score	Remission (0-2 partial Mayo) Mild (3-4 partial Mayo) Moderate/ severe (5+ partial Mayo)	To condition and treatment pathways: Health states appear appropriate; no surgery-related health states To economic analysis: 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.	None
Brown (2011)	N = 17 Physicians (gastroenterologists = 10, surgeons =	TTO method Subjects were asked to imagine themselves in each of the scenarios provided when completing the survey, as	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	None

First Author (Year)	Study Population[a]	Methods of Elicitation and Valuation[b]	Health-State Description	Appropriateness of Health States[c]	Mapping
	7) N = 69 UC patients living with moderate disease, defined by a SCCAI score between 4 and 9 N = 150 Postcolectomy patients	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 US life tables. Responses were converted to a utility scale ranging from 0 to 1.		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. 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 active UC; 59% male, median age 43.5 years PODIUM study (n = 359):	UC disease severity was classified according to the sum score with the UCDAI. Estimates of patients' HRQoL 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,	Remission (UCDAI score 0-2) Mild to moderate relapse (UCDAI score 3-8) Severe relapse (UCDAI score 9-12)	To condition and treatment pathways: 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.	Response mapping algorithm was used to predict EQ-5D domain response

First Author (Year)	Study Population[a]	Methods of Elicitation and Valuation[b]	Health-State Description	Appropriateness of Health States[c]	Mapping
	mild to moderate UC, remission with a relapse within the past year; 53% male, median age 48 years	to establish their EQ-5D index.			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 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.	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 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.	None
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 bootstrap simulation, using a response mapping algorithm to predict EQ-5D domain response from UCDAI item scores and applying the UK tariff for	Remission (UCDAI score: ≤ 2) Mild/moderate relapse (UCDAI score: 3-8) Severe relapse (UCDAI score: > 8)	To condition and treatment pathways: Health states appear appropriate; no surgery-related health states To economic analysis: This study is not appropriate for use in the economic analysis because it used different health states than those used in the economic model.	Response mapping algorithm was used to predict EQ-5D domain response

First Author (Year)	Study Population[a]	Methods of Elicitation and Valuation[b]	Health-State Description	Appropriateness of Health States[c]	Mapping
		preference-based utility.			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 surgery complications. These utilities were adopted from a study conducted by Arseneau et al. (2006).	Remission (SCAI: 0-2) Mild (SCAI: 3-5) Moderate-severe (SCAI: 6+) Temporary discontinuers Surgery Post surgery remission Post surgery remission Post surgery complications Death	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 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.	None
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 included in the economic analysis. Values for some states could be considered for use in the sensitivity analysis.	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		
Muir (2001)	Patients who underwent IPAA for UC	HRQoL 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; HRQoL, 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 71. 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.

Note: The header row represents the requirements of the NICE reference case, which states that measurement of changes in health-related quality of life should be reported directly by patients, and the value of changes in patients' health-related quality of life should be based on public preferences using a choice-based method. The EQ-5D is the preferred measure of health-related quality of life in adults (NICE, 2013).

[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.

Utility values based upon the EQ-5D are available from two sources: the GEMINI I study and the survey conducted in Cardiff Hospital referenced by Punekar et al. and Tsai et al. The most notable difference in utilities between these two sources is for patients with moderate to severe disease. The GEMINI I study suggests that patients with moderate to severe disease (a Mayo score of 6-12) have a utility of 0.68, whereas the Cardiff survey suggests that patients with an SCCAI score of more than 2 have a utility of 0.42.

The SCCAI scale has five clinical criteria: bowel frequency, bowel frequency at night, urgency of defecation, blood in stool and general wellbeing. Patients with higher scores have more severe symptoms.

The difference in these results could be explained by the differences in the definitions of the Mayo and SCCAI scales, it could indicate that more patients in the Cardiff study had more severe UC (patients in this group could have had a score between 3 and 15). Or it could possibly be explained by informative drop-out within the GEMINI I study or by differences in an observational study and a clinical trial where patients have frequent visits to health care providers.

In scenario analyses, alternative utilities are applied in the model (see Section 7.7.9).

Table 72. Summary of Utilities by Study and Health States

First Author (Year)	Study Population and Methods	Health-State Description	Utility Estimate (SD)
None GEMINI I trial data, posthoc analysis	UC patients Clinical trial of VEDO Posthoc analysis of EQ-5D data by Mayo scores	Remission (Mayo 0-2) Mild (Mayo 3-5) Moderate to Severe (Mayo 6-12)	0.88 (0.188) 0.80 (0.184) 0.68 (0.224)
Punekar (2010)	UC patients Survey carried out in Cardiff Hospital, using the EQ-5D and valued using UK tariffs	Remission (SCCAI 0-2) Active UC (SCCAI 3+) Surgical Remission (weighted average: 29% IPAA, 71% ileostomy) Surgical Complications (assumed to be the same as active UC)	0.88 (0.14) 0.42 (0.32) 0.60 (0.38) *0.42 (0.32)*
Tsai (2008)	UC patients Survey carried out in Cardiff Hospital, using the EQ-5D and valued using UK tariffs	Remission Mild Moderate to severe Surgery	0.88 (NR) 0.76 (NR) 0.42 (NR) 0.61 (NR)
Arseneau (2006)	48 UC patients TTO and VAS were used to collect preference data Utility weights obtained using a scripted structured review, which included written descriptions and visual aids for each health state	Post surgery complications Post surgery remission J pouch Ileostomy	0.49 (0.32) 0.68 (0.29) 0.57(0.30)

CI, confidence interval; EQ-5D, EuroQol 5 Dimensions; NR, not reported; TTO, time trade-off; UC, ulcerative colitis; UK, United Kingdom; VAS, visual analog scale.

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 I study has not been conducted. See Section 6.9.2 for a summary of the safety data related to VEDO in UC. Within the model, disutilities were applied for adverse events. The methods used to derive the proportion of patients with adverse events are 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 “Mayo health states” (remission, mild disease, moderate to severe disease) the model uses the observed EQ-5D scores from the GEMINI I study. For the surgery and post-surgery health states, values are taken from the literature because patients in the GEMINI I study were not followed for surgery. In scenario analyses, we consider alternative data sources including two systematically identified publications (Punekar and Hawkins, 2010; Arseneau et al., 2006; Tsai et al., 2008)

The utility estimates for the base-case and all scenario analyses are presented in Table 73.

Table 73. Health-State Utility Weights

Health State	VEDO Trial Data (Base-Case)	Punekar and Hawkins (2010)	Arseneau et al. (2006)	Tsai et al. (2008)
Remission	0.86	0.88	0.79	0.88
Mild	0.80	N/A[a]	N/A[a]	0.76
Moderate-severe	0.68	0.42	0.32	0.42
Surgery	0.42[a]	0.42	0.32	0.61
Post surgery remission	0.60[a]	0.60	0.63	0.61
Post surgery Complications	0.42[a]	0.42	0.49	0.55

[a] Due to lack of available data in the published article, we assumed the same value as presented in Punekar et al., 2010.

The utility data for the surgery and post surgery health states in the previous publications are limited. Tsai and colleagues (2008) assumed the utility weight for surgery to be similar to post surgery remission. However, the HODaR study surveyed patients at least 6 weeks following surgery. As the cycle length in the Markov model is 8 weeks, a survey response of at least 6 weeks later would not accurately reflect the quality of life for a surgery patient during the model cycle in which the surgery occurred. As such, the model does not use the HODaR study for our utility estimate for surgery. Instead, it is assumed that patients undergoing surgery would have the same utility as the moderate-severe disease patients. It is also assumed that patients would have a quality of life less than moderate-severe disease for the 2 weeks following the surgical procedure before progressively improving for the remainder of the cycle when they transition to postsurgical remission, postsurgical complication, or subsequent surgery. As such, we assumed the utility weight for surgery to be similar to that for moderate-severe disease. For post surgery remission, the model uses the data presented by Punekar and Hawkins (2010), who assumed post surgery remission utility to be a weighted average of two post surgery utility estimates and post surgery complications to have a utility similar to moderate-severe disease.

Adverse Event Disutilities

The models by Punekar et al and Tsai et al. did not consider adverse events. Therefore, utility decrements for adverse events were identified through a targeted review of the available published literature (Table 74). To incorporate these utility decrements into the model, these disutility estimates were multiplied 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 VEDO would have a health-state utility of 0.860. Based on the probability of each adverse event and the disutility associated with that adverse event, a patient treated with VEDO 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 VEDO patient in remission during that cycle.

Table 74. Disutility 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)

[a] Disutility based upon pyrexia.

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.

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. It is assumed that there is no patient variability in the quality of life experience within a health state but no formal analysis has been conducted to try to capture this.

[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.

7.4.12	**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 captured 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.

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

7.4.16 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 75 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 Appendix 17, Section 10.17.

Table 75. 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)	Tsai et al., 2008 for resource use; NHS reference costs 2011-2012 for unit costs
Mild (Mayo = 3-5)	Tsai et al., 2008 for resource use; NHS reference costs 2011-2012 for unit costs
Moderate-to-Severe (Mayo = 6-12)	Tsai et al., 2008 for resource use; NHS reference costs 2011-2012 for unit costs
Surgery	Buchanan et al., 2011 (inflated to 2012 using Pay and Price Index from Curtis, 2012); NHS reference costs 2011-2012
Post-surgical remission	Tsai et al., 2008 for resource use; NHS reference costs 2011-2012 for unit costs
Post-surgical complications	Tsai et al., 2008 for resource use; NHS reference costs 2011-2012 for unit costs
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

7.4.17 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

7.4.18	**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.

Table 76. Summary of Cost and Resource Use Studies Identified in the Literature Searches

First Author (Year)	Cost Type	Description of Available Data	Details of Methods	Country, Data Year, Cost Year	Applicability to UK Clinical Practices[a]
Lindsay (2013)	Direct costs	Direct cost parameters: elective surgical procedures, hospitalisations and healthcare provider consultations	Non-interventional retrospective analysis of Crohn's disease patient records to compare the cumulative healthcare resource utilisation for the 0-24 month period post-infliximab treatment with the 12 months preceding infliximab treatment from a UK NHS perspective	UK Data year: 2011 Cost year: 2009-2010	The UK-based study provided the cost of CD-related health care for infliximab patients; however, this was not applicable to the health states used in the economic model.
Ghosh (2014) Poster only	Direct costs	Direct cost parameters: cost of treatment, side-effects, complications	Default input values for costs, the percentage of patients receiving each treatment, and the percentage of patients experiencing side effects or complications were determined from national sources and published literature.	UK Data year: NR Cost year: NR	The UK-based study provided the cost of CD-related health care; however this was not applicable to the health states used in the economic model.
Vaizey (2013)	Direct costs	Direct cost parameters: Gastroenterologist visits, UC-related investigations; emergency department visits; hospitalisations,	UC-related health care resource utilisation was collected using a patient questionnaire and chart review for UC-related hospitalisations (over 1 year) and all other UC health care resource use (over 3 months) Unit costs were derived from government sources	UK Data year: NR Cost year: NR	The UK-based study provided the 3-month cost of UC-related health care; however, this was not provided by the health states

First Author (Year)	Cost Type	Description of Available Data	Details of Methods	Country, Data Year, Cost Year	Applicability to UK Clinical Practices[a]
		cost per patient for UC-related health care			used in the economic model.
Van der Valk (2012)	Resource use related to indirect costs	Indirect cost parameters: Mean number of days of sick leave of paid work (patients and caregivers) Mean number of days of sick leave of unpaid work (patients)	A secure web-based questionnaire was used After completing the baseline questionnaire, patients received an invitation to fill out the 3-month follow-up questionnaire Patients were asked which of the following situations applied best to their situation: being employed, fully or partially disabled, retired or early retired, homemaker, student or unemployed Employed patients or partially disabled patients with a paid job indicated the number of work hours and number of workdays per week Patients were asked to report the number of sick leave days from both paid and unpaid (voluntary work) work within the previous 3 months; additionally, patients were asked to report whether caregivers were absent from paid work in order to take care of them and for how many days	Netherlands Data year: 2011 Cost year: 2011	This study was based in the Netherlands, but the data on productivity losses might be applied to the UK. However, these data are not available by health state and assumptions will need to be made if the data are to be used in the economic analysis.
Punekar (2010)	Direct costs	Direct cost parameters: Drug acquisition and administration costs, hospitalisations	A Delphi panel of five experts estimated the resource use of UC patients during and after hospitalisation. The costs of comparator treatments and concomitant medications were calculated based on the average doses used in the clinical trials and was costed based on pack	Country: England and Wales Data years: 2006-2007 Cost years: 2006-2007	This study presented UK resource use and costs by health states (remission, surgical remission, and

First Author (Year)	Cost Type	Description of Available Data	Details of Methods	Country, Data Year, Cost Year	Applicability to UK Clinical Practices[a]
		and other assessments, consultant visits, surgical procedures, primarily ileostomy and IPAA, diagnostic endoscopy	sizes in the British National Formulary. Infliximab drug cost assumed a mean body weight of 80 kg and an administration cost of £62.66 per infusion. All patients were assumed to have 10 days of hospitalisation during initial treatment period. Patients suffering post surgery complications were assumed to have 10 days of hospital stay in addition to the stay due to their surgical procedure. The total cost of surgery was calculated using a weighted average based on the prevalence of 2 surgical techniques (29% IPAA, 71% ileostomy).		complications). The health states used here matched some of those included in the economic analysis; therefore, their corresponding costs could be considered in the economic analysis.
Buchanan (2011)	Direct costs	Direct cost parameters: Drugs, surgeries, tests, and procedures; and staff costs Costs for 27 disease stages were reported. Average costs were presented for the initial month in each disease stage, as well as for any subsequent months spent in that disease stage.	Decision models were built to simulate the natural disease history of UC, informed by UK and European clinical pathways. UK NHS perspective was used for UK costs; unit costs were extracted from NHS reference costs and the BNF. Definitions of disease stages and type of costs included at each disease stage were detailed in the study's supplementary appendix. UK costs were reported separately to costs for Europe.	Countries: UK and Europe Data year: NR Cost year: 2008	The study presented UK cost data by disease stages and could be considered applicable for use in the economic analysis.

First Author (Year)	Cost Type	Description of Available Data	Details of Methods	Country, Data Year, Cost Year	Applicability to UK Clinical Practices[a]
Tsai (2008)	Direct costs	Direct cost parameters: Surgical intervention, consultant visits, hospitalisation, blood tests, elective endoscopy, emergency endoscopy, and drug costs	This resource use was estimated by a panel of 6 UK gastroenterologists. The cost of ileostomy was assumed to be equivalent to 2 complex procedures; the cost of IPAA was assumed equivalent to 2 complex and 1 major procedure. The cost of a complex and major procedure was calculated as a weighted average of elective and non-elective IBD procedures, with or without complications, weighted by their frequency of occurrence in the UK clinical practice. The cost of surgical intervention then was calculated as the weighted average of ileostomies and IPAAs. The cost of hospitalisation was based on the ACT trials. Mean rates of hospitalisation were obtained from a posthoc analysis of the ACT trials and were costed using the NHS reference costs.	Country: UK Data years: 2006-2007 Cost years: 2006-2007	This study presented UK-based cost and resource use data for the same health states as those used in the economic model. The data from this study is appropriate for use in the base-case economic analysis.
Reinisch (2007)	Resource use related to indirect costs	Indirect cost parameters: Changes in employment, disability status, productivity, and hours worked per week, by clinical remission status	The study used prospectively collected data from the ACT 1 and 2 trials. Analyses included all 728 patients, regardless of their randomised treatment group (i.e., placebo and infliximab patients were grouped together for analysis). Clinical remission was defined as a total Mayo score of 2 points or lower, with no individual subscore greater than 1 point.	Countries: multiple countries Data year: NR Cost year: NR	The results of the study could be used in a secondary economic analysis that includes productivity losses.
Bassi (2004)	Resource use related	Direct cost parameters:	Perspective was that of the UK NHS. A prevalence approach to costing illness	Country: UK Data year:	The study presented UK-

First Author (Year)	Cost Type	Description of Available Data	Details of Methods	Country, Data Year, Cost Year	Applicability to UK Clinical Practices[a]
	to indirect costs	Outpatient services, inpatient services, investigations, medication, and surgery, secondary care products and services Indirect cost parameters: Out-of-pocket expenses, employment status, and number of lost working days and loss of social days	was used to quantify the economic burden of IBD over a 6-month time frame (June 2000-December 2000). A postal questionnaire was sent out to all patients with confirmed IBD cases, requesting information relating to the previous 6 months for the following items: (1) number of IBD-related visits to a primary care doctor (general practitioner); (2) estimated total IBD-related out-of-pocket expenses (for example, for travel, prescription charges, special diets, or clothing); (3) employment status and number of lost working days due to IBD; and (4) loss of ‘‘social’’ days (household and recreational activities). Direct cost for secondary care products and services were estimated (per 6 months) by multiplying units of resource by their unit cost. The cost estimates included staff salaries and training, heating and lighting, pharmacy services, and miscellaneous costs. Expenditure returns also incorporated an overheads element to reflect the cost of capital and support services in the provision of hospital services.	2000 Cost years: 2000-2001	based cost data and provided 6-month costs by extent of disease, which may be considered applicable for use in the economic analysis.

BNF, British National Formulary; IBD, inflammatory bowel disease; IPAA, ileal pouch anal anastomosis; NHS, National Health Service; NR, not reported; UC, ulcerative colitis; UK, United Kingdom.

[a] Appropriateness of each study also was assessed against the health states used in the economic model, which were defined as follows: “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.”

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

- 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 reviewed the model structure and answered questions about the costs of caring for patients with UC to verify the inputs to the model. Please see Section 7.3.5 for more information.

[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.

Intervention and comparators' costs

7.4.20	**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.**

For VEDO, 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. For infliximab, the induction phase consisted of three treatments at weeks 0 and 2 and 6, with subsequent 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. For golimumab, the induction phase included a loading dose of 200 mg at week 0, 100 mg at week 2, and 50 mg at week 6. Costs for each biologic per cycle during the induction and maintenance phases are shown in Table 77 and 0, respectively.

Table 77. Cost of Biologics During Induction Phase

Treatment	Total Vials Used	Cost Per Vial[a]	Cost Per Cycle
VEDO	2[b]	[redacted]	[redacted]
Infliximab	12[c]	£419.62	£5,035.44
Adalimumab	8[d]	£352.14	£2,817.12
Golimumab	6[e]	£762.97	£4,577.82

[a] Source: British National Formulary (2013).

[b] Patients treated with VEDO receive the standard dose (one vial for VEDO) in week 0 and week 2.

[c] Patients treated with infliximab receive the standard dose (four vials for infliximab) in weeks 0, 2, and 6.

[d] Patients treated with adalimumab receive 160 mg in week 0, 80 mg in week 2, and 40 mg every 2 weeks thereafter. As such, patients receive eight doses of adalimumab in the induction phase: four doses at week 0, two doses at week 2, and one dose each at weeks 4 and 6.

[e] Patients treated with golimumab are given induction doses of 200 mg at week 0, 100 mg at week 2. In the UK, golimumab is only available in a 50-mg dose. As such, the induction phase for golimumab includes six doses of 50 mg over 6 weeks (four doses in week 0 and two doses in week 2).

Table 78. Per-Cycle Cost of Biologics During 8-Week Cycle in the Maintenance Phase

Treatment	Administration	Vials/Admin	Total Vials	Cost per Cycle
VEDO	1	1	1	[redacted]
Infliximab	1	4	4	£1,678.48
Adalimumab	4	1	4	£1,408.56
Golimumab	2	1	2	£1,525.94

The mix of treatments that compose conventional therapy is based on interviews with clinician experts (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 for patients receiving the conventional therapy strategy are summarised in Table 79. The percentages sum to greater than 100% because patients may be on multiple therapies. We assume 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 conventional therapy costs for the biologic regimens are equivalent to those for the conventional therapy regimen.

Table 79. 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	13%
Mesalazine	1.2-2.4 g daily in divided doses	400 mg, 120-tab pack at £41.62	13%
Olsalazine	500 mg twice daily	250 mg, 112-cap pack at £19.77	13%
Sulfasalazine	500 mg 4 times daily	500 mg, 112-cap pack at £5.82	13%
Corticosteroids			
Budesonide	3 mg 3 times daily for up to 8 weeks	3 mg net price: 100-cap pack at £75.05	1%
Prednisolone	1 metered application (20 mg prednisolone) once or twice daily for 2 weeks	14-application canister at £48.00	36%
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	39%
Mercaptopurine	Initially 2.5 mg/kg, adjusted according to response	50 mg net price: 25-tab pack at £22.54	15%

Treatment	Dose and Frequency	Price	% Use
Methotrexate	10-25 mg once weekly	2.5 mg net price: 24-tab pack at £2.39; 28-tab pack at £3.27	9%

Source: British National Formulary (December 2013) for unit costs; UK IBD Audit Steering Group (Royal College of Physicians, 2013) for percentage use.

In addition to drug costs, VEDO and infliximab have costs of administration applied each time that a patient in the model receives a dose. The cost of an IV administration is £308 in the model (payment by results mandatory tariff 2012/13 FZ37F).

Health-state costs

7.4.21 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.

Resource-use estimates for all health states (apart from surgery) were adapted from Tsai et al, 2008. The study by Buchanan et al, 2011 was used to calculate the cost of surgery. The Tsai et al. article reported annual resource use for each of the model's health states as estimated by a panel of UK gastroenterologists. We then applied a unit cost to this resource use based on the NHS Reference Cost database to calculate the annual cost of each health state, and then adjusted that cost to an 8-week cycle cost. The estimated annual units of resource use and the annual and per-cycle cost per health state are presented in Table 80.

Table 80. Health Care Resource Use, by Health State

		Per-Cycle Resource Use, by Health State[a]					
Resource Item	Unit Cost	Remission	Mild	Moderate-Severe	Severe	Post surgery Remission	Post surgery Complications
Consultant visit	£105.73[b]	0.31	0.69	1	—	0.23	0.27
Hospitalisation	£3,399.36[b]	0.46	0.05	0.05	—	—	0.50
Surgery	£13,577.27[c]	—	—	—	1	—	—
Blood tests	£3.35[b]	0.50	0.6	1	—	0.23	0.50
Elective endoscopy	£1,497.12[b]	0.03	0.08	0.13	—	0.18	0.10
Emergency endoscopy	£2,026.09[b]	—	0.04	0.12	—	0.08	0.02
Per-cycle cost		£236.52	£424.02	£957.77	£13,577.27[d]	£467.65	£1,913.24

[a] Source: Tsai et al. (2008) present their data on an annual basis even though they consider 8-week cycles. We present 8-week cycle resource use in the table above and in the model. These are derived by dividing by the annual estimates from Tsai et al. (2008) by 6.5.

[b] Source: National Health Service reference costs 2011-2012.

[c] Source: Buchanan et al. (2011).

[d] The cost of surgery is based on the following assumptions as reported in the online supplement to Buchanan et al. (2011):

- Patient undergoes surgery (40% of patients undergo proctocolectomy with ileostomy, 60% undergo subtotal proctocolectomy with pouch formation +/− loop ileostomy) with a weighted average cost calculated to be £5,714.80.
- Surgeon appointment (1 × 10 minutes − £13.62).
- Inpatient day: Average stay of 10 days. The unit cost includes staff and resource-use costs (estimated to be £2,776.88), closure of ileostomy (required by 95% of patients with a pouch), and an additional inpatient stay of 7 days (average cost calculated to be £3,114.42).

Adverse-event costs

7.4.22 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 (Table 81). Full detail of these calculations is found in Appendix 17, Section 10.17.

Table 81. 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.

Miscellaneous costs

7.4.23 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.

7.5 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.

7.5.1 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.

7.5.2 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.

7.5.3 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.

7.6 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

7.6.1 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 I trial.

Table 82. Summary of Clinical Endpoints from the GEMINI I Trial and the Cost-Effectiveness Model

	Placebo / Conventional Therapy		Vedolizumab	
	Clinical Trial	Model Result	Clinical Trial	Model Result
Outcome				
End of induction				
Proportion with response	25.50%	26.11%	47.11%	47.71%
Proportion in remission	5.37%	5.37%	16.89%	16.88%
End of maintenance				
Proportion with mild disease*	2.02%	2.02%	6.95%	6.95%
Proportion in remission**	4.05%	4.05%	19.69%	19.69%

* 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.

** 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.

7.6.2	**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.**

Because the data does not allow for a reasonable comparison of vedolizumab with other biologic therapies in TNF-failure patients, Markov traces are displayed by patient population and comparator, and these are presented 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 13. Markov Trace: Vedolizumab for the Mixed Patient Population (ITT)

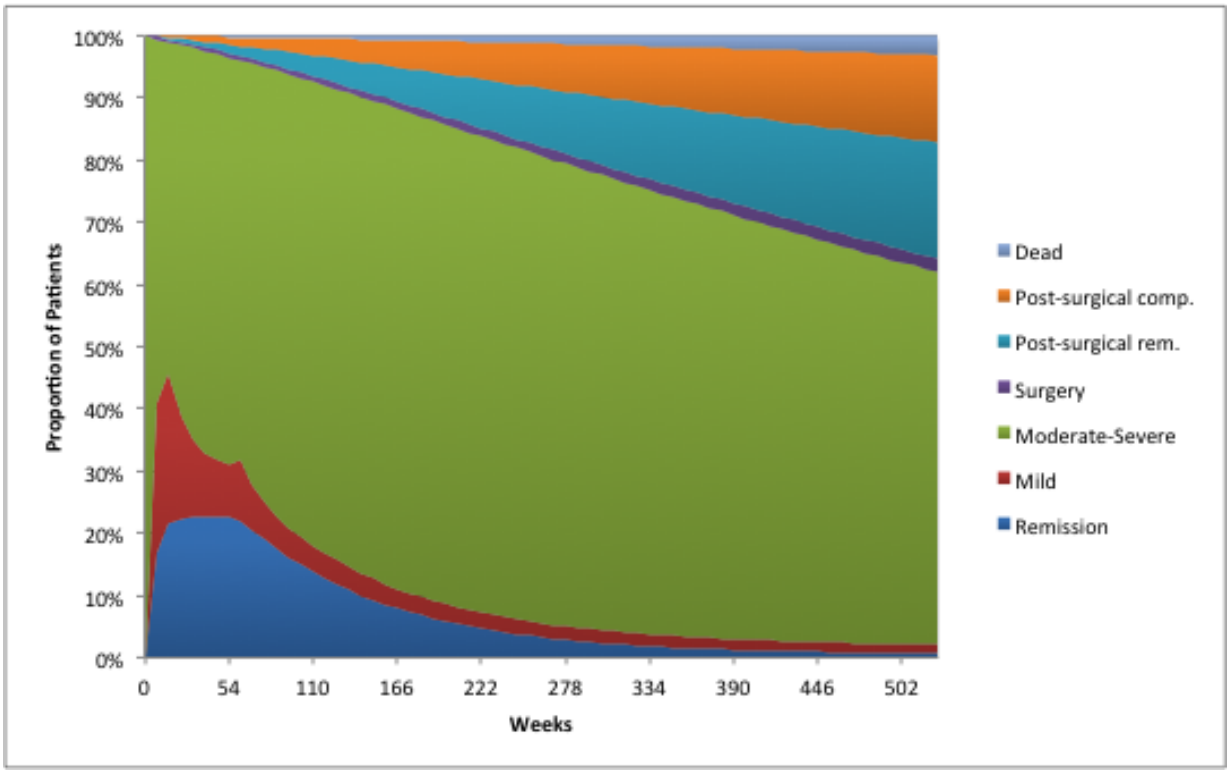


Figure 14. Markov Trace: Conventional Therapy for the Mixed Patient Population (ITT)

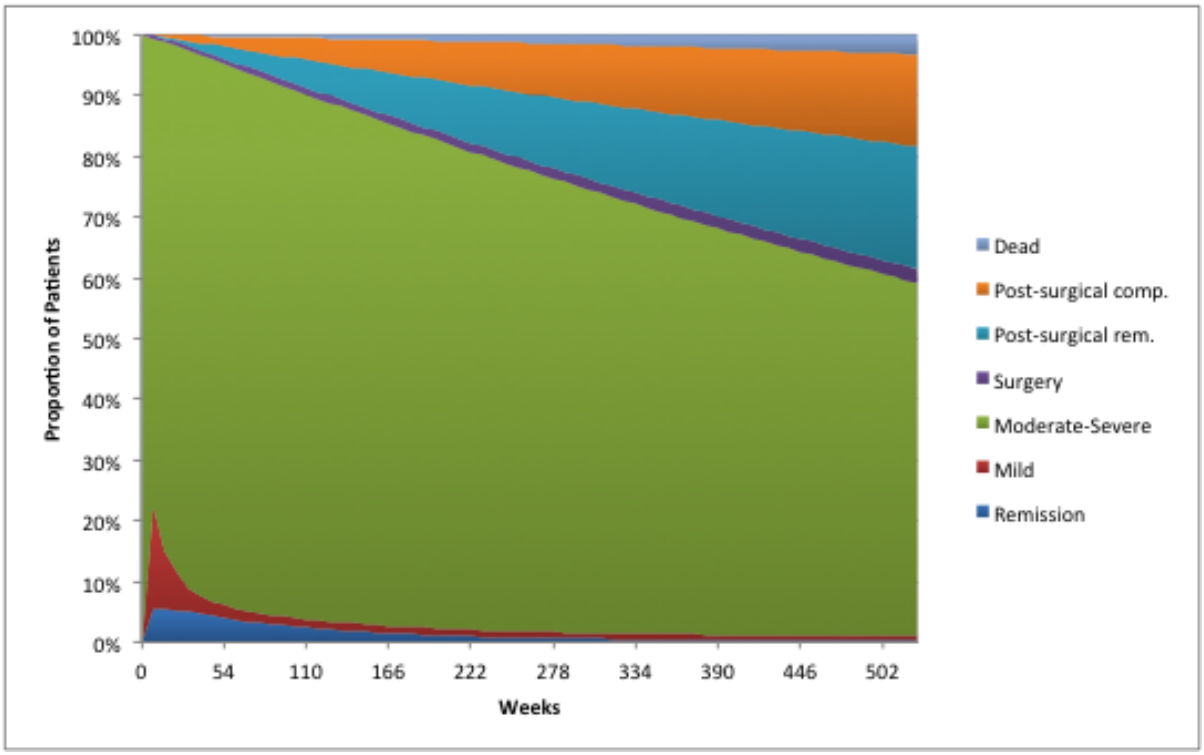
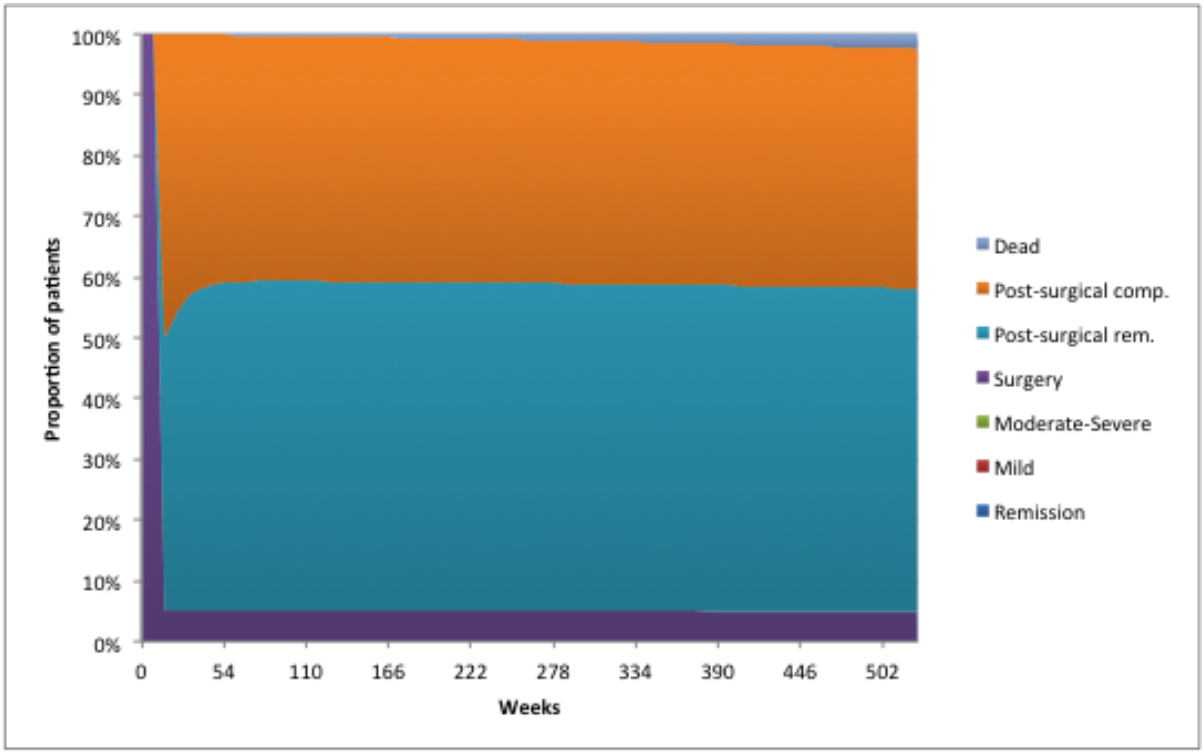


Figure 15. Markov Trace: Surgery for the Mixed Patient Population (ITT)



TNF-Naïve Population

Figure 16. Markov Trace: Vedolizumab for the TNF-Naïve Population (MTC-Based Estimates)

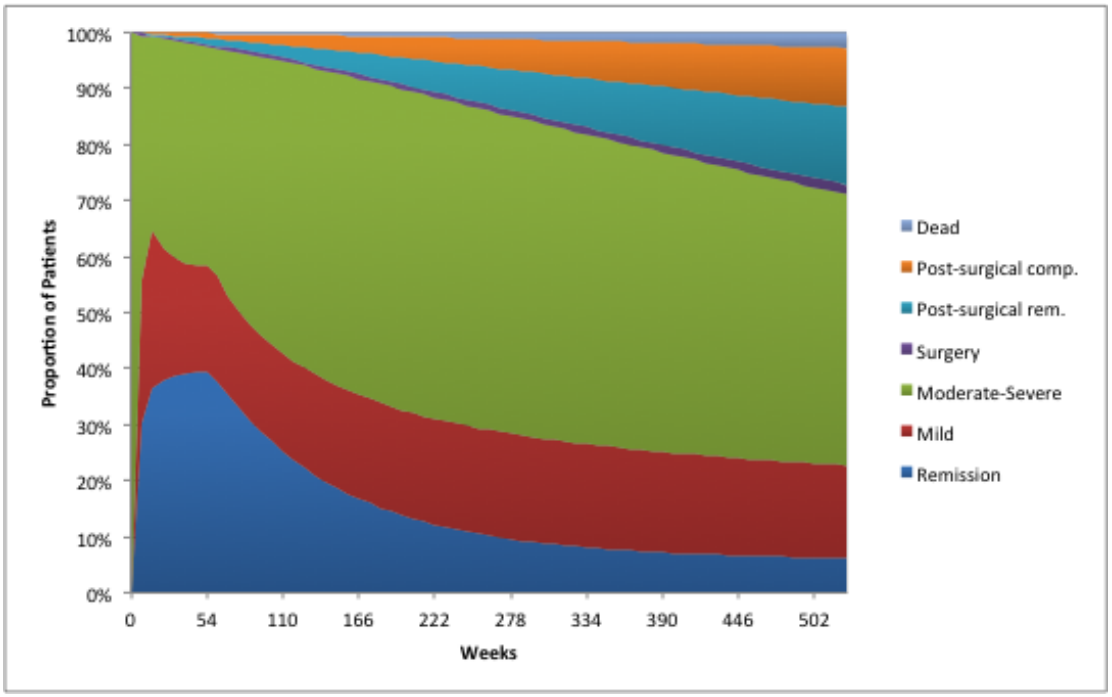


Figure 17. Markov Trace: Conventional Therapy for the TNF-Naïve Population (MTC-Based Estimates)

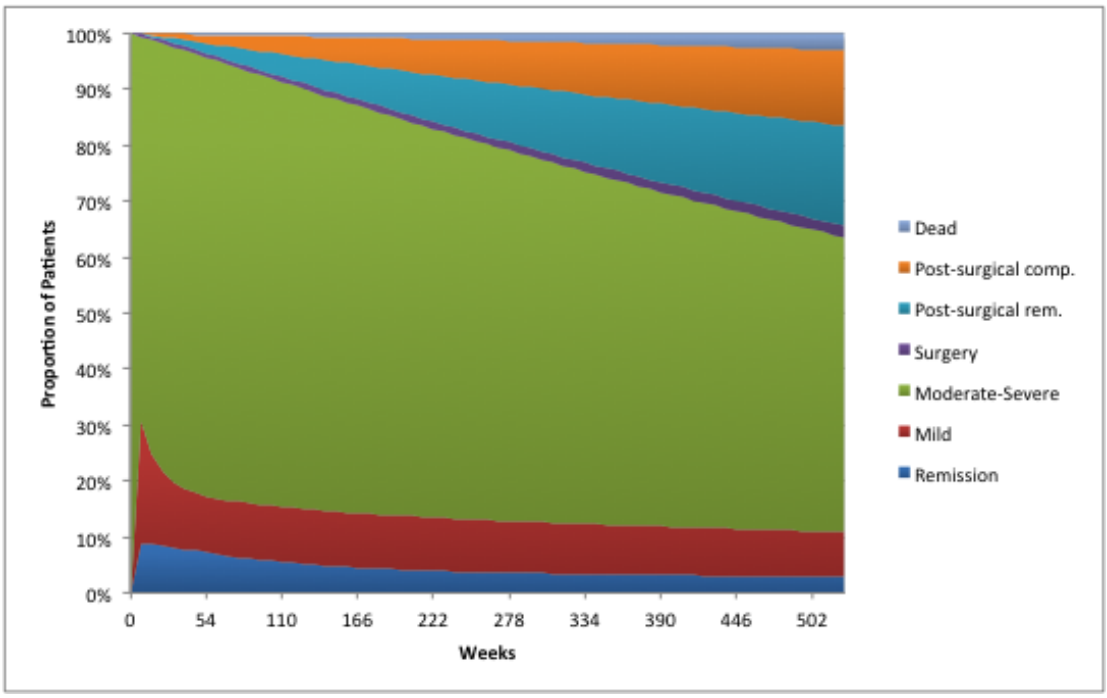


Figure 18. Markov Trace: Infliximab for the TNF-Naïve Population

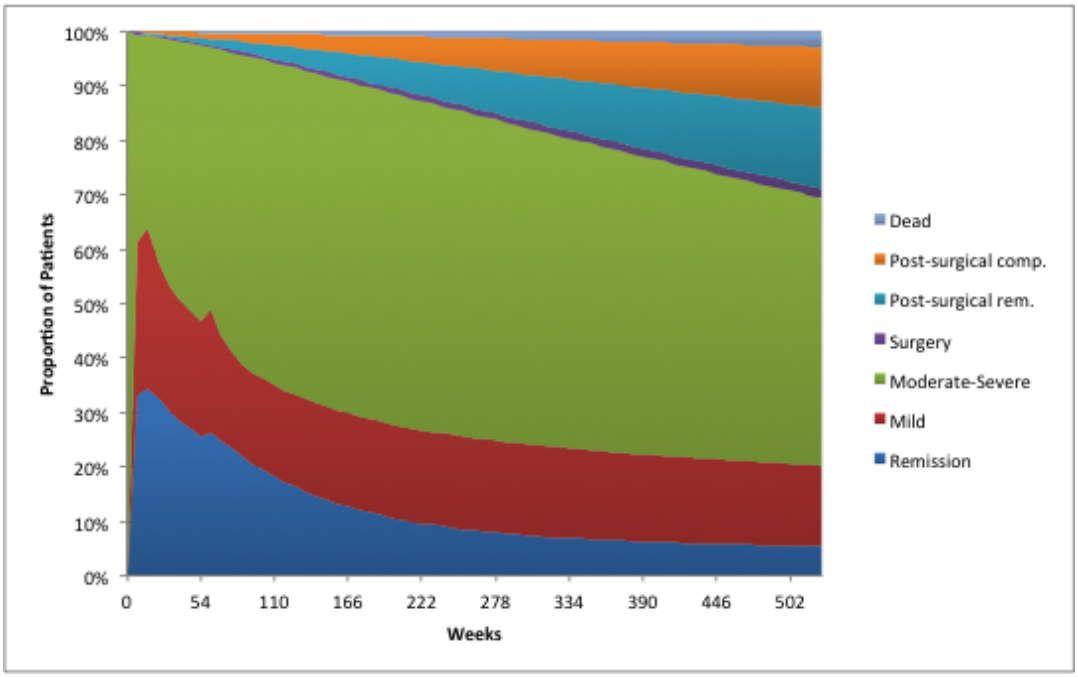


Figure 19. Markov Trace: Adalimumab for the TNF-Naïve Population

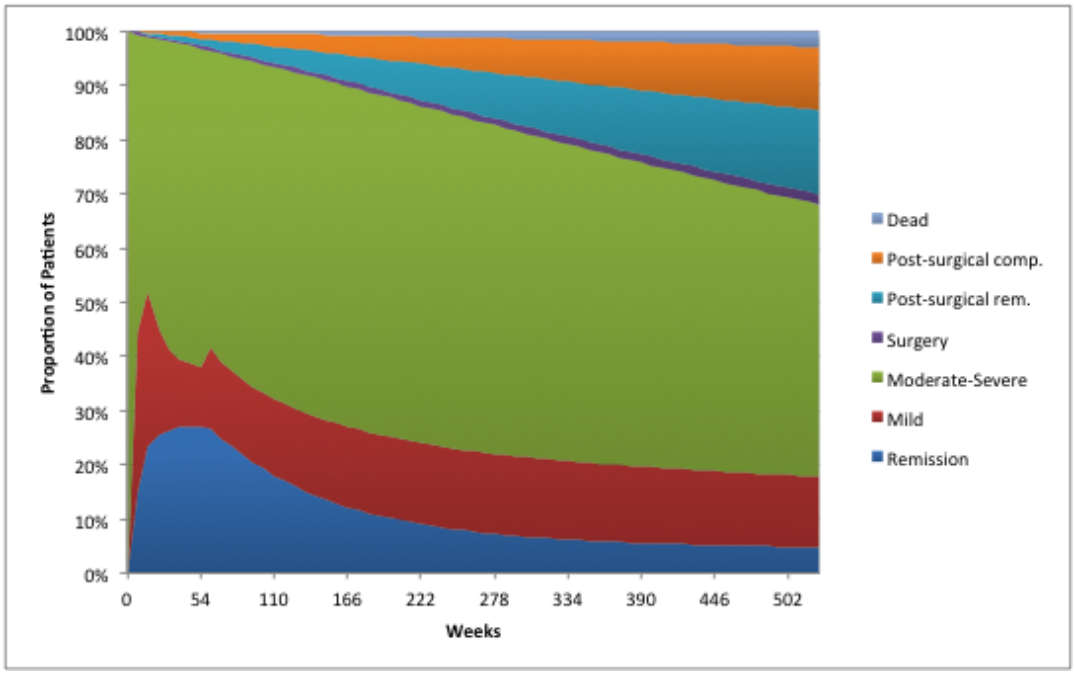
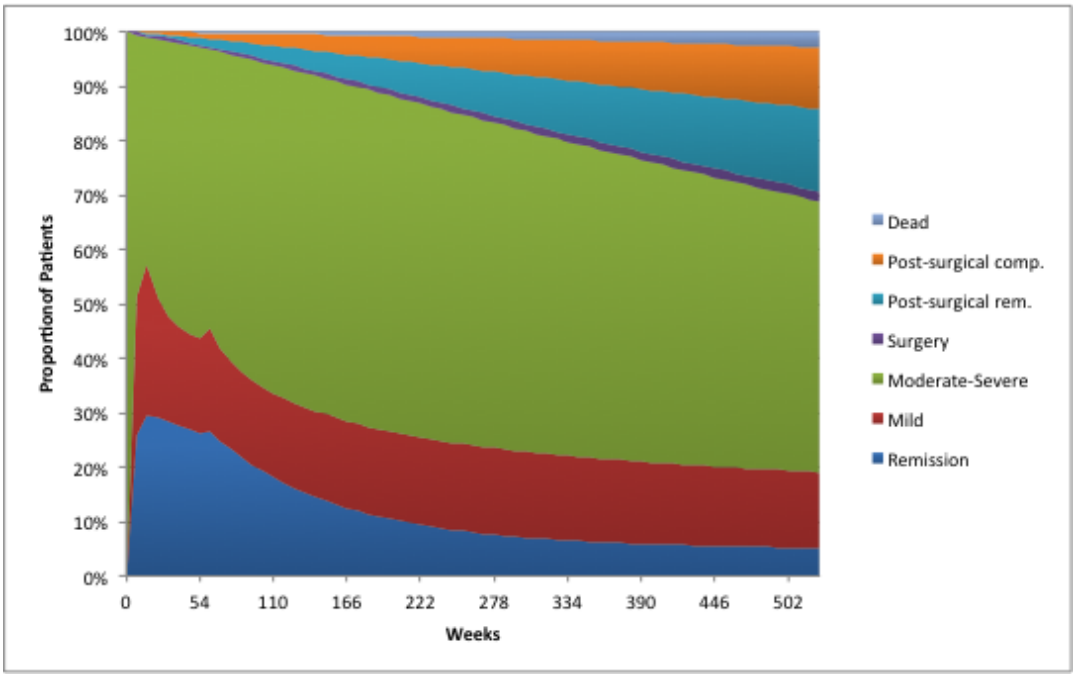


Figure 20. Markov Trace: Golimumab for the TNF-Naïve Population



Failure Population

Figure 21. Markov Trace: Vedolizumab for the TNF-Failure Population (Clinical Trial-Based Estimates)

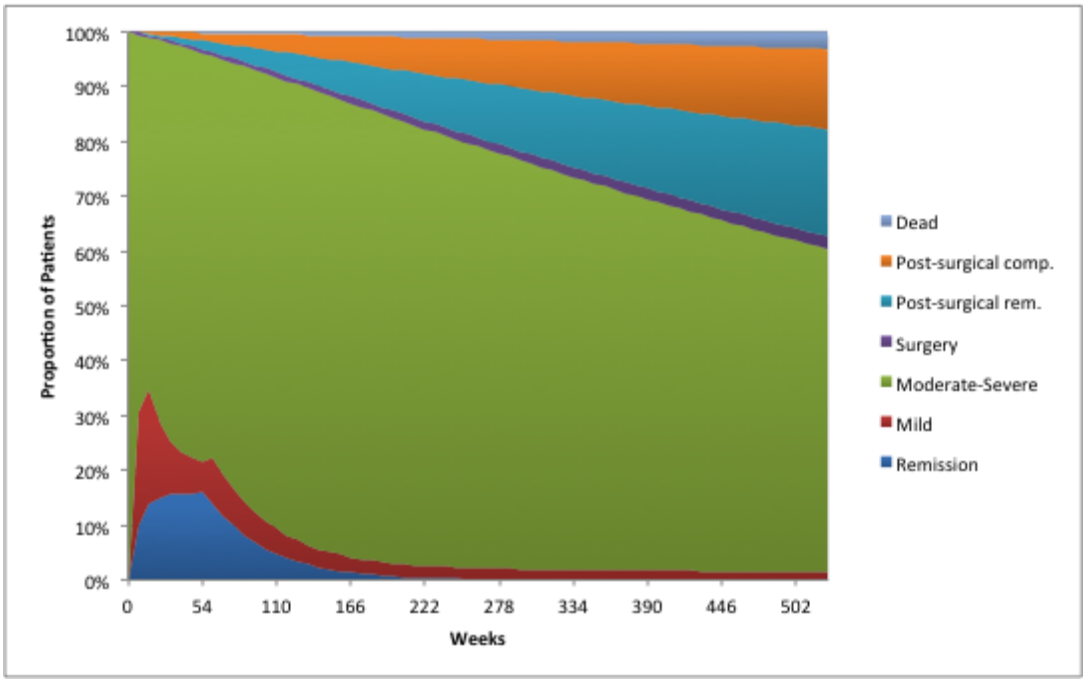
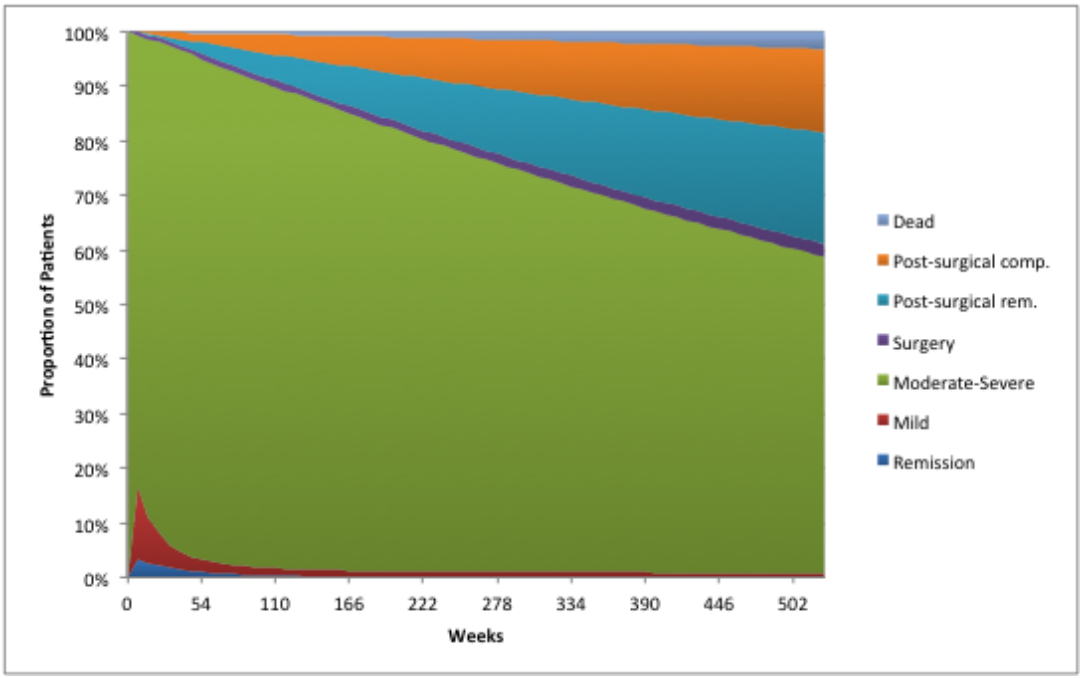


Figure 22. Markov Trace: Conventional Therapy for the TNF-Failure Population (Clinical Trial-Based Estimates)



7.6.3	**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 the data does not allow for a reasonable comparison of vedolizumab with other biologic 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 23. Utility Markov Trace: Vedolizumab for the Mixed Patient Population (ITT). Modelled Utility Scores by Health State per Cycle.

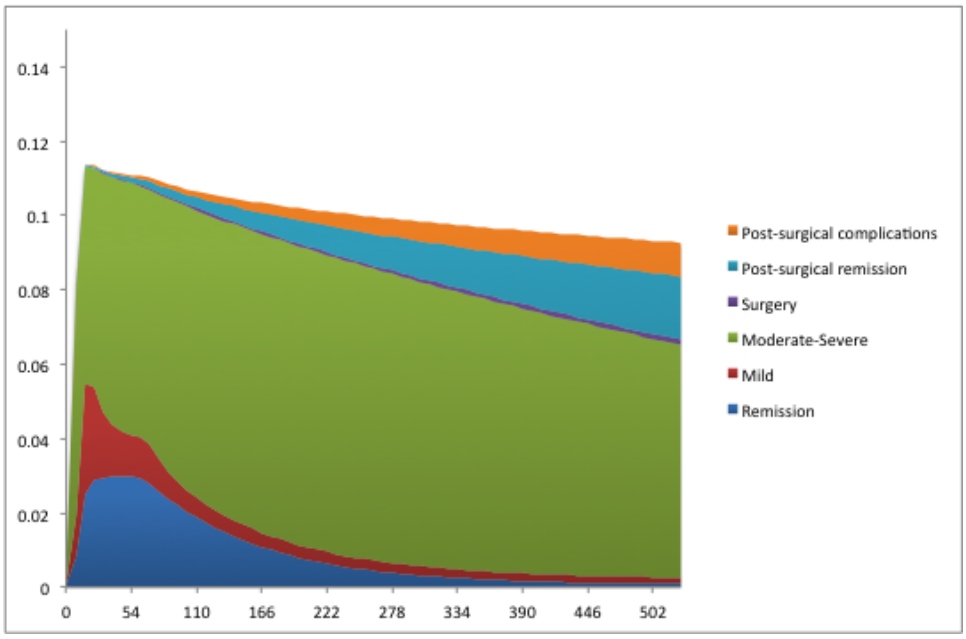


Figure 24. Utility Markov Trace: Conventional Therapy for the Mixed Patient Population (ITT). Modelled Utility Scores by Health State per Cycle.

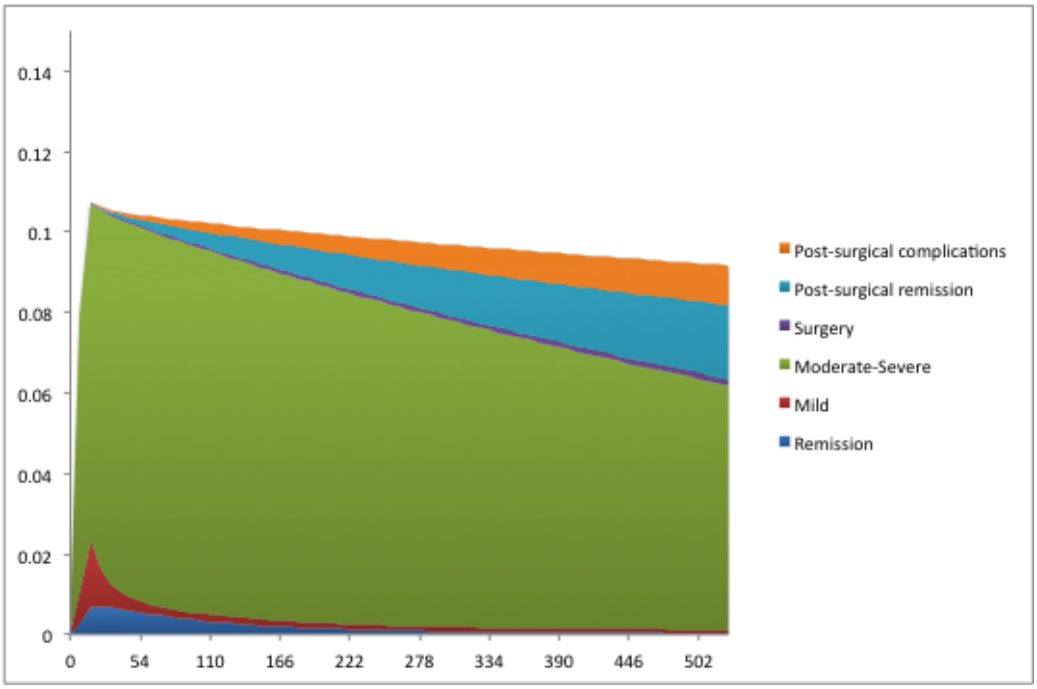
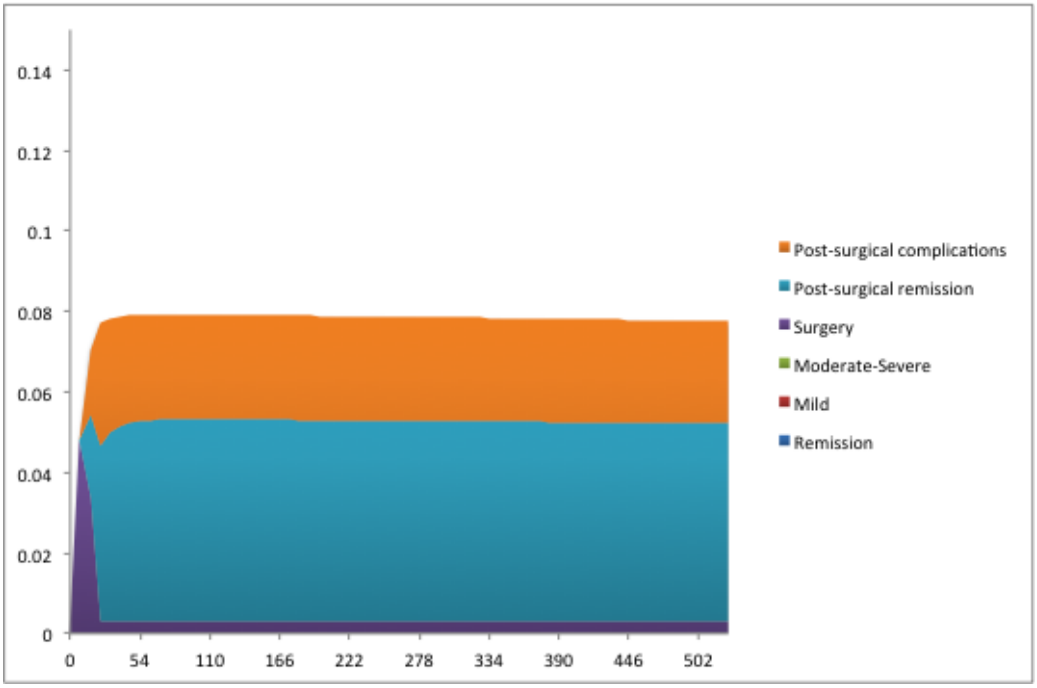


Figure 25. Utility Markov Trace: Surgery for the Mixed Patient Population (ITT). Modelled Utility Scores by Health State per Cycle.



TNF-Naïve Population

Figure 26. Utility Markov Trace: Vedolizumab for the TNF-Naïve Population (MTC-Based Estimates). Modelled Utility Scores by Health State per Cycle.

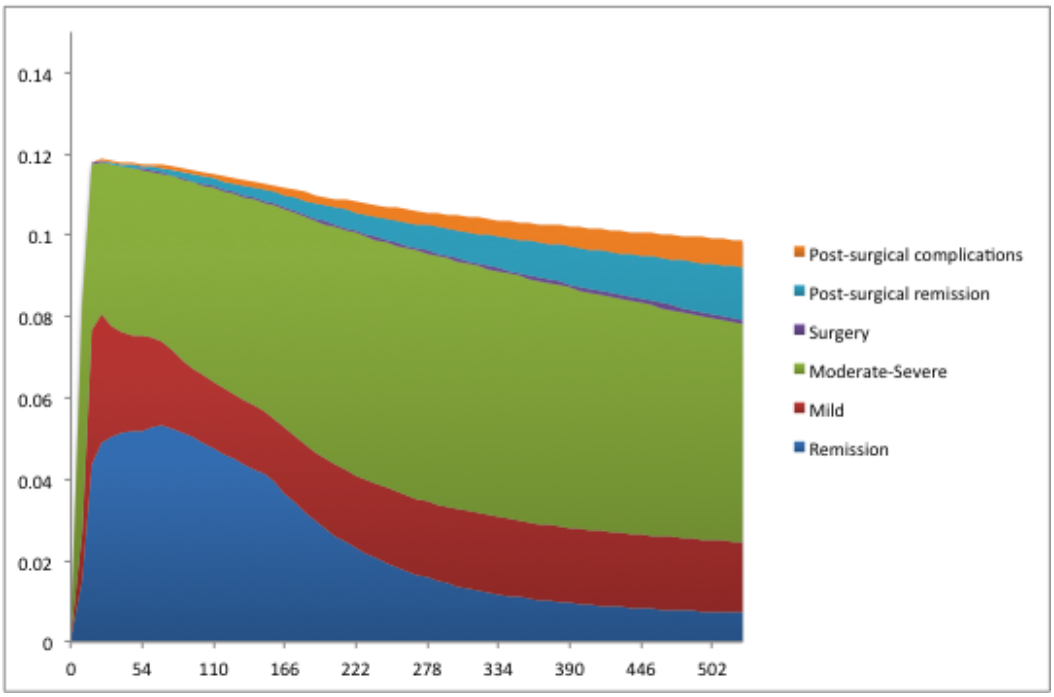


Figure 27. Utility Markov Trace: Conventional Therapy for the TNF-Naïve Population (MTC-Based Estimates). Modelled Utility Scores by Health State per Cycle.

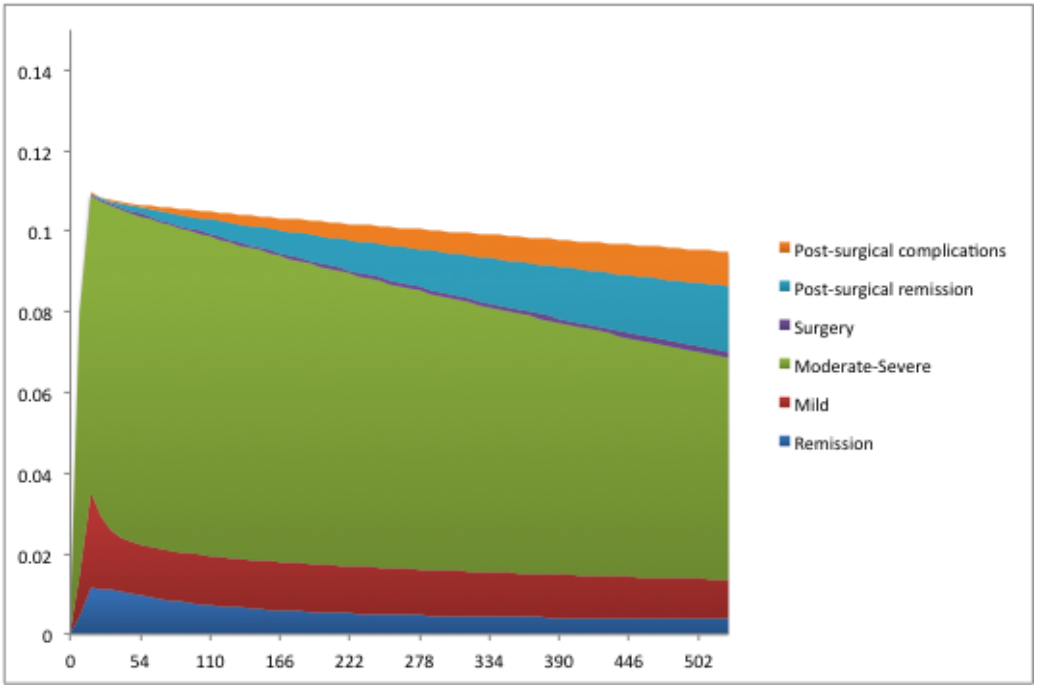


Figure 28. Utility Markov Trace: Infliximab for the TNF-Naïve Population. Modelled Utility Scores by Health State per Cycle.

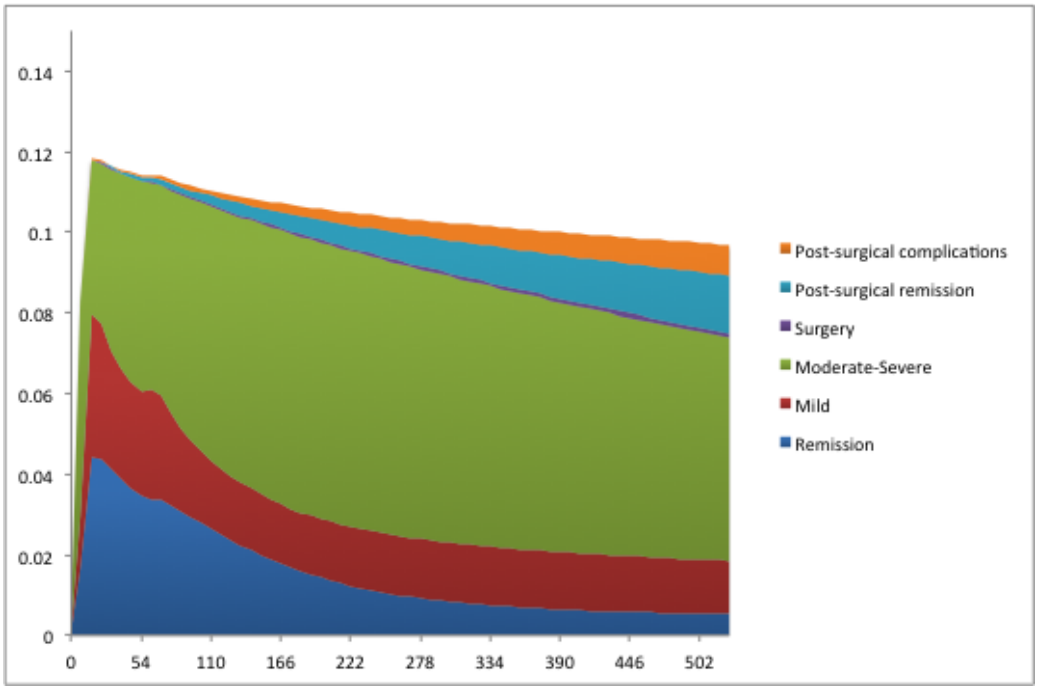


Figure 29. Utility Markov Trace: Adalimumab for the TNF-Naïve Population. Modelled Utility Scores by Health State per Cycle.

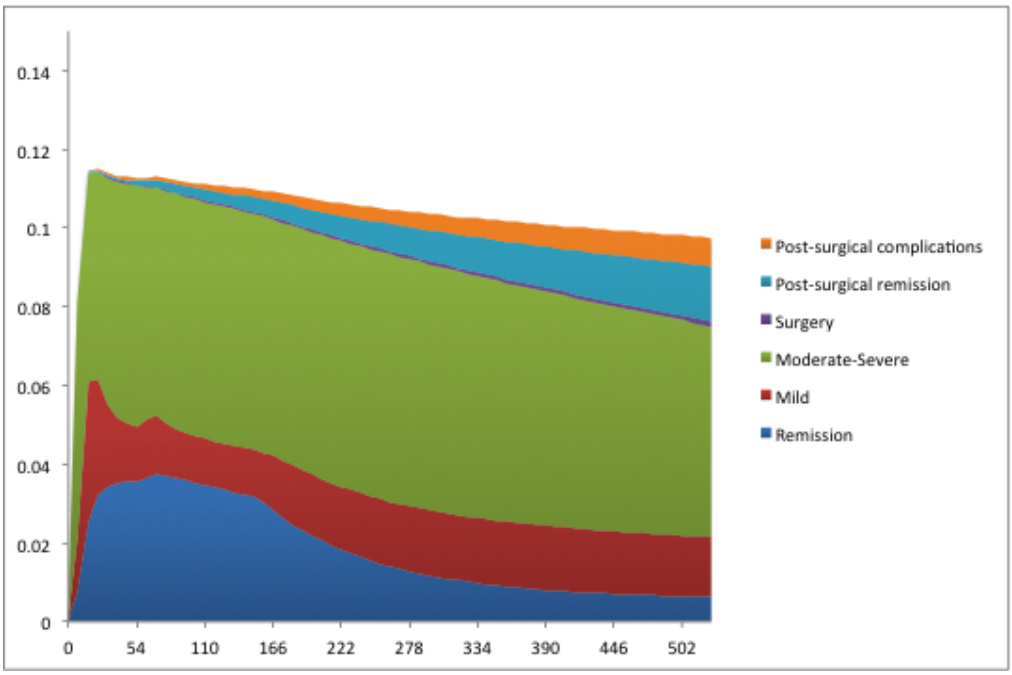
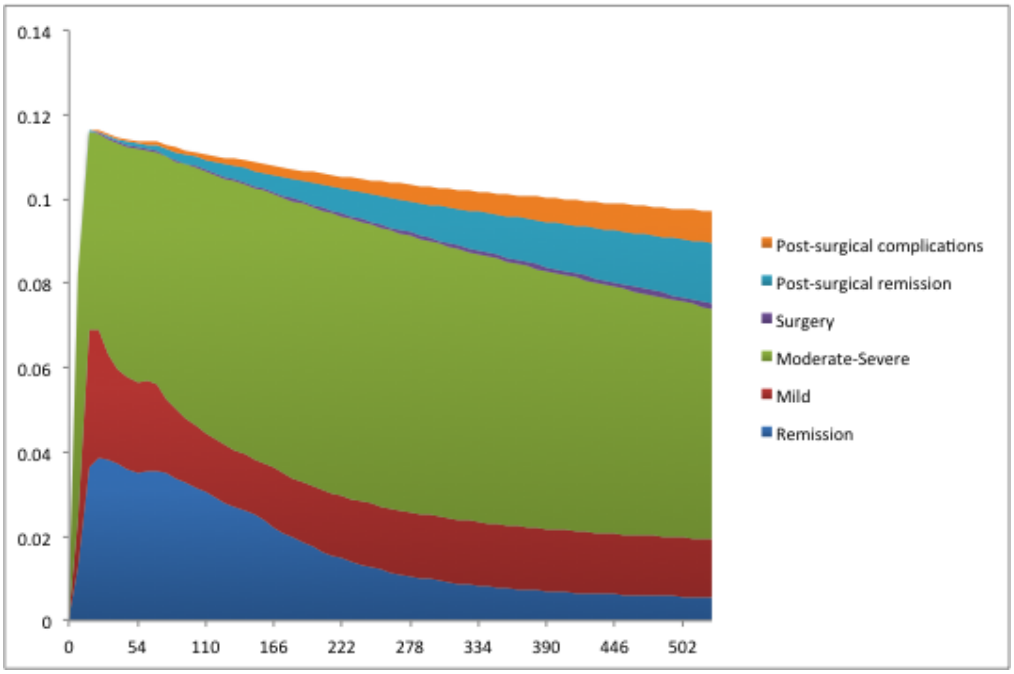


Figure 30. Utility Markov Trace: Golimumab for the TNF-Naïve Population. Modelled Utility Scores by Health State per Cycle.



TNF-Failure Population

Figure 31. Utility Markov Trace: Vedolizumab for the TNF-Failure Population (Trial-Based Estimates). Modelled Utility Scores by Health State per Cycle.

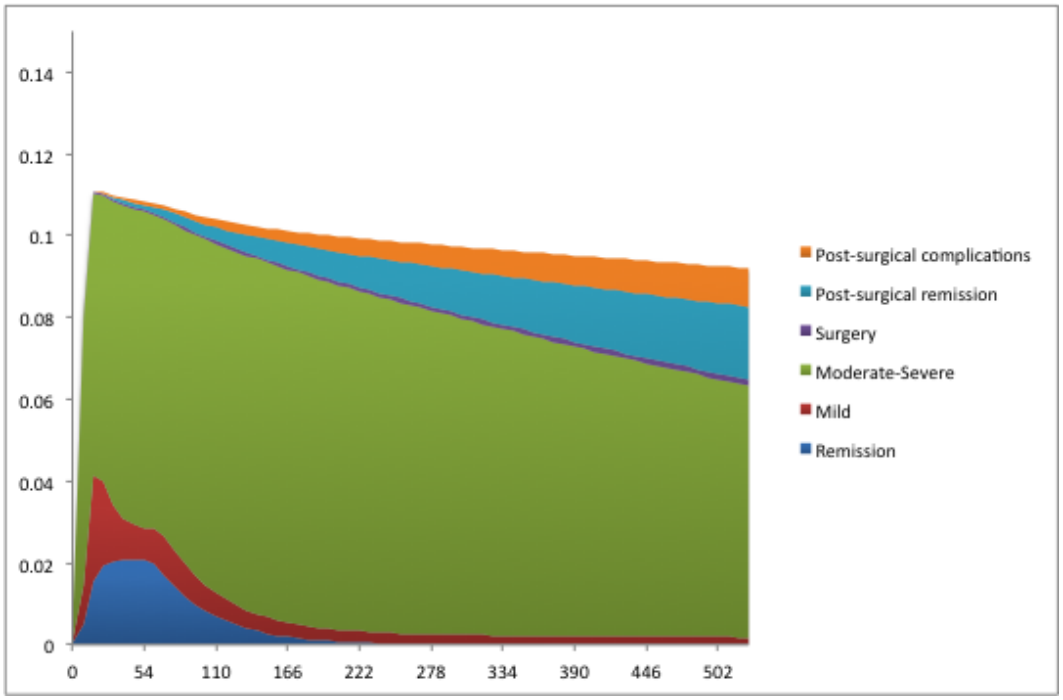
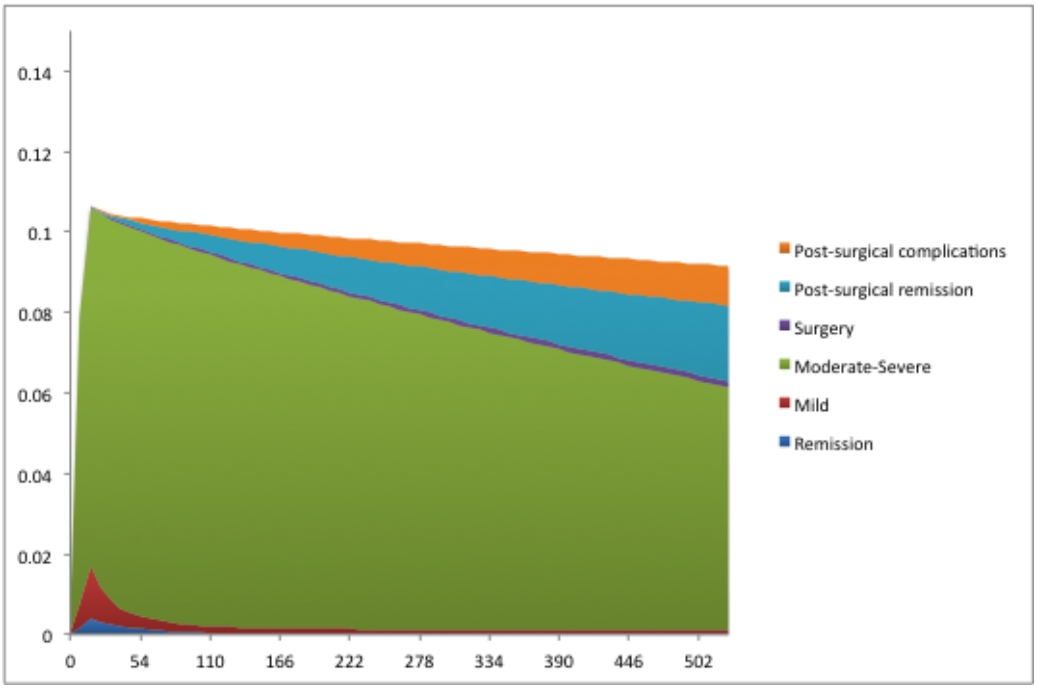


Figure 32. Utility Markov Trace: Vedolizumab for the TNF-Failure Population (Trial-Based Estimates). Modelled Utility Scores by Health State per Cycle.



7.6.4	**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 83. Life Years Estimated by the Model by Health State for the Mixed Population (ITT)

	VDZ	Conventional therapy	Surgery
Remission (Mayo = 0-2)	0.639	0.133	0.000
Mild (Mayo = 3-5)	0.356	0.141	0.000
Moderate-to-Severe (Mayo = 6-12)	5.903	6.411	0.000
Surgery	0.113	0.127	0.599
Post-surgical remission	0.724	0.833	4.396
Post-surgical complications	0.552	0.635	3.314
Total	8.286	8.281	8.309

Table 84. QALYs Estimated by the Model by Health State for the Mixed Population (ITT)

	VDZ	Conventional therapy	Surgery
Remission (Mayo = 0-2)	0.548	0.114	0.000
Mild (Mayo = 3-5)	0.284	0.113	0.000
Moderate-to-Severe (Mayo = 6-12)	4.006	4.350	0.000
Surgery	0.047	0.053	0.252
Post-surgical remission	0.434	0.500	2.637
Post-surgical complications	0.232	0.267	1.392
Total	5.551	5.397	4.281

Table 85. Costs Estimated by the Model by Health State for the Mixed Population (ITT)

	VDZ	Conventional therapy	Surgery
Initial Drug and Administration	[redacted]	£0	£0
Drug Switch (Conventional Therapy)	£8,813	£8,930	£0
Health State Costs			
Remission (Mayo = 0-2)	£985	£205	£0
Mild (Mayo = 3-5)	£984	£390	£0
Moderate-to-Severe (Mayo = 6-12)	£36,877	£40,050	£0
Surgery	£9,965	£11,237	£53,065
Post-surgical remission	£2,207	£2,542	£13,407
Post-surgical complications	£6,890	£7,925	£41,358
Adverse Events	£616	£645	£0
Total	£77,056	£71,925	£107,831

TNF-Naïve Patients

Table 86. Life Years Estimated by the Model by Health State for the TNF-Naive Population

	VDZ	Conventional therapy	Infliximab	Adalimumab	Golimumab
Remission (Mayo = 0-2)	1.379	0.379	1.079	0.985	1.036
Mild (Mayo = 3-5)	1.549	0.810	1.467	1.232	1.351
Moderate-to-Severe (Mayo = 6-12)	4.365	5.684	4.660	4.909	4.780
Surgery	0.082	0.112	0.089	0.094	0.091
Post-surgical remission	0.522	0.738	0.567	0.608	0.587
Post-surgical complications	0.399	0.563	0.433	0.464	0.448
Total	8.297	8.286	8.295	8.292	8.294

Table 87. QALYs Estimated by the Model by Health State for the TNF-Naive Population

	VDZ	Conventional therapy	Infliximab	Adalimumab	Golimumab
Remission (Mayo = 0-2)	1.184	0.325	0.926	0.846	0.890
Mild (Mayo = 3-5)	1.237	0.647	1.171	0.983	1.078
Moderate-to-Severe (Mayo = 6-12)	2.962	3.857	3.162	3.331	3.244
Surgery	0.034	0.047	0.037	0.040	0.038
Post-surgical remission	0.313	0.443	0.340	0.365	0.352
Post-surgical complications	0.168	0.236	0.182	0.195	0.188
Total	5.898	5.555	5.818	5.760	5.790

Table 88. Costs Estimated by the Model by Health State for the TNF-Naive Population

	VDZ	Conventional therapy	Infliximab	Adalimumab	Golimumab
Initial Drug and Administration	[redacted]	£0	£14,215	£6,817	£9,920
Drug Switch (Conventional Therapy)	£9,250	£9,181	£9,105	£9,125	£9,115
Health State Costs					
Remission (Mayo = 0-2)	£2,127	£584	£1,664	£1,520	£1,599
Mild (Mayo = 3-5)	£4,285	£2,241	£4,057	£3,406	£3,735
Moderate-to-Severe (Mayo = 6-12)	£27,270	£35,508	£29,110	£30,667	£29,860
Surgery	£7,272	£9,959	£7,838	£8,343	£8,083
Post-surgical remission	£1,593	£2,252	£1,730	£1,855	£1,791
Post-surgical complications	£4,978	£7,020	£5,403	£5,789	£5,591
Adverse Events	£645	£663	£830	£634	£693
Total	£69,075	£67,406	£73,952	£68,157	£70,387

TNF-Failure Population

Table 89. Life Years Estimated by the Model by Health State for the TNF-Failure Population

	VDZ	Conventional therapy	Surgery
Remission (Mayo = 0-2)	0.272	0.028	0.000
Mild (Mayo = 3-5)	0.322	0.139	0.000
Moderate-to-Severe (Mayo = 6-12)	6.197	6.489	0.000
Surgery	0.120	0.129	0.599
Post-surgical remission	0.778	0.849	4.396
Post-surgical complications	0.593	0.647	3.314
Total	8.283	8.280	8.309

Table 90. QALYs Estimated by the Model by Health State for the TNF-Failure Population

	VDZ	Conventional therapy	Surgery
Remission (Mayo = 0-2)	0.234	0.024	0.000
Mild (Mayo = 3-5)	0.257	0.111	0.000
Moderate-to-Severe (Mayo = 6-12)	4.205	4.403	0.000
Surgery	0.050	0.054	0.252
Post-surgical remission	0.467	0.509	2.637
Post-surgical complications	0.249	0.272	1.392
Total	5.463	5.373	4.281

Table 91. Costs Estimated by the Model by Health State for the TNF-Failure Population

	VDZ	Conventional therapy	Surgery
Initial Drug and Administration	[redacted]	£0	£0
Drug Switch (Conventional Therapy)	£8,722	£8,890	£0
Health State Costs			
Remission (Mayo = 0-2)	£420	£43	£0
Mild (Mayo = 3-5)	£891	£384	£0
Moderate-to-Severe (Mayo = 6-12)	£38,713	£40,534	£0
Surgery	£10,615	£11,417	£53,065
Post-surgical remission	£2,374	£2,589	£13,407
Post-surgical complications	£7,405	£8,070	£41,358
Adverse Events	£611	£642	£0
Total	£78,409	£72,570	£107,831

7.6.5 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 92. 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 (Mayo = 0-2)	0.548	0.114	0.434	0.434	41.1%
Mild (Mayo = 3-5)	0.284	0.113	0.172	0.172	16.2%
Moderate-to-Severe (Mayo = 6-12)	4.006	4.350	-0.345	0.345	32.6%
Surgery	0.047	0.053	-0.006	0.006	0.6%
Post-surgical remission	0.434	0.500	-0.066	0.066	6.2%
Post-surgical complications	0.232	0.267	-0.035	0.035	3.3%
Total	5.551	5.397	0.154	1.057	100.0%

Table 93. Disaggregated Costs for Vedolizumab and Conventional Therapy Estimated by the Model for the Mixed Population (ITT)

	Vedolizumab	Conventional therapy	Increment	Absolute Increment	% Absolute Increment
Initial Drug and Administration	[redacted]	£0	£9,719	£9,719	57.0%
Drug Switch (Conventional Therapy)	£8,813	£8,930	-£117	£117	0.7%
Health State Costs	£0	£0	£0	£0	0.0%
Remission (Mayo = 0-2)	£985	£205	£780	£780	4.6%
Mild (Mayo = 3-5)	£984	£390	£594	£594	3.5%
Moderate-to-Severe (Mayo = 6-12)	£36,877	£40,050	-£3,173	£3,173	18.6%
Surgery	£9,965	£11,237	-£1,272	£1,272	7.5%
Post-surgical remission	£2,207	£2,542	-£335	£335	2.0%
Post-surgical complications	£6,890	£7,925	-£1,035	£1,035	6.1%
Adverse Events	£616	£645	-£28	£28	0.2%
Total	£77,056	£71,925	£5,131	£17,053	100.0%

Table 94. Disaggregated QALYs for Vedolizumab and Surgery Estimated by the Model for the Mixed Population (ITT)

	Vedolizumab	Surgery	Increment	Absolute Increment	% Absolute Increment
Remission (Mayo = 0-2)	0.548	0.000	0.548	0.548	6.5%
Mild (Mayo = 3-5)	0.284	0.000	0.284	0.284	3.4%
Moderate-to-Severe (Mayo = 6-12)	4.006	0.000	4.006	4.006	47.7%
Surgery	0.047	0.252	-0.204	0.204	2.4%
Post-surgical remission	0.434	2.637	-2.203	2.203	26.2%
Post-surgical complications	0.232	1.392	-1.160	1.160	13.8%
Total	5.551	4.281	1.270	8.406	100.0%

Table 95. Disaggregated Costs for Vedolizumab and Surgery Estimated by the Model for the Mixed Population (ITT)

	Vedolizumab	Surgery	Increment	Absolute Increment	% Absolute Increment
Initial Drug and Administration	[redacted]	£0	£9,719	£9,719	6.6%
Drug Switch (Conventional Therapy)	£8,813	£0	£8,813	£8,813	6.0%
Health State Costs	£0	£0	£0	£0	0.0%
Remission (Mayo = 0-2)	£985	£0	£985	£985	0.7%
Mild (Mayo = 3-5)	£984	£0	£984	£984	0.7%
Moderate-to-Severe (Mayo = 6-12)	£36,877	£0	£36,877	£36,877	25.1%
Surgery	£9,965	£53,065	-£43,100	£43,100	29.4%
Post-surgical remission	£2,207	£13,407	-£11,201	£11,201	7.6%
Post-surgical complications	£6,890	£41,358	-£34,468	£34,468	23.5%
Adverse Events	£616	£0	£616	£616	0.4%
Total	£77,056	£107,831	-£30,775	£146,762	100.0%

TNF-Naïve Patients

Table 96. Disaggregated QALYs for Vedolizumab and Conventional Therapy Estimated by the Model for the TNF-Naïve Population (MTC-Based Estimates)

	Vedolizumab	Conventional therapy	Increment	Absolute Increment	% Absolute Increment
Remission (Mayo = 0-2)	1.184	0.325	0.859	0.859	33.6%
Mild (Mayo = 3-5)	1.237	0.647	0.590	0.590	23.1%
Moderate-to-Severe (Mayo = 6-12)	2.962	3.857	-0.895	0.895	35.0%
Surgery	0.034	0.047	-0.013	0.013	0.5%
Post-surgical remission	0.313	0.443	-0.129	0.129	5.1%
Post-surgical complications	0.168	0.236	-0.069	0.069	2.7%
Total	5.898	5.555	0.343	2.554	100.0%

Table 97. Disaggregated Costs for Vedolizumab and Conventional Therapy Estimated by the Model for the TNF-Naïve Population (MTC-Based Estimates)

	Vedolizumab	Conventional Therapy	Increment	Absolute Increment	% Absolute Increment
Initial Drug and Administration	[redacted]	£0	£11,655	£11,655	40.3%
Drug Switch (Conventional Therapy)	£9,250	£9,181	£69	£69	0.2%
Health State Costs	£0	£0	£0	£0	0.0%
Remission (Mayo = 0-2)	£2,127	£584	£1,543	£1,543	5.3%
Mild (Mayo = 3-5)	£4,285	£2,241	£2,044	£2,044	7.1%
Moderate-to-Severe (Mayo = 6-12)	£27,270	£35,508	-£8,238	£8,238	28.5%
Surgery	£7,272	£9,959	-£2,687	£2,687	9.3%
Post-surgical remission	£1,593	£2,252	-£658	£658	2.3%
Post-surgical complications	£4,978	£7,020	-£2,042	£2,042	7.1%
Adverse Events	£645	£663	-£18	£18	0.1%
Total	£69,075	£67,406	£1,669	£28,954	100.0%

Table 98. Disaggregated QALYs for Vedolizumab and Infliximab Estimated by the Model for the TNF-Naïve Population

	Vedolizumab	Infliximab	Increment	Absolute Increment	% Absolute Increment
Remission (Mayo = 0-2)	1.184	0.926	0.258	0.258	45.5%
Mild (Mayo = 3-5)	1.237	1.171	0.066	0.066	11.6%
Moderate-to-Severe (Mayo = 6-12)	2.962	3.162	-0.200	0.200	35.2%
Surgery	0.034	0.037	-0.003	0.003	0.5%
Post-surgical remission	0.313	0.340	-0.027	0.027	4.7%
Post-surgical complications	0.168	0.182	-0.014	0.014	2.5%
Total	5.898	5.818	0.081	0.567	100.0%

Table 99. Disaggregated Costs for Vedolizumab and Infliximab Estimated by the Model for the TNF-Naïve Population

	Vedolizumab	Infliximab	Increment	Absolute Increment	% Absolute Increment
Initial Drug and Administration	[redacted]	£14,215	-£2,559	£2,559	39.1%
Drug Switch (Conventional Therapy)	£9,250	£9,105	£144	£144	2.2%
Health State Costs	£0	£0	£0	£0	0.0%
Remission (Mayo = 0-2)	£2,127	£1,664	£463	£463	7.1%
Mild (Mayo = 3-5)	£4,285	£4,057	£228	£228	3.5%
Moderate-to-Severe (Mayo = 6-12)	£27,270	£29,110	-£1,840	£1,840	28.1%
Surgery	£7,272	£7,838	-£566	£566	8.6%
Post-surgical remission	£1,593	£1,730	-£137	£137	2.1%
Post-surgical complications	£4,978	£5,403	-£425	£425	6.5%
Adverse Events	£645	£830	-£185	£185	2.8%
Total	£69,075	£73,952	-£4,877	£6,546	100.0%

Table 100. Disaggregated QALYs for Vedolizumab and Adalimumab Estimated by the Model for the TNF-Naïve Population

	Vedolizumab	Adalimumab	Increment	Absolute Increment	% Absolute Increment
Remission (Mayo = 0-2)	1.184	0.846	0.338	0.338	32.3%
Mild (Mayo = 3-5)	1.237	0.983	0.254	0.254	24.3%
Moderate-to-Severe (Mayo = 6-12)	2.962	3.331	-0.369	0.369	35.4%
Surgery	0.034	0.040	-0.005	0.005	0.5%
Post-surgical remission	0.313	0.365	-0.051	0.051	4.9%
Post-surgical complications	0.168	0.195	-0.027	0.027	2.6%
Total	5.898	5.760	0.138	1.044	100.0%

Table 101. Disaggregated Costs for Vedolizumab and Adalimumab Estimated by the Model for the TNF-Naïve Population

	Vedolizumab	Adalimumab	Increment	Absolute Increment	% Absolute Increment
Initial Drug and Administration	[redacted]	£6,817	£4,838	£4,838	40.3%
Drug Switch (Conventional Therapy)	£9,250	£9,125	£124	£124	1.0%
Health State Costs	£0	£0	£0	£0	0.0%
Remission (Mayo = 0-2)	£2,127	£1,520	£607	£607	5.1%
Mild (Mayo = 3-5)	£4,285	£3,406	£879	£879	7.3%
Moderate-to-Severe (Mayo = 6-12)	£27,270	£30,667	-£3,398	£3,398	28.3%
Surgery	£7,272	£8,343	-£1,071	£1,071	8.9%
Post-surgical remission	£1,593	£1,855	-£261	£261	2.2%
Post-surgical complications	£4,978	£5,789	-£811	£811	6.8%
Adverse Events	£645	£634	£11	£11	0.1%
Total	£69,075	£68,157	£918	£12,000	100.0%

Table 102. Disaggregated QALYs for Vedolizumab and Golimumab Estimated by the Model for the TNF-Naïve Population

	Vedolizumab	Golimumab	Increment	Absolute Increment	% Absolute Increment
Remission (Mayo = 0-2)	1.184	0.890	0.294	0.294	36.9%
Mild (Mayo = 3-5)	1.237	1.078	0.159	0.159	19.9%
Moderate-to-Severe (Mayo = 6-12)	2.962	3.244	-0.281	0.281	35.3%
Surgery	0.034	0.038	-0.004	0.004	0.5%
Post-surgical remission	0.313	0.352	-0.039	0.039	4.9%
Post-surgical complications	0.168	0.188	-0.021	0.021	2.6%
Total	5.898	5.790	0.108	0.797	100.0%

Table 103. Disaggregated Costs for Vedolizumab and Golimumab Estimated by the Model for the TNF-Naïve Population

	Vedolizumab	Golimumab	Increment	Absolute Increment	% Absolute Increment
Initial Drug and Administration	[redacted]	£9,920	£1,736	£1,736	24.1%
Drug Switch (Conventional Therapy)	£9,250	£9,115	£134	£134	1.9%
Health State Costs	£0	£0	£0	£0	0.0%
Remission (Mayo = 0-2)	£2,127	£1,599	£528	£528	7.3%
Mild (Mayo = 3-5)	£4,285	£3,735	£549	£549	7.6%
Moderate-to-Severe (Mayo = 6-12)	£27,270	£29,860	-£2,591	£2,591	35.9%
Surgery	£7,272	£8,083	-£811	£811	11.3%
Post-surgical remission	£1,593	£1,791	-£197	£197	2.7%
Post-surgical complications	£4,978	£5,591	-£613	£613	8.5%
Adverse Events	£645	£693	-£48	£48	0.7%
Total	£69,075	£70,387	-£1,312	£7,207	100.0%

TNF-Failure Patients

Table 104. 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 (Mayo = 0-2)	0.234	0.024	0.210	0.210	33.7%
Mild (Mayo = 3-5)	0.257	0.111	0.146	0.146	23.5%
Moderate-to-Severe (Mayo = 6-12)	4.205	4.403	-0.198	0.198	31.8%
Surgery	0.050	0.054	-0.004	0.004	0.6%
Post-surgical remission	0.467	0.509	-0.042	0.042	6.8%
Post-surgical complications	0.249	0.272	-0.022	0.022	3.6%
Total	5.463	5.373	0.090	0.622	100.0%

Table 105. 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
Initial Drug and Administration	[redacted]	£0	£8,658	£8,658	65.4%
Drug Switch (Conventional Therapy)	£8,722	£8,890	-£169	£169	1.3%
Health State Costs	£0	£0	£0	£0	0.0%
Remission (Mayo = 0-2)	£420	£43	£377	£377	2.8%
Mild (Mayo = 3-5)	£891	£384	£507	£507	3.8%
Moderate-to-Severe (Mayo = 6-12)	£38,713	£40,534	-£1,822	£1,822	13.8%
Surgery	£10,615	£11,417	-£802	£802	6.1%
Post-surgical remission	£2,374	£2,589	-£215	£215	1.6%
Post-surgical complications	£7,405	£8,070	-£664	£664	5.0%
Adverse Events	£611	£642	-£30	£30	0.2%
Total	£78,409	£72,570	£5,839	£13,243	100.0%

Base-case analysis

7.6.6 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 106 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 £33,297. Versus surgery, vedolizumab has lower costs and greater QALYs and hence dominates.

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 (£4,000 - £6,000 approx) or dominates.

In the TNF failure group, vedolizumab derives more QALYs than both surgery and conventional therapy, dominating the former (due to lower cost) and deriving an ICER of £64,999 against the latter.

Table 106. Incremental Cost-Effectiveness Estimates for Vedolizumab Compared with each Alternative by Patient Sub-Group

Population / Technology	Total Costs	Total LYG	Total QALYs	Incremental Costs (£)	Incremental LYG	Incremental QALYs	ICER (Cost per QALY gained)
Mixed Population (ITT)							
Vedolizumab	£77,056	8.286	5.551				
Conventional Therapy	£71,925	8.281	5.397	£5,131	0.005	0.154	£33,297
Surgery	£107,831	8.309	4.281	-£30,775	-0.023	1.270	Vedo. dominates
TNF-Naïve Patients							
Vedolizumab	£69,075	8.297	5.898				
Conventional Therapy	£67,406	8.286	5.555	£1,669	0.011	0.343	£4,862
Infliximab	£73,952	8.295	5.818	-£4,877	0.002	0.081	Vedo. dominates
Adalimumab	£68,157	8.292	5.760	£918	0.004	0.138	£6,634
Golimumab	£70,387	8.294	5.790	-£1,312	0.003	0.108	Vedo. dominates
Surgery	£107,831	8.309	4.281	-£38,756	-0.012	1.617	Vedo. dominates
TNF-Failure Patients							
Vedolizumab	£78,409	8.283	5.463				
Conventional Therapy	£72,570	8.280	5.373	£5,839	0.003	0.090	£64,999
Surgery	£107,831	8.309	4.281	-£29,422	-0.026	1.182	Vedo. dominates

Sensitivity analyses

7.6.7	**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 68 (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)

Figures 33/ 34 below shows that the variables with the biggest impact upon the ICER when comparing against conventional therapy and surgery 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 33. Tornado Diagram: Cost-Effectiveness versus Conventional Therapy for the Mixed Patient Population (ITT).

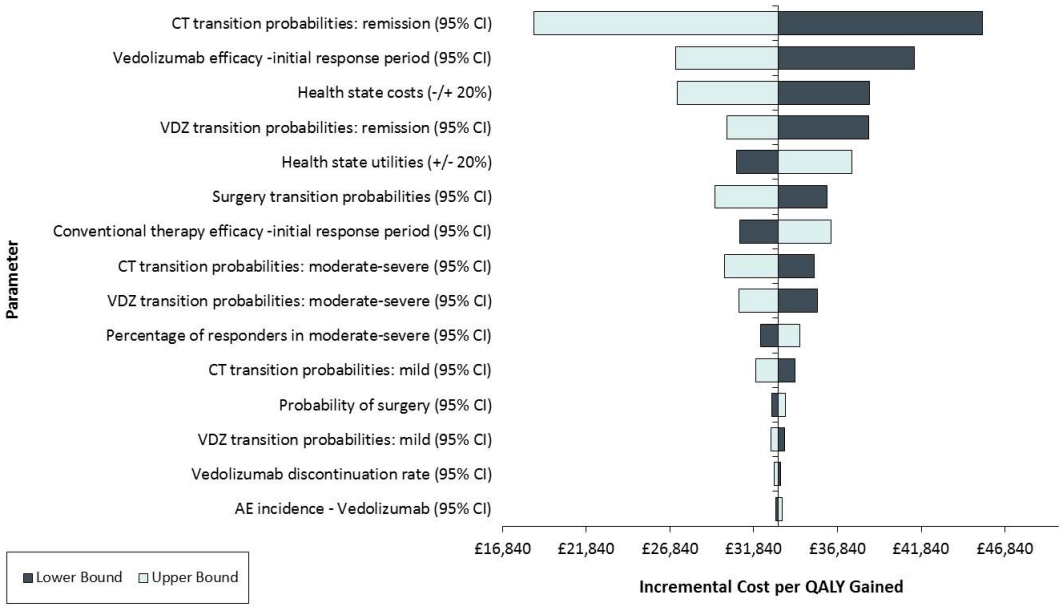
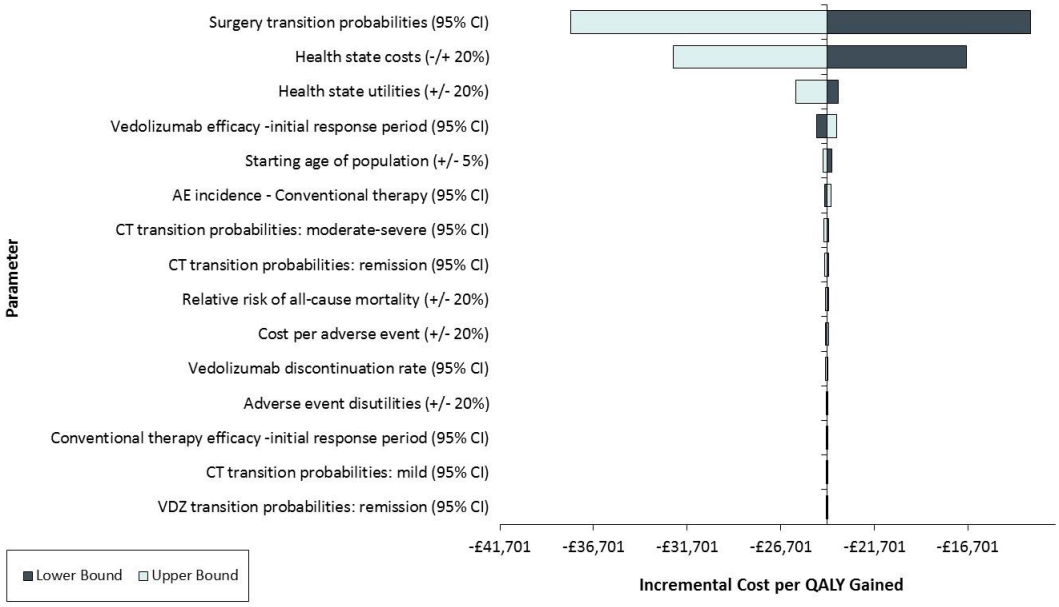


Figure 34. Tornado Diagram: Cost-Effectiveness versus Surgery for the Mixed Patient Population (ITT).



TNF-Naïve Population

Figures 35-39 below shows that the variables with the biggest impact upon the ICER when assessing the TNF naïve population (and against the other TNFα treatment options) are as follows:

- Transition probabilities for remission related to conventional therapy.
- Health state costs.
- Vedolizumab efficacy.
- Infliximab efficacy.
- Infliximab transition probability for remission.
- Vedolizumab transition probability for remission.
- Other TNF efficacy.
- Surgery transition probilities.

Figure 35. Tornado Diagram: Cost-Effectiveness versus Conventional Therapy for the TNF-Naive Population (MTC-Based Estimates)

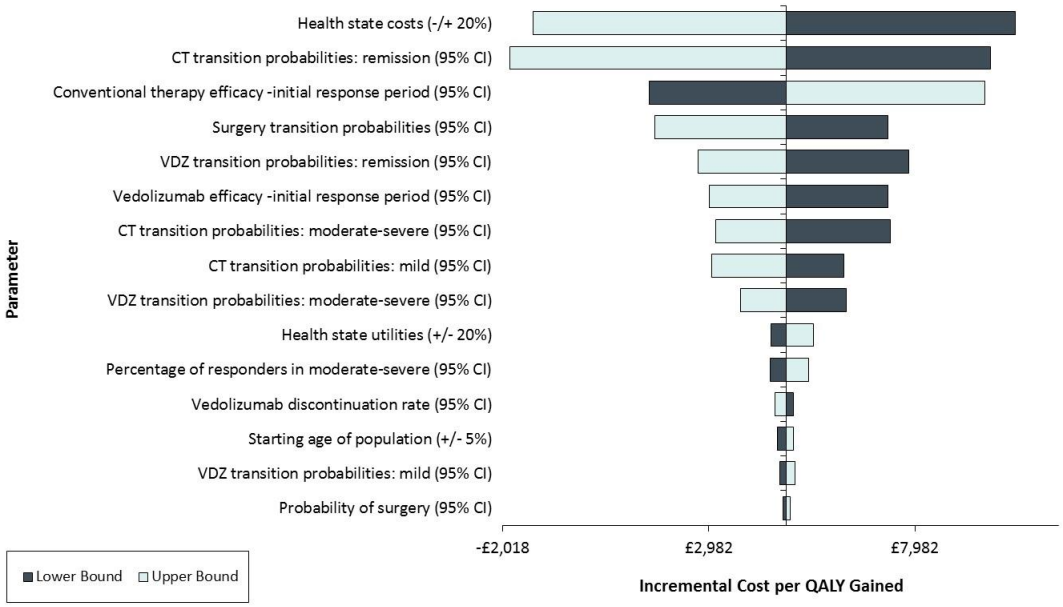


Figure 36. Tornado Diagram: Cost-Effectiveness versus Infliximab for the TNF-Naive Population

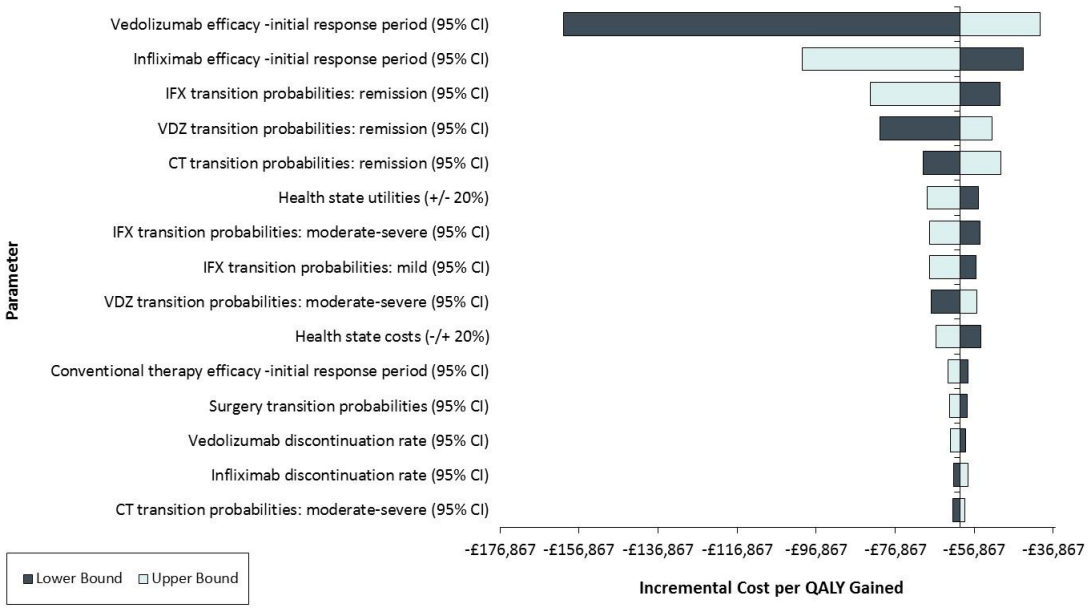


Figure 37. Tornado Diagram: Cost-Effectiveness versus Adalimumab for the TNF-Naive Population

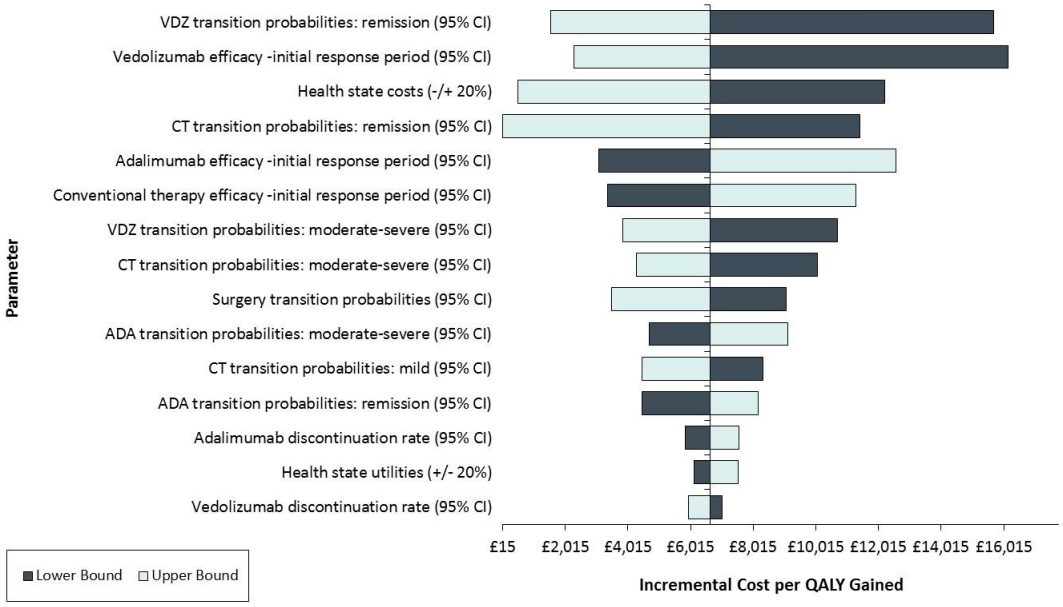


Figure 38. Tornado Diagram: Cost-Effectiveness versus Golimumab for the TNF-Naive Population

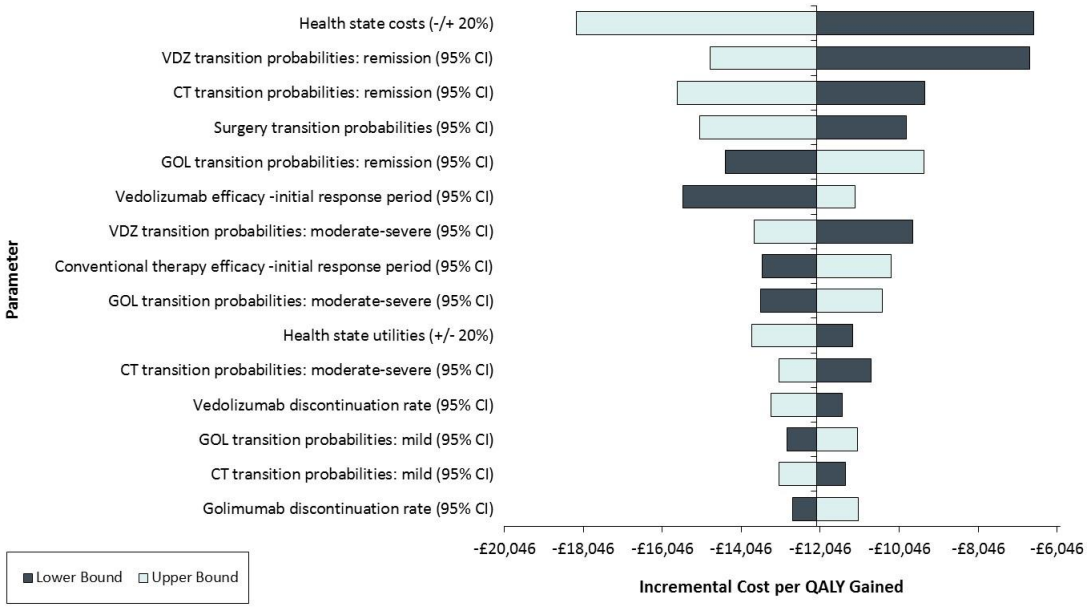
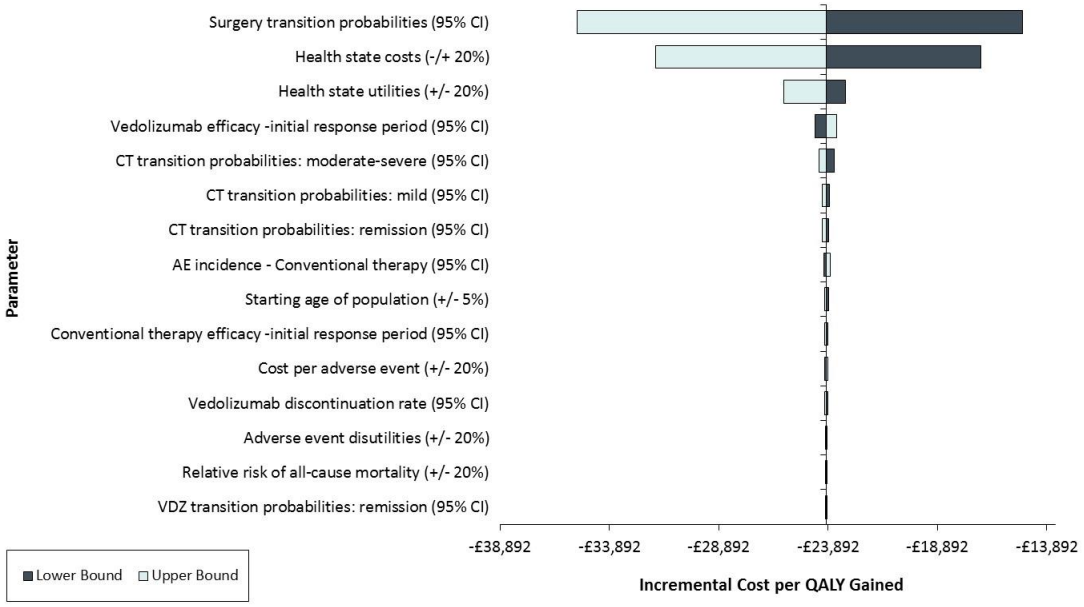


Figure 39. Tornado Diagram: Cost-Effectiveness versus Surgery for the TNF-Naive Population



TNF-Failure Patients

Figures 40 and 41 below shows that the variables with the biggest impact upon the ICER when assessing the TNF failure population are as follows:

- Vedolizumab efficacy.
- Conventional therapy transition probabilities.
- Health state costs.
- Surgery transition probilities.

Figure 40. Tornado Diagram: Cost-Effectiveness versus Conventional Therapy for the TNF-Failure Population (Trial-Based Estimates)

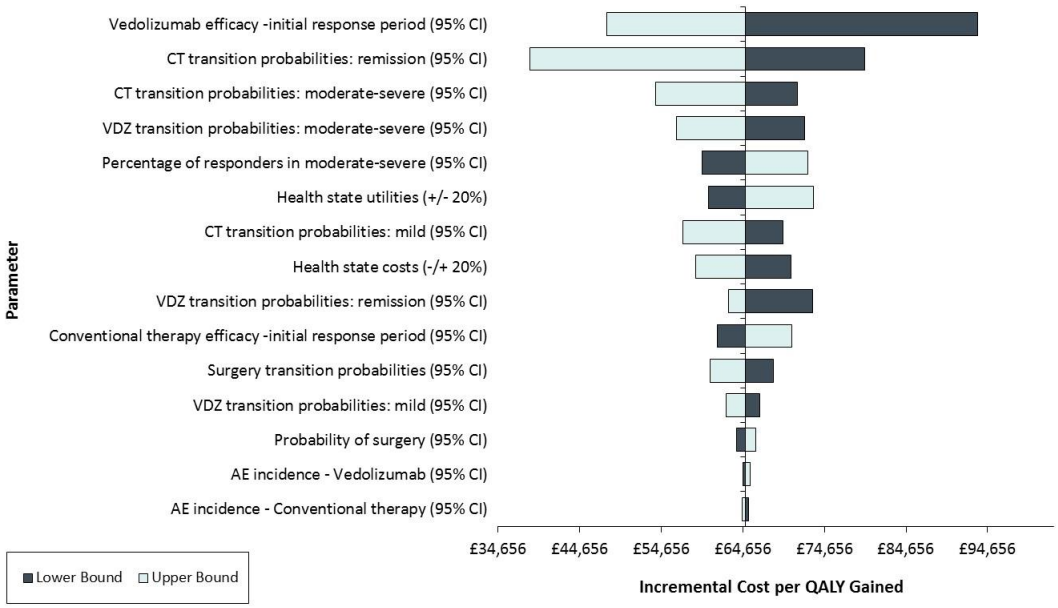
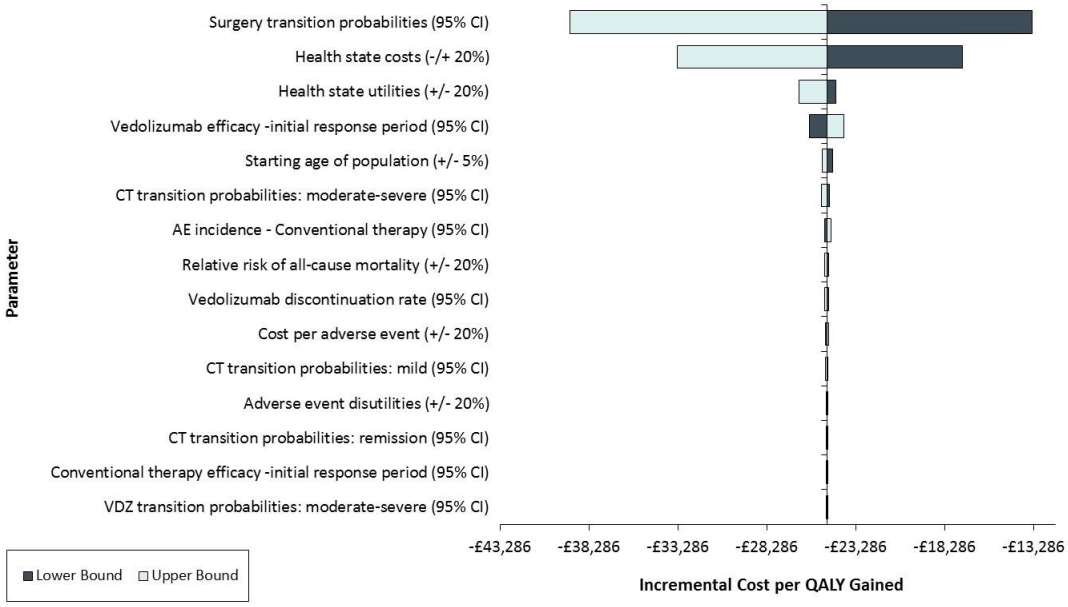


Figure 41. Tornado Diagram: Cost-Effectiveness versus Conventional Surgery for the TNF-Failure Population

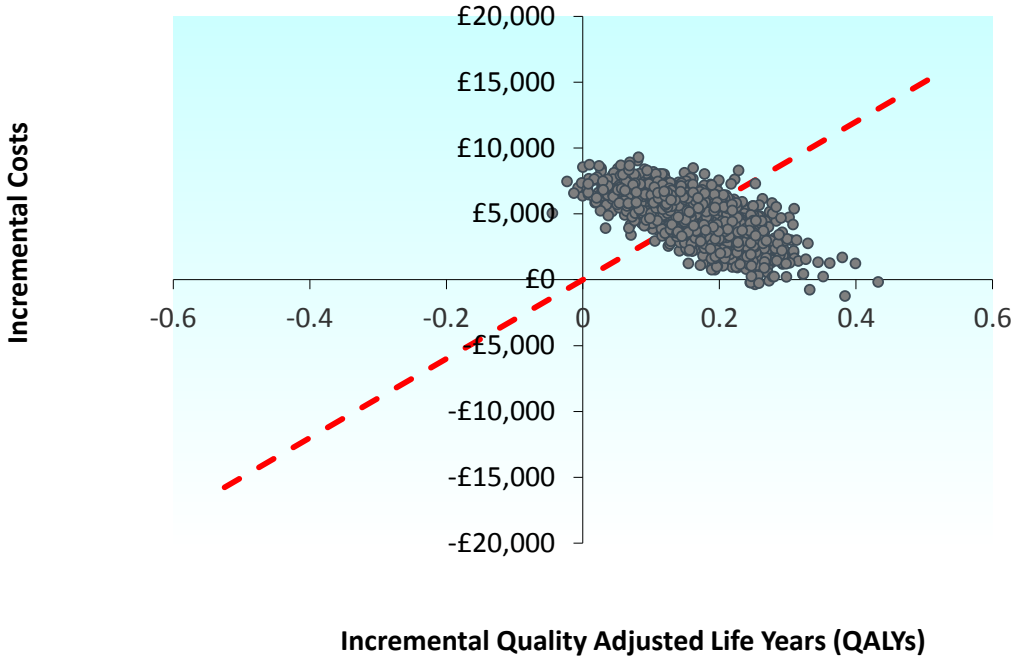


7.6.8	**Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.**

Probabilistic sensitivity analyses were run by patient population (for all patients, TNF-naïve and TNF-failure) and comparator, using the inputs listed in Table 68 (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 42. **PSA: Cost-Effectiveness Plane and CEAC for Vedolizumab versus Conventional Therapy for the Mixed Patient Population (ITT).**



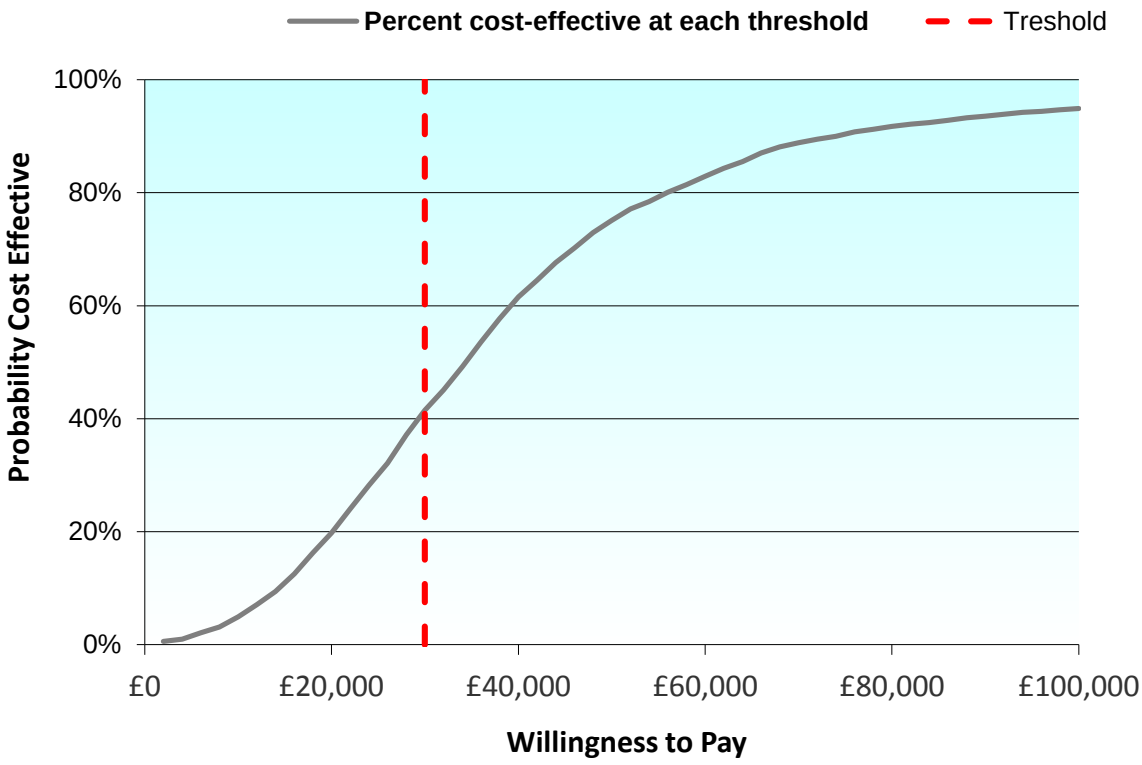
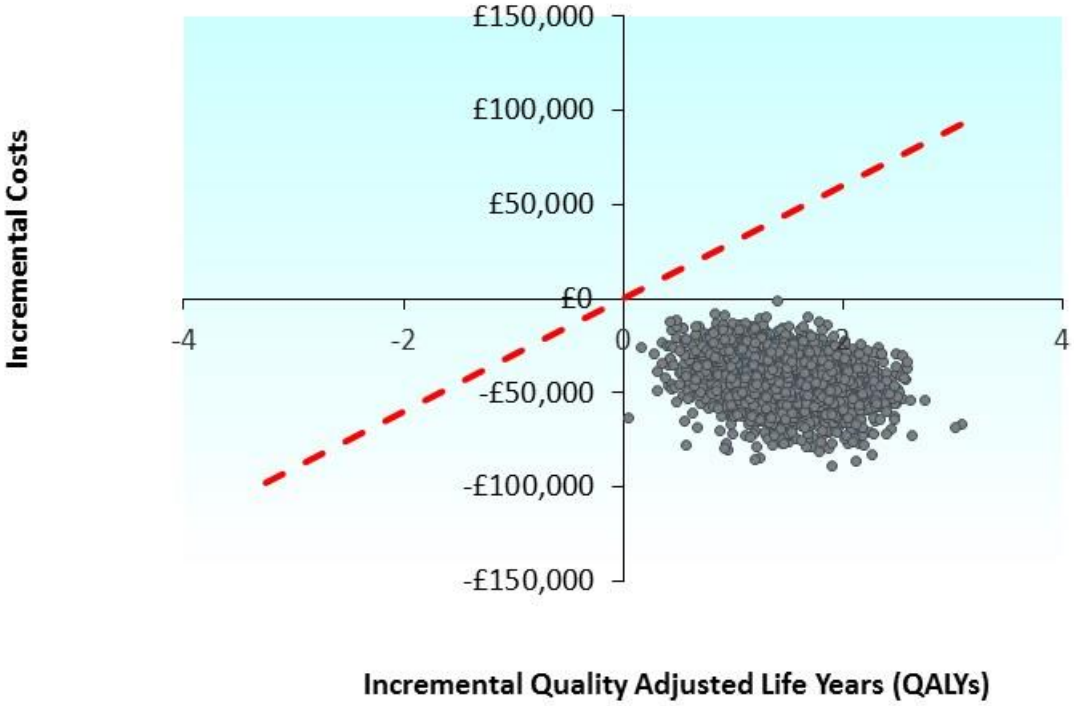
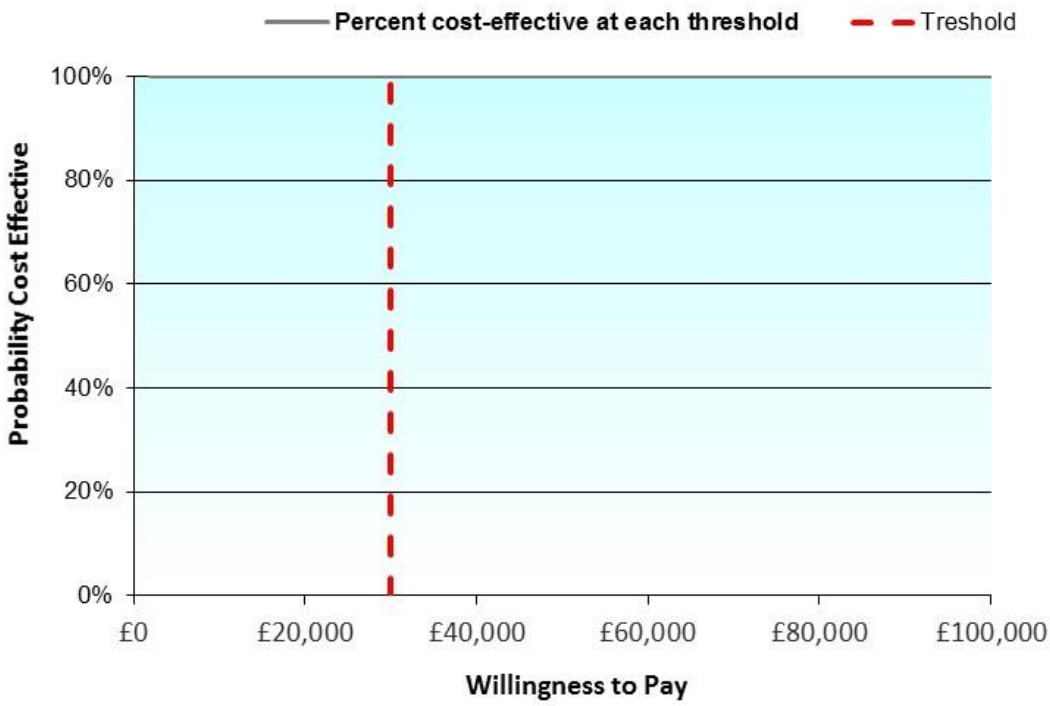


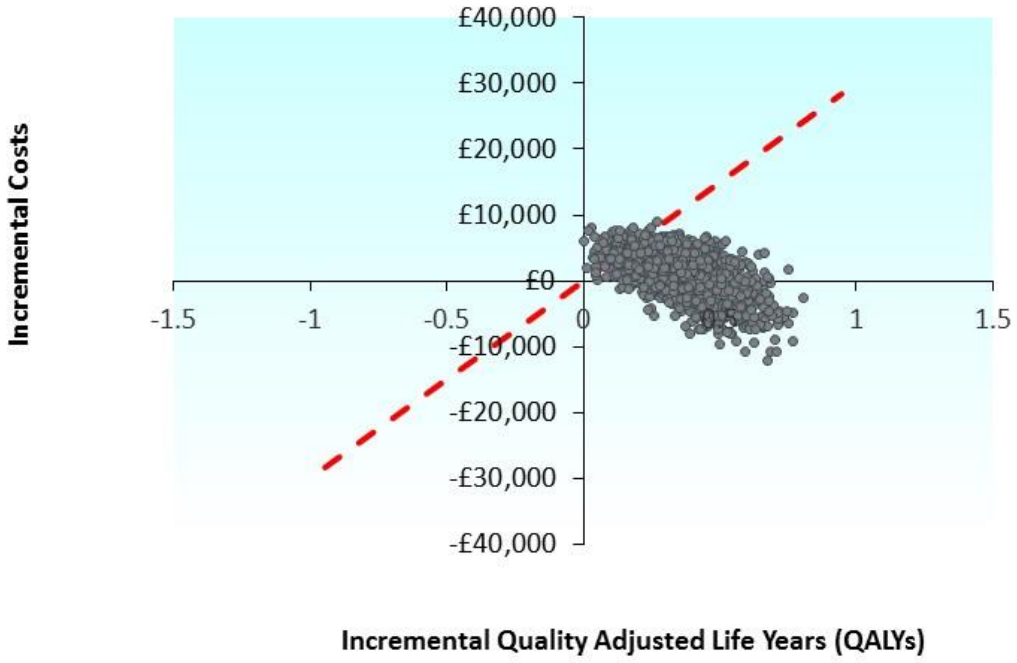
Figure 43. PSA: Cost-Effectiveness Plane and CEAC for Vedolizumab versus Surgery for the Mixed Patient Population (ITT).





TNF-Naïve Population

Figure 44. PSA: Cost-Effectiveness Plane and CEAC for Vedolizumab versus Conventional Therapy for the TNF-Naïve Population (Trial-Based Estimates)



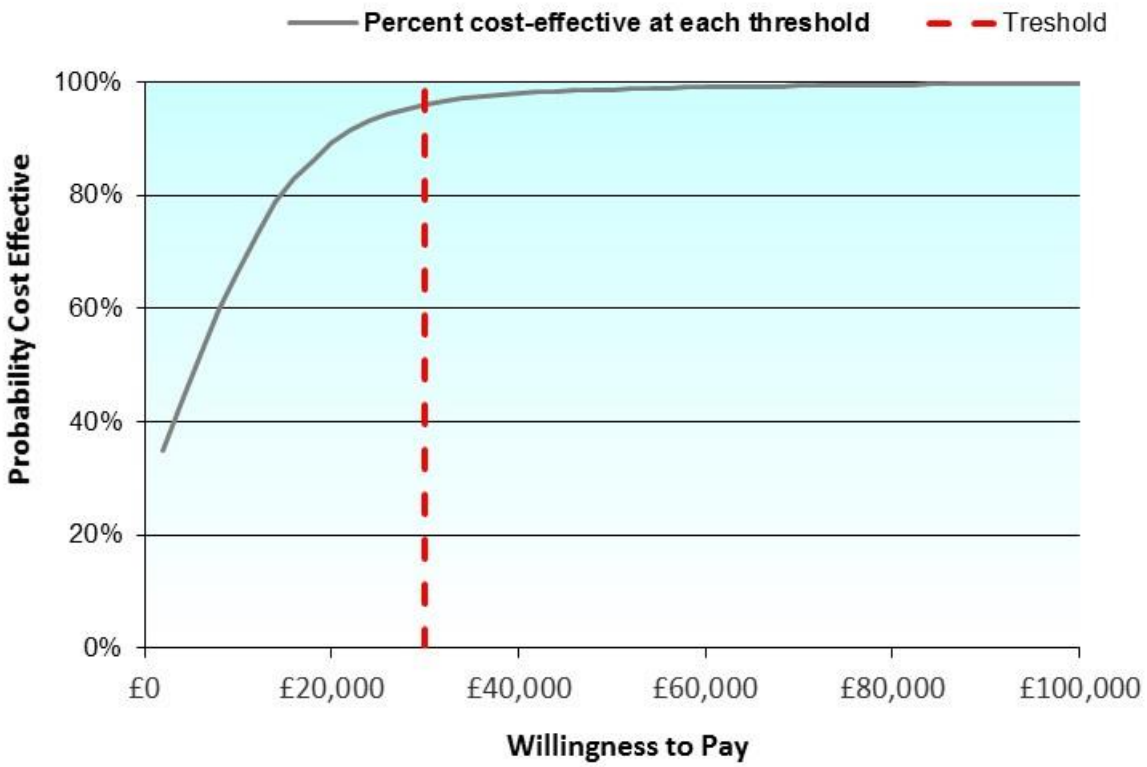
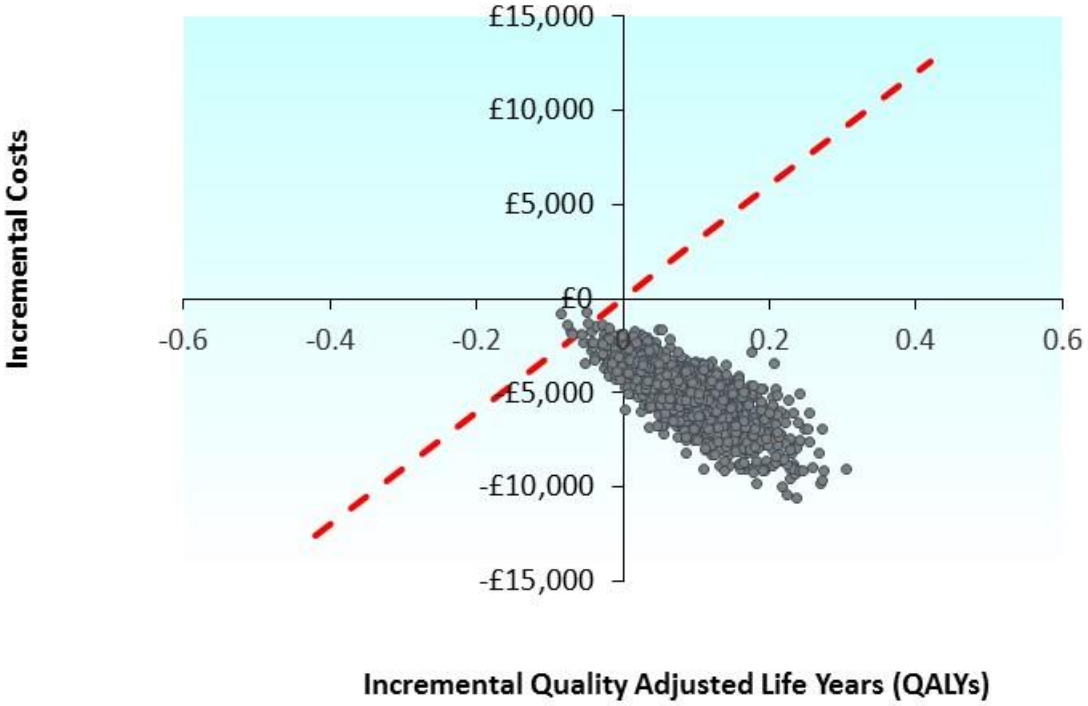


Figure 45. PSA: Cost-Effectiveness Plane and CEAC for Vedolizumab versus Infliximab for the TNF-Naïve Population



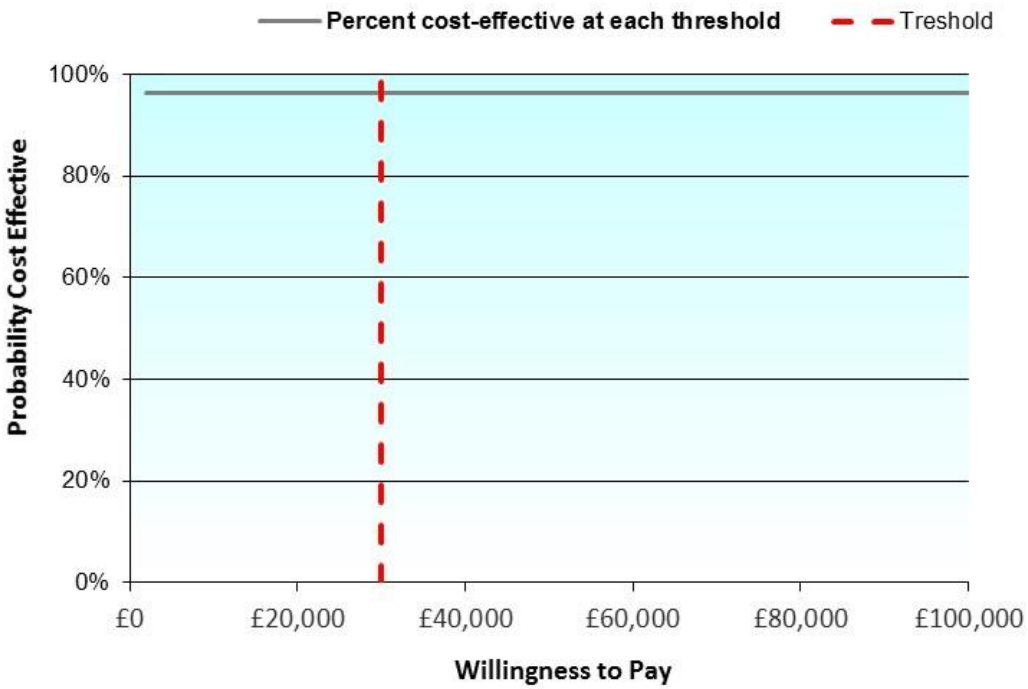
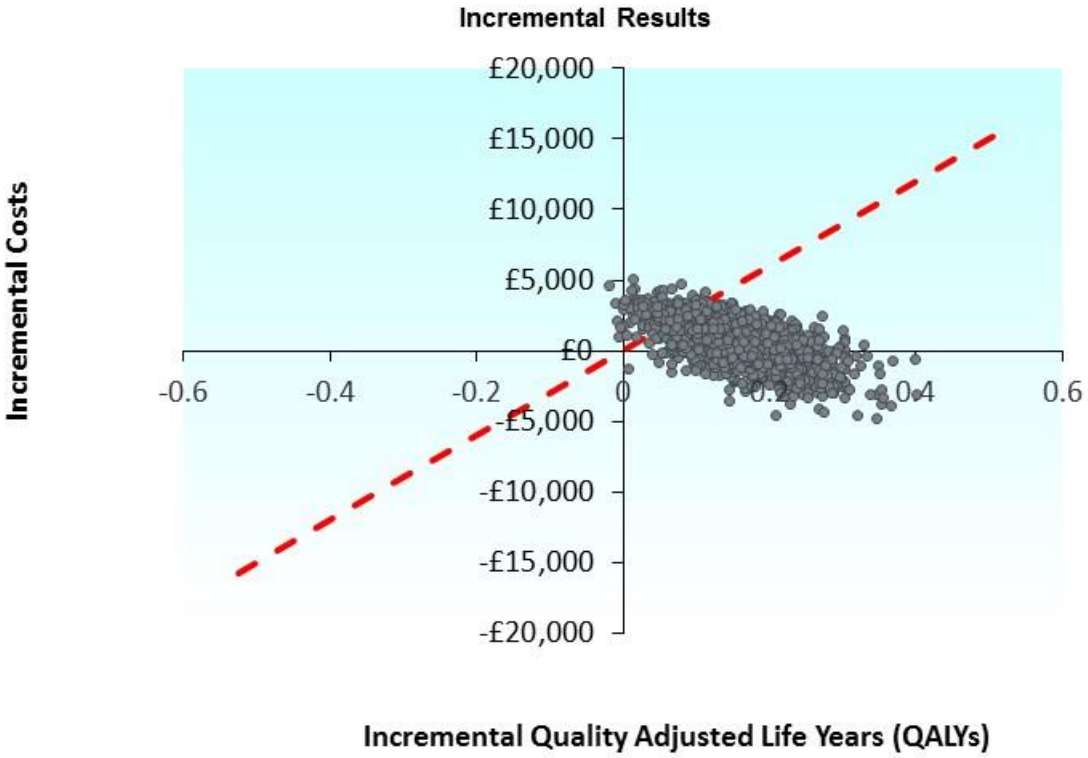


Figure 46. PSA: Cost-Effectiveness Plane and CEAC for Vedolizumab versus Adalimumab for the TNF-Naïve Population



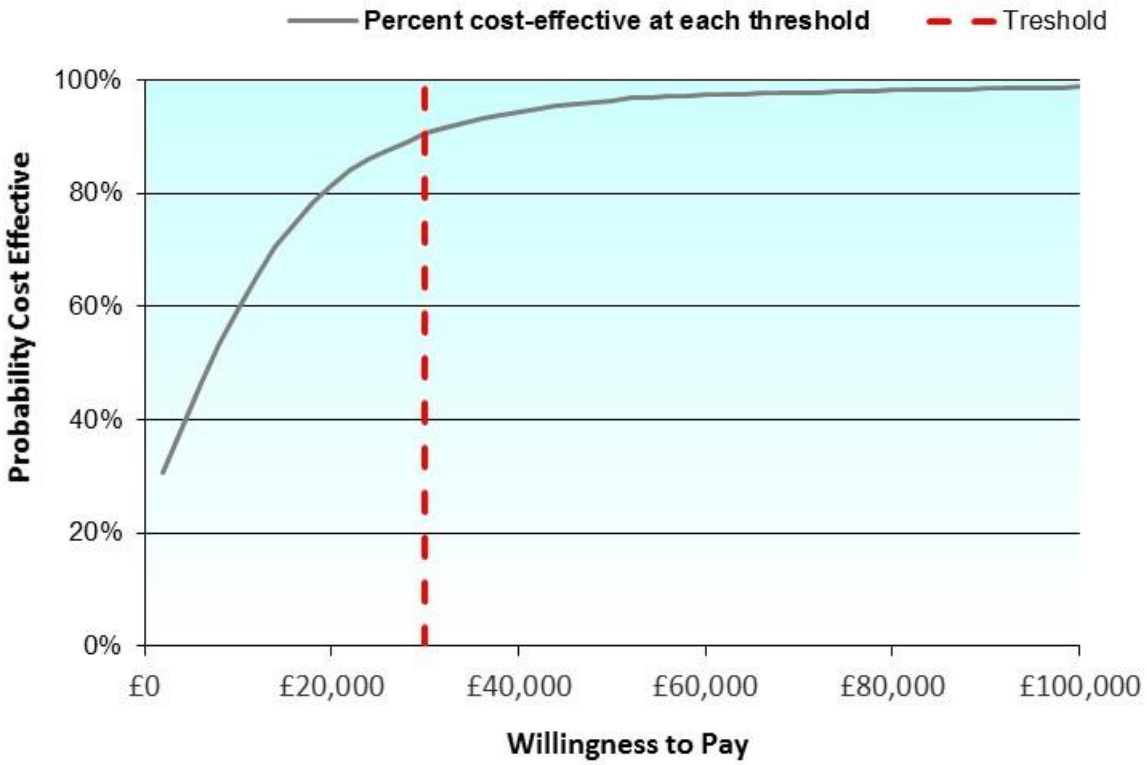
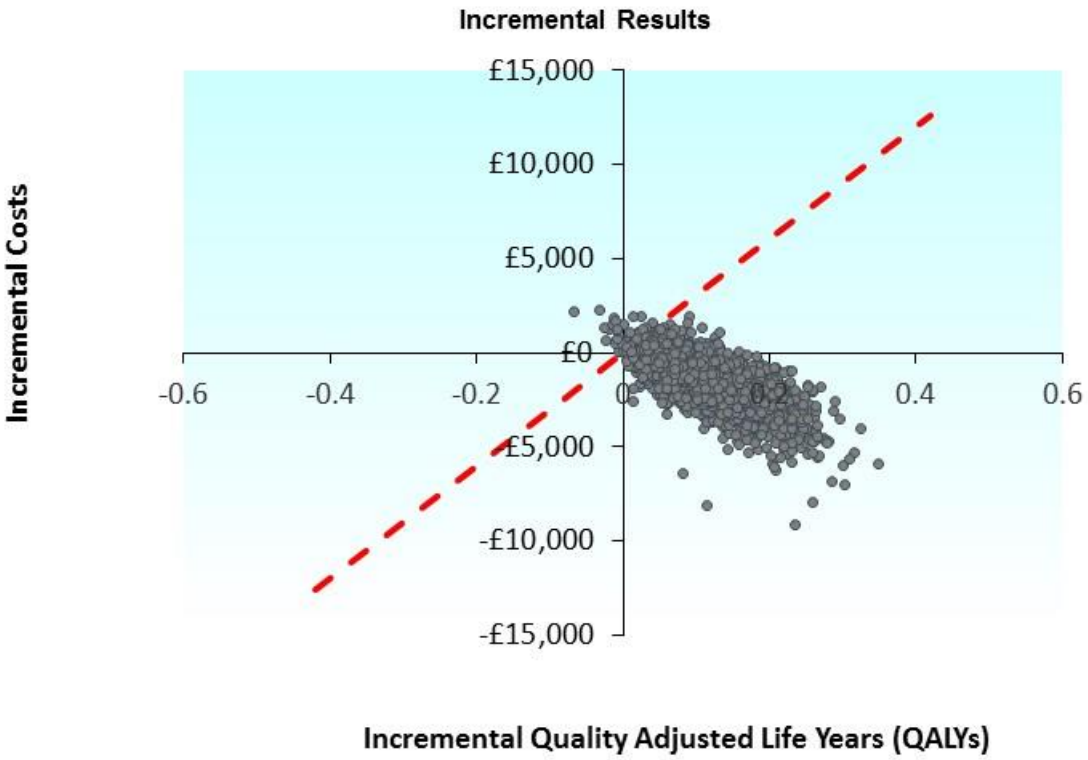


Figure 47. PSA: Cost-Effectiveness Plane and CEAC for Vedolizumab versus Golimumab for the TNF-Naïve Population



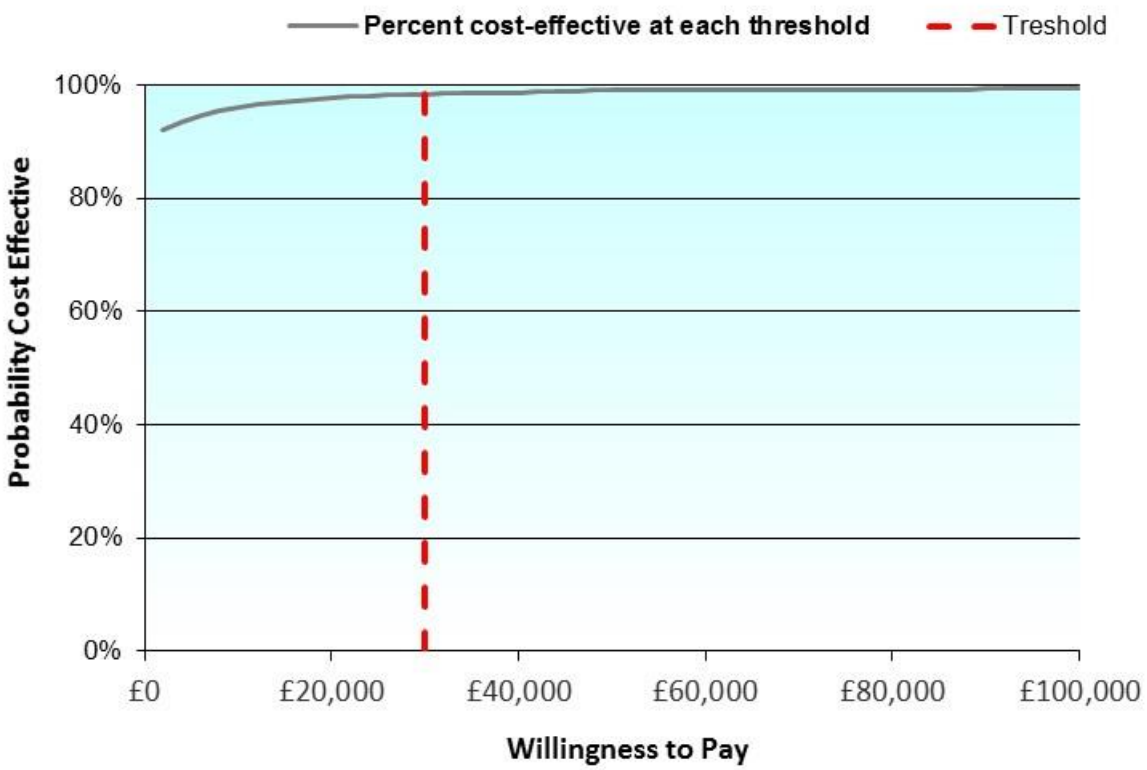
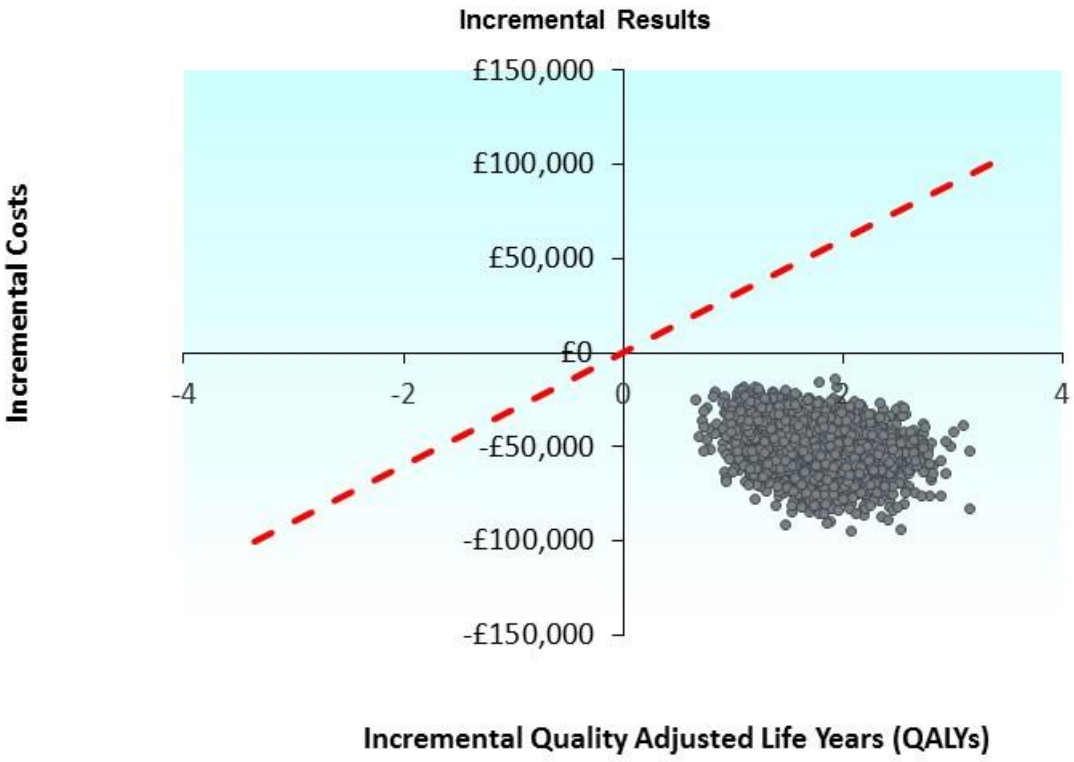
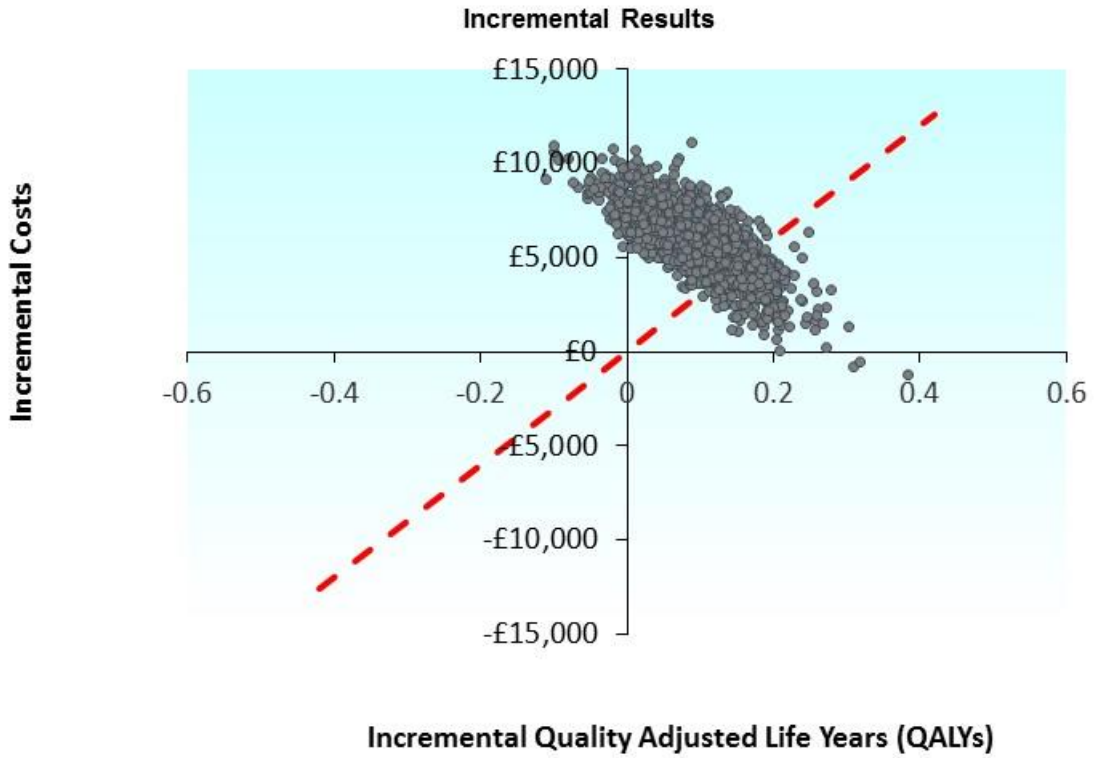


Figure 48. PSA: Cost-Effectiveness Plane and CEAC for Vedolizumab versus Surgery for the TNF-Naïve Population



TNF-Failure Patients

Figure 49. PSA: Cost-Effectiveness Plane and CEAC for Vedolizumab versus Conventional Therapy for the TNF-Failure Population (Trial-Based Estimates)



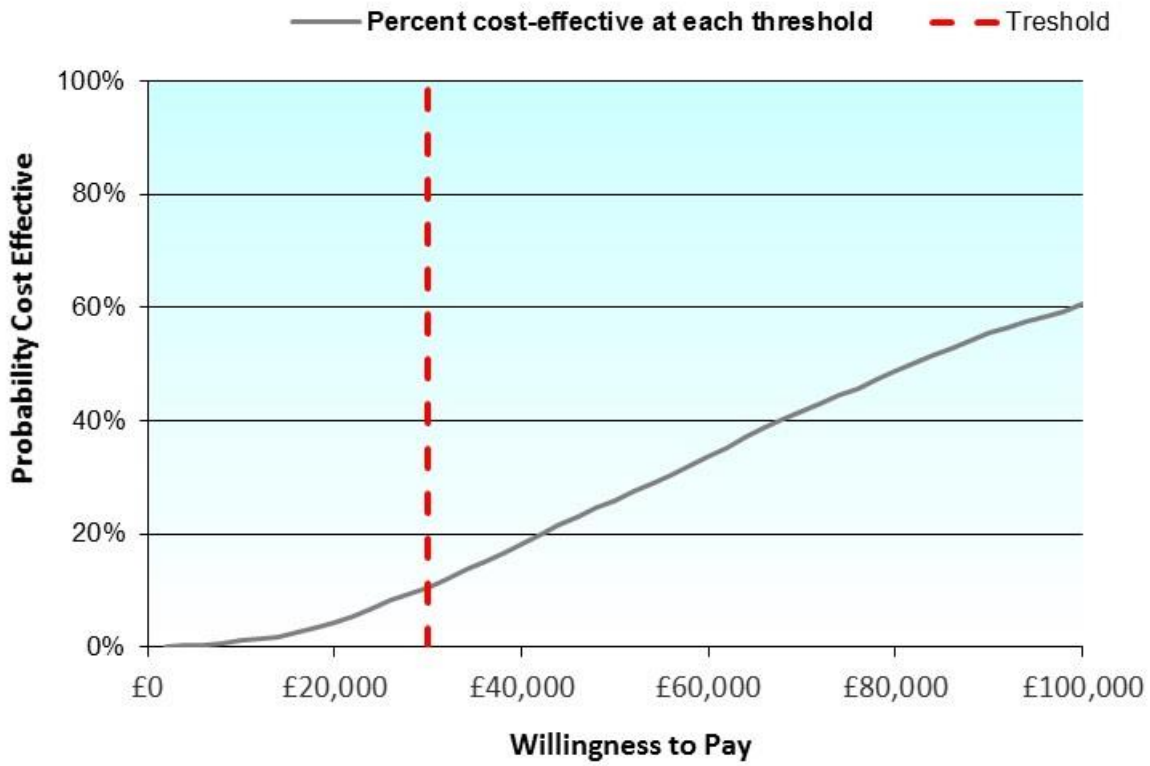
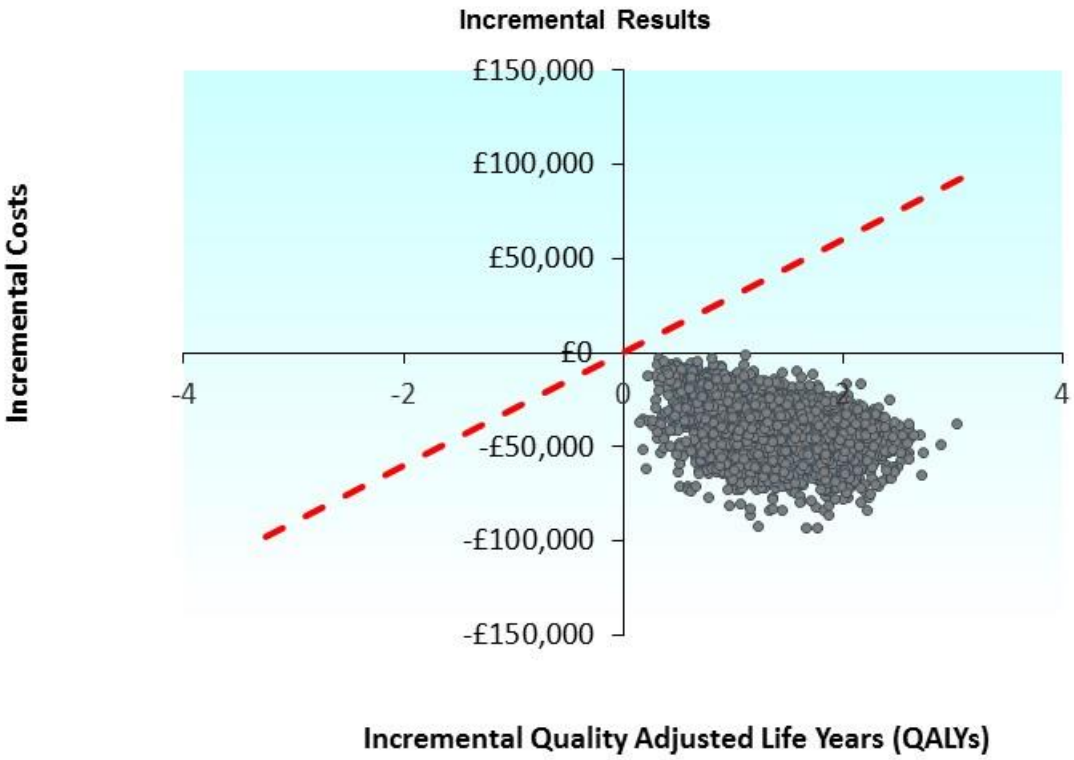


Figure 50. PSA: Cost-Effectiveness Plane and CEAC for Vedolizumab versus Surgery for the TNF-Failure Population



7.6.9 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.

- Unlike previous economic models in the disease area, the basecase model, presented here, includes additional risks of mortality associated with ulcerative colitis. In a scenario analysis, these relative risks were set to one, reflecting a scenario where patients with ulcerative colitis have a mortality rate that is the same as the general population.

- The basecase model uses the 6-week continuation rule that reflects the design of the GEMINI I 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, adalimumab or golimumab was set to 3 years.

The following tables detail the results of the scenario analyses by population and comparator.

Mixed Population (ITT)

Table 107. Scenario Analysis – Versus Conventional Therapy – Mixed Population (ITT)

Input(s)	Incremental Costs	Incremental QALYs	ICER
Base case			
Time horizon			
1 year	£7,665	0.041	£188,640
Lifetime	£4,144	0.201	£20,599
Utility weight source			
Punekar et al. (2010)	£5,131	0.287	£17,857
Arseneau et al. (2006)	£5,131	0.285	£18,008
Tsai et al. (2008)	£5,131	0.275	£18,627
Mortality risk			
No UC-related mortality risk	£5,087	0.151	£33,675
Vedolizumab response assessment			
Week 10	£7,132	0.227	£31,414
Maximum time on treatment			
3 years	£8,148	0.206	£39,575

Table 108. Scenario Analysis – Versus Surgery – Mixed Population (ITT)

Input(s)	Incremental Costs	Incremental QALYs	ICER
Base case	-£30,775	1.270	Vedo. dominates
Time horizon			
1 year	-£10,758	0.238	Vedo. dominates
Lifetime	-£48,285	1.820	Vedo. dominates
Utility weight source			
Punekar et al. (2010)	-£30,775	-0.263	£117,134*
Arseneau et al. (2006)	-£30,775	-1.164	£26,438*
Tsai et al. (2008)	-£30,775	-0.659	£46,733*
Mortality risk			
No UC-related mortality risk	-£30,613	1.288	Vedo. dominates
Vedolizumab response assessment			
Week 10	-£30,192	1.397	Vedo. dominates
Maximum time on treatment			
3 years	-£27,758	1.322	Vedo. dominates

- Results are in the south-west quadrant of the cost-effectiveness plane: the ICER represents the cost-effectiveness of surgery compared with vedolizumab.

TNF-Naïve Population

Table 109. Scenario Analysis – Versus Conventional Therapy – TNF-Naïve Population (MTC-Based Estimates)

Input(s)	Incremental Costs	Incremental QALYs	ICER
Base case	£1,669	0.343	£4,862
Time horizon			
1 year	£8,742	0.062	£139,885
Lifetime	-£5,413	0.683	Vedo. dominates
Utility weight source			
Punekar et al. (2010)	£1,669	0.676	£2,469
Arseneau et al. (2006)	£1,669	0.703	£2,375
Tsai et al. (2008)	£1,669	0.703	£2,375
Mortality risk			
No UC-related mortality risk	£1,564	0.337	£4,647
Vedolizumab response assessment			
Week 10	£4,368	0.343	£12,726
Maximum time on treatment			
3 years	£9,645	0.369	£26,152

Table 110. Scenario Analysis – Versus Infliximab – TNF-Naïve Population

Input(s)	Incremental Costs	Incremental QALYs	ICER
Base case	-£4,877	0.081	Vedo. dominates
Time horizon			
1 year	-£2,940	0.011	Vedo. dominates
Lifetime	-£6,375	0.153	Vedo. dominates
Utility weight source			
Punekar et al. (2010)	-£4,877	0.160	Vedo. dominates
Arseneau et al. (2006)	-£4,877	0.159	Vedo. dominates
Tsai et al. (2008)	-£4,877	0.155	Vedo. dominates
Mortality risk			
No UC-related mortality risk	-£4,900	0.079	Vedo. dominates
Vedolizumab response assessment			
Week 10	-£2,791	0.081	Vedo. dominates
Maximum time on treatment			
3 years	-£3,326	0.159	Vedo. dominates

Table 111. Scenario Analysis – Versus Adalimumab – TNF-Naïve Population

Input(s)	Incremental Costs	Incremental QALYs	ICER
Base case	£918	0.138	£6,634
Time horizon			
1 year	£3,667	0.027	£135,406
Lifetime	-£1,997	0.279	Vedo. dominates
Utility weight source			
Punekar et al. (2010)	£918	0.275	£3,342
Arseneau et al. (2006)	£918	0.288	£3,190
Tsai et al. (2008)	£918	0.265	£3,459
Mortality risk			
No UC-related mortality risk	£875	0.136	£6,452
Vedolizumab response assessment			
Week 10	£2,907	0.138	£21,006
Maximum time on treatment			
3 years	£6,556	0.130	£50,607

Table 112. Scenario Analysis – Versus Golimumab – TNF-Naïve Population

Input(s)	Incremental Costs	Incremental QALYs	ICER
Base case	-£1,312	0.108	Vedo. dominates
Time horizon			
1 year	£952	0.018	£51,918
Lifetime	-£3,490	0.213	Vedo. dominates
Utility weight source			
Punekar et al. (2010)	-£1,312	0.215	Vedo. dominates
Arseneau et al. (2006)	-£1,312	0.221	Vedo. dominates
Tsai et al. (2008)	-£1,312	0.208	Vedo. dominates
Mortality risk			
No UC-related mortality risk	-£1,344	0.106	Vedo. dominates
Vedolizumab response assessment			
Week 10	£747	0.108	£6,916
Maximum time on treatment			
3 years	£2,359	0.152	£15,548

TNF-Failure Population

Table 113. Scenario Analysis – Versus Conventional Therapy – TNF-Failure Population (Trial-Based Estimates)

Input(s)	Incremental Costs	Incremental QALYs	ICER
Base case	£5,839	0.090	£64,999
Time horizon			
1 year	£7,037	0.031	£230,671
Lifetime	£5,227	0.118	£44,132
Utility weight source			
Punekar et al. (2010)	£5,839	0.163	£35,830
Arseneau et al. (2006)	£5,839	0.165	£35,355
Tsai et al. (2008)	£5,839	0.155	£37,589
Mortality risk			
No UC-related mortality risk	£5,813	0.088	£66,025
Vedolizumab response assessment			
Week 10	£8,097	0.145	£55,763
Maximum time on treatment			
3 years	£7,757	0.141	£55,149

Table 114. Scenario Analysis – Versus Surgery – TNF-Failure Population (Trial-Based Estimates)

Input(s)	Incremental Costs	Incremental QALYs	ICER
Base case	-£29,422	1.182	Vedo. dominates
Time horizon			
1 year	-£11,213	0.222	Vedo. dominates
Lifetime	-£46,373	1.704	Vedo. dominates
Utility weight source			
Punekar et al. (2010)	-£29,422	-0.434	£67,866*
Arseneau et al. (2006)	-£29,422	-1.327	£22,164*
Tsai et al. (2008)	-£29,422	-0.823	£35,732*
Mortality risk			
No UC-related mortality risk	-£29,235	1.201	Vedo. dominates
Vedolizumab response assessment			
Week 10	-£28,091	1.272	Vedo. dominates
Maximum time on treatment			
3 years	-£27,505	1.233	Vedo. dominates

* Results are in the south-west quadrant of the cost-effectiveness plane: the ICER represents the cost-effectiveness of surgery compared with vedolizumab.

7.6.10 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 TNF-naïve population.

In a mixed patient population, at an acceptability threshold of £30,000 per QALY, the probability of vedolizumab being cost-effective is about 40%. In the TNF-naïve

population, this is approximately 95%. Compared with adalimumab, in a TNF-naïve population, the probability of the ICER being less than £30,000 is about 90%.

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. In particular, the basecase utility value for patients with moderate to severe disease is 0.68. The literature, to date has used a value in the range of 0.3 to 0.4. If the utility associated with moderate to severe disease is in that range, the cost-effectiveness of vedolizumab is considerably improved.

7.6.11 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.

7.7 Validation

7.7.1	**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 Table 82). We also compared the results to previous economic analyses (see Section 7.9.1).

7.8 Subgroup 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 subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups 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).

7.8.1	**Please specify whether analysis of subgroups was undertaken and how these subgroups 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, adalimumab and golimumab only in patients that were TNF-naïve.

Subgroups of patients defined by failure to TNF antagonist therapy were included in the scope of this appraisal. Patients randomized to the GEMINI I study were stratified by TNF antagonist therapy and the outcomes data from the trial were analysed by these strata.

7.8.2	**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.

7.8.3	**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 comparators in subgroups defined by prior TNF antagonist therapy outcomes.

7.8.4	**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 subgroups, results have been presented, above, by subgroup.

7.8.5	**Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 5.**

No obvious subgroups or subgroups identified in the decision problem have been excluded from the analysis.

7.9 Interpretation of economic evidence

7.9.1	**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?**

When set to similar settings, our model results for an anti-TNF–naive population are consistent with the 10-year results presented by Tsai and colleagues (2008). These authors found anti-TNF–naive infliximab patients to incur 4.591 QALYs compared with 3.838 QALYs for patients on conventional therapy over a 10-year period. Similarly, the NICE HTA submission for infliximab estimated 4.583 QALYs over 10 years for patients treated with infliximab and 3.824 QALYs for patients treated with conventional therapy (NICE, 2008). When our model uses the utility weights presented in by Tsai and colleagues (2008), and sets mortality to be independent of UC health state, we find QALYs of 4.650 for infliximab and 4.156 for conventional therapy.

Table 115. Estimated QALYs for Infliximab Treated UC Patients from Different Cost-Effectiveness Models

	Estimated QALYs	
Model	**Infliximab**	**Conventional Therapy**
Tsai et al. (2008)	4.591	3.838
Infliximab submission to NICE (2008)	4.583	3.824
Vedolizumab model (TNF-Naïve Population using same settings as infliximab models)	4.650	4.156

7.9.2 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.

7.9.3 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 a large, international, well-controlled clinical trial 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, adalimumab and golimumab in the TNF-naïve population demonstrating similar outcomes for the agents, and an improvement in discontinuation due to adverse events 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 very 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 other. Utilities in

the model are based upon the EQ-5D data in the GEMINI I study and are consistent with the reference case. Alternative utilities are explored in scenario analyses.

The model compares vedolizumab with all of the comparators in the scope, although the assessment comparing vedolizumab with surgery is limited by the relative scarcity of data on the outcomes and costs associated with surgery for UC. However, it is clear from the literature and expert clinical opinion that surgery is considered a last resort treatment and one associated with considerable morbidity.

Patients rarely gain normal life after a colectomy and can suffer from complications such as postoperative bleeding, faecal incontinence, depression, sexual dysfunction, female infertility, pouchitis, pouch leakage, pelvic abscesses, pouch fistulae, small bowel obstruction, and anastomotic stricture.

Even with a 'successful' pouch, patients rarely return to normal life. In cohort analyses, more than half the patients with IPAA had between 5-10 bowel movements per day, soiling or seepage at night was reported between 15%-25%. Up to 35% have reported ongoing need for continuous or occasional IBD-related medication

In a recent meta-analysis of seven studies, female fertility in 481 patients with IPAA was compared with that in 411 patients with UC without IPAA. In the surgical group, the risk of infertility was increased from 15% to 48%. In online survey of 424 patients, more than half the women survey (66%) reported difficulty conceiving post surgery while 31% said their sexual life was worse after surgery compared to before surgery

Whilst the model estimates that the utility associated with post-surgical remission is 0.60 and the utility associated with post-surgical complications is 0.42 it is likely that further research and more detailed assessment of post-surgical health states could inform this comparison in more detail.

7.9.4 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.

Brief introduction

A model was developed in Microsoft Excel to estimate the impact on health care budgets in the United Kingdom (UK) over a 5-year period of introducing vedolizumab b. The model calculated the budget impact for a population of patients with moderately to severely active UC who have had an inadequate response to, lost response to, or are intolerant to either a conventional therapy or a TNF-α antagonist.

The budget-impact model used the following key outputs:

- Total costs of treating patients with UC over a 5-year period with current treatments, including costs of treatments only or costs of both treatments and health care monitoring (these may include adalimumab, infliximab, golimumab, conventional therapy, and surgery)
- Incremental costs of introducing VEDO into the formulary over a 5-year period

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 subgroups considered. Also present results for the subsequent 5 years.

In 2014, 4,506 patients are eligible for treatment with VEDO in England and Wales. The total adult population for England and Wales is 56,948,200 (ONS, 2013) and the estimated prevalence of UC is 0.24%. This meant a total of 136,676 people had UC. The prevalence of moderate and severe UC is 52.33% of the UC population and 6.3% (4,506) of those are eligible for treatment. Over the next 5 years, it is assumed

that the projected prevalence of moderate to severe UC in England and Wales will remain at 52.33% of the total UC population. With a projected year on year increase in the total population of England and Wales, and the projected prevalence rate remaining at 0.24% there would be a yearly increase in the number of UC patients eligible for treatment with biologics. A five year projection for the market authorised (eligible) patient population is presented below.

Table 116. 5 year projection of VEDO market authorised UC patients

Year	2014	2015	2016	2017	2018
Total populationa	56,948,200	57,341,143	57,725,328	58,112,088	58,489,817
Prevalence rate (of total population)[a]	0.24%	0.24%	0.24%	0.24%	0.24%
Proportion of moderate to severe patients (biologic eligible in % of treated)[b]	52.33%	52.33%	52.33%	52.33%	52.33%
Proportion of patients treated with Biologic[c]	6.3%	8.9%	12.1%	14.3%	16.2%
Proportion of patients with moderate to severe UC	4,506	6,409	8,772	10,437	11,900

a= ONS, 2013, b= global assumption, c = UK assumption based on positive NICE HTA / MTA

8.2 What assumption(s) were made about current treatment options and uptake of technologies?

In addition to VEDO, it is assumed that the treatment options available to the eligible population are Adalimumab, Infliximab, and Golimumab. Takeda estimates that 82.3% of all patients, including patients with mild disease, are treated with a biologic. The treatment rate is 100% in moderate and severe patients. 6.3% of the moderate to severe UC patient population fail conventional therapy and are therefore eligible for treatment in 2014. The tables below show current uptake of existing technologies and the projected market uptake of VEDO.

Table 117. Current uptake of existing technologies

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	2014	2015	2016	2017	2018
Adalimumab	32.9%	37.9%	40.3%	40.3%	40.4%
Infliximab	65.9%	59.2%	54.4%	53.4%	52.1%
Golimumab	1.3%	2.9%	5.4%	6.4%	7.6%

Source: Informa UK, 2013, with market share data adjusted to reflect shares for those being treated with biologic therapy.

Table 118. Table 1: Projected uptake for VEDO

	2014	2015	2016	2017	2018
VEDO	0.1%	9.1%	19.7%	26.4%	30.0%

8.3 What assumption(s) were made about market share (when relevant)?

The 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 VEDO (VEDO) in the population of patients with moderately to severely active UC who have had an inadequate response to conventional therapy and who are being treated with a biologic therapy.

Table 119. Current market share estimates

Comparator	2014	2015	2016	2017	2018
Adalimumab	32.9%	37.9%	40.3%	40.3%	40.4%
Infliximab	65.9%	59.2%	54.4%	53.4%	52.1%
Golimumab	1.3%	2.9%	5.4%	6.4%	7.6%

Source: Informa UK, 2013, with market share data adjusted to reflect shares for those being treated with biologic therapy.

The base-case budget impact analysis assumed VEDO will take 30% of its market share from adalimumab, 60% from infliximab, and 10% from golimumab. The table below shows redistribution of the market share once VEDO is introduced taking yearly population increases into consideration.

Table 120. Market share estimates after introduction of VEDO

Drug	2014	2015	2016	2017	2018
VEDO	0.1%	9.1%	19.7%	26.4%	30.0%
Adalimumab	32.8%	35.2%	34.4%	32.3%	31.4%
Infliximab	65.8%	53.8%	42.5%	37.5%	34.1%
Golimumab	1.3%	2.0%	3.4%	3.7%	4.6%

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 administration cost of VEDO and cost accrued from treatment of VEDO related adverse events. The cost of surgery and postsurgical complications are also taken into consideration and since approximately 40% of patients require a stoma, the cost of stoma appliances are included. 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 121. Cost of treatments

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]
Golimumab	per 50 mg vial	£762.97[a]	£0.00[d]
VEDO	per 300 mg vial	[redacted]	£308.00[c]

Source: a = BNF, August 2014, b = Takeda Data on File, c = Assumed the cost of administering VEDO was equal to the cost for Infliximab administration, d = Assumptions, e = PbR mandatory tariff 2013/14 FZ37F

Table 122. 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 was £12,917 and was obtained from published literature (Buchanan et al., 2011) and inflated using the Pay and Prices Index (Curtis, 2012). It was assumed that 40% of patients require a stoma (Buchanan et al., 2011). The cost of stoma appliances was estimated at £445 and was obtained from published literature (Buchanan et al., 2011). The cost of stoma nurse was estimated at £259, based on six visits to a specialist nurse. Unit cost per visit was obtained from the NHS Reference Costs.

Postsurgical complication cost

The model incorporates the costs of postsurgical complications, so the overall cost of surgery depends on the outcome of surgery. The typical postsurgical complications

include postoperative sepsis, postoperative wound infections, pouch failure, and pouchitis (National Institute for Health and Care Excellence [NICE], 2007). The unit cost for postsurgical complications are presented in the table below.

Table 123. Postsurgical complications cost

Resource Item	Unit Cost[a]	Postsurgical Outcome	
		Complication	Remission
Consultant visit	**£115.48**	**1.75**	**1.5**
Hospitalisation episode	£2,574.02	3.25	0
Blood tests	£2.95	3.25	1.5
Elective endoscopy	£635.68	0.65	1.25
Emergency endoscopy	£950.00	0.125	0.5
Total cost per year		**£9,109**	**£1,447**

a= NHS reference cost 2012/2013

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, VEDO in the base case analysis led to resource savings in the costs associated with the management of drug-related adverse events. In other scenario analysis carried out, resource saving were also seen in the cost of surgery and other disease related cost (disease monitoring and symptomatic treatment). Estimates for resource saving over the 5 years period in this analysis after VEDO has been introduced are shown in the table below.

Table 124. Estimates of resource savings.

Type of Cost	2014	2015	2016	2017	2018
Drug related adverse events	-£766	-£82,277	-£244,401	-£388,998	-£502,609
Cost of surgery	–£349	–£37,431	–£111,187	–£176,969	–£228,654

Other disease-related costs	–£936	–£100,497	–£298,525	–£475,143	–£613,913

8.7 What is the estimated annual budget impact for the NHS in England and Wales?

In the base case analysis, the introduction of VEDO is likely to increase drug expenditure by £8,037 in the first year after launch and by £12,782,541 cumulatively over the 5 years considered in this analysis. A breakdown of the yearly budget impact is presented below.

Table 125. Base case estimated annual VEDO budget impact for the NHS in England and Wales.

Type of Cost	2014	2015	2016	2017	2018
Drug acquisition costs	£3,940	£422,915	£1,256,258	£1,999,506	£2,583,481
Drug administration	£4,864	£522,088	£1,550,849	£2,468,388	£3,189,304
Drug related AEs	-£766	-£82,277	-£244,401	-£388,998	-£502,609
Total annual costs	£8,037	£862,726	£2,562,706	£4,078,896	£5,270,176
Cumulative costs	£8,037	£870,763	£3,433,469	£7,512,365	£12,782,541

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 other disease-related costs associated with disease monitoring and symptomatic treatment were also included. The budget impact analysis results show that the introduction of VEDO is likely to reduce drug expenditure by £6,751 in the first year after launch and by £10,738,937 cumulatively over the 5 year period considered in this analysis. A yearly breakdown is presented below.

Table 126. Sensitivity analysis estimated annual VEDO budget impact for the NHS

Type of Cost	2014	2015	2016	2017	2018

Drug acquisition costs	£3,940	£422,915	£1,256,258	£1,999,506	£2,583,481
Drug administration	£4,864	£522,088	£1,550,849	£2,468,388	£3,189,304
Drug related AEs	-£766	-£82,277	-£244,401	-£388,998	-£502,609
Cost of surgery	-£349	-37,431	-111,187	-176,969	-228,654
Other disease-related costs	-£936	-100,497	-298,525	-475,143	-613,913
Total annual costs	£6,752	£724,798	£2,152,994	£3,426,784	£4,427,609
Cumulative costs	£6,752	£731,550	£2,884,544	£6,311,328	£10,738,937

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. The symptoms associated with UC 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 may be saved or better spent elsewhere. Also no equity issues are envisaged with the administering of VEDO.

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