NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

Ulcerative colitis (moderate, severe) - infliximab (review TA140), adalimumab (review TA262) & golimumab (2nd line) [ID695]

Manufacturer submission of evidence:

Infliximab (Remicade®)

MSD

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1. Executive Summary

1.1. Background

Ulcerative colitis (UC) is a chronic and debilitating condition that affects ~162,000 patients across the UK. The disease is characterised by diarrhoea, rectal bleeding, abdominal pain, and mucosal ulceration. The cause of UC is unknown and the condition can develop at any age, with peak incidence between 15 and 25 years of age, and a second, smaller peak between 55 and 65 years of age. UC is a lifelong disease that typically follows a relapsing-remitting pattern and is associated with significant morbidity, particularly if controlled poorly. Current medical approaches focus on treating active disease to address symptoms, to improve quality of life, and to maintain remission.

For 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, options for further treatment are currently limited and often involve surgical intervention (colectomy).

Colectomy is associated with unintended sequelae, including, but not limited to pouchitis, reduced fertility, nocturnal faecal incontinence, and pouch failure. Therefore, patients and their physicians will often want to delay or avoid surgery. Biologic therapy is an effective alternative but is not currently recommended for use by NICE for the treatment of patients with moderately to severely active UC.

Remicade® (henceforth referred to as infliximab), a chimeric human-murine monoclonal antibody, binds with high affinity to both soluble and transmembrane forms of tumour necrosis factor-alpha (TNF-α), thereby neutralising its activity. It is one of only three biologic drugs licensed for the treatment of moderately to severely active UC in the UK.

Infliximab, which is administered via intravenous (IV) infusion, has been shown to be effective in inducing and maintaining clinical response, clinical remission, and mucosal healing in patients with moderately to severely active UC.

Infliximab provides an efficacious option for the treatment of moderately to severely active UC and represents a cost-effective treatment in comparison with non-biologic standard of care (colectomy).

1.2. The Technology

The key features of infliximab are presented in Table 1:

Table 1: Key features of infliximab

Approved name	Infliximab
Brand name	Remicade®
Marketing status	European Commission granted marketing authorisation valid throughout the European Union on 28th February 2006
Pharmacological action	Chimeric human-murine monoclonal antibody that binds with high affinity to both soluble and transmembrane forms of TNF-α but not to lymphotoxin α (TNF-β)
Formulation	One 100mg vial of powder for reconstitution
Dosing frequency	5mg/kg given as an IV infusion followed by additional 5mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter
Average length of a course of treatment	Available data suggest that the clinical response is usually achieved within 14 weeks of treatment, i.e. three doses. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within this time period[1]
Indications	*Adult ulcerative colitis:* Infliximab 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-MP or AZA, or who are intolerant to or have medical contraindications for such therapies *Paediatric ulcerative colitis:* Infliximab is indicated for treatment of severely active UC, in children and adolescents aged 6 to 17 years, who have had an inadequate response to conventional therapy including corticosteroids and 6-MP or AZA, or who are intolerant to or have medical contraindications for such therapies *Rheumatoid arthritis:* Infliximab, in combination with MTX, is indicated for the reduction of signs and symptoms as well as the improvement in physical function in: • adult patients with active disease when the response to DMARDs, including MTX, has been inadequate • adult patients with severe, active and progressive disease not previously treated with MTX or other DMARDs In these patient populations, a reduction in the rate of the progression of joint damage, as measured by X-ray, has been demonstrated *Psoriatic arthritis:* Infliximab is indicated for treatment of active and progressive psoriatic arthritis in adult patients when the response to previous DMARD therapy has been inadequate. Infliximab should be administered: • in combination with MTX • or alone in patients who show intolerance to MTX or for whom MTX is

	contraindicated *Ankylosing spondylitis:* Infliximab is indicated for treatment of severe, active ankylosing spondylitis, in adult patients who have responded inadequately to conventional therapy *Adult Crohn's disease:* Infliximab is indicated for: • treatment of moderately to severely active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies • treatment of fistulising, active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage, and immunosuppressive therapy) *Paediatric Crohn's disease:* Infliximab is indicated for treatment of severe, active Crohn's disease, in children and adolescents aged 6 to 17 years, who have not responded to conventional therapy including a corticosteroid, an immunomodulator and primary nutrition therapy; or who are intolerant to or have contraindications for such therapies Infliximab has been studied only in combination with conventional immunosuppressive therapy *Psoriasis:* Infliximab is indicated for treatment of moderate to severe plaque psoriasis in adult patients who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including ciclosporin, MTX, or psoralen combined with ultraviolet A

6-MP, 6-mercaptopurine; AZA, azathioprine; DMARD, disease-modifying anti-rheumatic drug; IV, intravenous; MTX, methotrexate; TNF-α, tumour necrosis factor-alpha; TNF-β, tumour necrosis factor-beta; UC, ulcerative colitis.

1.3. Clinical Effectiveness

The efficacy and safety of infliximab was evaluated in two randomised, double-blind, placebo-controlled clinical studies in adult patients and long-term extension studies.

1.3.1. ACT 1 and ACT 2

ACT 1 and ACT evaluated the efficacy of infliximab for induction and maintenance therapy in adults with moderately to severely UC despite treatment with concurrent medications. Eligible patients (364 in ACT 1 and 364 in ACT 2) were randomly assigned in a 1:1:1 ratio to receive IV infusions of infliximab at a dose of 5mg/kg, 10mg/kg, or placebo at weeks 0, 2, and 6 and then every 8 weeks through week 46 in ACT 1 or week 22 in ACT 2. Patients were followed for 54 weeks in ACT 1 and 30 weeks in ACT 2.

The key efficacy outcomes included clinical response, defined as a decrease from baseline in the total Mayo score of ≥3 points and ≥30%, with an accompanying decrease in the sub-score for rectal bleeding of at least 1 point or an absolute score for rectal bleeding of 0 or 1, and clinical remission, defined as a total Mayo score of 2 points or lower, with no individual sub-score exceeding 1 point. Mucosal healing was also measured, and was defined as an absolute sub-score for endoscopy of 0 or 1. Additional outcomes included sustained clinical response, sustained clinical remission, and corticosteroid-free remission.

Clinical response, clinical remission, and mucosal healing were assessed at weeks 8 and 30 in both studies and at week 54 in ACT 1. Patients who had a clinical response or who were in clinical remission at each time point were considered to have a sustained clinical response or to be in sustained clinical remission, respectively. In both studies, AEs and concomitant medications were recorded at each visit.

In ACT 1 at week 8, 84 of 121 (69.4%) of patients in the group receiving 5mg/kg of infliximab and 75 of 122 (61.5%) of patients in the group receiving 10mg/kg of infliximab had a clinical response, compared with 45 of 121 (37.2%) of patients in the placebo group ($p<0.001$ for both comparisons). In ACT 2 at week 8, 78 of 121 patients (64.5%) of patients in the group receiving 5mg/kg of infliximab and 83 of 120 (69.2%) of patients in the group receiving 10mg/kg of infliximab had a clinical response, compared with 36 of 123 (29.3%) of patients in the placebo group ($p<0.001$ for both comparisons).

In both studies, the proportion of patients who had a clinical response or remission at weeks 8 and 30, and at week 54 in the ACT 1 trial, were higher by a factor of between 1.7 to more than 2.0 in the infliximab groups than in the placebo groups.

The proportion of patients with sustained clinical response or sustained clinical remission was significantly higher in the infliximab groups than in the placebo groups. Furthermore, the partial Mayo scores in both studies provide evidence of clinical improvement as early as week 2. Mucosal healing at weeks 8 and 30 in both studies and at week 54 in ACT 1 occurred in significantly more patients in the infliximab groups than in the placebo groups ($p\leq0.009$ for all comparisons). The proportion of patients who were in clinical remission and had discontinued corticosteroids at week 30 in both studies and at week 54 in ACT 1 was higher in the infliximab groups than in the placebo groups.

These studies demonstrate that an induction regimen of three doses of infliximab followed by maintenance infusions every 8 weeks in patients with moderately to severely active UC is superior to placebo in achieving clinical response and remission, mucosal healing, and corticosteroid-sparing effects during 30 to 54 weeks of therapy.

1.3.2. ACT 1 and ACT 2 Extension Studies

The aim of the extension studies was to evaluate long-term efficacy, quality of life, and safety in patients with UC who received infliximab during the original ACT 1 and ACT 2 studies.

Patients who, in the opinion of the investigator, could benefit from continued treatment were eligible to enter the extension study after completing their main study therapy and evaluations through weeks 46 and 54 (ACT 1), or weeks 22 and 30 (ACT 2). In the extension studies, infliximab treatment continued for a maximum of 3 years or until marketing authorisation was obtained and the drug was commercially available in that country. The first extension study infusion (Extension week 0, E0) was to occur at week 54 (ACT 1) or week 30 (ACT 2).

Disease activity was evaluated using the Physician's Global Assessment (PGA). PGA is a four point sub-score (0=normal, 1=mild, 2=moderate, and 3=severe) of the total Mayo score. At each visit, data regarding the use of corticosteroids to treat UC symptoms in the past 8 weeks were also collected. Patients were evaluated every 8 weeks up to 3 years (week E152).

A total of 291 patients participated in the long-term extension studies: 229 in the infliximab group and 62 in the placebo group. Overall, 230 patients received at least one infliximab infusion during the extension studies (including one patient in the placebo group who inadvertently received one infliximab infusion) and were evaluated for safety; 229 infliximab-treated patients were included in the efficacy analyses and had a mean (± standard deviation [SD]) duration of follow-up of 113 (±42) weeks (range 4-184 weeks; median 128 weeks; interquartile range [IQR] 96-144 weeks).

The proportion of patients who had scores indicative of no disease or mild disease (scores of 0 or 1) was maintained during the extension studies. At week E0, the proportion of patients with no disease or mild disease was 76.5% and ranged from 91.3%-94.3% between weeks E24 and E128. Twenty patients remained at week E152, of whom 18 (90.0%) had no disease or mild disease. The proportion of patients who had scores indicative of no disease (score of 0) was also maintained during the extension studies. At weeks E0 and E24, the proportions of patients with

no disease were 42.0% and 55.6%, respectively, ranging from 62.4%-72.2% between weeks E48 and E128. At week E152, 13 (65.0%) had no disease.

The proportion of patients with no disease or mild disease who did not use corticosteroids to treat their UC within the past 8 weeks ranged from 70.9%-90.0% and the proportion of patients with no disease who did not use corticosteroids to treat their UC ranged from 46.4%-65.0% between weeks E8 and E152. The proportion of patients who did not use corticosteroids to treat their UC within the past 8 weeks increased through the duration of the extension studies.

The long-term results from these extensions studies are consistent with previously-reported data which describe sustained clinical improvement and overall favourable safety profiles in patients who received maintenance infliximab therapy. Patients with moderately to severely active UC who achieved clinical benefit with infliximab therapy in the ACT studies maintained clinical benefit for up to an additional 3 years of infliximab therapy.

1.4. Cost-Effectiveness

The basecase results for all comparisons are shown in Table 2. The incremental cost relative to standard non-biologic therapy (colectomy) over a 10 year time horizon is £27,130, and in combination with the incremental quality-adjusted life year (QALY) gain of 0.72, an incremental cost-effectiveness ratio (ICER) of £37,682 was obtained.

Table 2: Basecase cost-effectiveness results

	Incremental discounted total direct cost				Incremental discounted QALYs				Incremental cost-effectiveness ratio			
	Det. value	Prob. value	95% CrI low	95% CrI high	Det. value	Prob. value	95% CrI low	95% CrI high	Det. value	Interpretation*	Prob. value	Interpretation*
Adalimumab 160/80/40mg vs. Standard non-biologic treatment (colectomy)	15,448	16,298	11,128	24,117	0.51	0.52	-0.16	1.30	30,319	Smaller NMB, hence not cost-effective	31,385	Smaller NMB, hence not cost-effective
Golimumab 200/100/50(100)mg vs. Standard non-biologic treatment (colectomy)	14,964	15,523	11,512	21,156	0.56	0.57	-0.11	1.39	26,569	Greater NMB, hence cost-effective	27,163	Greater NMB, hence cost-effective
Infliximab 5mg/kg vs. Standard non-biologic treatment (colectomy)	27,130	28,365	19,010	41,122	0.72	0.74	-0.08	1.72	37,682	Smaller NMB, hence not cost-effective	38,307	Smaller NMB, hence not cost-effective
Golimumab 200/100/50(100)mg vs. Adalimumab 160/80/40mg	-484	-776	-9,148	6,107	0.05	0.05	-0.10	0.24	Dominant	Greater NMB, hence cost-effective	Dominant	Greater NMB, hence cost-effective
Infliximab 5mg/kg vs. Adalimumab 160/80/40mg	11,682	12,066	626	25,865	0.21	0.22	0.00	0.58	55,507	Smaller NMB, hence not cost-effective	54,564	Smaller NMB, hence not cost-effective
Infliximab 5mg/kg vs. Golimumab 200/100/50(100)mg	12,166	12,842	2,493	25,846	0.16	0.17	-0.05	0.52	77,599	Smaller NMB, hence not cost-effective	75,998	Smaller NMB, hence not cost-effective

* Willingness-to-pay ratio of £30,000. CrI, credible interval; Det., deterministic; NMB, net monetary benefit; Prob., probabilistic; QALY, Quality-Adjusted Life Year; vs., versus.

1.5. Conclusion

Clinical and adverse event (AE) randomised-controlled trial (RCT) evidence supports the conclusion that patients would benefit substantially from an on-going recommendation of infliximab for the treatment of moderately to severely active UC.

A network meta-analysis (NMA) provided evidence that infliximab was statistically significantly superior to adalimumab after induction for mucosal healing. Infliximab and golimumab were shown to have similar efficacy profiles. The safety profiles of infliximab, golimumab, and adalimumab were generally similar across outcomes. Therefore, infliximab provides an equally effective treatment option for patients with moderately to severely active UC for whom IV treatment is more appropriate.

The ICER for infliximab versus standard non-biologic treatment (colectomy) is £37,682. The positive impact of infliximab in terms of reducing the Burden of Illness and mitigating the Wider Societal Impact of the condition represents additional value for consideration by the committee. Taking into account the shortfall in quality of life, and in the ability of people to contribute to society as a result of their experience with moderately to severely active UC, it is likely that infliximab represents a cost-effective treatment in first-line biologic treatment of UC.

2. Description of Technology

2.1. Brand Name, Generic Name, and Therapeutic Class

Infliximab is a TNF-α inhibitor and part of the biologic disease-modifying anti-rheumatic drug (DMARD) class. It is available in a 100mg vial of powder for reconstitution.

2.2. Mechanism of Action

Infliximab is a chimeric human-murine monoclonal antibody that binds with high affinity to both soluble and transmembrane forms of TNF-α but not to lymphotoxin α (TNF-β).

2.3. Marketing Authorisation

The European Commission granted a marketing authorisation valid throughout the European Union for infliximab on 28th February 2006.

2.4. Indications

The approved indications for infliximab are as follows:

Adult ulcerative colitis:
Infliximab 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-MP or AZA, or who are intolerant to or have medical contraindications for such therapies

Paediatric ulcerative colitis:
Infliximab is indicated for treatment of severely active UC, in children and adolescents aged 6 to 17 years, who have had an inadequate response to conventional therapy including corticosteroids and 6-MP or AZA, or who are intolerant to or have medical contraindications for such therapies

Rheumatoid arthritis:

Infliximab, in combination with methotrexate (MTX), is indicated for the reduction of signs and symptoms as well as the improvement in physical function in:

- adult patients with active disease when the response to disease-modifying anti-rheumatic drugs (DMARDs), including MTX, has been inadequate
- adult patients with severe, active and progressive disease not previously treated with MTX or other DMARDs

In these patient populations, a reduction in the rate of the progression of joint damage, as measured by X-ray, has been demonstrated

Psoriatic arthritis:

Infliximab is indicated for treatment of active and progressive psoriatic arthritis in adult patients when the response to previous DMARD therapy has been inadequate. Infliximab should be administered:

- in combination with MTX
- or alone in patients who show intolerance to MTX or for whom MTX is contraindicated

Ankylosing spondylitis:

Infliximab is indicated for treatment of severe, active ankylosing spondylitis, in adult patients who have responded inadequately to conventional therapy

Adult Crohn's disease:

Infliximab is indicated for:

- treatment of moderately to severely active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies
- treatment of fistulising, active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage, and immunosuppressive therapy)

Paediatric Crohn's disease:

Infliximab is indicated for treatment of severe, active Crohn's disease, in children and adolescents aged 6 to 17 years, who have not responded to conventional therapy including a

corticosteroid, an immunomodulator and primary nutrition therapy; or who are intolerant to or have contraindications for such therapies

Infliximab has been studied only in combination with conventional immunosuppressive therapy

Psoriasis:

Infliximab is indicated for treatment of moderate to severe plaque psoriasis in adult patients who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including ciclosporin, MTX, or psoralen combined with ultraviolet A

2.5. Costs

Table 3: Cost information for infliximab

Pharmaceutical formulation	One 100mg vial of powder for reconstitution
Acquisition cost (excluding Value Added Tax (VAT))	£419.62
Method of administration	Intravenous infusion
Doses	5mg/kg
Dosing frequency	5mg/kg given as an intravenous infusion followed by additional 5mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter
Average length of a course of treatment	Available data suggest that the clinical response is usually achieved within 14 weeks of treatment, i.e. three doses. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within this time period1
Average cost of a course of treatment	For an average patient weight of 78kg[2]: Cost in year 1: £13,427.84 Cost in subsequent years: £10,070.88
Dose adjustments	Not applicable

2.6. Additional Tests, Investigations, and Monitoring

Tests, investigations, precautions, and monitoring for infliximab are consistent with those for all other TNF-α inhibitors.

Treatment with infliximab is contraindicated in patients with tuberculosis (TB) or other severe infections such as sepsis, abscesses, and opportunistic infections and in patients with moderate or severe heart failure (NYHA class III/IV) and in patients with a history of hypersensitivity to infliximab, to other murine proteins, or to any of the following excipients[1]:

- Sucrose
- Polysorbate 80

- Monobasic sodium phosphate
- Dibasic sodium phosphate

3. Context

Ulcerative colitis is a chronic inflammatory disease of the colon, which is characterised by diarrhoea, rectal bleeding, abdominal pain, and mucosal ulceration. The cause of UC is unknown and the condition can develop at any age, with peak incidence between 15 and 25 years of age, and a second, smaller peak between 55 and 65 years of age. UC is a lifelong disease that typically follows a relapsing-remitting pattern and is associated with significant morbidity, particularly if controlled poorly. Current medical approaches focus on treating active disease to address symptoms, to improve quality of life, and to maintain remission. Advice and support for patients is crucial, particularly for people facing the possibility of surgery.

3.1. Number of Patients Covered by the Indication in the UK

Ulcerative colitis is the most common type of inflammatory bowel disease (IBD) with an incidence of ~10 per 100,000 people annually, and a prevalence of ~240 per 100,000 in the UK[3]. Therefore, ~162,000 people in the UK have a diagnosis of UC[4]. The total number of patients with moderately to severely active UC is estimated at 41% of the total: ~66,000 people[5]. Of these, 15% are eligible for treatment with biologic therapy: ~10,000 people[5]. It would then be expected that a third of these patients would receive treatment with a biologic therapy: ~3300[5].

3.2. Relevant NICE Guidance

NICE has performed three technology appraisals of TNF-α inhibitors licensed for the treatment of moderately to severely active UC and has produced one clinical guideline:

TA140: Infliximab for sub-acute manifestations of ulcerative colitis[6]

Infliximab is not recommended for people with sub-acute, moderately to severely active UC. Sub-acute UC is defined as UC that would normally be managed without needing to stay in hospital overnight or having urgent surgery.

TA163: Infliximab for the treatment of acute exacerbations of ulcerative colitis[7]

Infliximab is recommended as a possible treatment for people with acute, severely active UC only if:

- Ciclosporin is considered inappropriate for them, or

- They are taking part in a research study (clinical trial)

TA262: Adalimumab for the treatment of moderate to severe ulcerative colitis (terminated appraisal)[8]

NICE was unable to recommend the use of adalimumab for the treatment of moderately to severely active UC because no evidence submission was received from the manufacturer or sponsor of the technology. This appraisal relates to people whose disease has responded inadequately to conventional therapy including corticosteroids and 6-MP or AZA, or who are intolerant to or have medical contraindications for such therapies.

CG166: Ulcerative colitis: management in adults, children and young people[3]

This guidance outlines treatment options for inducing remission in patients with mild to moderate UC (two-step therapy dependent on the extent and location of disease, comprising aminosalicylates e.g. 5-aminosalicylate [5-ASA] and corticosteroids) and for patients with acute, severe UC (evaluation of surgical intervention and two-step therapy comprising corticosteroids and ciclosporin, and infliximab where ciclosporin is inappropriate). For the maintenance of remission, CG166 recommends the use of 5-ASA and AZA or 6-MP.

3.3. Current Clinical Practice

There is no cure for UC; therefore, timely diagnosis and treatment strategies that control symptoms are crucial. Currently, patients with moderately to severely active UC are treated initially with conventional therapies (including thiopurines [AZA, 6-MP] and corticosteroids). Where patients are contraindicated to these therapies or have an inadequate response, they would be eligible for a TNF-α inhibitor (as specified by the marketing authorisations of adalimumab, infliximab, and golimumab). If a TNF-α inhibitor is successful in inducing a clinical response, patients can either continue treatment with a TNF-α inhibitor in the maintenance setting or may be prescribed aminosalicylates (in combination with other conventional therapies)[7]. If patients are not prescribed a TNF-α inhibitor, they may undergo surgical intervention (colectomy).

3.4. Issues Relating to Current Practice

Infliximab has received a NICE recommendation for the treatment of moderately to severely active UC but only for induction treatment in patients with acute, severe UC (i.e. requiring hospitalisation)[7]. None of the TNF-α inhibitors licensed for the treatment of moderately to severely active UC has received a NICE recommendation outside of the acute, severe setting. This limits the treatment options available to patients when they have an inadequate response or contraindication to conventional therapies and accelerates the progression to surgery with its associated negative consequences (described in Section 3.5).

3.5. Comparators

Relevant comparators, as listed in the NICE scope for this appraisal, are standard clinical management (which may include a combination of thiopurines, corticosteroids, aminosalicylates, and surgical intervention) and other TNF-α inhibitors: adalimumab and infliximab. Calcineurin inhibitors (such as ciclosporin) are listed as a potential comparator but their use is only recommended in the acute, severe setting[3] which is outside the scope of this appraisal. Comparators are described in the following sections:

Thiopurines (AZA, 6-MP)

These drugs are purine anti-metabolites, which inhibit ribonucleotide synthesis and effect immunomodulation through altering cell signalling (via action on the Rac1 pathway) and consequently inducing T-cell apoptosis. Azathioprine is metabolised to 6-MP and subsequently to 6-thioguanine nucleotides. Thioguanine has been successfully used for the treatment of IBD, but caution is appropriate due to potential hepatotoxicity. Thiopurines are effective for both active disease and maintaining remission in UC.

Corticosteroids

This class of therapy includes a wide range of molecules delivered by a variety of methods including topical suppositories, enemas, oral tablets, and IV infusions. Many strategies attempt to maximise topical effects while limiting the systemic side effects of steroids e.g. raised blood pressure, raised blood sugar, reduced bone density, gastritis, and proximal muscle wasting. Intravenous corticosteroids are given in the event of UC flares requiring rapid control. Corticosteroids have powerful anti-inflammatory effects, but are not recommended as

maintenance therapy for UC because of their side effect profile and the potential for dependency.

Aminosalicylates (5-ASA)

These drugs are available in tablet, liquid, suspension, enema, or suppository forms, and act in a variety of ways to control the action of epithelial cells in releasing lipid mediators, cytokines, and other molecules. Aminosalicylates are prescribed as an alternative to TNF-α inhibitors in the maintenance setting.

Surgery

Surgery for UC is indicated for the following broad scenarios:

- Emergency surgery is infrequently undertaken for life-threatening complications such as toxic megacolon, colonic perforation, and massive haemorrhage
- Surgery is more commonly undertaken for acute or severe disease characterised by treatment refractoriness, frequent flare-ups, extra-colonic manifestations, chronic corticosteroid dependence, side effects/intolerance/complications from medications (in particular corticosteroids), or according to clinical judgment
- Epithelial dysplasia in biopsies or proven cancer may also necessitate surgery

Around one in four people with UC will require surgery at some point during their illness and epidemiologic studies have reported 10 year cumulative risks of colectomy ranging from 9%-21%[9,10]. Surgery may not be successful in the long-term and can result in potential complications requiring further intervention and/or hospitalisation; consultation with clinicians has indicated that complications occur in more than half of patients undergoing colectomy. For example, following colectomy with ileoanal pouch, patients are at risk for pouchitis (50% by 5 years), female infertility, nocturnal faecal incontinence, and pouch failure[10]. Pouch-related issues resulting from surgery require up to a third of patients to take medication to reduce stool frequency, though despite this, patients can still have a high level of bowel movements (~6 per day) and experience distressing soiling events (~25% of patients)[11].

TNF-α Inhibitors

TNF-α inhibitors are a class of biologic medicines targeted against TNF-α, a mediator of inflammation implicated in UC and other autoimmune conditions. TNF-α inhibitors are administered intravenously or subcutaneously and are licensed for the treatment of moderately to severely active UC in patients who have failed to respond to conventional therapy, in both the induction and maintenance settings.

Patients treated with TNF-α inhibitors benefit from delayed time to surgery and reduced surgical outcomes overall. One study of infliximab demonstrated that the cumulative incidence of colectomy through 54 weeks was 10% for infliximab and 17% for placebo (p=0.02), yielding an absolute risk reduction of 7%[10]. Compared with placebo, fewer UC-related hospitalisations and surgeries/procedures per 100 patient-years of treatment occurred with infliximab therapy: 40 versus 20 (p=0.003) and 34 versus 21 (p=0.03), respectively[10]. This trend has also been observed in a study of adalimumab; colectomy rates were reduced in responders to adalimumab compared to non-responders (14.7% vs. 42.9%, p=0.035), with a significantly reduced time free of colectomy in non-responders (148 days, 95% confidence interval [CI] 82.1-214.2) compared to responders (226 days, 95% CI 197.4-255.8) (p<0.01)[12].

4. Identification of Equality Issues

MSD do not anticipate any equality issues during this appraisal.

5. Clinical Evidence

5.1. Key Clinical Trial Data

The efficacy and safety of infliximab was evaluated in two randomised, double-blind, placebo-controlled clinical studies in adult patients with UC, and long-term extension studies.

5.1.1. ACT 1 and ACT 2[2]

The marketing authorisation for infliximab for the treatment of moderately to severely active UC was granted on the basis of two Phase 3 studies: ACT 1 and ACT 2. These were two randomised, double-blind, placebo-controlled studies which evaluated the efficacy and safety of infliximab for induction and maintenance therapy in adults with UC.

Study Design

In these studies eligible patients (with moderately to severely active UC despite treatment with concurrent medications) were randomly assigned in a 1:1:1 ratio to receive IV infusions of infliximab at a dose of 5mg/kg, 10mg/kg, or placebo at weeks 0, 2, and 6 and then every 8 weeks through week 46 in ACT 1 or week 22 in ACT 2. Patients were followed for 54 weeks in ACT 1 and 30 weeks in ACT 2.

Doses of concomitant medications remained constant except for corticosteroids, which were tapered by 5mg weekly after week 8 until a dose of 20mg per day was reached. Thereafter the dose was reduced by 2.5mg weekly until discontinuation.

Patients in both studies were evaluated at weeks 0, 2, 6, 8, 14, 22, and 30 for patients in both studies and at weeks 38, 46, and 54 in ACT 1. The Mayo score was determined at weeks 0, 8, and 30 for patients in both studies and at week 54 for patients in ACT 1. A partial Mayo score (Mayo score without endoscopy) was determined at all visits.

Clinical response was defined as a decrease from baseline in the total Mayo score of ≥3 points and ≥30%, with an accompanying decrease in the sub-score for rectal bleeding of at least 1 point or an absolute score for rectal bleeding of 0 or 1. Clinical remission was defined as a total Mayo score of ≤2, with no individual sub-score >1. Mucosal healing was defined as an absolute sub-score for endoscopy of 0 or 1.

Clinical response, clinical remission, and mucosal healing were assessed at weeks 8 and 30 in both studies and at week 54 in ACT 1. Patients who had a clinical response or who were in clinical remission at each time point were considered to have a sustained clinical response or to be in sustained clinical remission, respectively.

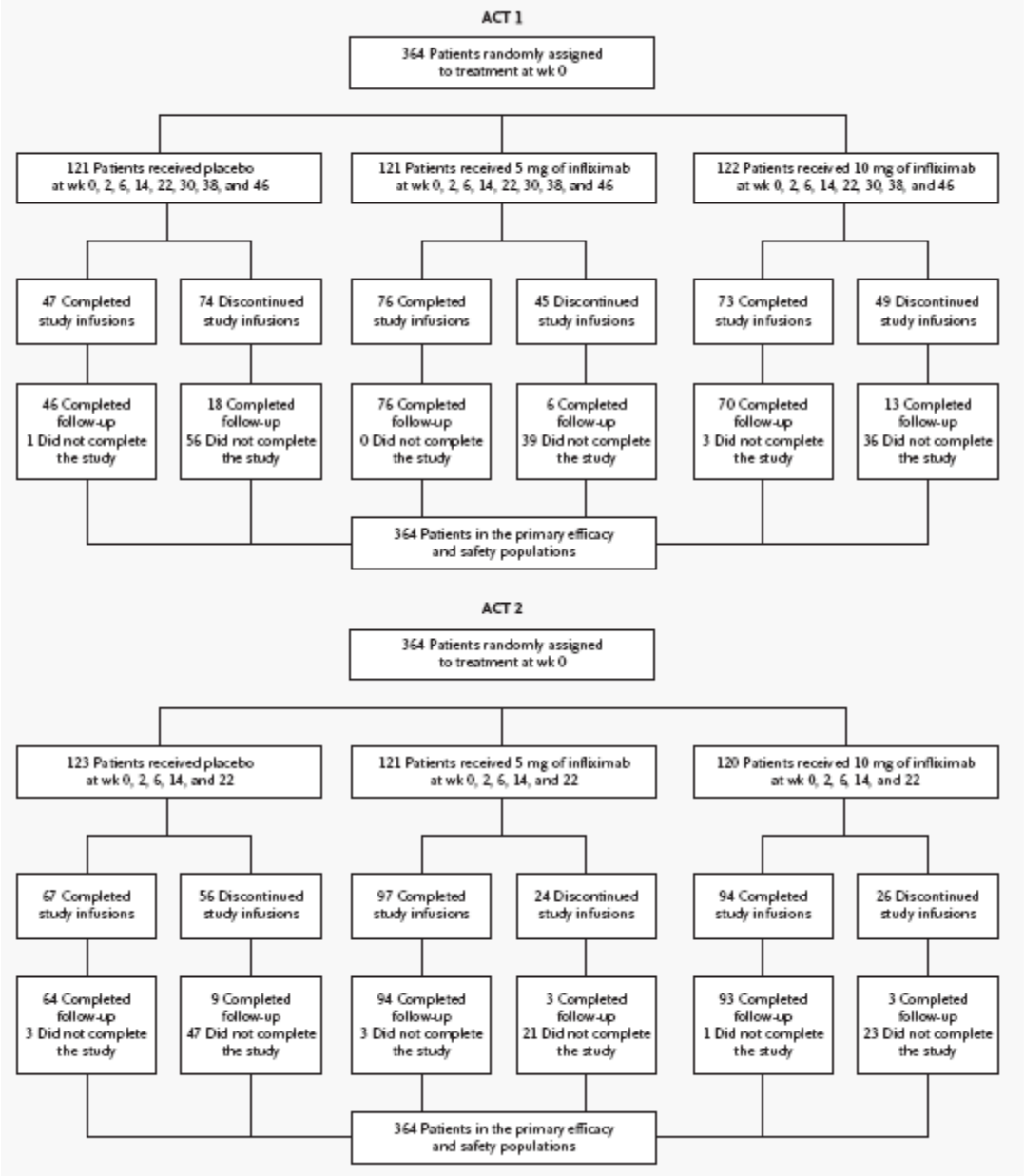
In both studies, AEs and concomitant medications were recorded at each visit. Serum specimens for the identification of antibodies against infliximab and anti-nuclear antibodies were collected at weeks 0 and 30 in both studies and at week 54 in ACT 1. Samples positive for anti-nuclear antibodies were tested for antibodies against double-stranded DNA.

Baseline Patient Characteristics

In ACT 1, 364 patients underwent randomisation: 121 were assigned to receive placebo, 121 to receive 5mg/kg of infliximab, and 122 to receive 10mg/kg of infliximab (Figure 1). The baseline characteristics of the patients were similar, although the mean duration of disease among patients who received 10mg/kg of infliximab was longer than among those who received 5mg/kg or placebo. Treatment was discontinued prematurely by 74 (61.2%) patients in the placebo group, 45 (37.2%) patients in the group receiving 5mg/kg of infliximab, and 49 (40.2%) patients in the group receiving 10mg/kg of infliximab.

In ACT 2, 364 patients underwent randomisation: 123 were assigned to receive placebo, 121 to receive 5mg/kg of infliximab, and 120 to receive 10mg/kg of infliximab (Figure 1). The baseline characteristics of the patients were similar. More than twice as many patients in the placebo group as in the other two groups prematurely discontinued the study infusions.

Figure 1: Patient enrolment and treatment in ACT 1 and ACT 2



Efficacy Results

In ACT 1 at week 8, 84 of 121 (69.4%) of patients in the group receiving 5mg/kg of infliximab and 75 of 122 (61.5%) of patients in the group receiving 10mg/kg of infliximab had a clinical response, compared with 45 of 121 (37.2%) of patients in the placebo group ($p<0.001$ for both comparisons). In ACT 2 at week 8, 78 of 121 patients (64.5%) of patients in the group receiving 5mg/kg of infliximab and 83 of 120 (69.2%) of patients in the group receiving 10mg/kg of infliximab had a clinical response, compared with 36 of 123 (29.3%) of patients in the placebo group ($p<0.001$ for both comparisons).

In both studies, the proportion of patients who had a clinical response or remission at weeks 8 and 30, and at week 54 in the ACT 1 trial, were higher by a factor of between 1.7 to more than 2.0 in the infliximab groups than in the placebo groups. The rates of clinical response were similar between the subpopulations of patients who were corticosteroid-refractory and those who were not.

The proportion of patients with sustained clinical response or sustained clinical remission was significantly higher in the infliximab groups than in the placebo groups. The partial Mayo scores in both studies provide evidence of clinical improvement as early as week 2. Mucosal healing at weeks 8 and 30 in both studies and at week 54 in ACT 1 occurred in significantly more patients in the infliximab groups than in the placebo groups ($p \leq 0.009$ for all comparisons).

At baseline, 222 of 364 (61.0%) of patients were receiving corticosteroids in ACT 1, as were 186 of 364 (51.1%) of patients in ACT 2. The baseline median daily corticosteroid dose was 20mg per day in both studies. The proportion of patients who were in clinical remission and had discontinued corticosteroids at week 30 in both studies and at week 54 in ACT 1 was higher in the infliximab groups than in the placebo groups. Similarly, the decreases in the median daily corticosteroid doses were greater among patients in the infliximab groups than among those in the placebo group.

Safety Results

The ACT 1 and ACT 2 trials collected extensive safety information. A summary of data from these trials is given in this section.

The proportion of patients experiencing any AE was similar in both the placebo group and in the infliximab 5mg/kg group. There was a slight increase in the number of AEs reported among patients receiving infliximab in ACT 1 compared to ACT 2 (Table 4) but this may be a product of the increased length of the study rather than a cumulative effect of the medication, as the placebo group in ACT 1 showed a similarly increased number of AEs. The majority of AEs (reported by ≥10% of either treatment group) involved the gastrointestinal tract, including worsening of UC, abdominal pain, and nausea (Table 5). There were more serious adverse events (SAEs) reported by patients receiving placebo than by those receiving active treatment in both studies (Table 6). A single patient in the 5mg/kg infliximab study arm of ACT 2 experienced a lupus-like reaction which was also considered a SAE. Neurological AEs in the form of optic neuritis occurred in two patients receiving 5mg/kg infliximab (one in each study). Other SAEs included infections (upper respiratory tract infections, TB, and pneumonia), basal

cell carcinoma, prostatic adenocarcinoma, and a colonic dysplasia. The incidence of these SAEs was low.

There was one death during the ACT 2 study in a patient receiving 5mg/kg infliximab. It occurred in the post 30 week extension period when patients deemed to be benefiting from infliximab were continued on the treatment. The death was due to a complication of histoplasmosis pneumonia.

Table 4: Summary of main AEs in ACT 1 and ACT 2

	ACT 1		**ACT 2**	
	Placebo	**Infliximab 5mg/kg**	**Placebo**	**Infliximab 5mg/kg**
Any AE, n (%)	103 (85.1)	100 (87.6)	90 (73.2)	99 (81.8)
SAE, n (%)	32 (26.4)	26 (21.5)	24 (19.5)	13 (10.7)
Infection, n (%)	47 (38.8)	53 (43.8)	29 (23.6)	33 (27.3)
Serious infection, n (%)	5 (4.1)	3 (2.5)	1 (0.8)	2 (1.7)
Acute infusion reaction, n (%)	13 (10.7)	12 (9.9)	10 (8.1)	14 (11.6)

AE, adverse event; SAE, serious adverse event.

Table 5: AEs occurring in ≥10% of either treatment group in ACT 1 and ACT 2

	ACT 1		**ACT 2**	
	Placebo	**Infliximab 5mg/kg**	**Placebo**	**Infliximab 5mg/kg**
Worsening of UC, n (%)	40 (33.1)	23 (19.0)	20 (16.3)	11 (9.1)
Abdominal pain, n (%)	16 (13.2)	11 (9.1)	14 (11.4)	10 (8.3)
Nausea, n (%)	14 (11.6)	14 (11.6)	9 (7.3)	6 (5.0)
Upper RTI, n (%)	28 (23.1)	20 (16.5)	14 (11.4)	16 (13.2)
Pharyngitis, n (%)	10 (8.3)	12 (9.9)	3 (2.4)	7 (5.8)
Pain, n (%)	19 (15.7)	14 (11.6)	11 (8.9)	9 (7.4)
Rash, n (%)	16 (13.2)	14 (11.6)	3 (2.4)	2 (1.7)
Arthralgia, n (%)	18 (14.9)	21 (17.4)	6 (4.9)	16 (13.2)
Headache, n (%)	27 (22.3)	22 (18.2)	18 (14.6)	19 (15.7)
Fever, n (%)	10 (8.3)	14 (11.6)	12 (9.8)	13 (10.7)
Anaemia, n (%)	12 (9.9)	4 (3.3)	13 (10.6)	6 (5.0)
Fatigue, n (%)	11 (9.1)	14 (11.6)	6 (4.9)	6 (5.0)

RTI, respiratory tract infection; UC, ulcerative colitis.

Table 6: Number of subjects with ≥1 SAEs (by WHOART System-Organ Class) in ACT 1 and ACT 2

	ACT 1		ACT 2	
	Placebo	**Infliximab 5mg/kg**	**Placebo**	**Infliximab 5mg/kg**
Gastrointestinal disorders, n (%)	18 (14.9)	17 (14.0)	19 (15.4)	11 (9.1)
Body general disorders, n (%)	2 (1.7)	2 (1.7)	0 (0.0)	3 (2.5)
Musculoskeletal disorders, n (%)	1 (0.8)	2 (1.7)	0 (0.0)	1 (0.8)
Respiratory system disorders, n (%)	2 (1.7)	1 (0.8)	0 (0.0)	0 (0.0)
Cardiovascular disorders, n (%)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Central & peripheral nervous system disorders, n (%)	1 (0.8)	1 (0.8)	0 (0.0)	0 (0.0)
Red blood cell disorders, n (%)	2 (1.7)	1 (0.8)	2 (1.6)	1 (0.8)
Resistance disorders, n (%)	4 (3.3)	0 (0.0)	2 (1.6)	2 (1.7)
Myo-, endo-, pericardial, coronary, & valve disorders, n (%)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Vascular (extra-cardiac) disorders, n (%)	3 (2.5)	1 (0.8)	1 (0.8)	0 (0.0)
Ear and hearing disorders, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Metabolic disorders, n (%)	3 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)
Neoplasms, n (%)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.8)
Skin and appendages disorders, n (%)	2 (1.7)	1 (0.8)	0 (0.0)	0 (0.0)
Urinary system disorders, n (%)	3 (2.5)	1 (0.8)	1 (0.8)	0 (0.0)
White cell and RES disorders, n (%)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Blood disorders, n (%)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Psychiatric disorders, n (%)	2 (1.7)	0 (0.0)	1 (0.8)	0 (0.0)
Reproductive disorders, n (%)	3 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)

RES, reticuloendothelial system.

Discontinuation of Treatment

Discontinuation of treatment was greater in the placebo arms of both studies than the treatment arms (Table 7). Discontinuation due to AEs in the ACT 1 study was similar for the placebo and 5mg/kg infliximab groups (11 [9.1%] and 10 [8.3%], respectively) but in the ACT 2 study there were 12 (9.8%) AE-related discontinuations in the placebo group compared with two (1.7%) in the 5mg/kg infliximab group. Rates of infusion reactions (defined as any AE occurring within 2 hours of an infusion) were similar across the placebo and 5mg/kg infliximab groups. A possible delayed hypersensitivity reaction occurred in two patients receiving placebo and two patients receiving 5mg/kg infliximab in ACT 1. In ACT 2, no patients receiving placebo or 5mg/kg infliximab experienced possible delayed hypersensitivity reactions.

Table 7: Discontinuation of infusions in ACT 1 and ACT 2

	ACT 1		ACT 2	
	Placebo	**Infliximab 5mg/kg**	**Placebo**	**Infliximab 5mg/kg**
Discontinued infusions, n/N (%)	74/121 (61.2)	45/121 (37.2)	56/123 (45.5)	24/121 (19.8)
Discontinued due to AE, n (%)	11 (9.1)	10 (8.3)	12/123 (9.8)	2/121 (1.7)
Discontinued due to infusion reaction, n (%)	0 (0.0)	2 (1.7)	0 (0.0)	0 (0.0)

AE, adverse event.

Positive tests for anti-nuclear antibodies and anti-double-stranded DNA antibodies was only seen in those subjects receiving infliximab, specifically 10.7% of subjects in ACT 1 and 4.9% in ACT 2. Subjects receiving infliximab also developed antibodies to the drug in a small number of cases: 7.8% in ACT 1 and 9.5% in ACT 2. This may have led to an elevated number of subjects experiencing infusion reactions (Table 8).

Table 8: Infusion reactions, by antibodies to infliximab result in ACT 1 and ACT 2 *

	ACT 1	ACT 2
	Infusion reaction (at week 54)	**Infusion reaction (at week 30)**
Positive test for antibodies, n/N (%)	5/14 (35.7)	6/12 (50)
Negative or inconclusive test for antibodies, n/N (%)	21/215 (9.8)	17/176 (9.7)

* Data includes 10mg/kg infliximab groups.

There were no serious infusion reactions or anaphylaxis in the subjects testing positive for infliximab antibodies in either study, but during the ACT 1 study a single patient receiving 5mg/kg infliximab testing positive for antibodies experienced a serious delayed hypersensitivity reaction.

In the ACT 1 trial patients in the 5mg/kg infliximab group experienced half the number of UC-related hospitalisations within the study period compared to patients in the placebo group (Table 9). In the ACT 2 trial patients receiving infliximab had even fewer hospitalisations, a third of those observed in the placebo group. The numbers of colectomies and ostomies within the study period are similar, with slightly more occurring in the placebo group of both studies.

Table 9: Hospitalisations, colectomies, and ostomies through week 54 in ACT 1 and ACT 2

	ACT 1		ACT 2	
	Placebo	**Infliximab 5mg/kg**	**Placebo**	**Infliximab 5mg/kg**
UC-related hospitalisation, mean ±SD (p value)	0.22 ±0.57	0.11 ±0.34 (p=0.061)	0.21 ±0.55	0.07 ±0.29 (p=0.009)
Colectomy, n (%)	9 (7.4)	7 (5.8)	1 (0.7)	0 (0.0)
Ostomy, n (%)	5 (4.1)	3 (2.5)	1 (0.7)	0 (0.0)

SD, standard deviation; UC, ulcerative colitis.

Summary

An induction regimen of three doses of infliximab followed by maintenance infusions every 8 weeks in patients with moderately to severely active UC was superior to placebo in achieving clinical response and remission, mucosal healing, and corticosteroid-sparing effects during 30 to 54 weeks of therapy.

5.1.2. ACT 1 and ACT 2 Extension Studies[13]

The aim of the extension studies was to evaluate long-term efficacy, quality of life, and safety in patients with UC who received infliximab during the original ACT 1 and ACT 2 studies.

The ACT 1 and ACT 2 studies were conducted globally at 62 (ACT 1) and 55 (ACT 2) sites between March 2002 and March 2005. Patients who continued into the long-term extension studies were evaluated at 44 (ACT 1) and 38 (ACT 2) sites between December 2003 and August 2007.

Patient eligibility criteria for ACT 1 and ACT 2 have been described. In summary, eligible patients had moderately to severely active UC (Mayo score of 6 to 12 points), including an endoscopic sub-score of at least 2, despite concurrent treatment with corticosteroids, and/or AZA or 6-MP (ACT 1 and ACT 2), and/or 5-ASA-containing medications (ACT 2).

Study Design

No specific eligibility criteria were predefined for the long-term extension studies. Patients who, in the opinion of the investigator, could benefit from continued treatment were eligible to enter the extension study after completing their main study therapy and evaluations through weeks 46 and 54 (ACT 1), or weeks 22 and 30 (ACT 2). Patients participating in the extension studies continued to receive the blinded treatment to which they had been randomised. Investigational sites were unblinded to study medication assignment beginning September 2005 after the week

54 (ACT 1) and extension week 24 (ACT 2) analyses were completed. At this time, patients receiving placebo were discontinued from the study and those receiving infliximab 5mg/kg or 10mg/kg continued to receive open-label treatment every 8 weeks. Patients receiving 10mg/kg infliximab were permitted to decrease their dose to 5mg/kg. Any patient who, in the opinion of the investigator, lost response while receiving infliximab 5mg/kg was permitted to increase the dose to 10mg/kg for subsequent infusions.

In the extension studies, infliximab treatment continued for a maximum of 3 years or until marketing authorisation was obtained and the drug was commercially available in that country. Thus, patients had different lengths of follow-up and the number of patients who completed each visit decreased over time in the extension studies.

For those enrolled, the first extension study infusion (Extension week 0, E0) was to occur at week 54 (ACT 1) or week 30 (ACT 2). By the time the extension studies were approved for the ACT trials, some patients had already completed their week 54 (ACT 1) or week 30 (ACT 2) main study final visit. Because of the potential for a loss of the response achieved during the main study, patients with a treatment gap of greater than 8 weeks could receive an extra infusion 2 weeks after their week E0 infusion at the discretion of the investigator. Patients who had used ciclosporin, tacrolimus, sirolimus, or mycophenolate mofetil during the treatment gap were required to discontinue these medications at least 8 weeks before infliximab maintenance therapy was resumed. Patients who received experimental medication for the treatment of UC after completion of the main study were ineligible for the extension studies.

Disease activity was evaluated using the Physician's Global Assessment (PGA). PGA is a four point sub-score (0=normal, 1=mild, 2=moderate, and 3=severe) of the total Mayo score[14]. At each visit, data regarding the use of corticosteroids to treat UC symptoms in the past 8 weeks were also collected. Patients were evaluated every 8 weeks up to 3 years (week E152).

Baseline Patient Characteristics

A total of 291 patients participated in the long-term extension studies: 229 in the infliximab group and 62 in the placebo group (Figure 2). Patients receiving placebo at the time that investigative sites were unblinded to treatment assignment were discontinued from the extension study, and thus, were not included in the analyses.

During the extension, infliximab dosage adjustments were made at the discretion of the treating physicians; total Mayo scores were not collected during the study extension, and no criteria

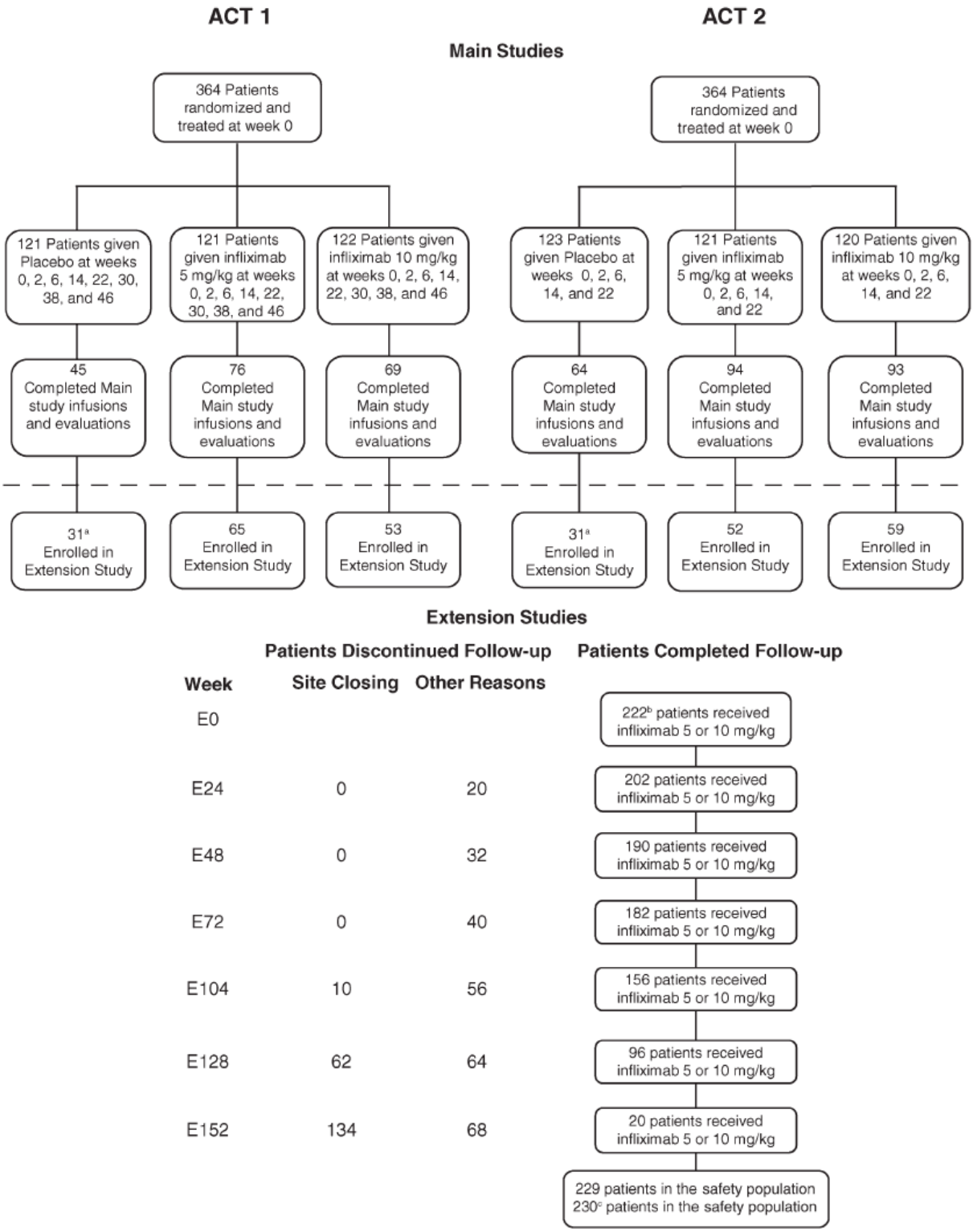
were pre-specified for patients who lost response or responded to infliximab dosage adjustments.

Among the 229 infliximab-treated patients, 16 (7.0%) who entered the extension studies and received infliximab 5mg/kg increased their dose to 10mg/kg. Of those, 12 (75%) patients completed the extension studies, one (6.3%) was lost to follow-up, one (6.3%) withdrew consent, and two (12.5%) discontinued because of AEs (one each: worsening UC or adenocarcinoma of the lung). Overall, 82 (35.8%) patients either discontinued study drug or escalated from 5mg/kg to 10mg/kg.

Twenty-two (9.6%) patients who entered the extension studies and received infliximab 10mg/kg decreased their dose to 5mg/kg. Of those, 20 (90.9%) patients completed the extension studies at the lower dose and two (9.1%) discontinued (one each: left the study site or withdrew consent) the extension studies. Additionally, two (0.9%) patients who entered the extension study and received infliximab 10mg/kg decreased their dose to 5mg/kg, then returned to 10mg/kg dose and completed the studies.

Overall, 230 patients received at least one infliximab infusion during the extension studies (including one patient in the placebo group who inadvertently received one infliximab infusion) and were evaluated for safety; 229 infliximab-treated patients were included in the efficacy analyses and had a mean (± SD) duration of follow-up of 113 (±42) weeks (range 4-184 weeks; median 128 weeks; interquartile range [IQR] 96-144 weeks).

Figure 2: Patient enrolment and treatment in the extension studies



[a]Patients who received placebo were discontinued after study unblinding and were not included in the analyses
[b]Seven patients do not have study termination data and are not included in this figure.
[c]One placebo-treated patient inadvertently received an infliximab infusion and is included in the safety analysis.

Of the 229 patients in the infliximab group, 70 (30.6%) patients permanently discontinued extension study infusions: 24 (10.5%) due to an AE, 11 (4.8%) due to lack of efficacy, one

(0.4%) due to a requirement for a colectomy, and 34 (14.8%) for 'other reasons' (including withdrawal of consent, loss to follow-up, investigator discretion, and patient non-compliance).

In the infliximab group, 190 and 156 patients completed follow-up through weeks E48 and E104, respectively. Through week E152, 134 patients discontinued follow-up due to termination of the study in their country and were considered to have completed the extension study per protocol. At the end of 3 years of the extensions (week E152), 20 patients had completed follow-up and extension study infusions (Figure 2).

Patients in the infliximab group who entered the extension studies had similar baseline patient and disease characteristics at the commencement of the main study compared to all patients randomised to receive infliximab in the ACT main studies (Table 10).

Table 10: Demographic and clinical characteristics of patients in ACT 1, ACT 2, and extension studies

	Infliximab Group Main Studies ($N = 484$)	Infliximab Group Extension Study ($N = 229$)
Patient characteristics		
Sex, *n* (%)		
Male	294 (60.7)	134 (58.5)
Race, *n* (%)		
Caucasian	456 (94.2)	219 (95.6)
Black	7 (1.4)	5 (2.2)
Asian	8 (1.7)	3 (1.3)
Other	13 (2.7)	2 (0.9)
Age (yrs)		
Mean ± SD	41.3 ± 13.88	41.0 ± 13.38
Median	40.0	40.0
IQ range	(30.0, 52.0)	(30.0, 50.0)
Range	(18, 81)	(18, 74)
Weight (kg)		
Mean ± SD	78.7 ± 18.35	79.8 ± 19.93
Median	77.0	77.0
IQ range	(66.0, 89.0)	(66.4, 89.3)
Range	(40.0, 177.3)	(40.0, 177.3)
Disease characteristics		
Mayo score		
Mean ± SD	8.4 ± 1.56	8.2 ± 1.63
Median	8.0	8.0
IQ range	(7.0, 9.0)	(7.0, 9.0)
Range	(4, 12)	(5, 12)
PGA, *n* (%)		
Normal or inactive disease	0 (0.0)	0 (0.0)
Mild disease	20 (4.1)	13 (5.7)
Moderate disease	384 (79.3)	178 (77.7)
Severe disease	80 (16.5)	38 (16.6)
Endoscopy, *n* (%)		
Normal or inactive disease	0 (0.0)	0 (0.0)
Mild disease	2 (0.4)	0 (0.0)
Moderate disease	309 (63.8)	138 (60.3)
Severe disease	173 (35.7)	91 (39.7)
CRP (mg/dL)		
N	480	228
Mean ± SD	1.4 ± 2.17	1.3 ± 1.94
Median	0.80	0.70
IQ range	(0.2, 1.6)	(0.2, 1.5)
Range	(0.2, 22.7)	(0.2, 17.0)
Ulcerative colitis disease duration (yrs)		
Mean ± SD	6.9 ± 6.31	7.6 ± 6.70
Median	4.9	5.7
IQ range	(2.5, 9.0)	(2.8, 10.6)
Range	(0.2, 42.1)	(0.2, 34.7)
Extent of disease, *n* (%)		
N	478	226
Limited to left side of colon	275 (57.5)	138 (61.1)
Extensive	203 (42.5)	88 (38.9)
Refractory to corticosteroids, *n* (%)		
Yes	143 (29.5)	70 (30.6)
Ulcerative colitis-related medical history		
Previous segmental resection, *n* (%)		
Yes	4 (0.8)	5 (0.7)
Other ulcerative colitis-related surgical procedure, *n* (%)		
Yes	9 (1.9)	15 (2.1)

CRP, C-reactive protein; IQ, interquartile range; kg, kilograms; PGA, Physician's Global Assessment; SD, standard deviation; yrs, years.

Efficacy Results

The proportion of patients who had scores indicative of no disease or mild disease (scores of 0 or 1) was maintained during the extension studies. At week E0, the proportion of patients with no disease or mild disease was 76.5% and ranged from 91.3%-94.3% between weeks E24 and E128. Twenty patients remained at week E152, of whom 18 (90.0%) had no disease or mild disease.

The proportion of patients who had scores indicative of no disease (score of 0) was also maintained during the extension studies. At weeks E0 and E24, the proportions of patients with no disease were 42.0% and 55.6%, respectively, ranging from 62.4%-72.2% between weeks E48 and E128. At week E152, 13 (65.0%) had no disease.

When the ACT 1 and ACT 2 data were analysed separately, the proportion of patients who had no disease or mild disease activity were generally similar between the two extension studies, but the proportion of patients with no disease was higher in the ACT 1 extension study than in the ACT 2 extension study. Less than half of patients had a treatment gap of more than 8 weeks between the last infusion of the main study and the extension study week E0 infusion (n=95). Among these patients, the mean (± SD) treatment gap duration was 146 (±117) days (median 115 days; range 1-512 days; IQR 57-213 days). At week E0, a greater proportion of patients without a treatment gap had scores indicative of no disease or mild disease when compared with those with a treatment gap (111 of 132 patients [84.1%] versus 62 of 94 patients [66.0%]). Greater proportions of patients without a treatment gap had scores indicative of no disease when compared with those with a treatment gap at weeks E0 (69 of 132 patients [52.3%] versus 26 of 94 patients [27.7%]) and E8 (76 of 128 patients [59.4%] versus 41 of 92 patients [44.6%]). The proportion of patients with scores indicative of no disease or mild disease, or no disease, were similar between patients with and without a treatment gap at all other extension study visits.

The proportion of patients with no disease or mild disease who did not use corticosteroids to treat their UC within the past 8 weeks ranged from 70.9%-90.0% and the proportion of patients with no disease who did not use corticosteroids to treat their UC ranged from 46.4%-65.0% between weeks E8 and E152. The proportion of patients who did not use corticosteroids to treat their UC within the past 8 weeks increased through the duration of the extension studies.

Safety Results

AEs, vital signs, and concomitant medications were recorded at each study visit. Serum samples were collected to allow determination of the presence of antibodies to infliximab and anti-nuclear antibodies at weeks E0 (only in patients with a treatment gap of more than eight weeks), E48, E104, E152, and E164. Serum samples positive for anti-nuclear antibodies were tested for anti-double-stranded DNA antibodies. A colonoscopic dysplasia questionnaire was administered to all patients approximately every 6 months.

On average, patients received an additional 2 years of infliximab therapy during the extension studies (Table 11). During the long-term extension studies, the overall rates of AEs were 506 per 100 patient-years. Infections occurred at a rate of 99 per 100 patient-years. Infliximab was discontinued due to an AE at a rate of less than 5 patients per 100 patient-years of therapy.

Table 11: Long-term safety in infliximab-treated patients in the extension studies

	Per 100 Patient-years
No. Patients	230
Mean treatment duration, years	1.99
Mean follow-up duration, years	2.16
No. Adverse events	506
No. Serious adverse events	21
No. Infections	99
No. Serious infections	3.4
No. Infections requiring antimicrobial therapy	41
No. Possible delayed hypersensitivity-like reactions	0
No. Patients discontinuing infliximab because of an adverse event	4.63
No. Patients who died	0.20
No. Patients with malignancy	1.01
No. Patients with infusion reaction	7.25
No. Patients with appropriate samples[a]	227
Mean follow-up duration, years	2.18
No. Patients with antibodies to infliximab at any time during extension studies	6.46

[a]Patients with appropriate samples either had antibodies to infliximab at some timepoint following their first infusion or had 1 or more samples obtained after their last infusion.

Among all 230 infliximab-treated patients, 49 (21.3%) experienced SAEs giving an overall rate of 21 SAEs per 100 patient-years of therapy. Ten patients (4.3%) experienced a serious infection (3.4 serious infections per 100 patient-years of therapy). Serious adverse events experienced by more than one patient were UC flare (11 patients, 4.8%); pneumonia (five patients, 2.2%; including pneumonia [four patients] and lobar pneumonia [one patient]), gastrointestinal bleeding (four patients, 1.7%; including gastrointestinal haemorrhage [two patients], haemorrhagic gastritis [one patient], and haemorrhagic gastric ulcer [one patient]), nausea and bone fracture (three patients each, 1.3%); abdominal pain, intestinal obstruction, and fever (two patients each, 0.9%).

One patient died during the extension studies as a result of histoplasmosis pneumonia. At the commencement of the main study this patient was receiving AZA and mesalazine for UC. During the extension studies there were no reports of TB or other opportunistic infections.

Five malignancies were reported during the extension studies for infliximab-treated patients. Adenocarcinoma of the lung was diagnosed in a 19 year old patient receiving infliximab 5mg/kg 1 month after the week E128 infusion. This patient was a non-smoker and died 18 months after completing the extension study.

One patient each developed breast cancer and prostate cancer; both were receiving infliximab 5mg/kg. Breast cancer was diagnosed after the week E72 infusion in a 33 year old patient with no family history of breast cancer. Infliximab was discontinued and the patient was treated with partial mastectomy, radiation therapy, and chemotherapy. Prostate cancer was diagnosed 2 months after the week E72 infusion in a 64 year old patient with pre-existing prostatitis (elevated prostate-specific antigen levels) at week E32. Infliximab was discontinued after the week E88 infusion and the patient's levels decreased with radiation therapy.

Two patients, each receiving infliximab 10mg/kg, developed a skin neoplasm (one each, basal cell carcinoma and skin cancer of the nose and forearm). Neither skin neoplasm resulted in discontinuation of treatment.

One patient with extensive disease and a 10 year history of UC at the main study baseline visit received infliximab 5mg/kg and showed evidence of colonic dysplasia during the extension studies.

No cases of optic neuritis or multifocal motor neuropathy were reported during the extension studies.

Overall, infusion reactions occurred in 36 of 230 patients (7.25 per 100 patient-years of therapy) who received an infliximab infusion. Three patients experienced a serious infusion reaction, including one patient who discontinued treatment because of a serious infusion reaction. Four patients discontinued infliximab because of non-serious infusion reactions.

Among 227 patients with serum samples analysable for antibodies to infliximab (mean duration of follow-up of 2.18 per 100 patient-years), 32 patients (6.46 per 100 patient-years of therapy) were positive for antibodies to infliximab. Among the 227 patients with appropriate serum samples for antibody to infliximab analysis, 16 of 132 (12.1%) patients without a treatment gap and 16 of 95 (16.8%) patients with a treatment gap were positive for antibodies to infliximab.

Among 214 patients analysed for anti-nuclear antibodies, 178 (83.2%) were negative at the extension study baseline, and 53 (24.8%) subsequently tested positive (i.e. 1:320 titer) at any time during the extension study. Additionally, 197 of 214 (92.1%) evaluated patients were negative for anti-double-stranded DNA antibodies at the extension study baseline, and 23 (10.7%) subsequently tested positive at any time during the extension study.

During the extension study, 15 of 53 infliximab-treated patients who developed anti-nuclear antibodies reported clinically-relevant AEs. These AEs included lupus arthritis (n=1), lupus-like reaction (n=1), arthralgia (n=7), or joint pain (n=7). None of these AEs were serious; however, two patients discontinued therapy. Additionally, one patient receiving infliximab 5mg/kg developed a lupus-like facial rash; however, this patient was not found to be positive for anti-nuclear or anti-double-stranded DNA antibodies. No anaphylactic or possible delayed hypersensitivity reactions were observed.

In the extension studies, infliximab was generally well-tolerated. These long-term results are consistent with previously reported data which describe overall favourable safety profiles in patients who received maintenance infliximab therapy[15,16,17,18.] No new or unexpected safety trends emerged in this review, suggesting that the AE profile found in the main ACT 1 and ACT 2 studies reflect the safety issues in subsequent years.

Summary

The long-term results from these extensions studies are consistent with previously-reported data which describe sustained clinical improvement and overall favourable safety profiles in patients who received maintenance infliximab therapy.

Patients with moderately to severely active UC who achieved clinical benefit with infliximab therapy in the ACT studies maintained clinical benefit for up to an additional 3 years of infliximab therapy.

5.2. Identification of Studies for Network Meta-Analysis

The objective for this submission is to assess the clinical and cost-effectiveness of infliximab for the treatment of moderately to severely active UC in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-MP or AZA, or who are intolerant to or have medical contraindications for such therapies. The acute, severe treatment setting is excluded from this appraisal, with guidance pertaining to this setting issued in TA163[7].

Relevant comparators, as listed in the NICE scope for this appraisal, are standard clinical management (which may include a combination of aminosalicylates, corticosteroids, thiopurines, calcineurin inhibitors, and surgical intervention) and other TNF-α inhibitors: adalimumab and golimumab. In the absence of active-controlled studies evaluating infliximab for the UC indication, a NMA was performed to compare the efficacy and safety of conventional therapy, adalimumab, golimumab, and infliximab for the treatment of adult patients with moderately to severely active UC (described in the following sections).

5.2.1. Searching

To identify data to inform the NMA, two reviewers working independently, in duplicate, conducted a systematic literature search. MEDLINE®, Embase®, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched (from inception to week 2, 2014). The search terms included "ulcerative colitis" and the generic and brand names of each of the agents ("golimumab" or "Simponi" and "adalimumab" or "Humira" and "infliximab" or "Remicade") (Table 12). Searches were limited to studies in humans and were not limited by language. Conference abstracts provided through the Embase® search were also reviewed to determine whether any relevant studies had completed recently. Additionally, hand searches of the

bibliographies of published systematic reviews and health technology assessments were performed.

Table 12: MEDLINE® and Embase® search strategy – OVID database, week 2, 2014

No.	Search term	Hits
1	ulcerative colitis.mp.	79799
2	golimumab.mp.	2190
3	simponi.mp.	289
4	2 or 3	2202
5	adalimumab.mp.	18031
6	humira.mp.	2308
7	5 or 6	18054
8	infliximab.mp.	37663
9	remicade.mp.	3844
10	8 or 9	37689
11	4 or 7 or 10	43472
12	1 and 11	5711
13	remove duplicates from 12	4735

5.2.2. Study Selection

All identified citations were scanned by two independent reviewers for eligibility according to the types of patients, interventions, comparisons, and outcomes outlined in Table 13. The researchers then obtained the full-text publications of those citations potentially matching the eligibility criteria. After obtaining these full-text publications, the same two researchers independently assessed for eligibility again, with disagreements assessed by a third adjudicator.

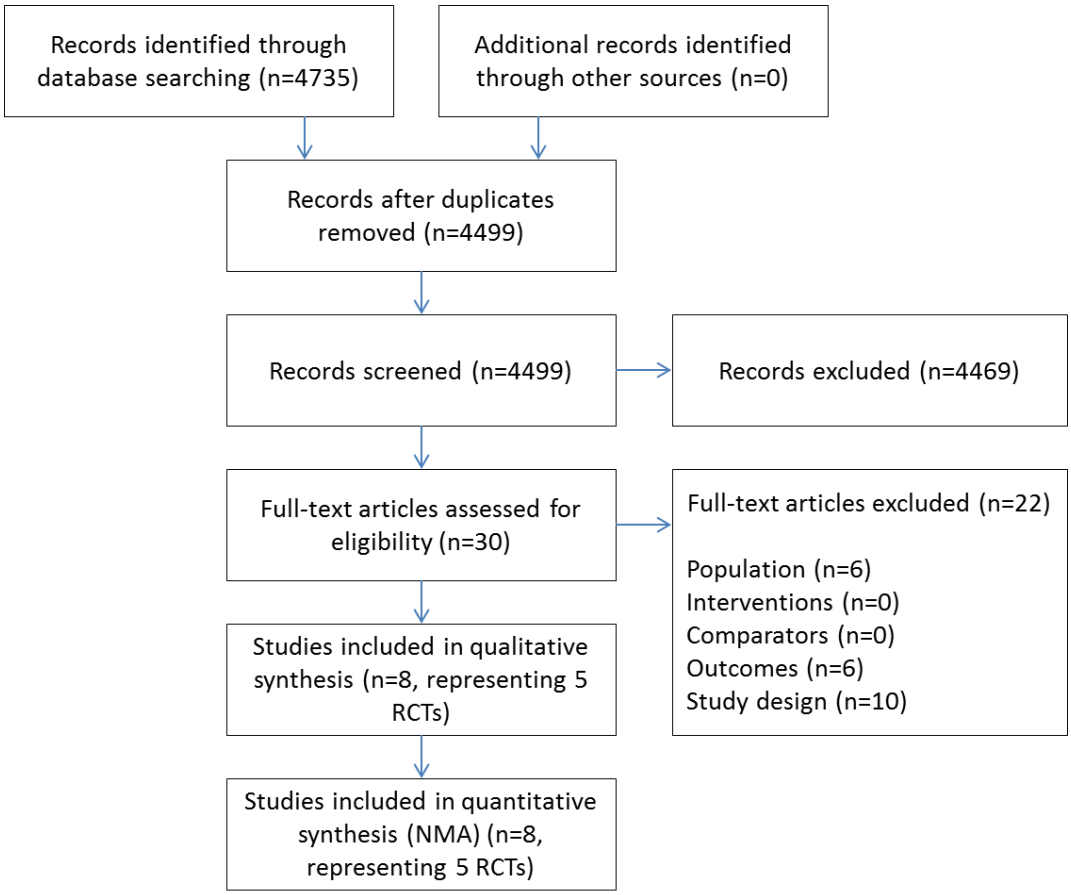
Table 13: Types of patients, interventions, controls, and outcomes considered

Component	Eligibility criteria
Population	Adults over 18 years of age diagnosed with moderately to severely active UC who have not previously received treatment with an TNF-α inhibitor
Interventions	• Adalimumab * • Golimumab ** • Infliximab ***
Comparisons (controls)	Any standard of care/conventional therapy such as 5-ASAs, corticosteroids, and immunomodulators (AZA or 6-MP)
Primary efficacy outcomes	• Clinical remission • Clinical response • Colectomy • Mucosal healing • Sustained clinical remission • Sustained clinical response
Secondary efficacy outcomes	• IBDQ response (>16 point improvement) • UCSS • UC-related hospitalisation • Reduction in use of corticosteroids • Steroid-free remission • Survival • Discontinuations due to lack of efficacy
Safety outcomes	• Any SAE • Discontinuations due to AE • Injection- or infusion-site reaction
Time points	Induction (6-8 weeks) and maintenance (52-60 weeks of treatment)

* Induction: 160mg at week 0, 80mg at week 2, and 40mg at weeks 4 and 6. Maintenance: 40mg every other week, starting at week 8; ** Induction: 200mg at week 0, 100mg at week 2, or 400mg at week 0, 200mg at week 2. Maintenance: 50mg or 100mg every 4 weeks, starting at week 6; *** Induction: 5mg/kg or 10mg/kg at weeks 0, 2, and 6. Maintenance: 5mg/kg or 10mg/kg every 8 weeks, starting at week 8. 5-ASA, 5-aminosalicylate; 6-MP, 6-mercaptopurine; AE, adverse event; AZA, azathioprine; IBDQ, Inflammatory Bowel Disease Questionnaire; SAE, serious adverse event; TNF-α, tumour necrosis factor-alpha; UC, ulcerative colitis; UCSS, Ulcerative Colitis Symptom Score.

The flow of citations through the screening process is outlined in Figure 3. In total, eight publications were identified that met the eligibility criteria, representing five RCTs. Data were extracted from the included studies by two reviewers working independently and recorded in a Microsoft Excel® spreadsheet. A third reviewer checked all data extraction.

Figure 3: Schematic of the publication selection process



NMA, network meta-analysis; RCT, randomised-controlled trial.

5.3. List of Relevant Clinical Trials

Of the five eligible RCTs (summarised in Table 14), two assessed infliximab (ACT 1 and ACT 2)[2,10,19], one assessed golimumab (the respective phases of PURSUIT were considered as one study)[20,21], and two assessed adalimumab (ULTRA 1 and ULTRA 2)[22,23,24]. All RCTs compared a TNF-α inhibitor of interest with a placebo arm where patients were receiving conventional background therapy. All RCTs reported results at the end of the induction period (6-8 weeks), and four reported the effect of the TNF-α inhibitors at the end of maintenance period (52-60 weeks). The 22 full-text articles excluded after the full-text screening are listed in Table 15, with the justification for their exclusion.

Table 14: Summary of RCTs eligible for inclusion in the NMA

Trial identifier	Trial design	Interventions	Number of patients randomised	Evaluation of induction	Evaluation of maintenance	Evaluation of sustained response
ACT 1	Multicentre, randomised, double-blind, placebo-controlled trial	Placebo	121	Week 8	Week 54	Responders at weeks 30 and 54 out of responders to induction
		Infliximab 5mg/kg	121			
		Infliximab 10mg/kg	122			
ACT 2	Multicentre, randomised, double-blind, placebo-controlled trial	Placebo	123	Week 8	Week 30	Responders at week 30 out of responders to induction
		Infliximab 5mg/kg	121			
		Infliximab 10mg/kg	120			
PURSUIT	Multicentre, randomised, double-blind, placebo-controlled trial	Placebo	407	Week 6	Week 60	Responders through weeks 36 and 60 out of responders to induction
		Golimumab (induction total)	949			
ULTRA 1	Multicentre, randomised, double-blind, placebo-controlled trial	Placebo	130	Week 8	N/A	N/A
		Adalimumab 160/80/40mg	130			
ULTRA 2	Multicentre, randomised, double-blind, placebo-controlled trial	Placebo	246	Week 8	Week 52	Responders at week 52 out of responders to induction
		Adalimumab 160/80/40mg	248			

N/A, not applicable.

Table 15: Studies excluded after full-text screening

Study	Principal reason for exclusion
Colombel *et al.* 2011 [25]	Follow-up to Rutgeerts *et al.* 2005; no relevant data for current analysis
Gustavsson *et al.* 2010 [26]	Follow-up to Järnerot *et al.* 2005; no relevant data for current analysis
Oussalah *et al.* 2008 [27]	All patients have an inadequate clinical response to infliximab
Ferrante *et al.* 2007 [28]	Follow-up to Rutgeerts *et al.* 2005; no relevant data for current analysis
Reinisch *et al.* 2007 [29]	Follow-up to Rutgeerts *et al.* 2005; no relevant data for current analysis
Järnerot *et al.* 2005 [30]	Included only hospitalised patients with severe UC
Armuzzi *et al.* 2004 [31]	Not all patients were inadequate responders to conventional therapy
Ochsenkühn *et al.* 2004 [32]	Not all patients were inadequate responders to conventional therapy
Gornet *et al.* 2003 [33]	Not all patients had UC, outcomes not stratified by disease
Probert *et al.* 2003 [34]	Used different definition of remission and response than other trials
Sands *et al.* 2001 [35]	Outcomes only provided at 2 weeks
Jürgens *et al.* 2010 [36]	Non-randomised/observational study
Olsen *et al.* 2012 [37]	Non-randomised/observational study
Halpin *et al.* 2013 [38]	Non-randomised/observational study
Molander *et al.* 2012 [39]	Non-randomised/observational study
Rostholder *et al.* 2012 [40]	Non-randomised/observational study
Steenholdt *et al.* 2012 [41]	Non-randomised/observational study
Steenholdt *et al.* 2013 [42]	Non-randomised/observational study
Gies *et al.* 2010 [43]	Non-randomised/observational study
Italian Group *et al.* 2013 [44]	Non-randomised/observational study
Reinisch *et al.* 2013 [45]	Non-randomised/observational study
Suzuki *et al.* 2013 [46]	Japanese-only population

UC, ulcerative colitis.

5.4. Summary of Methodology, Participants, and Outcomes of Relevant Clinical Trials

Eligibility criteria for enrolment into the included studies were similar (please see **Error! Reference source not found.**). Baseline patient characteristics (including disease severity and concomitant therapies) were similar across all included studies (Table 7). All studies measured similar outcomes and utilised the Mayo score to assess clinical response and remission, defining these outcomes similarly (Table 8). The study outcomes were relevant to clinical practice in the UK. The included studies followed similar methodology, with the exception of PURSUIT for which the adaptive trial design necessitated a number of adjustments to the Bayesian methodology utilised in the NMA (described in Section 5.8.1).

Table 16: Baseline patient characteristics of RCTs eligible for inclusion in the NMA

Trial identifier	Interventions	Male patients (%)	Age (years)	Weight (kg)	Disease duration (years)	Mayo score (median)	CRP (mg/l)	Disease location: extensive/left-sided/other (%)	Steroid-refractory disease (%)	Concomitant therapy: corticosteroids/ aminosalicylates/ AZA/immunosuppressants
ACT 1	Placebo	59.5	41.4 *	76.8 *	6.2 *	8.4 *	8.0 **	45.0/55.0/0.0	31.4	65.3/70.2/29.8/43.8
	Infliximab 5mg/kg	64.5	42.4 *	80.0 *	5.9 *	8.5 *	9.0 **	47.1/52.9/0.0	29.8	57.9/67.8/37.2/54.5
	Infliximab 10mg/kg	59.0	41.8 *	76.9 *	8.4 *	8.4 *	10.0 **	44.6/55.4/0.0	31.1	59.8/70.5/36.1/48.4
ACT 2	Placebo	57.7	39.3 *	76.1 *	6.5 *	8.5 *	6.0 **	41.7/58.3/0.0	29.3	48.8/72.4/28.5/43.9
	Infliximab 5mg/kg	62.8	40.5 *	78.4 *	6.7 *	8.3 *	8.0 **	40.7/59.3/0.0	28.9	49.6/76.0/33.9/43.0
	Infliximab 10mg/kg	56.7	40.3 *	79.6 *	6.5 *	8.3 *	6.0 **	37.5/62.5/0.0	28.3	55.0/75.8/30.8/41.7
PURSUIT	Placebo	52.9	39.0 *	NR	6.0 *	8.3 *	4.5 **	43.0/57.0/0.0	NR	40.5/83.4/30.8/32.1
	Golimumab (induction total)	57.4	40.4 *	NR	6.4 *	8.5 *	4.9 **	41.8/58.2/0.0	NR	43.9/81.2/31.3/31.7
ULTRA 1	Placebo	63.1	37.0 **	78.7 *	5.4 **	8.7 *	3.2 **	56.2/32.3/11.5	NR	68.5/75.4/NR/40.0
	Adalimumab 160/80/40mg	63.8	36.5 **	75.5 *	6.1 **	8.8 *	3.3 **	46.2/46.9/6.9	NR	54.6/80.8/NR/39.2
ULTRA 2	Placebo	61.8	41.3 *	77.1 *	8.5 *	8.9 *	4.2 **	48.8/39.0/12.2	NR	56.9/63.0/32.5/NR
	Adalimumab 160/80/40mg	57.3	39.6 *	75.3 *	8.1 *	8.9 *	4.1 **	48.4/38.7/12.9	NR	60.5/58.9/37.5/NR

The baseline characteristics presented for the PURSUIT trial are provided as those listed in PURSUIT-SC. The baseline characteristics for the ULTRA 2 trial were not stratified by prior TNF-α inhibitor experience and are therefore presented for the entire population. * Mean; ** Median. AZA, azathioprine; CRP, C-reactive protein; NR, not reported.

Table 17: Primary and secondary outcomes of RCTs eligible for inclusion in the NMA

Trial identifier	Primary outcome(s)	Definition	Secondary outcome(s)
ACT 1	Proportion of patients with clinical response at week 8	Decrease from baseline in the Mayo score by ≥30% and ≥3 points, with a decrease in the rectal bleeding sub-score of >1 or a rectal bleeding sub-score of 0 or 1	http://clinicaltrials.gov/show/NCT00036439
ACT 2	Proportion of patients with clinical response at week 8	Decrease from baseline in the Mayo score by ≥30% and ≥3 points, with a decrease in the rectal bleeding sub-score of >1 or a rectal bleeding sub-score of 0 or 1	http://clinicaltrials.gov/show/NCT00096655
PURSUIT	(Induction) number of participants with clinical response at week 6 (Maintenance) number of participants in clinical response through week 54	Decrease from baseline in Mayo score by greater than or equal to 30% and greater than or equal to 3 points, with either a decrease from baseline in rectal bleeding sub-score of greater than or equal to 1 or a rectal bleeding sub-score of 0 or 1. The Mayo score is sum of 4 sub-scores (i.e. stool frequency, rectal bleeding, endoscopic findings, and physician's global assessment); each rated on a scale from 0 to 3, with higher scores indicating more severe disease. The total Mayo score value ranges from 0 to 12	http://clinicaltrials.gov/show/NCT00487539 http://clinicaltrials.gov/show/NCT00488631
ULTRA 1	Proportion of participants with clinical remission per Mayo score at week 8	Total Mayo score ≤2 and no individual sub-score >1. The Mayo score is a discrete ordinal scale ranging from 0 (normal or inactive disease) to 12 (severe disease) and is a composite of 4 sub-scores: Stool Frequency Sub-score, Rectal Bleeding Sub-score, Endoscopy Sub-score, and Physician's Global Assessment Sub-score, each of which ranges from 0 (normal) to 3 (severe disease)	http://clinicaltrials.gov/show/NCT00385736
ULTRA 2	Proportion of participants who achieved clinical remission per Mayo score at week 8 Proportion of participants who achieved clinical remission per Mayo score at week 52	Total Mayo score of at least 2 and no individual sub-score greater than 1. The Mayo score is a discrete ordinal scale ranging from 0 (normal or inactive disease) to 12 (severe disease) and is a composite of 4 sub-scores: Stool Frequency Sub-score, Rectal Bleeding Sub-score, Endoscopy Sub-score, and Physician's Global Assessment Sub-score, each of which ranges from 0 (normal) to 3 (severe disease)	http://clinicaltrials.gov/show/NCT00408629

UC, ulcerative colitis.

5.5. Statistical Analyses in Included Studies

Please see **Error! Reference source not found.** for details of statistical analyses conducted in included studies.

5.6. Critical Appraisal of Included Studies

Please see **Error! Reference source not found.** for the critical appraisal of included studies. The quality of included RCTs was assessed according to NICE criteria and all were found to be of high methodological quality.

5.7. Results of Included Studies

Extracted data for analysis are presented in Table 18 to Table 24.

Primary Outcomes Data

Table 18: Primary outcomes data considered within the NMA - induction

Trial identifier	Interventions	Number of patients with outcome (n/N)		
		Remission	Response	Mucosal healing
ACT 1	Placebo	18/121	45/121	41/121
	Infliximab 5mg/kg	47/121	84/121	75/121
	Infliximab 10mg/kg	39/122	75/122	72/122
ACT 2	Placebo	7/123	36/123	38/123
	Infliximab 5mg/kg	41/121	78/121	73/121
	Infliximab 10mg/kg	33/120	83/120	74/120
PURSUIT Phase 2	Placebo	7/69	26/69	22/69
	Golimumab 200/100mg	13/71	33/71	29/71
	Golimumab 400/200mg	18/68	35/68	32/68
PURSUIT Phase 3	Placebo	16/256	76/256	73/256
	Golimumab 200/100mg	48/257	133/257	111/257
	Golimumab 400/200mg	46/258	142/258	117/258
ULTRA 1	Placebo	12/130	58/130	54/130
	Adalimumab 160/80mg	24/130	71/130	61/130
ULTRA 2	Placebo	16/145	56/145	51/145
	Adalimumab 160/80mg	32/150	89/150	74/150

Table 19: Primary outcomes data considered within the NMA - maintenance

Trial identifier	Interventions	Number of patients with outcome (n/N)			
		Remission	Response	Mucosal healing	Colectomy
ACT 1	Placebo	20/121	24/121	22/121	36/244 *
	Infliximab 5mg/kg	42/121	55/121	55/121	28/242 *
	Infliximab 10mg/kg	42/122	54/122	57/122	18/242 *
PURSUIT	Placebo	32/407	46/407	43/407	NR
	Golimumab 50mg	55/289	112/289	96/289	NR
	Golimumab 100mg	66/289	121/289	100/289	NR
ULTRA 2	Placebo	18/145	35/145	28/145	19/483 †
	Adalimumab 40mg	33/150	55/150	47/150	15/480 †

* Combined data from ACT 1 and ACT 2; † Combined data from ULTRA 1 and ULTRA 2. NR, not reported.

Table 20: Primary outcomes data considered within the NMA - maintenance, sustained outcomes

Trial identifier	Interventions	Number of patients with outcome (n/N)	
		Sustained remission	Sustained response
ACT 1	Placebo	8/121	17/121
	Infliximab 5mg/kg	24/121	47/121
	Infliximab 10mg/kg	25/122	45/122
PURSUIT	Placebo	7/256 [a]	28/256 [f]
	Golimumab 200/100/50mg	18/257 [b]	63/257 [g]
	Golimumab 200/100/100mg	19/257 [c]	67/257 [h]
	Golimumab 400/200/50mg	17/258 [d]	67/258 [i]
	Golimumab 400/200/100mg	19/258 [e]	72/258 [j]
ULTRA 2	Placebo	9/145	24/145
	Adalimumab 40mg	16/150	44/150

[a] Number of cases calculated by multiplying the probability of induction remission with placebo from the induction phase of PURSUIT with the probability of maintaining remission with placebo from the non-randomised maintenance phase of PURSUIT, multiplied with the sample size at the beginning of the induction phase: (16/256)*(9/22)*256

[b] Number of cases calculated by multiplying the probability of induction remission with golimumab 200/100mg from the induction phase of PURSUIT with the probability of maintaining remission with golimumab 50mg from the randomised maintenance phase of PURSUIT, multiplied with the sample size at the beginning of the induction phase: (48/257)*(19/52)*257

[c] Number of cases calculated by multiplying the probability of induction remission with golimumab 200/100mg from the induction phase of PURSUIT with the probability of maintaining remission with golimumab 100mg from the randomised maintenance phase of PURSUIT, multiplied with the sample size at the beginning of the induction phase: (48/257)*(23/57)*257

[d] Number of cases calculated by multiplying the probability of induction remission with golimumab 400/200mg from the induction phase of PURSUIT with the probability of maintaining remission with golimumab 50mg from the randomised maintenance phase of PURSUIT, multiplied with the sample size at the beginning of the induction phase: (46/258)*(19/52)*258

[e] Number of cases calculated by multiplying the probability of induction remission with golimumab 400/200mg from the induction phase of PURSUIT with the probability of maintaining remission with golimumab 100mg from the randomised maintenance phase of PURSUIT, multiplied with the sample size at the beginning of the induction phase: (46/258)*(23/57)*258

[f] Number of cases calculated by multiplying the probability of induction response with placebo from the induction phase of PURSUIT with the probability of maintaining response with placebo from the non-randomised maintenance phase of PURSUIT, multiplied with the sample size at the beginning of the induction phase: (76/256)*(46/124)*256

[g] Number of cases calculated by multiplying the probability of induction response with golimumab 200/100mg from the induction phase of PURSUIT with the probability of maintaining response with golimumab 50mg from the randomised maintenance phase of PURSUIT, multiplied with the sample size at the beginning of the induction phase: (133/257)*(72/153)*257

[h] Number of cases calculated by multiplying the probability of induction response with golimumab 200/100mg from the induction phase of PURSUIT with the probability of maintaining response with golimumab 100mg from the randomised maintenance phase of PURSUIT, multiplied with the sample size at the beginning of the induction phase: (133/257)*(78/154)*257
[i] Number of cases calculated by multiplying the probability of induction response with golimumab 400/200mg from the induction phase of PURSUIT with the probability of maintaining response with golimumab 50mg from the randomised maintenance phase of PURSUIT, multiplied with the sample size at the beginning of the induction phase: (142/258)*(72/153)*258
[j] Number of cases calculated by multiplying the probability of induction response with golimumab 400/200mg from the induction phase of PURSUIT with the probability of maintaining response with golimumab 100mg from the randomised maintenance phase of PURSUIT, multiplied with the sample size at the beginning of the induction phase: (142/258)*(78/154)*258

Secondary Outcomes Data

Table 21: Secondary outcomes data considered within the NMA - induction

Trial identifier	Interventions	Number of patients with outcome (n/N)	
		IBDQ response	Discontinuation due to lack of efficacy
ACT 1	Placebo	121/244 *	NR
	Infliximab 5mg/kg	169/242 *	NR
	Infliximab 10mg/kg	166/242 *	NR
PURSUIT	Placebo	NR	11/330
	Golimumab 200/100mg	NR	7/331
	Golimumab 400/200mg	NR	6/332
ULTRA 1	Placebo	NR	4/130
	Adalimumab 160/80mg	NR	1/130
ULTRA 2	Placebo	75/145	NR
	Adalimumab 160/80mg	102/150	NR

* Combined data from ACT 1 and ACT 2. IBDQ, Inflammatory Bowel Disease Questionnaire; NR, not reported.

Table 22: Secondary outcomes data considered within the NMA - maintenance

Trial identifier	Interventions	Number of patients with outcome (n/N)			
		UC-related hospitalisation	Corticosteroid-free remission	IBDQ response	Cessation of steroid use
ACT 1	Placebo	60/244 *	7/121	54/121	NR
	Infliximab 5mg/kg	39/242 *	18/121	85/121	NR
	Infliximab 10mg/kg	37/242 *	12/122	83/122	NR
ACT 2	Placebo	NR	2/123	NR	NR
	Infliximab 5mg/kg	NR	11/121	NR	NR
	Infliximab 10mg/kg	NR	18/120	NR	NR
PURSUIT	Placebo	NR	14/389 [a]	NR	NR
	Golimumab 50mg	NR	22/289	NR	32/289
	Golimumab 100mg	NR	19/289	NR	28/289
ULTRA 1	Placebo	68/483 †	NR	NR	NR
	Adalimumab 40mg	47/480 †	NR	NR	NR
ULTRA 2	Placebo	NR	5/145	31/145	34/145
	Adalimumab 40mg	NR	15/150	48/150	51/150

* Combined data from ACT 1 and ACT 2, † Combined data from ULTRA 1 and ULTRA 2, [a] not available, assumed proportion based on other trials. IBDQ, Inflammatory Bowel Disease Questionnaire; NR, not reported; UC, ulcerative colitis.

Safety Outcomes Data

Table 23: Safety outcomes data considered within the NMA - induction

Trial identifier	Interventions	Number of patients with outcome (n/N)		
		Discontinuation due to AEs	Any SAEs	Injection-site reactions
PURSUIT	Placebo	3/330	20/330	5/330
	Golimumab 200/100mg	1/331	9/331	11/331
	Golimumab 400/200mg	1/332	11/332	10/332
ULTRA 1	Placebo	5/130	17/130	7/223
	Adalimumab 160/80mg	4/130	9/130	13/223

AE, adverse event; SAE, serious adverse event.

Table 24: Safety outcomes data considered within the NMA - maintenance

Trial identifier	Interventions	Number of patients with outcome (n/N)		
		Discontinuation due to AEs	Any SAEs	Injection- or infusion-site reactions
ACT 1	Placebo	11/121	31/121	13/121
	Infliximab 5mg/kg	10/121	26/121	12/121
	Infliximab 10mg/kg	11/121	29/121	15/121
ACT 2	Placebo	12/123	24/121	10/121
	Infliximab 5mg/kg	2/121	13/121	14/121
	Infliximab 10mg/kg	5/120	11/121	14/121
PURSUIT	Placebo	10/156	12/156	3/156
	Golimumab 50mg	8/154	13/154	3/154
	Golimumab 100mg	14/154	22/154	11/154
ULTRA 2	Placebo	34/260	32/260	10/260
	Adalimumab 40mg	23/257	31/257	31/257

AE, adverse event; SAE, serious adverse event.

5.8. Network Meta-Analysis

5.8.1. Methodology of Network Meta-Analysis

Bayesian NMA[47] was performed for all outcomes listed in Table 25. All outcomes are binary and were therefore modelled in a logistic regression model. While this model inherently produces odds ratios (ORs) as the effect measure, relative risks (RRs) are presented here for ease of interpretation. Standard methodology for converting ORs to expected treatment effect proportions and subsequently to RRs were employed[47]. The RRs were accompanied by 95% credible intervals (CrIs) to represent uncertainty surrounding the estimation. When only one RCT informed each treatment (which was predominantly the case for end of maintenance outcomes), heterogeneity could not be estimated and therefore a fixed-effects model was employed. If this was not the case, a random-effects approach was followed.

Incorporating PURSUIT in NMA

The design of PURSUIT creates a challenge in establishing indirect comparative efficacy of golimumab versus adalimumab and infliximab since the placebo arm in PURSUIT-M was induced on active therapy (responders to golimumab in the induction trial). Moreover, patients initially randomised to placebo in induction were allowed to cross-over to golimumab 100mg at 6 weeks if they did not achieve response. The design of PURSUIT-M differs substantially from the more classical designs of the long-term RCTs of adalimumab and infliximab (ULTRA 2 and ACT 1, respectively). In those RCTs, patients randomised to placebo comparator arms were induced on placebo, and both responders and non-responders to placebo remained on placebo throughout completion of the maintenance phase in a parallel group design. Therefore, the placebo arms in PURSUIT are significantly different from those in the ULTRA and ACT trials. It should also be noted that while both ACT 1 and ACT 2 provide fully randomised long-term data for both infliximab and placebo, the ULTRA 2 trial allowed optional cross-over from placebo to adalimumab 40mg after induction, in addition to permitting cross-over from adalimumab 40mg to 80mg after the induction period for those patients who were not responding.

As patients randomised to placebo during the maintenance phase of PURSUIT were responders to golimumab induction treatment, they were expected to have better outcomes than a hypothetical cohort of patients in a classical placebo randomisation where no active intervention had been received previously and where continued randomisation is not contingent on response at induction. For this reason, the 156 patients randomised to placebo after golimumab induction response should not form the basis of the placebo control. The patients originally randomised to placebo were non-randomly allocated to continue placebo or receive golimumab 100mg depending on their response. Following the intention-to-treat (ITT) principle, it can be assumed that all patients re-allocated to golimumab 100mg after induction would not have responded had they continued placebo. The ITT principle can also be used for the ULTRA 2 data where non-responding patients originally randomised to placebo had the option of crossing over to adalimumab 40mg (in ULTRA 2 a 'non-responder' imputation was employed, meaning that all cross-overs were assumed prospective placebo non-responders). This assumption is likely to downward bias the estimated placebo proportion, and thus overestimates the relative efficacy of both golimumab and adalimumab.

PURSUIT also created challenges in estimating the proportion of patients with a positive outcome in the golimumab 50mg and golimumab 100mg groups. For golimumab 100mg, outcomes were separated by golimumab induction responders and non-responders. Simply combining the two is not viable since only a third of the patients responding to golimumab

induction therapy were re-randomised to golimumab 100mg. The solution is to downgrade the precision in the non-responder group correspondingly. That is, it can be assumed that like the responder group, only a third of non-responders received golimumab 100mg. For each outcome, the number of patients and events can therefore be divided by three, and the adjusted numbers can be added to the number of patients and events in the induction responder group. For example, clinical response at end of maintenance was achieved in 78/154 (50.6%) of patients responding to golimumab induction therapy and in 129/405 (31.8%) of patients not responding. To obtain a fair average of the two, the number of events and patients in the non-responder group can be divided by three, giving ~43/135 patients. Subsequently, the two are combined giving (78+43)/(154+135)=121/289 (41.8%) of patients on golimumab 100mg with a maintenance response.

For golimumab 50mg, no data are available for patients not responding at 6 weeks to induction therapy. Therefore, the existing relationships between the available data components were used to impute the expected proportions in this missing subgroup. For the imputation, it was assumed that for patients receiving a 54 week course of golimumab, the relative difference in 54 week efficacy (post-induction) between early golimumab responders and non-responders is independent of the dose of golimumab given for 54 weeks. In other words, if golimumab induction responders receiving a further 54 week course of 100mg respond twice as well at the end of maintenance as non-responders receiving a 54 week course of 100mg golimumab, then it can be assumed that same relationship holds true had the 54 week course been golimumab 50mg. PURSUIT provides golimumab 50mg maintenance data only for golimumab induction responders. To calculate the hypothetical proportion among golimumab induction non-responders, one simply needs to multiply the relative efficacy between the two golimumab 100mg groups (i.e. golimumab induction responders versus non-responders). As with the above calculations for golimumab 100mg, because only a third of induction responders were randomised to golimumab 50mg, it should also be assumed that only a third of induction non-responders were hypothetically randomised to golimumab 50mg. That is, the imputed proportion should be multiplied with the hypothetical sample size of 405/3=135.

To illustrate this imputation approach the clinical response outcome can be considered. The estimated efficacy of golimumab for induction non-responders and responders is 129/405=31.8% and 78/154=50.6%, respectively. The relative efficacy of golimumab between the two groups is therefore 31.8%/50.6%=0.628. The efficacy of golimumab 50mg among golimumab induction responders is 72/154=46.8%. Assuming the relative efficacy between induction non-responders and responders across maintenance doses, the expected efficacy of

golimumab 50mg among induction non-responders is 0.628*46.8%=29.4%. Further assuming a hypothetical sample size of 135, it would be expected that 0.294*135=40 of these patients would have clinical responses at the end of maintenance. Combining these numbers gives (72+40)/(154+135)=112/289 (38.8%) as the semi-imputed number and proportion of patients receiving golimumab 50mg that were in clinical response by the end of maintenance.

In order to obtain the proportion of patients in sustained response and sustained remission out of all patients starting induction treatment in PURSUIT and to have similar data as for ULTRA 2 and ACT 1, the probability of induction response or remission with golimumab from the induction phase of PURSUIT was first multiplied with the probability of maintaining response or remission with golimumab from the randomised maintenance phase of PURSUIT. For the placebo intervention, the probability of induction response or remission with placebo from the induction phase of PURSUIT was multiplied with the probability of maintaining response or remission with placebo from the non-randomised maintenance phase of PURSUIT. Refer to the footnote of Table 20 for more detail regarding the calculations.

NMA Treatment Network

Treatment networks at the end of induction and the end of maintenance are shown in Figure 4 and Figure 5, respectively. Non-licensed doses are included in the treatment networks (infliximab 10mg/kg and golimumab 400/200mg), however, their inclusion or exclusion does not impact the networks as no included trials investigated those doses alone.

Figure 4: Treatment network for the analyses of outcomes at the end of induction therapy

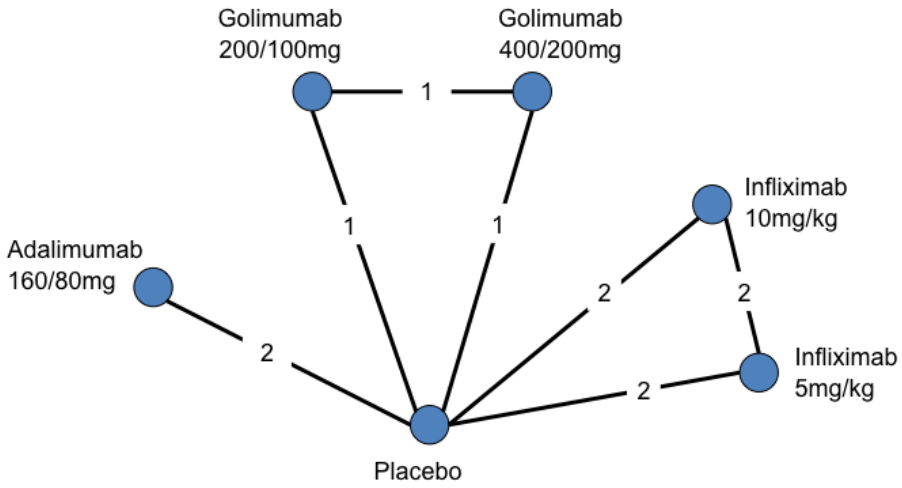
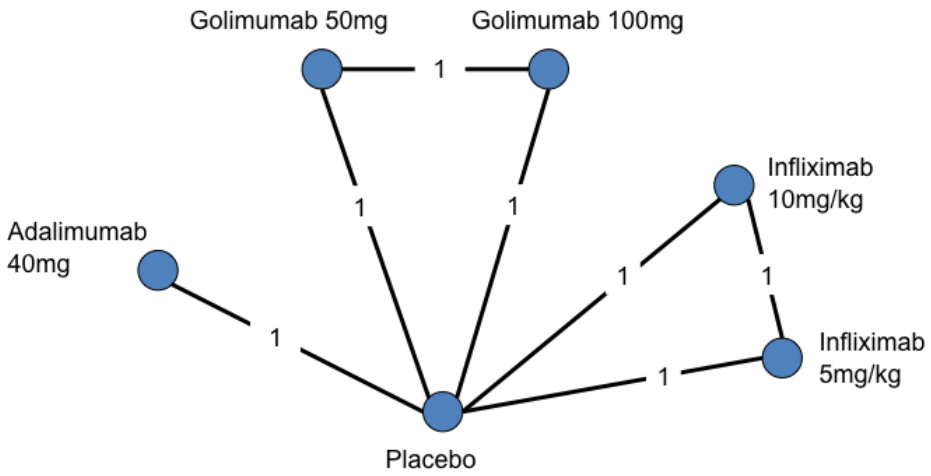


Figure 5: Treatment network for the analyses of outcomes at the end of maintenance therapy



5.8.2. Results of Network Meta-Analysis

Relevant data from included studies were analysed in the NMA, including primary and secondary efficacy outcomes and safety outcomes (Table 25). Outcomes were reported at the end of induction therapy and/or at the end of maintenance therapy.

Table 25: Outcomes analysed in the NMA

	Induction	Maintenance
Primary efficacy outcomes		
Clinical remission	✓	✓
Clinical response	✓	✓
Mucosal healing	✓	✓
Colectomy		✓
Sustained clinical remission		✓
Sustained clinical response		✓
Secondary efficacy outcomes		
Discontinuation due to lack of efficacy	✓	
IBDQ response	✓	✓
UC-related hospitalisation		✓
Corticosteroid-free remission		✓
Safety outcomes		
Discontinuation due to AEs	✓	✓
Any SAEs	✓	✓
Injection- or infusion-site reactions	✓	✓

AE, adverse event; IBDQ, Inflammatory Bowel Disease Questionnaire; SAE, serious adverse event; UC, ulcerative colitis.

Primary Outcomes Analyses

Efficacy after Induction Therapy

Clinical Remission, Clinical Response, and Mucosal Healing

Table 18 presents the relative efficacy estimates between infliximab, golimumab, and adalimumab after induction therapy for the primary outcomes of clinical remission, clinical response, and mucosal healing. Each TNF-α inhibitor had significantly greater efficacy compared to placebo for each outcome, with the exception of adalimumab for clinical response and mucosal healing. Infliximab was significantly superior to adalimumab for mucosal healing.

Table 18: RRs and 95% CrIs for primary outcomes after induction therapy, between infliximab, golimumab, and adalimumab for clinical remission, clinical response, and mucosal healing

Comparison	Clinical remission	Clinical response	Mucosal healing
IFX 5 vs. PBO	**3.81 (2.25 to 6.22)**	**1.95 (1.49 to 2.35)**	**1.88 (1.50 to 2.26)**
IFX 10 vs. PBO	**3.09 (1.74 to 5.27)**	**1.91 (1.45 to 2.32)**	**1.86 (1.47 to 2.23)**
GOL 200/100 vs. PBO	**2.54 (1.29 to 4.39)**	**1.51 (1.01 to 1.96)**	**1.42 (1.07 to 1.78)**
ADA 160/80 vs. PBO	**2.03 (1.07 to 3.60)**	1.43 (0.97 to 1.89)	1.29 (0.96 to 1.64)
IFX 5 vs. IFX 10	1.23 (0.77 to 1.96)	1.02 (0.82 to 1.27)	1.01 (0.84 to 1.22)
IFX 5 vs. GOL 200/100	1.50 (0.73 to 3.42)	1.29 (0.91 to 1.98)	1.33 (0.99 to 1.82)
IFX 5 vs. ADA 160/80	1.88 (0.87 to 4.13)	1.36 (0.94 to 2.06)	**1.47 (1.06 to 2.03)**
IFX 10 vs. GOL 200/100	1.22 (0.57 to 2.91)	1.26 (0.89 to 1.94)	1.32 (0.96 to 1.80)
IFX 10 vs. ADA 160/80	1.52 (0.69 to 3.46)	1.33 (0.91 to 2.01)	**1.45 (1.04 to 2.00)**
GOL 200/100 vs. ADA 160/80	1.25 (0.51 to 2.82)	1.06 (0.65 to 1.64)	1.10 (0.77 to 1.58)

Statistically significant estimates, i.e. estimates where the 95% credible intervals do not overlap 1.00, are presented in bold. ADA, adalimumab; GOL, golimumab; IFX, infliximab; PBO, placebo; vs., versus.

Efficacy after End of Maintenance Therapy

Clinical Remission, Clinical Response, and Mucosal Healing

Table 19 presents the relative efficacy between infliximab, golimumab, and adalimumab after maintenance therapy for the primary outcomes of clinical remission, clinical response, and mucosal healing. Each TNF-α inhibitor had significantly greater efficacy compared to placebo for each outcome. For clinical remission, golimumab 100mg yielded the largest treatment effect followed by golimumab 50mg, infliximab 5mg/kg, infliximab 10mg/kg, and adalimumab 40mg. However, no significant differences were detected between the TNF-α inhibitors. For clinical response and mucosal healing, both golimumab doses yielded the largest estimates of effect and were significantly superior to adalimumab. There were no significant comparisons for infliximab against other TNF-α inhibitors.

Table 19: RRs and 95% CrIs for primary outcomes after maintenance therapy, between infliximab, golimumab, and adalimumab for clinical remission, clinical response, and mucosal healing

Comparison	Clinical remission	Clinical response	Mucosal healing
IFX 5 vs. PBO	**2.26 (1.40 to 3.60)**	**2.39 (1.64 to 3.37)**	**2.65 (1.79 to 3.82)**
IFX 10 vs. PBO	**2.24 (1.39 to 3.55)**	**2.32 (1.59 to 3.28)**	**2.73 (1.86 to 3.92)**
GOL 50 vs. PBO	**2.30 (1.60 to 3.28)**	**2.93 (2.34 to 3.67)**	**2.81 (2.18 to 3.62)**
GOL 100 vs. PBO	**2.71 (1.93 to 3.78)**	**3.11 (2.51 to 3.87)**	**2.91 (2.27 to 3.75)**
ADA 40 vs. PBO	**1.79 (1.08 to 2.97)**	**1.60 (1.09 to 2.30)**	**1.67 (1.10 to 2.51)**
IFX 5 vs. IFX 10	1.01 (0.68 to 1.50)	1.03 (0.76 to 1.39)	0.97 (0.72 to 1.30)
IFX 5 vs. GOL 50	0.98 (0.56 to 1.73)	0.81 (0.56 to 1.16)	0.94 (0.62 to 1.39)
IFX 5 vs. GOL 100	0.83 (0.48 to 1.43)	0.77 (0.53 to 1.09)	0.91 (0.60 to 1.35)
IFX 5 vs. ADA 40	1.26 (0.64 to 2.45)	1.49 (0.91 to 2.45)	1.58 (0.93 to 2.66)
IFX 10 vs. GOL 50	0.97 (0.55 to 1.71)	0.79 (0.54 to 1.13)	0.97 (0.64 to 1.43)
IFX 10 vs. GOL 100	0.83 (0.48 to 1.42)	0.75 (0.51 to 1.06)	0.94 (0.62 to 1.38)
IFX 10 vs. ADA 40	1.25 (0.64 to 2.42)	1.45 (0.88 to 2.38)	1.63 (0.97 to 2.74)
GOL 50 vs. GOL 100	0.79 (0.53 to 1.19)	0.88 (0.63 to 1.23)	0.94 (0.67 to 1.32)
GOL 50 vs. ADA 40	1.28 (0.70 to 2.34)	**1.84 (1.24 to 2.78)**	**1.68 (1.08 to 2.66)**
GOL 100 vs. ADA 40	1.51 (0.85 to 2.70)	**1.95 (1.33 to 2.93)**	**1.74 (1.12 to 2.74)**

Statistically significant estimates, i.e. estimates where the 95% credible intervals do not overlap 1.00, are presented in bold. ADA, adalimumab; GOL, golimumab; IFX, infliximab; PBO, placebo; vs., versus.

Colectomy, Sustained Remission, and Sustained Response

Table 20 presents the relative efficacy estimates between infliximab and adalimumab for colectomy and Table 21 presents the relative efficacy estimates between infliximab, golimumab, and adalimumab for sustained clinical remission and sustained clinical response. For colectomy, no placebo data were available for golimumab and due to substantial differences in placebo colectomy rates between the ACT 1 (infliximab versus placebo) and ULTRA 2 (adalimumab versus placebo) trials, no trial data-based prior distribution was constructed for imputing the placebo response in PURSUIT. In the PURSUIT trial, only 2%-3% of golimumab induction responders re-randomised to golimumab 50mg or 100mg had a colectomy at the end of maintenance. No data were available for golimumab induction non-responders. Both infliximab and adalimumab yielded lower RR estimates of colectomy than placebo, but only infliximab 10mg/kg was significantly superior to placebo. No significant differences were observed between infliximab and adalimumab.

For sustained clinical remission, infliximab yielded the highest efficacy estimate, followed by golimumab and then adalimumab. Both golimumab and infliximab doses were significantly superior to placebo, whereas adalimumab was not. For sustained clinical response, all agents were significantly superior to placebo. Again, infliximab was associated with the largest RR estimates and adalimumab with the lowest. No significant differences were detected between the TNF-α inhibitors for either of the outcomes.

Table 20: RRs and 95% CrIs for primary outcomes after maintenance therapy, between adalimumab and infliximab for colectomy

Comparison	Colectomy
IFX 5 vs. PBO	0.78 (0.49 to 1.24)
IFX 10 vs. PBO	**0.50 (0.29 to 0.86)**
ADA 40 vs. PBO	0.79 (0.41 to 1.54)
IFX 5 vs. IFX 10	1.56 (0.86 to 2.83)
IFX 5 vs. ADA 40	0.98 (0.32 to 3.04)
IFX 10 vs. ADA 40	0.63 (0.19 to 2.10)

Statistically significant estimates, i.e. estimates where the 95% credible intervals do not overlap 1.00, are presented in bold. ADA, adalimumab; IFX, infliximab; PBO, placebo; vs., versus.

Table 21: RRs and 95% CrIs for primary outcomes after maintenance therapy, between infliximab, golimumab, and adalimumab for sustained clinical remission and sustained clinical response

Comparison	Sustained clinical remission	Sustained clinical response
IFX 5 vs. PBO	**3.23 (1.53 to 6.97)**	**2.81 (1.80 to 4.30)**
IFX 10 vs. PBO	**3.33 (1.59 to 7.22)**	**2.67 (1.71 to 4.10)**
GOL 200/100/50 vs. PBO	**2.57 (1.15 to 6.05)**	**2.17 (1.51 to 3.10)**
GOL 200/100/100 vs. PBO	**2.71 (1.23 to 6.30)**	**2.30 (1.61 to 3.26)**
ADA 160/80/40 vs. PBO	1.77 (0.81 to 4.02)	**1.83 (1.17 to 2.82)**
IFX 5 vs. IFX 10	0.97 (0.57 to 1.65)	1.05 (0.76 to 1.47)
IFX 5 vs. ADA 160/80/40	1.82 (0.62 to 5.37)	1.54 (0.86 to 2.74)
IFX 5 vs. GOL 200/100/50	1.25 (0.43 to 3.69)	1.30 (0.76 to 2.19)
IFX 5 vs. GOL 200/100/100	1.19 (0.41 to 3.48)	1.22 (0.72 to 2.04)
IFX 10 vs. ADA 160/80/40	1.89 (0.64 to 5.55)	1.46 (0.81 to 2.62)
IFX 10 vs. GOL 200/100/50	1.29 (0.44 to 3.82)	1.23 (0.72 to 2.09)
IFX 10 vs. GOL 200/100/100	1.23 (0.42 to 3.58)	1.16 (0.68 to 1.95)
GOL 200/100/50 vs. GOL 200/100/100	0.95 (0.52 to 1.71)	0.94 (0.71 to 1.24)
GOL 200/100/50 vs. ADA 160/80/40	1.46 (0.48 to 4.51)	1.19 (0.69 to 2.04)
GOL 200/100/100 vs. ADA 160/80/40	1.53 (0.51 to 4.72)	1.26 (0.73 to 2.16)
GOL 200/100/100 vs. GOL 200/100/50	1.06 (0.58 to 1.92)	1.06 (0.80 to 1.40)

Statistically significant estimates, i.e. estimates where the 95% credible intervals do not overlap 1.00, are presented in bold. ADA, adalimumab; GOL, golimumab; IFX, infliximab; PBO, placebo; vs., versus.

Secondary Outcomes Analyses

Efficacy after Induction Therapy

Data at 6-8 weeks were available for IBDQ response and discontinuation due to lack of efficacy. IBDQ response data at 8 weeks were only available for infliximab (ACT 1 and ACT 2 combined) and adalimumab (ULTRA 1). Compared with placebo, the RR of IBDQ response was 1.39 (95% CrI 1.20-1.57) with infliximab 5mg/kg, 1.37 (95% CrI 1.22-1.59) with infliximab 10mg/kg, and 1.33 (95% CrI 1.10-1.57) with adalimumab 160/80mg. The comparison of infliximab and adalimumab yielded RRs of 1.05 and 1.03 with wide CrIs. Data on discontinuation due to lack of efficacy after induction were only available for golimumab and adalimumab. No significant differences between these biologics and placebo were identified.

Efficacy after End of Maintenance Therapy

Table 22 presents the relative efficacy estimates between infliximab, golimumab, and adalimumab for UC-related hospitalisations, corticosteroid-free remission, and IBDQ response. For UC-related hospitalisations, no data were available for golimumab. Both infliximab and adalimumab yielded significant ~30%-40% relative reductions in UC-related hospitalisations compared with placebo, and no significant difference was observed between the two. For corticosteroid-free remission, all agents were significantly more effective than placebo, except golimumab 100mg. However, the estimates for golimumab should be interpreted with caution since no control proportion was available and was therefore imputed from the infliximab and adalimumab trials. No significant differences were observed between the TNF-α inhibitors. For IBDQ response, no data were available for golimumab. Both infliximab and adalimumab showed statistical superiority over placebo; infliximab had slightly higher RR estimates, but no significant difference was observed between the two TNF-α inhibitors.

Table 22: RRs and 95% CrIs for secondary outcomes after maintenance therapy, between infliximab, golimumab, and adalimumab for UC-related hospitalisation, corticosteroid-free remission, and IBDQ response

Comparison	UC-related hospitalisation	Corticosteroid-free remission	IBDQ response
IFX 5 vs. PBO	**0.64 (0.42 to 0.93)**	**3.36 (1.71 to 7.05)**	**1.82 (1.39 to 2.34)**
IFX 10 vs. PBO	**0.60 (0.40 to 0.88)**	**3.46 (1.77 to 7.27)**	**1.74 (1.32 to 2.26)**
GOL 50 vs. PBO	--	**2.13 (1.13 to 4.10)**	--
GOL 100 vs. PBO	--	1.84 (0.94 to 3.60)	--
ADA 40 vs. PBO	**0.70 (0.50 to 0.98)**	**3.06 (1.20 to 8.36)**	**1.40 (1.02 to 1.90)**
IFX 5 vs. IFX 10	1.05 (0.68 to 1.65)	0.97 (0.60 to 1.57)	1.05 (0.83 to 1.33)
IFX 5 vs. GOL 50	--	1.57 (0.63 to 4.20)	--
IFX 5 vs. GOL 100	--	1.82 (0.71 to 4.96)	--
IFX 5 vs. ADA 40	0.90 (0.53 to 1.52)	1.09 (0.34 to 3.54)	1.29 (0.90 to 1.86)
IFX 10 vs. GOL 50	--	1.62 (0.65 to 4.32)	--
IFX 10 vs. GOL 100	--	1.88 (0.74 to 5.12)	--
IFX 10 vs. ADA 40	0.85 (0.50 to 1.46)	1.13 (0.35 to 3.65)	1.24 (0.86 to 1.80)
GOL 50 vs. GOL 100	--	1.17 (0.62 to 2.25)	--
GOL 50 vs. ADA 40	--	0.70 (0.21 to 2.16)	--
GOL 100 vs. ADA 40	--	0.60 (0.18 to 1.87)	--

Statistically significant estimates, i.e. estimates where the 95% credible intervals do not overlap 1.00, are presented in bold. ADA, adalimumab; GOL, golimumab; IBDQ, Inflammatory Bowel Disease Questionnaire; IFX, infliximab; PBO, placebo; UC, ulcerative colitis; vs., versus.

Safety Analyses

Safety after Induction Therapy

Table 23 presents the relative safety estimates between golimumab and adalimumab for discontinuations due to AEs, any SAEs, and injection-site reactions after induction therapy. Safety data on infliximab were only available at 30 and 54 weeks, and therefore, only comparisons of golimumab and adalimumab after induction were possible. For discontinuations due to AEs, golimumab yielded a greater relative reduction compared to placebo than adalimumab compared to placebo. However, the number of events was low for both agents, and therefore, the differences between the two were not significant. Both golimumab and adalimumab yielded close to half as many SAEs as placebo. Golimumab 50mg was significantly superior to placebo for SAEs, and the upper 95% CrI limits for both golimumab 100mg and adalimumab were only slightly larger than 1.00. Lastly, the risk of injection-site reactions was approximately twice that of placebo with both golimumab and adalimumab. For SAEs and injection-site reactions no significant differences between golimumab and adalimumab were observed.

Table 23: RRs and 95% CrIs for safety outcomes after induction therapy, between golimumab and adalimumab for discontinuations due to AEs, any SAEs, and injection-site reactions

Comparison	Discontinuation due to AEs	Any SAEs	Injection-site reactions
IFX 5 vs. PBO	--	--	--
IFX 10 vs. PBO	--	--	--
GOL 50 vs. PBO	0.26 (0.01 to 2.38)	**0.45 (0.20 to 0.94)**	2.28 (0.83 to 6.93)
GOL 100 vs. PBO	0.26 (0.01 to 2.38)	0.54 (0.25 to 1.09)	2.06 (0.73 to 6.41)
ADA 40 vs. PBO	0.78 (0.18 to 3.06)	0.50 (0.21 to 1.11)	1.92 (0.79 to 4.96)
IFX 5 vs. IFX 10	--	--	--
IFX 5 vs. GOL 50	--	--	--
IFX 5 vs. GOL 100	--	--	--
IFX 5 vs. ADA 40	--	--	--
IFX 10 vs. GOL 50	--	--	--
IFX 10 vs. GOL 100	--	--	--
IFX 10 vs. ADA 40	--	--	--
GOL 50 vs. GOL 100	1.00 (0.03 to 37.0)	0.82 (0.22 to 1.97)	1.10 (0.48 to 2.61)
GOL 50 vs. ADA 40	0.33 (0.01 to 4.83)	0.88 (0.28 to 2.77)	1.19 (0.30 to 4.81)
GOL 100 vs. ADA 40	0.33 (0.01 to 4.80)	1.09 (0.36 to 3.29)	1.07 (0.27 to 4.39)

Statistically significant estimates, i.e. estimates where the 95% credible intervals do not overlap 1.00, are presented in bold. ADA, adalimumab; AE, adverse event; GOL, golimumab; IFX, infliximab; PBO, placebo; SAE, serious adverse event; vs., versus.

Safety after End of Maintenance Therapy

Table 24 presents the relative safety estimates between infliximab, golimumab, and adalimumab for discontinuations due to AEs, any SAEs, and injection- or infusion-site reactions after maintenance therapy. For discontinuations due to AEs, all agents yielded a lower risk

compared with placebo with the exception of golimumab 100mg although none of the comparisons were significant. For SAEs, there were no significant differences between infliximab, golimumab, adalimumab, and placebo, though infliximab was significantly superior to golimumab 100mg. For injection-site reactions, golimumab 100mg and adalimumab were associated with a significantly higher risk compared with placebo. Similar infusion-site reactions were observed with infliximab 5mg/kg and infliximab 10mg/kg. Golimumab 50mg was associated with significantly fewer injection-site reactions than golimumab 100mg. It is important to note that infliximab is administered intravenously whereas golimumab and adalimumab are administered subcutaneously, and therefore some caution is needed in interpreting comparative risks between the interventions. Lastly, for all three outcomes the results for golimumab should be interpreted with caution since no placebo data were available; the placebo risks were imputed using data from the other trials.

Table 24: RRs and 95% CrIs for safety outcomes after maintenance therapy, between infliximab, golimumab, and adalimumab for discontinuations due to AEs, any SAEs, and injection- or infusion-site reactions

Comparison	Discontinuation due to AEs	Any SAEs	Injection- or infusion-site reactions
IFX 5 vs. PBO	0.51 (0.25 to 1.00)	0.68 (0.45 to 1.02)	1.14 (0.65 to 2.00)
IFX 10 vs. PBO	0.69 (0.36 to 1.27)	0.70 (0.46 to 1.04)	1.28 (0.74 to 2.22)
GOL 50 vs. PBO	0.81 (0.31 to 1.93)	1.09 (0.53 to 2.11)	1.01 (0.18 to 4.86)
GOL 100 vs. PBO	1.42 (0.65 to 2.94)	1.76 (0.98 to 3.04)	**3.67 (1.24 to 11.7)**
ADA 40 vs. PBO	0.67 (0.39 to 1.13)	0.98 (0.62 to 1.51)	**3.11 (1.66 to 6.05)**
IFX 5 vs. IFX 10	0.74 (0.35 to 1.54)	0.97 (0.63 to 1.51)	--
IFX 5 vs. GOL 50	0.63 (0.20 to 2.05)	0.63 (0.29 to 1.44)	--
IFX 5 vs. GOL 100	0.36 (0.13 to 1.00)	**0.39 (0.20 to 0.79)**	--
IFX 5 vs. ADA 40	0.76 (0.32 to 1.82)	0.70 (0.38 to 1.28)	--
IFX 10 vs. GOL 50	0.85 (0.29 to 2.67)	0.64 (0.29 to 1.47)	--
IFX 10 vs. GOL 100	0.49 (0.19 to 1.32)	**0.40 (0.20 to 0.81)**	--
IFX 10 vs. ADA 40	1.03 (0.45 to 2.34)	0.72 (0.39 to 1.32)	--
GOL 50 vs. GOL 100	0.54 (0.21 to 1.31)	0.55 (0.26 to 1.12)	**0.24 (0.05 to 0.80)**
GOL 50 vs. ADA 40	1.20 (0.41 to 3.38)	1.11 (0.47 to 2.50)	0.32 (0.05 to 1.73)
GOL 100 vs. ADA 40	2.10 (0.83 to 5.29)	1.80 (0.86 to 3.67)	1.18 (0.35 to 4.22)

Statistically significant estimates, i.e. estimates where the 95% credible intervals do not overlap 1.00, are presented in bold. ADA, adalimumab; AE, adverse event; GOL, golimumab; IFX, infliximab; PBO, placebo; SAE, serious adverse event; vs., versus.

Summary of NMA Results

At the end of induction therapy, all TNF-α inhibitors were significantly superior to placebo for primary efficacy outcomes (clinical remission, clinical response, and mucosal healing) with the exception of adalimumab for clinical response and mucosal healing. Infliximab was associated with the largest RR estimates for all outcomes. All TNF-α inhibitors were broadly similar to each other, except for infliximab which was significantly superior to adalimumab for mucosal healing.

There were no significant comparisons for any of the secondary efficacy outcomes after induction. In terms of safety, no data were available for infliximab at the end of induction, though golimumab and adalimumab demonstrated similar outcomes.

At the end of maintenance therapy, all TNF-α inhibitors were significantly superior to placebo for primary efficacy outcomes. When compared to each other, infliximab and golimumab demonstrated similar non-significant effects for all outcomes, though golimumab was significantly superior to adalimumab for clinical response and mucosal healing. For colectomy outcomes, infliximab was associated with a significantly lower risk than placebo but was similar to adalimumab (non-significant comparison). Regarding sustained clinical remission and sustained clinical response, all TNF-α inhibitors were significantly more effective than placebo except for adalimumab for sustained clinical remission. For both outcomes, infliximab was associated with the highest RRs, followed by golimumab. When compared against each other, no TNF-α inhibitor was significantly better than the others for the sustained outcomes.

For secondary efficacy outcomes after maintenance, all TNF-α inhibitors were significantly better than placebo, barring golimumab 100mg for corticosteroid-free remission. For these secondary outcomes the magnitude of effect was again greatest for infliximab. Comparisons within the TNF-α inhibitor class demonstrated broadly similar effects (though there were no data for adalimumab or golimumab in UC-related hospitalisation or IBDQ response).

Finally, analyses of safety outcomes following maintenance therapy demonstrated that infliximab was associated with fewer discontinuations due to AEs and fewer SAEs than placebo, albeit with a non-significant comparison. However, infliximab was significantly better than golimumab 100mg for the SAEs comparison. For injection- or infusion-site reactions, infliximab and golimumab 50mg were similar to placebo, and golimumab 100mg and adalimumab had a significantly higher risk than placebo.

The NMA suggests superior efficacy of infliximab in inducing mucosal healing when compared with adalimumab and similar efficacy profiles of infliximab and golimumab. The safety profiles of infliximab, golimumab, and adalimumab were generally similar across outcomes. Therefore, infliximab provides an equally effective treatment option for patients with moderately to severely active UC for whom IV treatment is more appropriate.

Strengths and Limitations of NMA

The NMA has several strengths and limitations. First, several outcomes were analysed. Most of the considered outcomes are closely related, but not all were reported in the included trials. The observed consistency in magnitudes and direction of effects across outcomes therefore adds confidence to the validity of the findings. Secondly, the characteristics of the patient and intervention characteristics in the included RCTs are highly similar, thus supporting the validity of combining the included trials in a NMA. Thirdly, PURSUIT used a non-conventional trial design, and thus, conventional NMA techniques would not have sufficed for producing comparative effect estimates between golimumab, infliximab, and adalimumab. This NMA employed novel techniques of optimising the use of all available data. The assumptions supporting the novel NMA techniques employed were conservative to avoid overestimating the efficacy and safety of golimumab.

A main limitation of the NMA is the small number of trials and patients available for analysis. Nevertheless, the consistency in magnitude and direction of effects across all outcomes supports the reliability of the current findings. Another limitation is related to the safety outcomes, particularly in ULTRA 2 and PURSUIT. In ULTRA 2, safety data were not reported separately for TNF-α inhibitor-naïve and -inadequate responders. Patients with previous inadequate clinical response to TNF-α inhibitors comprised ~40% of the trial population in ULTRA 2. Since this population is further progressed in their condition and treatments are less likely to reduce condition-related AEs, it is likely that the inclusion of these groups could have attenuated differences between placebo and adalimumab, and thus bias results against adalimumab. For PURSUIT, the rules for reporting of safety outcomes were not identical to those of the ACT and ULTRA trials. PURSUIT required efficacy assessments every 4 weeks, which could all be factors leading to increased safety signals for golimumab.

For outcomes at the end of maintenance therapy, differences in patient follow-up should be noted between ULTRA 2 and ACT 1. The former allowed patients with inadequate clinical response at 12 weeks or later to either switch to adalimumab (if originally randomised to placebo) or escalate their dose (if originally randomised to adalimumab). The latter randomised patients to a 52 week course of treatment or placebo and did not allow any modifications to the assigned intervention (or placebo) during those 52 weeks. However, patients who chose to switch were analysed using 'non-responder imputation', which assumes that patients would have remained non-responders had they continued the full 52 weeks of treatment. Since more patients receiving placebo are likely to switch, this approach may underestimate the 52 week

clinical response in the placebo group, and thus overestimate the comparative efficacy of adalimumab versus placebo.

Finally, the measurement of efficacy outcomes (sustained clinical remission and sustained clinical response) was more stringent in PURSUIT-M than all previous trials; in PURSUIT-M, patients not only reported full Mayo scores at weeks 0, 30, and 54, but also reported Partial Mayo scores every month. In contrast, only full Mayo scores were measured in the maintenance phases of the ULTRA and ACT trials (at weeks 0, 30, and 54). Therefore, the standards for sustained clinical remission and sustained clinical response were much stricter for participants in PURSUIT-M, which may lead to a conservative estimation of the maintenance efficacy of golimumab in the NMA.

6. Cost-Effectiveness

6.1. Published Cost-Effectiveness Evaluations

6.1.1. Identification of Studies

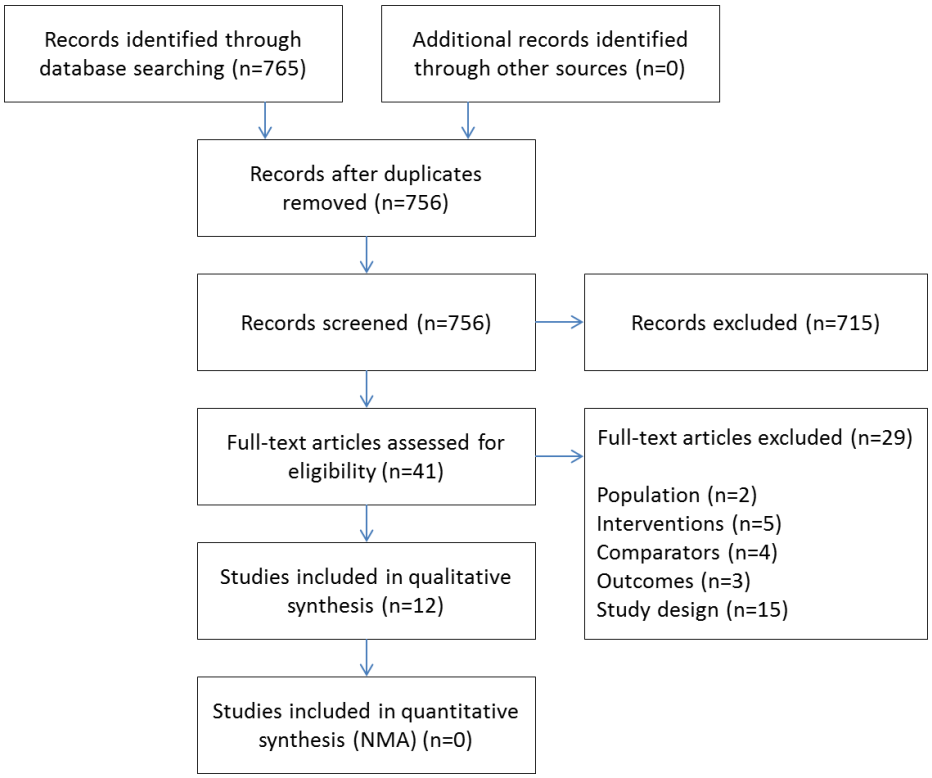
Searches were conducted in Embase®, PubMed®, and the National Health Service Economic Evaluation Database (NHSEED) (from inception to week 29, 2013) to identify published economic evaluations in UC to help inform the model structure and relevant parameters. The search strategies developed for each of these databases are shown in **Error! Reference source not found.**.

Publication titles and abstracts identified through the searches were scanned for inclusion/exclusion by a single reviewer and the full-texts of selected relevant studies were again reviewed for inclusion/exclusion prior to data extraction. The inclusion and exclusion criteria were as follows:

- Inclusion criteria:
  - Cost-effectiveness model/analysis in UC
  - Any severity of UC
  - Interventions: golimumab, adalimumab, infliximab, aminosalicylates, 6-MP, AZA, immunomodulators, ciclosporin, or surgery
- Exclusion criteria:
  - Non-English language
  - Population including patients with Crohn's disease

Searches in Embase®, PubMed®, and NHSEED identified 544, 189, and 32 publications, respectively. Of the total of 765 identified publications, 41 were deemed relevant to the decision problem during the title and abstract screening and 12 studies were finally included after full-text review (Figure 6).

Figure 6: Schematic of the publication selection process



NMA, network meta-analysis.

6.1.2. Description of Identified Studies

An overview of the 12 relevant studies is provided in Table 26.

Table 26: Summary of published cost-effectiveness models

Study	Country/ perspective	Target population	Model structure	Data	Time horizon/cycle length	Intervention/ comparator	Health states	Key outcomes
Tsai *et al.* 2008 [48]	UK NHS	Moderate-to-severe active UC	Markov model	ACT 1, ACT 2	Time horizon: Basecase: 5 years Sensitivity analyses: 1 year, lifetime Cycle length: First cycle: 8 weeks Second cycle: 6 weeks Followed by 8 week cycles	• Infliximab • Scheduled maintenance treatment	• Remission • Mild • Moderate-to-severe • Surgery • Post-surgery remission • Post-surgery complication	• ICERS • Costs • QALYs
Xie *et al.* 2009 [49]	Canada Public-funded healthcare system	Moderate-to-severe UC	Markov model	ACT 1, ACT 2	Time horizon: 5 years Cycle length First cycle: 0-8 weeks Second cycle: 9-30 weeks Third cycle: 31-54 weeks Then every 27 weeks beyond week 55	• 5mg/kg infliximab + adalimumab • 5mg/kg and 10mg/kg infliximab + adalimumab • Usual care	• Remission • Active UC • Surgery • Surgical remission • Surgical complication	• ICUR
Chaudhary & Fan 2013 [50]	Netherlands National payer	Moderate-to-severe UC with inadequate response or intolerant to corticosteroids, 5-ASA, 6-MP, or AZA	Decision tree + Markov model	ACT 1, ACT 2	Time horizon: Base case: 1 year Sensitivity analysis: 10 years Cycle length: First cycle: 3 months Second cycle: 9 months	• 5mg/kg infliximab • Ciclosporin • Surgery	• Remission • Surgery • Surgical complications • Surgical remission	• ICER

Brereton *et al.* 2010 [51]	UK NHS	Mild-to-moderate UC	Markov model	2 MMX trials, 1 open-label extension study	Time horizon: 5 years Cycle length: 8 weeks	• MMX mesalazine • Mesalazine •	• Active line: first-line • Active UC: first-line increased dosage • Active UC: 5-ASA failure/severe relapse • Surgery • Post-surgery • Remission • Death	• ICER • Effects of remission on CRC rates
Connolly *et al.* 2009 [52]	UK NHS	Mild-to-moderate active UC	Markov model	Randomised trial reporting efficacy of mesalazine	Time horizon: unclear Cycle length: 8 weeks	• Concomitant oral and topical mesalazine • Oral mesalazine	• Active UC • Mesalazine-refractory active UC • Steroid-refractory active UC • Infliximab active response UC • Remission	• Incremental QALYs • Incremental costs • ICER
Saini *et al.* 2012 [53]	US Health insurance provider	Newly UC-diagnosed adult population	Markov model	Cochrane meta-analysis, Cochrane review of ACT 1	Time horizon: 5 years Cycle length: 3 months	• Symptom targeted therapy • 5-ASA maintenance therapy • Continuous 5-ASA maintenance therapy • Inflammatio n targeted therapy	• No medication • 5-ASA • Azathioprine • Infliximab • Active disease • Colectomy	• Average flare per patient • Proportion of patients undergoing colectomy • QALYs • Costs • ICER
Punekar & Hawkins 2010 [54]	UK NHS	Patients hospitalised with acute exacerbation	Markov model	ACT 1, D'Haens 2001	Time horizon: Basecase: 1 year Sensitivity analysis: 10 years Cycle length: 3 months	• Infliximab • Standard of care • Ciclosporin • Surgery	• Multiple health states	• ICER

Odes *et al.* 2010 [55]	European N/A	Prospective cohort of UC patients	Markov model	European prospective data comprising UC patients	Time horizon: 10 years Cycle length: 3 months	• N/A	• Medical remission • Mild • Drug-responsive • Drug-dependent • Drug-refractory • Surgery • Surgical remission	• Distribution of patients across different health states • Transition probabilities
Connolly *et al.* 2012 [56]	Netherlands Health service	Active and quiescent UC	Decision tree	Marteau 2005, Dignass 2009	Time horizon: less than a year Cycle length: N/A	• 1g topical and 4g oral mesalazine • 4g oral mesalazine	• Combination therapy with oral mesalazine and topical mesalazine or oral mesalazine • Mesalazine-refractory active UC • Steroid-refractory active UC • Infliximab-responsive active UC • Remission	• Costs • QALYs •
Buckland & Bodger 2008 [57]	UK NHS	Hypothetical cohort of patients with moderately active UC	Decision tree	ASCEND I, ASCEND II	Time horizon: 12 weeks Cycle length: N/A	• HD mesalazine • SD mesalazine	• First-line (HD/SD mesalazine) • Second-line (oral steroids) • Third-line (intensive steroids) • Fourth-line: IV ciclosporin • Fifth-line: Surgery	• Cost per patient • QALYs •
Prenzler *et al.* 2011 [58]	Germany Statutory health insurance	Mild-to-moderate UC	Markov cohort model	Phase III trial of Mezavant® + Asacol® Open label study for Mezavant®	Time horizon: Basecase: 5 years Sensitivity analysis: lifetime Cycle length: 8 weeks	• Mezavant® • Asacol®	• Active UC: 1 line • Active UC: 1 line increased dosage • Active UC: 2 line • Active UC: failure/relapse • Surgery • Post-surgery • Remission • Death	• Costs • QALYs

Yen *et al.* 2008 [59] *	US Third party payer	Mild-to-moderate UC	Markov model	Published literature (multiple sources)	Time horizon: 2 years Cycle length: NR	• 5-ASA 4.8g/day induction dose with no maintenance • 5-ASA 4.8g/day induction dose followed by 2.4g/day maintenance dose, escalated to 4.8g/day in case of flare	• Remission - no maintenance • Remission on maintenance (5-ASA) • Remission on maintenance (infliximab or 6-MP) • Outpatient flare • Inpatient flare • Colectomy with ileal pouch • Pouch complications	• Mean flare per person • Cost per flare prevented • QALYs • Costs • ICER

* Some health states are missing for this study due to lack of clarity. 5-ASA, 5-aminosalicylate; 6-MP, 6-mercaptopurine; AZA, azathioprine; CRC, colorectal cancer; HD, high dosage; ICER, Incremental Cost-Effectiveness Ratio; ICUR, Incremental Cost-Utility Ratio; IV, intravenous; MMX, multi-matrix; N/A, not applicable; NHS, National Health Service; NR, not reported; QALY, Quality-Adjusted Life Year; SD, standard dosage; UC, ulcerative colitis; UK, United Kingdom; US, United States.

Based on the review detailed in previous sections, the two following model structures seem to be the most common:

- Structure based on sequence therapy: classification of health states in remission and active disease, where patients followed sequential therapy (different lines of treatment) based on their response to therapy
- Structure based on severity measure (using Mayo scores): classification of health states using the Mayo score indicators. This approach does not consider sequential therapy and this model was implemented for TA140[6]

Markov modelling is the most common approach used in nine of the selected 12 studies; five studies used a UK NHS perspective. None of the included studies compared all therapies in the same study. All the included studies reported health outcomes and/or QALYs. Variability in sources and values was noted. The review of previous economic models highlighted poor reporting of cost data. Where resource use estimates were reported, they were typically derived from interviews with experts in the field.

6.2. De Novo Analysis

6.2.1. Patients

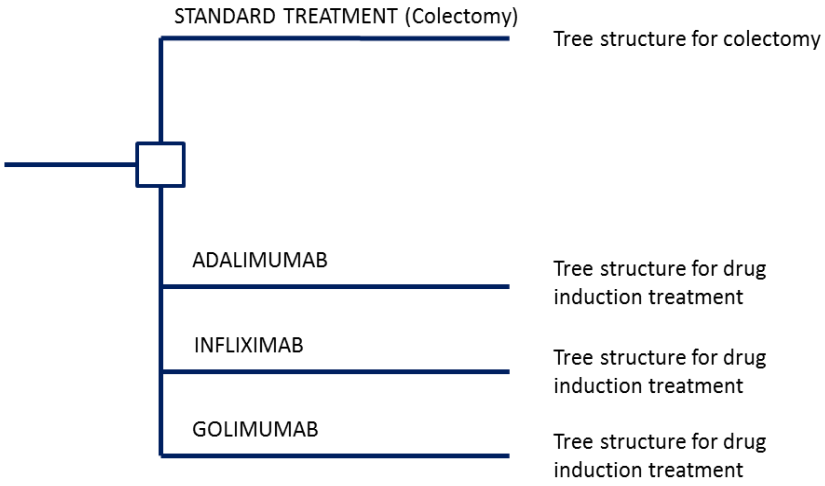
Infliximab is indicated for the treatment of moderately to severely active UC in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-MP or AZA, or who are intolerant to or have medical contraindications for such therapies. The target population in the model follows this indication.

6.2.2. Model Structure

The model demonstrates the cost-effectiveness of infliximab for the treatment of patients with moderately to severely active UC who have failed conventional drug treatment, from an NHS perspective.

The model compares golimumab against current non-biologic standard of care, where patients failing treatment with conventional therapy progress to colectomy. The cost-effectiveness of golimumab against infliximab and adalimumab, the other biologic drugs licensed for the treatment of UC, was also analysed. The economic model consists of four “arms” that represent the four intervention strategies as shown in Figure 7.

Figure 7: Model structure showing the four intervention strategies compared



Depending on the intervention strategy, the course of moderately to severely active UC is characterised by the following treatment phases:

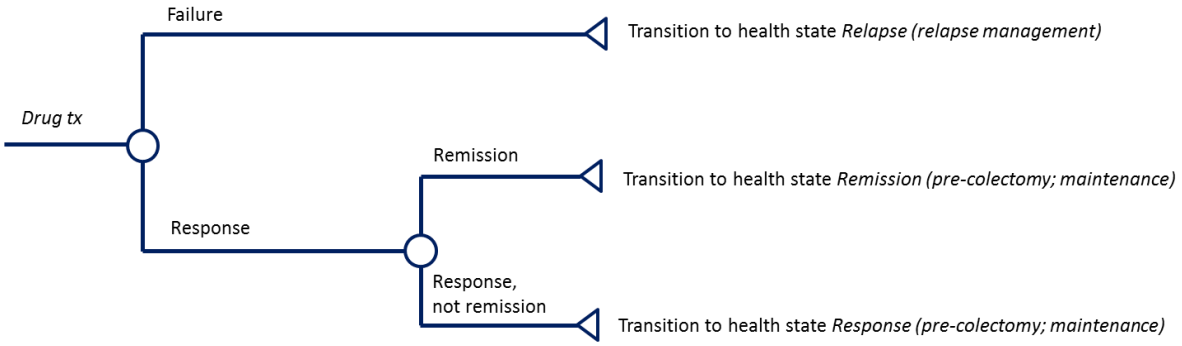
- Patients receiving a biologic (i.e. golimumab, infliximab, or adalimumab) as the initial treatment go through the following phases: drug induction treatment, drug maintenance treatment if a responder to induction treatment, relapse management, colectomy, and post-colectomy
- Patients receiving colectomy upon failure of conventional therapy progress to the post-colectomy phase

Biologic Induction Treatment

The outcomes with biologic induction treatment as the initial treatment for the population of interest are captured with a tree structure as illustrated in Figure 8.

With each treatment there is a probability of response with remission, a probability of response without remission, and a probability of failure. Remission was defined as a Mayo score of 0-2 and represents a state where most or all symptoms were completely suppressed. Response was defined as a Mayo score of 3-5, and failure was defined as moderately to severely active UC with a Mayo score of 6-12. Patients in response or remission continue with drug maintenance treatment. Patients with a failed induction treatment transition to the relapse management phase. According to general mortality figures, a small fraction will have died at the end of induction treatment.

Figure 8: Tree structure reflecting outcomes with drug induction treatment as initial treatment in model

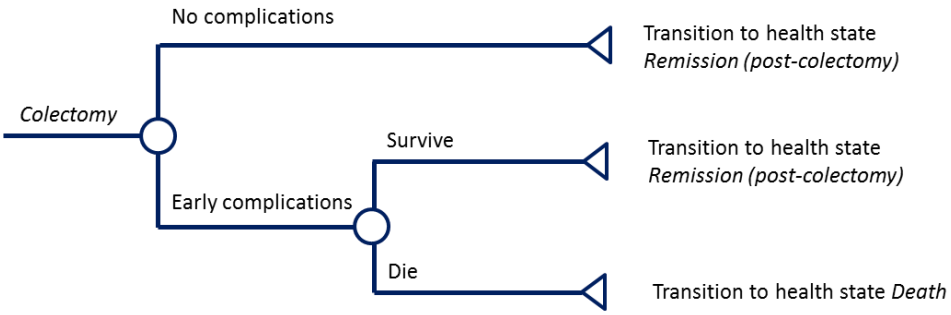


Colectomy as Induction Treatment

The outcomes with colectomy as standard of care for patients with moderately to severely active UC who fail to respond to conventional drug treatment are presented in Figure 9.

With colectomy there is a probability of early complications. All patients who undergo colectomy and do not die of complications remain in a post-colectomy phase. Patients who undergo colectomy without complications transition to a post-colectomy health state.

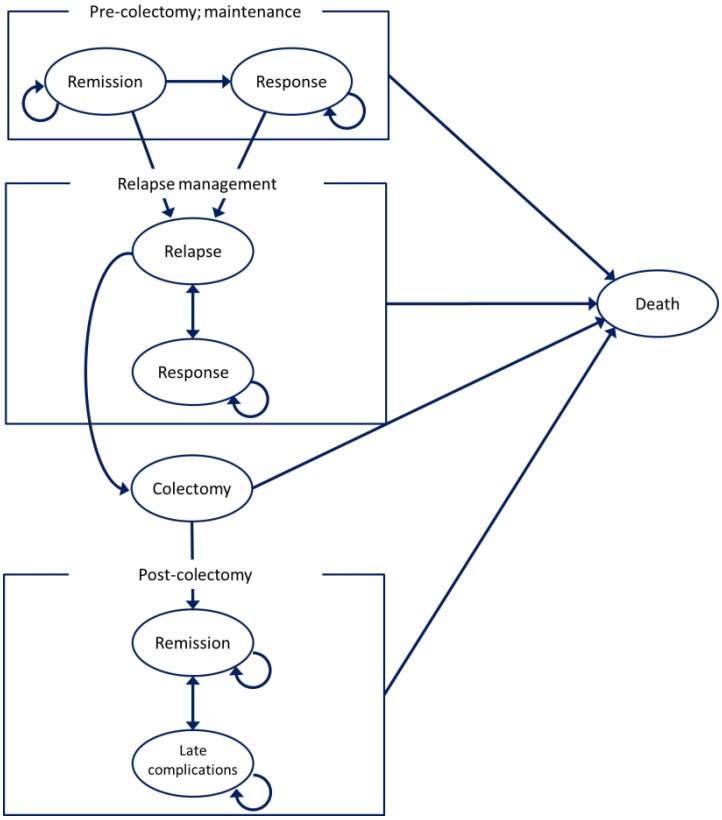
Figure 9: Tree structure reflecting outcomes with colectomy as treatment in model



Maintenance Treatment and Long-Term Follow-up

Maintenance treatment, relapse management, colectomy, and the post-colectomy phase following the initial treatment of choice are reflected with a Markov state-transition structure as presented in Figure 10.

Figure 10: Markov state-transition structure for maintenance treatment and long-term follow-up



6.2.3. Disease Progression

The model consists of the following mutually exclusive health states: *Response (pre-colectomy; maintenance)*; *Remission (pre-colectomy; maintenance)*; *Response (relapse management)*; *Relapse (relapse management)*; *Colectomy*; *Remission (post-colectomy)*; *Late complications (post-colectomy)*; and *Death*.

The cycle length of the model is 2 months. The possible transitions between the different health states at the end of each 2 month cycle are presented in Figure 11 and occur according to constant transition probabilities.

Figure 11: Possible transitions between health states (grey) with maintenance treatment and long-term follow-up

to / *from*	**Response** (pre-colectomy; maintenance)	**Remission** (pre-colectomy; maintenance)	**Response** (relapse management)	**Relapse** (relapse management)	**Colectomy**	**Remission** (post-colectomy)	**Late complications** (post-colectomy)	**Death**
Response (pre-colectomy; maintenance)								
Remission (pre-colectomy; maintenance)								
Response (relapse management)								
Relapse (relapse management)								
Colectomy								
Remission (post-colectomy)								
Late complications (post-colectomy)								
Death								

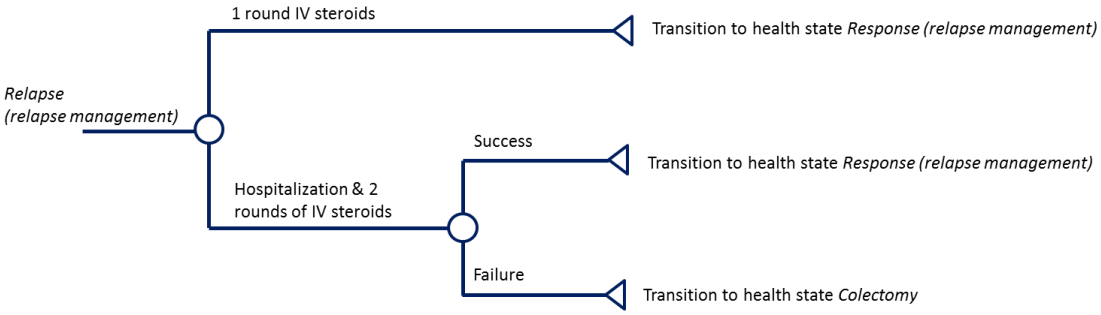
Patients who showed a response with biologic induction treatment but are not in remission start the Markov state-transition structure in the health state *Response (pre-colectomy; maintenance)*. Patients who experienced remission with induction treatment start the Markov state-transition structure in the health state *Remission (pre-colectomy; maintenance)*. Patients who failed to respond to induction treatment start the Markov structure in the health state *Relapse (relapse management).* Patients who did not receive biologic induction treatment, but instead underwent colectomy, start the Markov state-transition structure in the health state *Colectomy*.

The duration of drug maintenance treatment is reflected by the time spent in the health states *Response (pre-colectomy; maintenance)* and *Remission (pre-colectomy; maintenance)* and is based upon efficacy. Upon losing remission patients transition to the health state *Response (pre-colectomy; maintenance)*. Upon losing response, patients transition to the health state *Relapse (relapse management)*. To ensure that the modelled duration of biologic treatment matched the observed discontinuation rates of biologic treatment in the trial for golimumab, it was assumed that patients losing remission do not transition straight to *Relapse (relapse management)*.

All patients who enter the relapse management phase (either due to failed induction or maintenance treatment) as represented with the health state *Relapse (relapse management)*, are treated first with IV steroids. If they respond to IV steroids, a transition to the health state *Response (relapse management)* will occur. If patients fail the first course of IV steroids, they are

assumed to be hospitalised and receive a second round of IV steroids. With response to this second round of IV steroids they will also transition to the health state *Response (relapse management)*. However, when patients fail IV steroids they are assumed inadequate responders to all treatment options, and therefore in need of colectomy and so transition to the health state *Colectomy* (Figure 12). Patients in the health state *Response (relapse management)* who relapse, transition back to *Relapse (relapse management)* and receive another course of IV steroids.

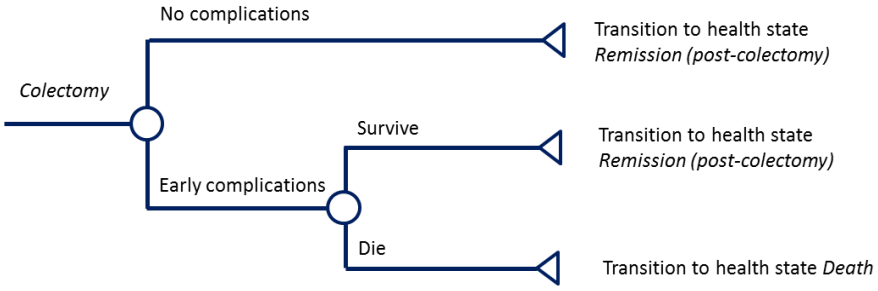
Figure 12: Possible transitions from health state relapse during relapse management phase



to / *from*	**Response** (pre-colectomy; maintenance)	**Remission** (pre-colectomy; maintenance)	**Response** (relapse management)	**Relapse** (relapse management)	**Colectomy**	**Remission** (post-colectomy)	**Late complications** (post-colectomy)	**Death**
Response (pre-colectomy; maintenance)								
Remission (pre-colectomy; maintenance)								
Response (relapse management)								
Relapse (relapse management)								
Colectomy								
Remission (post-colectomy)								
Late complications (post-colectomy)								
Death								

In a similar fashion to that described above for colectomy as initial treatment, the complications and mortality with colectomy in the Markov structure are reflected in Figure 13.

Figure 13: Possible transitions from health state colectomy



to / *from*	Response (pre-colectomy; maintenance)	Remission (pre-colectomy; maintenance)	Response (relapse management)	Relapse (relapse management)	Colectomy	Remission (post-colectomy)	Late complications (post-colectomy)	Death
Response (pre-colectomy; maintenance)								
Remission (pre-colectomy; maintenance)								
Response (relapse management)								
Relapse (relapse management)								
Colectomy								
Remission (post-colectomy)								
Late complications (post-colectomy)								
Death								

All patients who undergo colectomy and do not die of complications transition to the health state *Remission (post-colectomy).* Patients who have a colectomy may experience a number of long-term complications, which is reflected with a temporary transition to the health state *Late complications (post-colectomy)*. Complications included were: pouchitis, bowel obstruction, and anal fistula.

For each health state there is probability of dying according to mortality figures for the general UK population.

6.2.4. Technologies

NICE recommends the use of infliximab within its marketing authorisation, for the treatment of acute exacerbations of severely active UC. It relates to an induction course of three doses of infliximab[7]. Infliximab is recommended as an option for the treatment of acute exacerbations of severely active UC only in patients in whom ciclosporin is contraindicated or clinically inappropriate, based on a careful assessment of the risks and benefits of treatment in the individual patient.

At present, no biologic treatment is recommended by NICE for the treatment of moderately to severely active UC. In the absence of biologic treatment, patients failing to respond to conventional therapy progress to colectomy which is widely accepted as the standard of care in the UK. As such, golimumab was compared with colectomy.

In-line with the scope for this appraisal, other comparators for infliximab were biologic treatments that are licensed for use in the treatment of UC and have robust evidence of efficacy at the appropriate stage of the treatment pathway.

The dosing regimen for infliximab was 5mg/kg given as an IV infusion followed by additional 5mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter.

Golimumab is given as an initial dose of 200mg, followed by 100mg at week 2, then 50mg every 4 weeks, thereafter for patients with body weight less than 80kg. For those patients with body weight greater than or equal to 80kg, golimumab is given as an initial dose of 200mg, followed by 100mg at week 2, then 100mg every 4 weeks, thereafter.

The recommended adalimumab induction dose regimen for adult patients with moderately to severely active UC is 160mg at week 0 (dose can be administered as four injections in 1 day or as two injections per day for 2 consecutive days) and 80mg at week 2. After induction treatment, the recommended dose is 40mg every other week (EOW) via subcutaneous injection. Some patients who experience a decrease in their response may benefit from an increase in dosing frequency to 40mg adalimumab every week (EW)[60]. In the ULTRA study 22.9% of patients required dose escalation from 40mg EOW to 40mg EW. UK clinical experts have advised that up to 80% of patients with moderately to severely active UC treated with adalimumab receive 40mg EW. As such, in the model a conservative assumption that 50% of patients treated with adalimumab receive the weekly dose was applied.

6.3. Clinical Parameters and Variables

6.3.1. Efficacy of Each Intervention Strategy

The probabilities of response, remission, and failure with drug induction treatment and the transition probabilities related to drug maintenance treatment prior to the relapse management phase vary according to the intervention strategy evaluated.

Transition probabilities related to the relapse management phase, colectomy, and post-colectomy phase are the same for all intervention strategies compared.

Biologic-specific (transition) probabilities for response and remission were obtained by transforming the probabilities expected with non-biologic drug treatment into odds of (sustained) response and (sustained) remission. These were subsequently multiplied with ORs for each biologic treatment relative to placebo (obtained from RCT data) in order to obtain the odds of (sustained) response and (sustained) remission for each biologic, and then transformed into (transition) probabilities (more information is provided in Section 6.3.3). It was assumed that ORs of relative treatment effect are constant over time.

Adverse events associated with drug induction and maintenance treatment, as well as treatment during the relapse management phase, were limited to serious infections resulting in hospitalisations. The probability of this event was not used for any transition between health states, but simply to adjust the expected costs for each health state where drug treatment was considered. Any injection- or infusion-site reactions, infections not leading to hospitalisation, and malignancies were excluded as there were no significant differences in these AEs between the biologic interventions.

6.3.2. Efficacy of Drug Induction Treatment

The efficacy of drug induction treatment with each of the biologics and conventional treatment were obtained with a NMA of RCTs (identified by means of a systematic literature search). The trials ULTRA 1 and ULTRA 2 were included for adalimumab, ACT 1 and ACT 2 for infliximab, and PURSUIT for golimumab. Each of these trials were placebo-controlled. In Table 27 the observed data regarding induction response in each of the trials are presented. Note: response does include remission. Observed data for induction remission is shown in Table 28.

Table 27: Observed data for induction response in RCTs used for NMA presented as cases/sample size (proportion)

Trial identifier	Placebo	Adalimumab 160/80mg	Infliximab 5mg/kg	Infliximab 10mg/kg	Golimumab 200/100mg	Golimumab 400/200mg
ULTRA 1	58/130 (0.446)	71/130 (0.546)				
ULTRA 2	56/145 (0.386)	89/150 (0.593)				
ACT 1	45/121 (0.372)		84/121 (0.694)	75/122 (0.615)		
ACT 2	36/123 (0.293)		78/121 (0.645)	83/120 (0.692)		
PURSUIT Phase 2	26/69 (0.377)				33/71 (0.465)	35/68 (0.515)
PURSUIT Phase 3	76/256 (0.297)				133/257 (0.518)	142/258 (0.555)

Table 28: Observed data for induction remission in RCTs used for NMA presented as cases/sample size (proportion)

Trial identifier	Placebo	Adalimumab 160/80mg	Infliximab 5mg/kg	Infliximab 10mg/kg	Golimumab 200/100mg	Golimumab 400/200mg
ULTRA 1	12/130 (0.092)	24/130 (0.185)				
ULTRA 2	16/145 (0.110)	32/150 (0.213)				
ACT 1	18/121 (0.149)		47/121 (0.388)	39/122 (0.320)		
ACT 2	7/123 (0.057)		41/121 (0.339)	33/120 (0.275)		
PURSUIT Phase 2	7/69 (0.101)				13/71 (0.183)	18/68 (0.265)
PURSUIT Phase 3	16/256 (0.063)				48/257 (0.187)	46/258 (0.178)

In Table 29 the ORs of response and remission with each treatment relative to placebo as obtained with a random-effects NMA model for dichotomous endpoints are presented. The average of the estimated log odds of a response with placebo of each trial (as obtained with the NMA model) was transformed into the probability of response with placebo (0.355, 95% CrI 0.322-0.390). This estimate was assumed to reflect the outcome with non-biologic drug induction treatment. In the same way the probability of remission with placebo was obtained (0.089, 95% CrI 0.071-0.110).

Table 29: Relative treatment effects for induction response and remission with golimumab, adalimumab, and infliximab relative to placebo as obtained with random-effects NMA

Intervention	Odds ratio	95% credible interval	
		Low	High
Induction response			
Infliximab 5mg/kg	4.12	2.08	8.14
Infliximab 10mg/kg	3.81	1.95	7.59
Golimumab 200/100mg	2.12	1.01	3.95
Golimumab 400/200mg	2.47	1.19	4.65
Adalimumab 160/80mg	1.87	0.96	3.65
Induction remission			
Infliximab 5mg/kg	5.27	2.60	11.64
Infliximab 10mg/kg	3.90	1.88	8.56
Golimumab 200/100mg	2.99	1.32	6.28
Golimumab 400/200mg	3.32	1.56	7.23
Adalimumab 160/80mg	2.25	1.08	4.72

6.3.3. Efficacy of Drug Maintenance Treatment

For the model, the efficacy in terms of maintaining response and remission among patients that demonstrated response and remission with induction treatment was required. More specifically, the ORs of sustained response and remission with biologic maintenance treatment following biologic induction treatment relative to sustained response and remission with placebo following placebo induction treatment. The efficacy of drug maintenance treatment with each of the biologics and conventional treatment was obtained with a NMA of the ULTRA 2 trial for adalimumab, ACT 1 for infliximab, and PURSUIT for golimumab.

In the placebo-controlled trials ULTRA 2 and ACT 1 patients were randomised at the beginning of the induction treatment and remained on the same treatment (either biologic or placebo) during the long-term or maintenance phase. Sustained response or remission was the proportion of patients demonstrating response or remission at the end of the induction phase and still demonstrating response and remission at the end of the maintenance phase at 52/54 weeks of follow-up out of the patients starting induction treatment. In order to obtain the required estimates of relative treatment effects in terms of sustained response for the model, the observed number of patients with a sustained response at the end of the maintenance phase (numerator) out of the number of patients showing an induction response (denominator) were used from both trials. The same approach was used for sustained remission.

In PURSUIT-M, responders to golimumab 200/100mg or 400/200mg in the 6 week induction phase were re-randomised to placebo, golimumab 50mg, or golimumab 100mg groups for the maintenance phase. Hence, sustained response or remission was the proportion of patients showing a response or being in remission at 54 weeks out of patients randomised to

maintenance treatment. Since only responders to induction treatment with golimumab were included in the randomised maintenance trial, the sustained responders with placebo maintenance treatment given placebo induction response were obtained from the non-randomised maintenance patients who had been randomised to induction placebo.

Table 30 and Table 31 present the observed data for sustained response and remission out of patients showing induction response and remission (as synthesised with fixed-effects NMA models), respectively. The results of the analyses are presented in Table 32. A fixed-effects model was used because there is only one trial for each direct comparison in this placebo-controlled "star-network" meaning there are no data to estimate between-study heterogeneity.

For the model the combined results for golimumab 50mg and golimumab 100mg were used for biologic maintenance treatment. For a scenario with conventional drug maintenance treatment following biological induction treatment, the OR of sustained response and remission with placebo following golimumab induction was used for all biologics.

Table 30: Observed data for response at end of maintenance treatment out of patients demonstrating response with induction treatment in RCTs used for NMA presented as cases/sample size (proportion)

Trial identifier	Placebo *	Adalimumab 40mg **	Infliximab 5mg/kg	Infliximab 10mg/kg	Golimumab 50mg ***	Golimumab 100mg ***	Golimumab 50mg or 100mg ***	Placebo following golimumab induction ***
ULTRA 2	24/56 (0.429)	44/89 (0.494)						
ACT 1	17/45 (0.378)		47/84 (0.560)	45/75 (0.600)				
PURSUIT	46/124 (0.371)				72/153 (0.471)	78/154 (0.506)	150/307 (0.489)	49/156 (0.314)

* Placebo maintenance following placebo induction; ** Adalimumab 160/80mg induction; *** Golimumab 200/100mg or golimumab 400/200mg induction.

Table 31: Observed data for remission at end of maintenance treatment out of patients demonstrating remission with induction treatment in RCTs used for NMA presented as cases/sample size (proportion)

Trial identifier	Placebo *	Adalimumab 40mg **	Infliximab 5mg/kg	Infliximab 10mg/kg	Golimumab 50mg ***	Golimumab 100mg ***	Golimumab 50mg or 100mg ***	Placebo following golimumab induction***
ULTRA 2	9/16 (0.563)	16/32 (0.500)						
ACT 1	8/18 (0.444)		24/47 (0.510)	25/39 (0.641)				
PURSUIT	9/22 (0.409)				19/52 (0.365)	23/57 (0.404)	42/109 (0.385)	13/54 (0.241)

* Placebo maintenance following placebo induction; ** Adalimumab 160/80mg induction; *** Golimumab 200/100mg or 400/200mg induction.

Table 32: Relative treatment effects for sustained response and remission with golimumab, adalimumab, and infliximab relative to placebo out of patients showing response and remission with induction treatment, respectively (as obtained with fixed-effects NMA model)

Intervention	Odds ratio	95% credible interval	
		Low	High
Sustained response			
Placebo *	Reference		
Adalimumab 40mg **	1.31	0.67	2.59
Infliximab 5mg	2.12	1.02	4.54
Infliximab 10mg	2.51	1.17	5.51
Golimumab 50mg ***	1.51	0.94	2.47
Golimumab 100mg ***	1.75	1.08	2.84
Golimumab 50mg - 100mg ***	1.62	1.07	2.50
Placebo following golimumab ***	0.78	0.47	1.28
Sustained remission			
Placebo *	Reference		
Adalimumab 40mg **	0.76	0.22	2.56
Infliximab 5mg	1.30	0.44	4.05
Infliximab 10mg	2.26	0.73	7.49
Golimumab 50mg ***	0.83	0.29	2.40
Golimumab 100mg ***	0.98	0.36	2.78
Golimumab 50mg-100mg ***	0.92	0.36	2.45
Placebo following golimumab ***	0.45	0.15	1.34

* Placebo maintenance following placebo induction; ** Adalimumab 160/80mg induction; *** Golimumab 200/100mg or golimumab 400/200mg induction.

Please note that an OR less than 1 in Table 32 reflects that the conditional probability of maintaining response or remission with a biologic (given induction with the same biologic) is smaller than the conditional probability of response or remission with placebo following induction treatment with placebo. This does *not* mean that biologic maintenance treatment following biologic induction is less efficacious than placebo maintenance following biologic induction, as illustrated with a NMA of sustained response or sustained remission among all patients starting randomised induction treatment and receiving the same maintenance treatment. Such an analysis where the effect of the same induction and maintenance treatment is combined does show that biologics are more efficacious (i.e. OR>1) than placebo. Furthermore, an OR less than 1 of a biologic relative to placebo in Table 32 does not mean that biologic maintenance treatment among subjects receiving induction with the same biologic is less efficacious than placebo maintenance among subjects receiving induction treatment with the biologic; the PURSUIT maintenance trial demonstrated that among golimumab induction responders, maintenance treatment is more efficacious than placebo maintenance. The findings of Table 32 are simply needed to ensure that the economic model estimates appropriate probabilities of response and remission at 1 year follow-up that matches the findings of a NMA

of sustained response or sustained remission among all patients starting randomised induction treatment and receiving the same maintenance treatment.

The average of the estimated log odds of a sustained response with placebo of each trial as obtained with the NMA model was transformed into a 2 month probability (0.829, 95% CrI 0.797-0.858) assuming a time-independent constant underlying loss of response rate. This estimate was assumed to reflect the 2 month sustained response with non-biologic drug treatment. In a similar fashion, the 2 month probability of sustained remission with placebo was obtained (0.861, 95% CrI 0.806-0.908).

6.3.4. Relapse Management

According to the meta-analysis by Turner *et al.*[61] the probability of colectomy due to a failure of IV steroid treatment for severe UC is 0.27 (95% CI 0.26-0.29). In the model it was assumed that patients received up to two rounds of IV steroids for each cycle. Given the possible outcomes as presented in Figure 12, this 27% corresponds to a probability of success of 0.480 (95% CI 0.468-0.493) for both the first and second round of IV steroids.

The 2 month probability of loss of response in the relapse management phase, i.e. the transition from *Response (relapse management)* back to *Relapse (relapse management)*, was assumed to be the same as the 2 month probability of losing response as estimated with placebo maintenance in the NMA: 1-0.829=0.171 (95% CrI 0.142-0.203).

Given the source data and resulting transition probabilities for drug induction, maintenance, and relapse management, the 2 year risk of colectomy among patients starting infliximab predicted with the model matched figures reported in the literature (Oussalah *et al.*[27], Armuzzi *et al.*[31], Rostholder *et al.*[40]).

6.3.5. Safety of Drug Treatment

Evidence for the occurrence of serious infections leading to hospitalisation with biologic and conventional drug induction and maintenance treatment was obtained from the large scale registry study comparing TNF-α inhibitors with AZA or 6-MP among patients with IBD by Grijalva *et al.*[62]. With AZA or 6-MP 87 hospitalisations were observed out of 906 person-years of exposure. This translates into a 2 month probability of 0.016 (95% CI 0.011-0.021) assuming a time-independent incidence rate (i.e. exponentially-distributed time to event) used for drug induction treatment, maintenance treatment, and the relapse management phase. The reported

hazard ratio of serious infections leading to hospitalisations with TNF-α inhibitors relative to AZA or 6-MP was 1.10 (95% CI 0.83-1.46). It was assumed that this hazard ratio remains constant over time. Given the small risk of the event of interest over a 2 month period, it was also assumed that this hazard ratio would be similar to an OR, and was used in the model as such.

6.3.6. Colectomy

The risk of early complications with colectomy was assumed to be independent of previous drug treatment (Nelson *et al.*[63]), i.e. similar risk of complications with prior biologic and non-biologic treatment for UC. The risk of early complications related to elective surgery was obtained from the UK IBD Audit 2010 (2012)[64]: wound infection 36/490 (7%); rectal stump complications 7/490 (1%); intra-abdominal bleeding 8/490 (2%); intra-abdominal sepsis 23/490 (5%); anastomotic leakage 6/490 (1%); stoma complications 13/490 (3%); deep vein thrombosis 2/490 (0.4%); ileus requiring total parenteral nutrition 13/490 (3%); small bowel obstruction 14/490 (3%); cardiac 6/490 (1%); respiratory 13/490 (3%); other 81/490 (17%). For the model these complications were aggregated resulting in a probability of 164/490=0.335 (95% CrI 0.294-0.377).

With the model it was assumed that mortality associated with colectomy is only as a result of complications. In the UK IBD Audit 2010 (2012)[64] a total of 28 patients out of 3049 admitted UC patients died. Given the aforementioned complications related to elective surgery it was assumed that of the 28 observed deaths, the following 13 deaths were associated with the complications: heart disease (3/28); respiratory disease (6/28); gastrointestinal bleeding (1/28); and post-operative complications (3/28) (the 15 deaths due to other reasons were not considered). With a total of 13 deaths out of 164 complications, the probability of dying given a complication was estimated to be 13/164=0.079 (95% CrI 0.043-0.125).

6.3.7. Post Colectomy Phase

The probability of late complications, implying a transition from the health state *Remission (post-colectomy)* to *Late complications (post-colectomy)*, was estimated based on the occurrence of pouchitis, bowel obstruction, and anal fistula as reported by Arai *et al.*[65]. The mean time when pouchitis occurred for the 16 out of 296 patients experiencing pouchitis was 1.72 years, the mean time when bowel obstruction occurred for the 15 out of the 296 patients was 1.35 years, and the mean time when fistula occurred for the 12 patients experiencing fistula was at 1.9 years of follow-up. As such, the rate for long-term complications (events per person-year)

among all patients at risk was calculated according to 16/196*(1/1.72)+15/296*(1/1.35) +12/296*(1/1.9)=0.09, which was transformed into a 2 month probability of experiencing late complications: 1-exp(-0.09/6)=0.01494. The corresponding CI was based on the 296 subjects (95% CI 0.004-0.032). It was assumed that all complications are cured within a 2 month period and therefore the probability of transitioning from the health state *Late complications (post-colectomy)* back to *Remission (post-colectomy)* was set at 1.

6.3.8. Mortality

Other than mortality associated with colectomy, it was assumed that the mortality among UC patients was the same as the mortality rate for the UK general population (Bernstein *et al.*)[66]. A weighted average for male- and female-specific annual mortality (informed by the proportion of men [60%] and women [40%]) in the ACT 1 and ACT 2 trials was applied. The average age of the population at the beginning of the initial treatment was set at 41 years, also informed by the ACT trials.

6.3.9. Outcomes

Utility and cost estimates were assigned to the outcomes with the initial treatment (Figure 8 and Figure 9), and each of the eight health states of the Markov structure (Figure 10 and Figure 11). Given the 2 month cycle length used with the Markov structure and to facilitate model computation, it was assumed that the induction phase also lasted 2 months.

The utility values associated with failure, response, and remission as a result of induction treatment, and utility values assigned to the health states *Response (pre-colectomy; maintenance)* and *Remission (pre-colectomy; maintenance)* were assumed to be the same for golimumab and adalimumab. They were based on the EQ-5D data from the ACT 1 and ACT 2 trials. An additional disutility for the occurrence of AEs (i.e. serious infections) with drug treatment was not incorporated because the utilities related to the health states response, remission, and failure with drug treatment as obtained from the trial already include AEs. The same utility values were also assigned to the health states *Response (relapse management)* and *Relapse (relapse management)*.

Utility values for the health states *Colectomy, Remission (post-colectomy),* and *Late complications (post-colectomy)* were taken from literature as shown in Table 33. These health states have lower utility values than the health states related to remission and response prior to colectomy,

but are greater than the utility value of moderately to severely active UC in the relapse management phase.

Table 33: Health state utility values from literature

Health state	Utility data source
Response (relapse management	Woehl *et al.* [67], Tsai *et al.* [48], HODaR [68] mild disease: 0.76 (se=0.014)
Relapse (relapse management) without hospitalisation	Woehl *et al.* [67], Tsai *et al.* [48], Punekar & Hawkins [54], Chaudhary & Fan [50], HODaR [68] moderate to severe: 0.42 (se=0.093)
Colectomy	Woehl *et al* .[67], HODaR [68] colectomy (ileostomy: 0.63 se=0.10, IPAA: 0.56 se=0.13, assumed 50% IPAA)
Remission (post-colectomy)	Woehl *et al.* [67], Punekar & Hawkins [54], Chaudhary & Fan [50]
Late complications (post-colectomy)	Assumed same as *Remission (post-colectomy)*

IPAA, ileal pouch-anal anastomosis; se, standard error.

Costs associated with UC include costs related to drug acquisition, consultant visits, endoscopy, inpatient stay, complications, blood tests, and AEs. Costs related to drug treatment of UC were assigned to the induction phase and the following health states: *Response (pre-colectomy; maintenance), Remission (pre-colectomy; maintenance), Response (relapse management),* and *Relapse (relapse management)*. Costs related to consultant visits and blood tests were assigned to all health states, as were the costs due to elective endoscopies. Emergency endoscopies did not occur if a patient was in remission. Costs for inpatient stay were incurred after failure of the first course of IV steroid treatment, i.e. health state *Relapse (relapse management)*, with colectomy, and late complications of colectomy during the post-colectomy phase. Costs related to AEs were a function of the drug treatment specific risk of serious infections for which hospitalisation was required and included respiratory tract infections, skin and soft tissue infections, genitourinary tract infections, gastrointestinal infections, CNS infections, and septicaemia.

Expected outcomes associated with the initial treatment (i.e. drug induction or colectomy) were calculated by folding back the trees of Figure 8 and Figure 9. Outcomes accrued for each Markov cycle were calculated according to Sonnenberg & Beck[69], i.e. the multiplication of the distribution of health states at each cycle with the corresponding values (outcomes and costs) of each health state. By summing the results over the time horizon of interest the following outcomes were obtained for each of the model arms:

- Expected duration of the pre-colectomy phase (in months), i.e. the time on drug treatment prior to the relapse management phase;

- Expected duration of the relapse management phase (in months);
- Expected duration of post-colectomy phase (in months);
- Expected life years;
- Expected discounted life years;
- Expected discounted QALYs;
- Expected discounted drug acquisition and administration cost;
- Expected discounted AE cost related to drug treatment;
- Expected discounted consultant visit cost;
- Expected discounted endoscopy cost;
- Expected discounted inpatient stay cost;
- Expected discounted colectomy cost;
- Expected discounted costs late complications;
- Expected discounted other UC cost;
- Expected discounted total direct cost;
- Net monetary benefit (NMB) at a willingness-to-pay ratio (WTP) of £30,000 calculated as QALYs multiplied with the WTP minus costs

Quality-adjusted life years and costs were discounted at 3.5%.

The following key assumptions were made in the modelling:

- Only patients that demonstrate induction response or remission continue with drug maintenance treatment prior to the relapse management phase
- Duration of drug maintenance treatment is the same as duration of sustained response or remission. With a relapse, patients discontinue maintenance treatment
- Since the risk of discontinuation of biologic maintenance treatment due to AEs is smaller than the loss of response or remission, the discontinuation of biologic maintenance treatment is only determined by loss of efficacy
- After failure of drug induction or maintenance treatment, patients transition first to a relapse management phase, before undergoing colectomy
- Transition probabilities between health states are constant over time
- Duration of the relapse management phase and risk of early and late complications with colectomy is independent of drug treatment received prior to the relapse management phase
- No increased mortality due to UC, other than due to early complications of colectomy

- Utility associated with remission, response, and failure prior to relapse management is the same for all treatments and based on EQ-5D data from the ACT 1 and ACT 2 trials
- No disutility related to serious infections is incorporated. It was assumed that the utilities related to the health states response, remission, and failure with drug treatment as obtained from the trial already include AEs
- Post-colectomy remission (with or without late complications) is associated with a smaller utility than response or remission prior to colectomy

6.4. Measurement and Valuation of Health Effects

6.4.1. Health-Related Quality of Life Data Derived from Clinical Trials

The EQ-5D utilities associated with moderately to severely active UC (treatment failure), response, and remission expected with drug induction and maintenance treatment in the pre-colectomy phase were based on the observed EQ-5D estimates in the ACT 1 trial where results for placebo and golimumab were combined. The utility estimates at week 8 of follow-up were assumed to be applicable to the outcomes with induction treatment. The utilities at 54 weeks of the ACT 1 trial were assumed to be applicable to the health states with biologic maintenance treatment.

The utility estimates related to failure and response in the relapse management phase, colectomy, and post-colectomy phase were based on estimates reported in the literature as shown in Table 34.

Table 34: EQ-5D utility estimates by outcome and health state as used in the model

	Utility estimate	Standard error	95% CI low	95% CI high	Source
Response with drug induction treatment	0.79	0.021	0.75	0.83	ACT 1 week 8
Remission with drug induction treatment	0.84	0.018	0.80	0.87	ACT 1 week 8
Failure with drug induction treatment	0.70	0.018	0.66	0.73	ACT 1 week 8
Health state: *Response (pre-colectomy; maintenance)*	0.82	0.033	0.75	0.88	ACT 1 week 54
Health state: *Remission (pre-colectomy; maintenance)*	0.88	0.017	0.84	0.91	ACT 1 week 54
Health state: *Response (relapse management)*	0.76	0.014	0.73	0.79	Woehl *et al.* [67], Tsai *et al.* [48], HODaR [68] mild disease
Health state: *Relapse (relapse management)* w/o hospitalisation	0.42	0.093	0.24	0.61	Woehl *et al.* [67], Tsai *et al.* [48], Punekar & Hawkins [54], Chaudhary & Fan [50], HODaR [68] moderate to severe
Health state: *Colectomy*	0.60	0.110	0.37	0.80	Woehl *et al.* [67], HODaR [68] colectomy (ileostomy: 0.63 se=0.10, IPAA: 0.56 se=0.13, assumed 50% IPAA)
Health state: *Remission (post-colectomy)*	0.60	0.110	0.37	0.80	Woehl *et al.* [67], Punekar & Hawkins [54], Chaudhary & Fan [50]
Health state: *Late complications (post-colectomy)*	0.60	0.110	0.37	0.80	Assumed same as *Remission (post-colectomy)*

CI, confidence interval; IPAA, ileal pouch-anal anastomosis; se, standard error; w/o, without.

The utility value post-colectomy is greater than the utility value assigned to relapse in the relapse management phase and smaller than the utility associated with response which reflects that colectomy is a favourable health state in comparison to relapsed moderately to severely active UC. Given the unclear impact of late complications related to colectomy on EQ-5D utility, the same utility value was assigned to the health states *Remission (post-colectomy)* and *Late complications (post-colectomy)* to reflect an average utility in which a subset of patients do experience late complications. Several studies show that functional outcome and quality of life after colectomy is stable over time (McIntyre *et al.*[70], Meagher *et al.*[71], Bullard *et al.*[72], Weinryb *et al.*[73], Michelassi *et al.*[74], Hahnloser *et al.* 2004[75], Hahnloser *et al.* 2007[76], Tulchinsky *et al.*[77], McCormick *et al.*[78]). As such, arbitrary assumptions were made on how utility would change over time in the post-colectomy phase. A constant value was assumed as in previously published economic evaluations of interventions for UC (Woehl *et al.*[67], Chaudhary & Fan[50], Punekar & Hawkins[54]).

Arseneau *et al.*[79] reported a time-trade-off utility of 0.49 related to surgical complications among UC patients. For the model the difference between the value used for colectomy (0.60) and this value of 0.49 was calculated to obtain a "disutility" of 0.11 associated with early complications.

6.4.2. Adverse Events

Adverse events associated with drug induction and maintenance treatment, as well as treatment during the relapse management phase were limited to serious infections resulting in hospitalisations. The probability of this event was not used for any transition between health states, but simply to adjust the expected costs for each health state where drug treatment was considered. Any injection- or infusion-site reactions, infections not leading to hospitalisation, and malignancies were excluded as there were no significant differences in these AEs between the biologic interventions.

6.5. Resource Identification, Measurement, and Valuation

6.5.1. Drug Acquisition and Administration Costs

Drug acquisition costs are presented in Table 35, Table 36, and Table 37. Drug costs were assumed only for the pre-colectomy phase and relapse management phase. The distribution of drugs was based on the ACT 1 and ACT 2 trials.

After induction treatment, the recommended dose of adalimumab is 40mg EOW via subcutaneous injection. Some patients who experience a decrease in their response may benefit from an increase in dosing frequency to 40mg adalimumab EW[60]. In the ULTRA studies, ~23% of patients received once weekly maintenance dosing with 40mg adalimumab, however clinicians have advised that in clinical practice up to 80% of patients receive EW dosing. The model applies the conservative assumption that 50% of patients receiving adalimumab have weekly maintenance dosing.

The administration frequency of biologics used for maintenance treatment is on a weekly, bi-weekly, 4 week, or 8 week cycle, depending on the drug. Given the 2 month cycle length of the model, 8 week costs with biologics were inflated with a factor of 52/6/8.

Table 35: Drug acquisition and administration costs associated with drug induction treatment

	Description (details about dosage, administration and schedule)	Proportion of patients	Drugs, dosage, administration	Description of unit	Unit cost	Number units for induction period	Cost for total induction period
Adalimumab 160/80/40mg	Day 1: 160mg (4 pens); day 15: 80mg (2 pens); day 29: 40mg (1 pen); EOW 40mg (1 pen). 2 month time frame to evaluate response (in-line with trial evidence)	1.000	Adalimumab 160mg		£1408.56	1	£1408.56
		1.000	Adalimumab 80mg		£704.28	1	£704.28
		1.000	Adalimumab 40mg		£352.14	3	£1056.42
		0.812	Mesalazine	500mg, 100 tabs	£30.74	4.867	£149.60
		0.157	AZA	50mg, 56 tabs	£3.85	3.259	£12.55
		0.157	6-MP	50mg, 25 tabs	£50.47	4.867	£245.62
		0.439	Prednisolone	25mg, 56 tabs	£40.00	2.173	£86.90
						Total	£3369.29
Golimumab 200/100/50 (100)mg	Week 0 200mg (2 injections); week 2 100mg (1 injection); week 6 100mg (1 injection). 2 month induction period to evaluate response (minimum for the model). Note: According to schedule maintenance regimen starts at week 6. Patients <80kg 50mg; patients ≥80kg 100mg	1.000	Golimumab 200mg	100mg injection	£1525.94 without PAS/ £762.97 with PAS *	2	£3051.88 without PAS/ £1525.94 with PAS *
		1.000	Golimumab 100mg	100mg injection	£1525.94 without PAS/ £762.97 with PAS *	2	£3051.88 without PAS/ £1525.94 with PAS *
		0.812	Mesalazine	500mg, 100 tabs	£30.74	4.867	£149.60
		0.157	AZA	50mg, 56 tabs	£3.85	3.259	£12.55
		0.157	6-MP	50mg, 25 tabs	£50.47	4.867	£245.62
		0.439	Prednisolone	25mg, 56 tabs	£40.00	2.173	£86.90
						Total	£6303.79 without PAS/ £3251.91 with PAS *
Infliximab 5mg/kg	Weeks 0, 2, and 6. 2 month time frame to evaluate response (in-line with trial evidence)	1.000	Infliximab 5mg/kg	100mg vial	£419.62	12	£5035.44
		1.000	Infliximab administration	Day treatment	£154.00	3	£462.00
		0.812	Mesalazine	500mg, 100 tabs	£30.74	4.867	£149.60
		0.157	AZA	50mg, 56 tabs	£3.85	3.259	£12.55
		0.157	6-MP	50mg, 25 tabs	£50.47	4.867	£245.62
		0.439	Prednisolone	25mg, 56 tabs	£40.00	2.173	£86.90
						Total	£5697.47

* Patient Access Scheme, golimumab 100mg is flat priced to golimumab 50mg. 6-MP, 6-mercaptopurine; AZA, azathioprine; EOW, every other week; PAS, Patient Access Scheme.

Table 36: Drug acquisition and administration costs associated with drug maintenance treatment

	Description (details about dosage, administration and schedule)	Proportion of patients	Drugs, dosage, administration	Description of unit	Unit cost	Number units per 2 month cycle	Cost for 2 month cycle
Adalimumab 160/80/40mg	Every (other) week 40mg (1 pen) (4 per 8 week period)	0.500/0.770/1 *	Adalimumab 40mg EOW		£352.14	4.333	£1525.94
		0.500/0.230/0 *	Adalimumab 40mg EW		£352.14	8.667	£3051.88
		0.802	Mesalazine	500mg, 100tabs	£30.74	2.433	£74.80
		0.151	AZA	50mg, 56tabs	£3.85	3.259	£12.55
		0.151	6-MP	50mg, 25tabs	£50.47	4.867	£245.62
		0.507	Prednisolone	25mg, 56tabs	£40.00	1.086	£43.45
						Total	£2409.89
Golimumab 200/100/50 (100)mg	1 injection every 4 weeks. Patients <80kg 50mg; patients ≥80kg 100mg	0.316	Golimumab 100mg	100mg injection	£1525.94 without PAS/£762.97 with PAS **	2.167	£3306.20 without PAS/£1653.10 with PAS **
		0.684	Golimumab 50mg	50mg injection	£762.97	2.167	£1653.10
		0.802	Mesalazine	500mg, 100tabs	£30.74	2.433	£74.80
		0.151	AZA	50mg, 56tabs	£3.85	3.259	£12.55
		0.151	6-MP	50mg, 25tabs	£50.47	4.867	£245.62
		0.507	Prednisolone	25mg, 56tabs	£40.00	1.086	£43.45
						Total	£2296.40 without PAS/£1774.08 with PAS **
Infliximab 5mg/kg	Once every 8 weeks	1.000	Infliximab 5mg/kg	100mg vial	£419.62	4.333	1818.35
		0.000	Infliximab 10mg/kg	100mg vial	£419.62	7.583	3182.12
		1.000	Infliximab administration	Outpatient	£154.00	1.083	166.83
		0.802	Mesalazine	500mg, 100tabs	£30.74	2.433	74.80
		0.151	AZA	50mg, 56tabs	£3.85	3.259	12.55
		0.151	6-MP	50mg, 25tabs	£50.47	4.867	245.62
		0.507	Prednisolone	25mg, 56tabs	£40.00	1.086	43.45
						Total	£2106.17

* Basecase scenario 50% EOW/50% EW; ** Patient Access Scheme, golimumab 100mg is flat priced to golimumab 50mg. 6-MP, 6-mercaptopurine; AZA, azathioprine; EW, every week; EOW, every other week; PAS, Patient Access Scheme.

Table 37: Drug acquisition and administration costs associated with relapse management

	Description (details about dosage, administration and schedule)	Proportion of patients	Drugs, dosage, administration	Description of unit	Unit cost	Number units per 2 month cycle	Cost for 2 month cycle
Health state response	Mesalazine 4g daily (acute); 2g daily (chronic) AZA 2-2.5mg/kg daily 6-MP 1-1.5mg/kg daily Ciprofloxacin 500mg twice daily Prednisolone	0.796	Mesalazine	500mg, 100tabs	£30.74	2.433	£74.80
		0.157	AZA	50mg, 56tabs	£3.85	3.259	£12.55
		0.157	6-MP	50mg, 25tabs	£50.47	4.867	£245.62
		0.488	Prednisolone	25mg, 56tabs	£40.00	1.086	£43.45
						Total	£121.15
Health state relapse (1 round of IV steroids)	Mesalazine 4g daily (acute); 2g daily (chronic) AZA 2-2.5mg/kg daily 6-MP 1-1.5mg/kg daily Ciprofloxacin 500mg twice daily Prednisolone	0.834	Mesalazine	500mg, 100tabs	£30.74	4.867	£149.60
		0.154	AZA	50mg, 56tabs	£3.85	3.259	£12.55
		0.154	6-MP	50mg, 25tabs	£50.47	4.867	£245.62
		1.000	Prednisolone	25mg, 56tabs	£40.00	2.173	£86.90
		1.000	IV prednisolone	Outpatient	£154.00	1	£154.00
						Total	£405.43

6-MP, 6-mercaptopurine; AZA, azathioprine; IV, intravenous.

6.5.2. Costs due to Consultant Visits, Endoscopy, and Blood Tests

Resource use related to consultant visits, endoscopy, and blood tests were obtained by means of interviewing nine UK gastroenterologists treating UC patients. In Table 38 the average number of reported units expressed per 2 month cycle is presented, along with the corresponding cost estimate. The unit cost for a consultant visit was £157.00 (PSSRU [2012] p. 235), the unit cost for an elective endoscopy was £807.70 (NHS Reference Costs 2011-12: Elective Inpatient: Diagnostic Colonoscopy, 19 years and over [FZ51Z]), and the unit cost for emergency endoscopy was £502.99 (NHS Reference Costs 2011-12: Non Elective Inpatient [Short Stay]: Diagnostic Colonoscopy, 19 years and over [FZ51Z]). For a blood test a cost of £3.08 was assumed (NHS Reference Costs 2011-12: Haematology [Excluding anti-coagulant services] [DAPS DAP823]).

Table 38: Resource use and cost estimates per 2 month cycle related to consultant visits, endoscopy, and blood tests

	Response		Remission		Failure/relapse		Colectomy		Remission (post-colectomy)		Late complications (post-colectomy)	
	Units	Costs *	Units	Costs *	Units	Costs *	Units	Costs *	Units	Costs *	Units	Costs *
Consultant visits	0.58	91.58 (74.52 – 110.38)	0.28	43.70 (35.55 – 52.67)	1.04	162.76 (132.43 – 196.17)	1.04	162.76 (132.43 – 196.17)	0.34	53.12 (43.22 – 64.02)	0.43	67.77 (40.57 – 101.83)
Elective endoscopy	0.08	12.30 (10.01 – 14.82)	0.03	4.97 (4.05 – 5.99)	0.13	20.41 (16.61 – 24.60)	0.13	20.41 (16.61 – 24.60)	0.22	33.76 (27.46 – 40.68)	0.13	20.67 (16.82 – 24.92)
Emergency endoscopy	0.04	6.02 (4.90 – 7.25)	0.00	0.00	0.13	19.89 (16.18 – 23.97)	0.13	19.89 (16.18 – 23.97)	0.07	11.51 (9.37 – 13.88)	0.04	5.50 (4.47 – 6.62)
Blood tests	0.58	1.80 (1.46 – 2.17)	0.58	1.80 (1.46 – 2.17)	0.58 (induction) 1.11 (relapse management)	1.80 (1.46 – 2.17) 3.44 (2.79 – 4.14)	1.11	3.44 (2.79 – 4.14)	0.30	0.92 (0.75 – 1.10)	0.60	1.85 (1.51 – 2.23)

* Uncertainty associated with resource use, expressed as standard deviation of the uncertainty distribution ("se") was assumed to be 10% of the point estimate.

6.5.3. Costs due to Inpatient Stay, Colectomy, and Related Complications

In Table 39 the cost estimates related to hospitalisations, colectomy, early complications, and late complications are presented.

Table 39: Cost estimates related to hospitalisation during the relapse management phase, colectomy, and related complications

	Units	Unit cost	Costs	Source
Hospitalisation in relapse management phase; after failure of first round of IV steroids	1 episode	£675.25	£675.25	NHS reference costs 2011-2012: Non-Elective Inpatient (Short Stay): Major Gastrointestinal or Metabolic Disorders without CC (PA25B)
Colectomy without early complications			£7619.25	NHS Reference costs 2011-2012: Elective Inpatient: Very Complex Large Intestine Procedures without Major CC (FZ73B)
Additional costs related to early complications			£4029.61	NHS Reference costs 2011-2012: Elective Inpatient: Very Complex Large Intestine Procedures with Major CC (FZ73A) MINUS costs without Major CC (FZ73B)
Late complications; pouchitis	0.348	£807.70		NHS Reference Costs 2011-12: Elective Inpatient: Diagnostic Colonoscopy, 19 years and over (FZ51Z)
Late complications; bowel obstruction	0.415	£3321.97		NHS reference costs 2011-2012: Elective Inpatient: Major Gastrointestinal Disorders without CC (PA25B)
Late complications; anal fistula	0.237	£3321.97		NHS reference costs 2011-2012: Elective Inpatient: Major Gastrointestinal Disorders without CC (PA25B)
Late complications; total			£2446.85	

IV, intravenous; NHS, National Health Service.

6.5.4. Adverse Event Costs

The unit cost related to AEs leading to hospitalisations with drug induction treatment, maintenance treatment, and drug treatment during the relapse management phase is presented in Table 40. The types of infections included were based on the study by Grijalva *et al.*[62]. This study reported that about 50% of the infections were respiratory tract or skin and soft tissue infections. We assumed that the proportion of other infections were the same.

Table 40: Costs related to serious infections

Proportion	Infection	Cost	Source
0.250	Respiratory tract	£1524.48	NHS reference costs 2011-2012: Unspecified Acute Lower Respiratory Infection without CC (DZ22C)
0.250	Skin and soft tissue	£1329.56	NHS reference costs 2011-2012: Intermediate Infections without CC (PA17B)
0.125	Genitourinary tract	£1933.81	NHS reference costs 2011-2012: Other Infections (Genito-Urinary Medicine) (WA10Z)
0.125	Gastrointestinal	£918.73	NHS reference costs 2011-2012: Infectious or Non-Infectious Gastroenteritis, without CC (PA21B)
0.125	CNS	£2806.07	NHS reference costs 2011-2012: Non-Transient Stroke or Cerebrovascular Accident, Nervous System Infections or Encephalopathy, without CC (AA22B)
0.125	Septicemia	£2107.84	NHS reference costs 2011-2012: Septicaemia without CC (WA03Y)
Total cost of infection leading to hospitalisation		£1684.32	

CNS, central nervous system; NHS, National Health Service.

6.6. Results

6.6.1. Development of Health States and Outcomes over Time

The time horizon of 10 years can be considered sufficiently long to capture differences in the distribution of health states between the compared biologics; after 10 years of follow-up all patients are expected to have discontinued biologic treatment.

Given the design of the model, the differences in the duration of maintenance treatment with the different biologics is a direct result of their differences in induction and maintenance response and remission. The expected total duration of biologic treatment was estimated as 10.5 months with adalimumab, 22.2 months with infliximab, and 13.4 months with golimumab.

From Figure 15, Figure 16, and Figure 17 it can be observed that, depending on the biologic of choice, between 25%-30% of patients have undergone colectomy within 2 years from the start of biologic treatment. The corresponding expected time to colectomy from the start of biologic treatment was 44.2 months with adalimumab, 54.4 months with infliximab, and 46.8 months with golimumab.

In Figure 18 the development of utility among patients alive with the different intervention strategies is presented.

Figure 14: Distribution of health states over time with colectomy

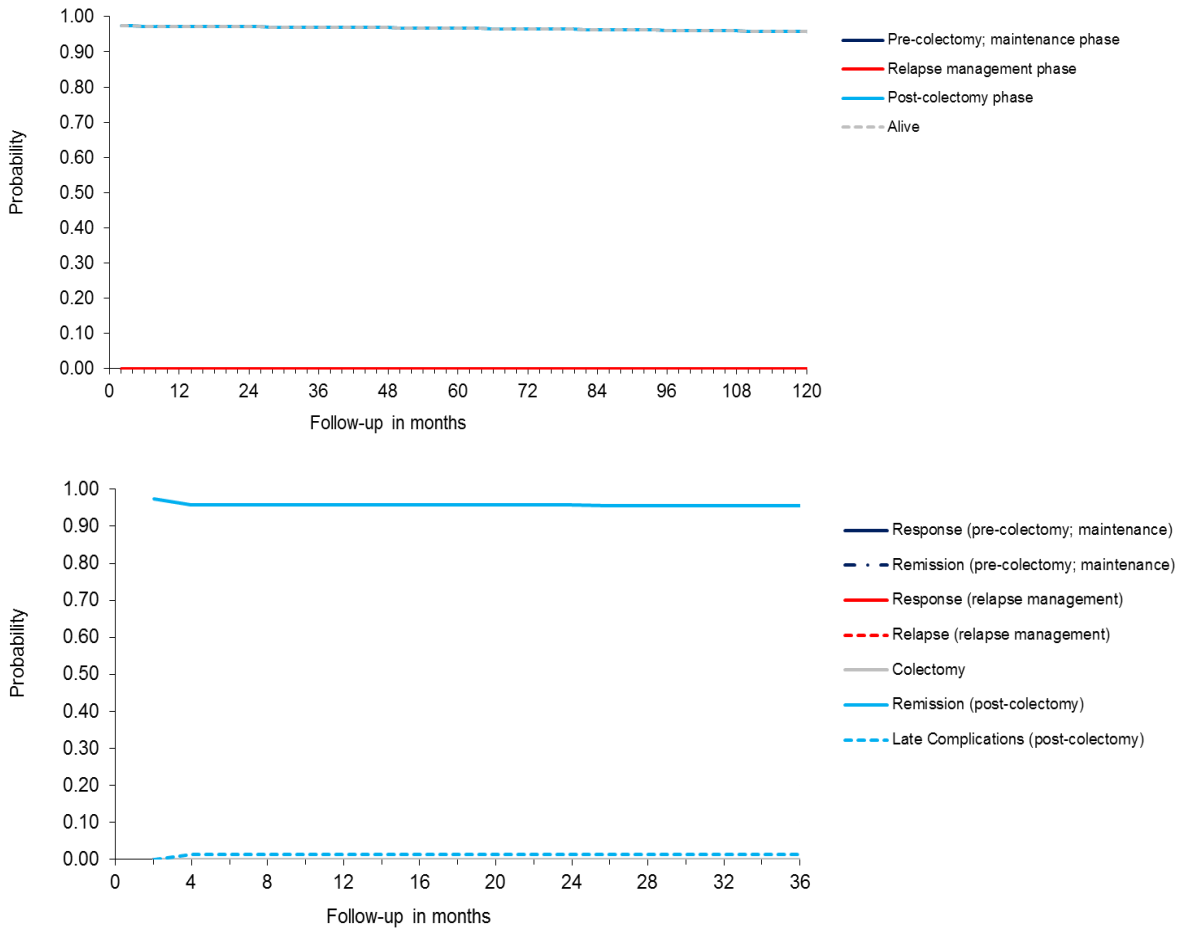


Figure 15: Distribution of health states over time with golimumab

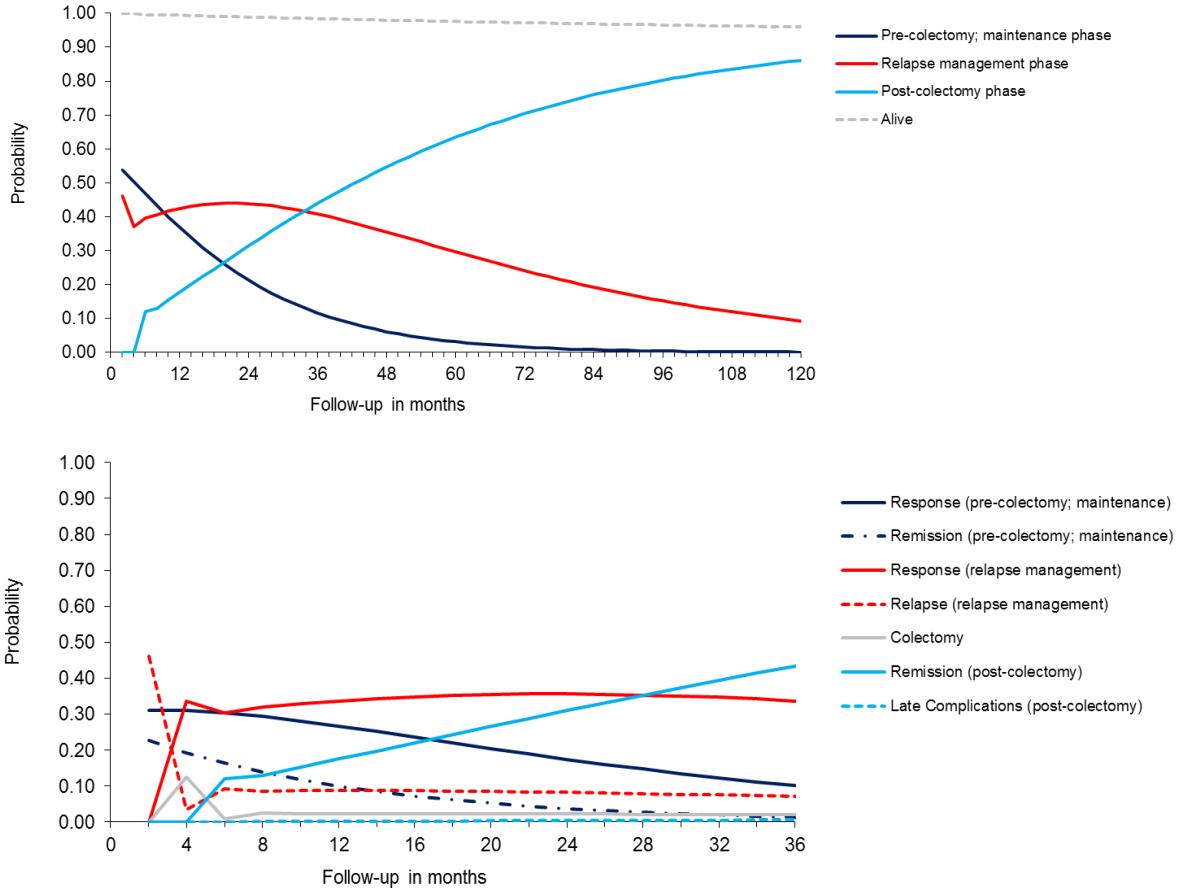


Figure 16: Distribution of health states over time with adalimumab

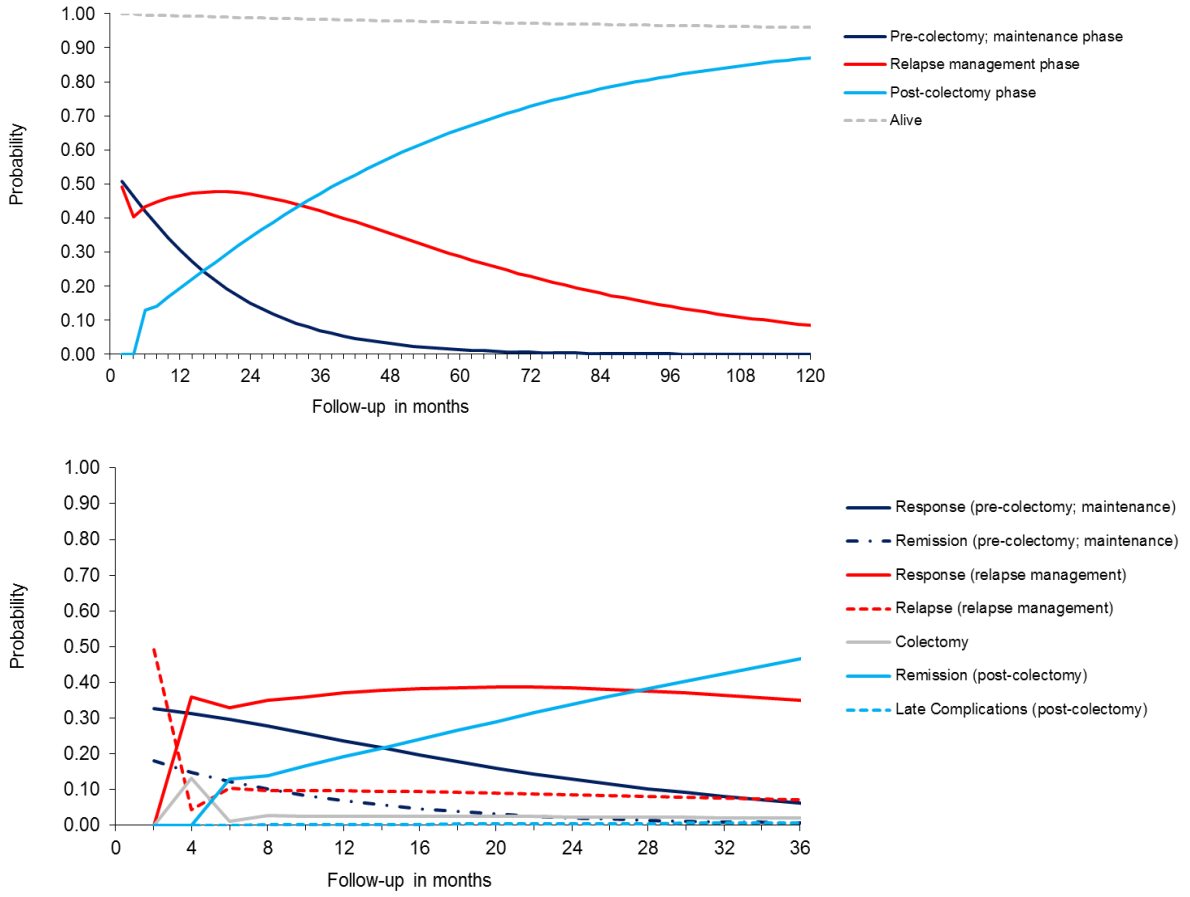


Figure 17: Distribution of health states over time with infliximab

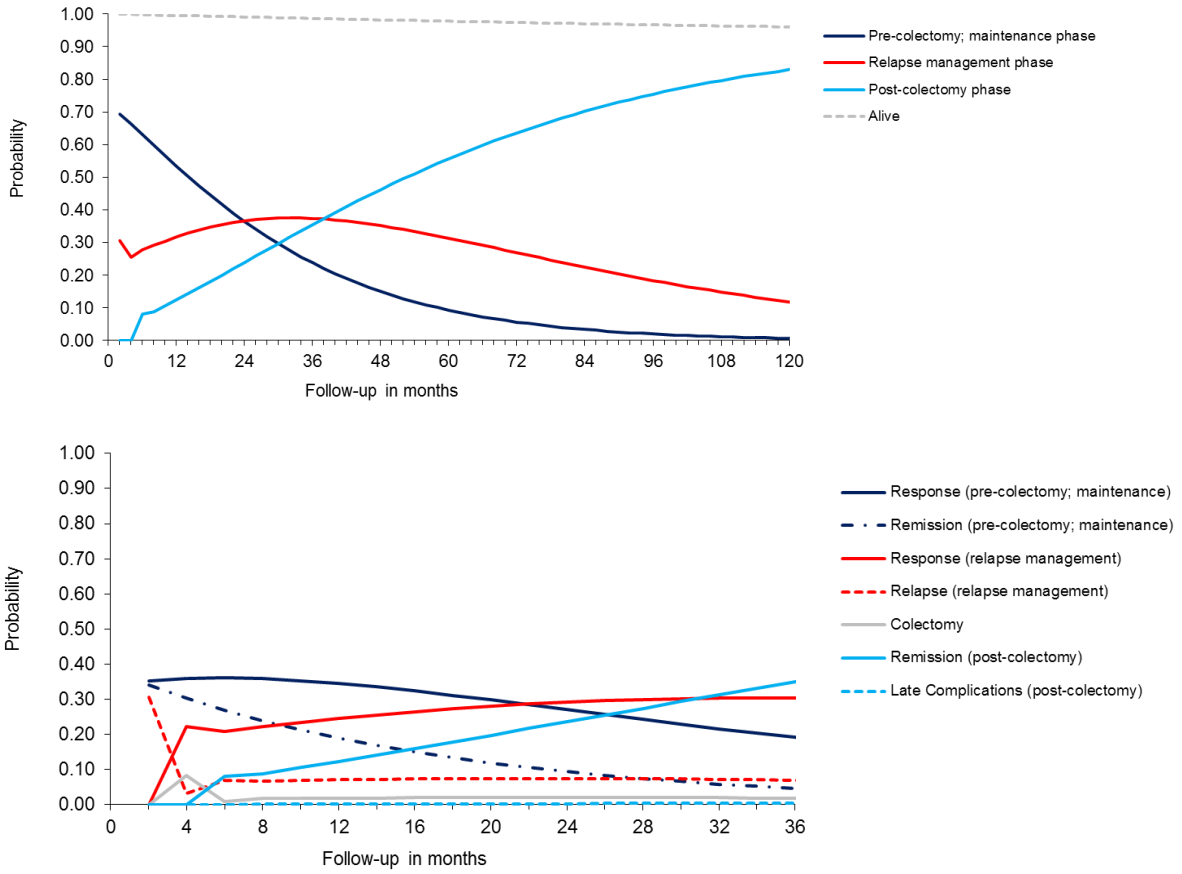
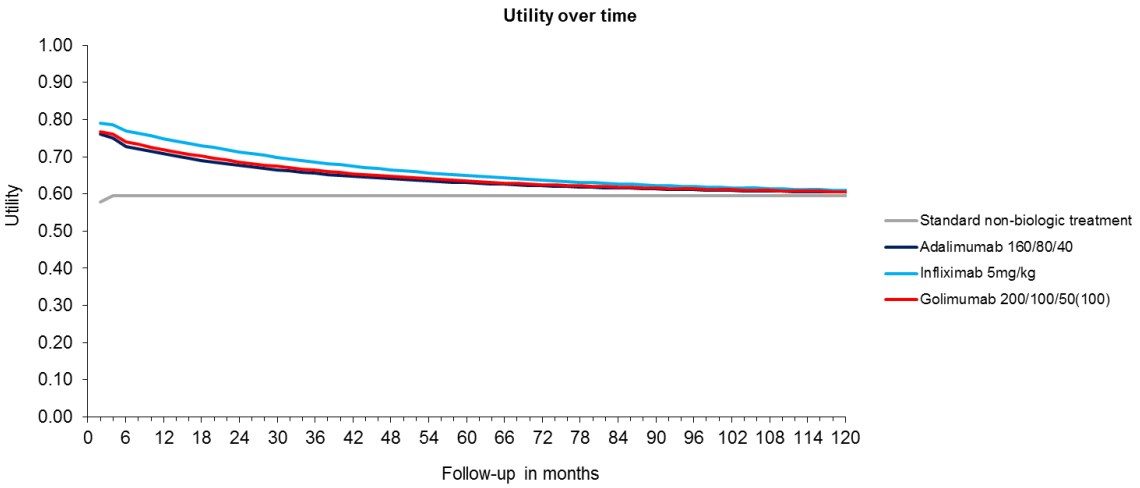


Figure 18: Development of utility over time (among patients alive)



6.6.2. Model Evaluations

A Patient Access Scheme (PAS) has been submitted in support of the parallel MSD submission for golimumab (made to NICE for this MTA), whereby the 100mg dose of golimumab is flat priced to the 50mg dose. The 100mg formulation will be provided to the NHS with a 50% discount on list price. The discount will be provided on the original invoice. The NHS will be invoiced £762.97 rather than the full list price of £1525.94.

The basecase analysis includes the PAS for golimumab, and applies the conservative assumption that 50% of patients treated with adalimumab receive weekly dosing in the maintenance phase.

6.6.3. Model Calculations

As the input parameters of the model are characterised by uncertainty, one-way sensitivity analysis and probabilistic sensitivity analysis (PSA) were performed to assess the robustness of the model and to quantify the uncertainty in the model outcomes, respectively.

With the PSA, new parameter values were sampled from the (posterior) distributions for efficacy, safety, utility, and costs for each iteration of the model. The model was evaluated by averaging output values over many iterations (i.e. 1.000), allowing uncertainty in model parameters to be accounted for. Next, the incremental cost, incremental QALYs, and ICER (ICER = incremental costs/incremental QALYs) were calculated. The probability of cost-effectiveness was expressed with cost-effectiveness acceptability curves. Furthermore, the probability of cost-effectiveness for golimumab relative to each of the three other strategies was calculated.

6.6.4. Basecase Analysis

The results of the basecase analysis are presented in Table 41 and. In the basecase the acquisition costs for golimumab 100mg were set to be the same as for golimumab 50mg.

Given the medical resource use considered in the model, the discounted cumulative total direct cost over a 10 year time horizon as presented in Figure 19 were obtained. The expected costs stratified by type of resource use are presented in Table 41.

The discounted QALYs over a 10 year time horizon were estimated to be 4.94 with colectomy and 5.66 with infliximab (Table 41). When the difference in total cost between infliximab and colectomy, i.e. £27,130, was expressed per unit QALY gained with infliximab relative to colectomy, an ICER of £37,682 was obtained (Table 42).

In Figure 20, Figure 21, and Figure 22 the results of one-way sensitivity analysis in terms of incremental costs, QALYs, and NMB (at a WTP of £30,000 per QALY) are presented. The uncertainty in the efficacy of induction and maintenance treatment with infliximab (and the associated uncertainty in the duration of treatment) has the greatest impact on the uncertainty in incremental cost estimates. In terms of QALYs and cost-effectiveness, the uncertainty regarding the utility estimate for health states after colectomy is the greatest driver of uncertainty in these model outcomes.

In Figure 23 the joint uncertainty distribution of incremental costs and QALYs with the biologics relative to colectomy are presented. In Figure 24 the implications of model uncertainty in terms of decision uncertainty are presented with cost-effectiveness acceptability curves.

Figure 19: Development of costs over time by intervention

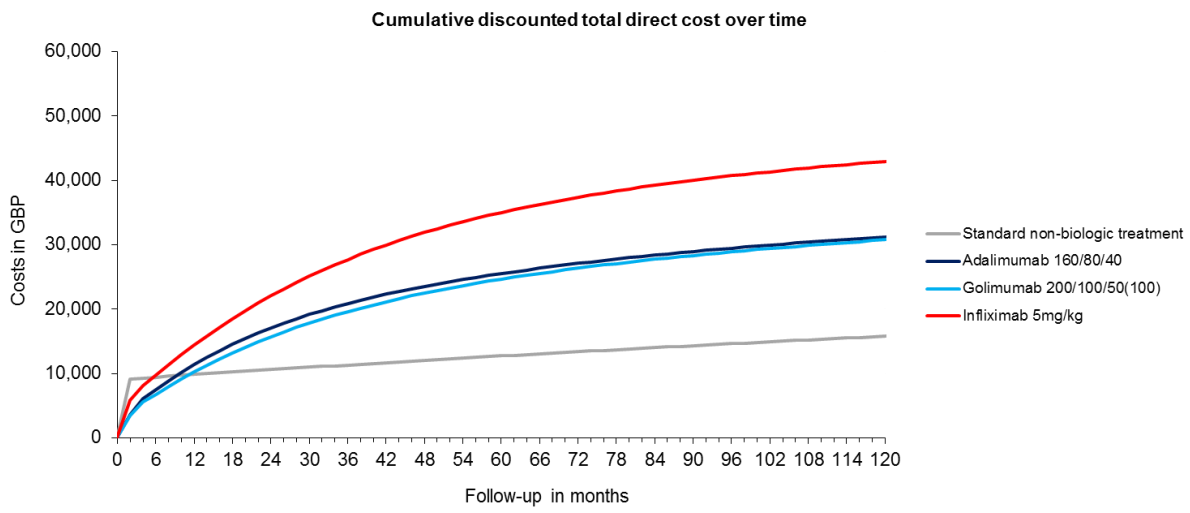


Table 41: Expected outcomes and costs for a 10 year time horizon

	Colectomy				Adalimumab 160/80/40mg				Golimumab 200/100/50(100)mg				Infliximab 5mg/kg			
	Det. value	Prob. value	95% CrI low	95% CrI high	Det. value	Prob. value	95% CrI low	95% CrI high	Det. value	Prob. value	95% CrI low	95% CrI high	Det. value	Prob. value	95% CrI low	95% CrI high
Duration of induction and maintenance treatment (pre-colectomy phase) (in months)	0.0	0.0	0.0	0.0	10.5	11.4	6.5	18.9	13.4	14.3	9.2	22.2	22.1	23.9	13.0	39.4
Time to colectomy (in months)	0.0	0.0	0.0	0.0	44.2	44.9	38.7	52.2	46.8	47.4	41.5	54.5	54.3	55.4	45.9	67.7
Duration of post-colectomy phase (in months)	113.9	113.9	111.8	115.3	71.1	70.4	63.2	76.3	68.6	67.9	60.9	73.5	61.3	60.2	48.7	69.6
Life years	9.65	9.65	9.48	9.77	9.76	9.76	9.65	9.83	9.76	9.76	9.66	9.83	9.78	9.78	9.69	9.84
Disc. life years	8.31	8.31	8.16	8.42	8.41	8.41	8.32	8.47	8.41	8.41	8.33	8.47	8.43	8.43	8.35	8.48
Discounted QALYs	4.94	4.97	3.19	6.58	5.45	5.48	4.44	6.45	5.51	5.54	4.54	6.47	5.66	5.71	4.73	6.54
Discounted drug acquisition and admin. cost	0	0	0	0	15,706	16,641	11,130	24,923	15,370	16,017	11,870	22,193	27,986	29,412	19,380	43,203
Discounted AE cost related to drug treatment	0	0	0	0	554	565	427	736	588	597	457	764	687	703	524	976
Disc. consultant visit cost	2,772	2,776	2,288	3,306	3,727	3,732	3,345	4,115	3,744	3,747	3,361	4,144	3,788	3,786	3,404	4,194
Discounted endoscopy cost	2,241	2,238	1,918	2,575	1,781	1,768	1,544	1,999	1,745	1,732	1,528	1,945	1,638	1,618	1,381	1,864
Discounted inpatient stay cost	0	0	0	0	916	909	835	978	910	903	825	975	911	890	756	985
Discounted colectomy cost	8,966	8,966	8,810	9,135	7,452	7,398	6,931	7,779	7,333	7,280	6,828	7,637	6,957	6,826	5,879	7,448
Discounted costs late complications	1,762	1,796	578	3,834	1,030	1,040	321	2,231	992	1,001	315	2,144	879	879	278	1,860
Discounted other UC cost	49	49	41	58	71	71	64	79	72	72	65	80	75	75	67	83
Discounted total direct cost	15,790	15,825	14,355	17,900	31,237	32,123	26,703	39,772	30,753	31,348	27,367	37,010	42,920	44,189	34,745	57,090
NMB at WTP of £30,000	132,554	133,133	81,299	179,410	132,391	132,414	106,499	153,746	134,486	134,755	108,789	156,962	127,023	126,982	107,025	139,126

Admin., administration; AE, adverse event; CrI, credible interval; Det., deterministic; Disc., discounted; NMB, net monetary benefit; Prob., probabilistic; QALY, Quality-Adjusted Life Year; UC, ulcerative colitis; WTP, willingness-to-pay.

Table 42: Pairwise comparisons; incremental costs, QALYs, and cost-effectiveness ratio for a 10 year time horizon

	Incremental discounted total direct cost				Incremental discounted QALYs				Incremental cost-effectiveness ratio			
	Det. value	**Prob. value**	**95% CrI low**	**95% CrI high**	**Det. value**	**Prob. value**	**95% CrI low**	**95% CrI high**	**Det. value**	**Interpretation***	**Prob. value**	**Interpretation***
Adalimumab 160/80/40mg vs. Standard non-biologic treatment (colectomy)	15,448	16,298	11,128	24,117	0.51	0.52	-0.16	1.30	30,319	Smaller NMB, hence not cost-effective	31,385	Smaller NMB, hence not cost-effective
Golimumab 200/100/50(100)mg vs. Standard non-biologic treatment (colectomy)	14,964	15,523	11,512	21,156	0.56	0.57	-0.11	1.39	26,569	Greater NMB, hence cost-effective	27,163	Greater NMB, hence cost-effective
Infliximab 5mg/kg vs. Standard non-biologic treatment (colectomy)	27,130	28,365	19,010	41,122	0.72	0.74	-0.08	1.72	37,682	Smaller NMB, hence not cost-effective	38,307	Smaller NMB, hence not cost-effective
Golimumab 200/100/50(100)mg vs. Adalimumab 160/80/40mg	-484	-776	-9,148	6,107	0.05	0.05	-0.10	0.24	Dominant	Greater NMB, hence cost-effective	Dominant	Greater NMB, hence cost-effective
Infliximab 5mg/kg vs. Adalimumab 160/80/40mg	11,682	12,066	626	25,865	0.21	0.22	0.00	0.58	55,507	Smaller NMB, hence not cost-effective	54,564	Smaller NMB, hence not cost-effective
Infliximab 5mg/kg vs. Golimumab 200/100/50(100)mg	12,166	12,842	2,493	25,846	0.16	0.17	-0.05	0.52	77,599	Smaller NMB, hence not cost-effective	75,998	Smaller NMB, hence not cost-effective

* Willingness-to-pay ratio of £30,000. CrI, credible interval; Det., deterministic; NMB, net monetary benefit; Prob., probabilistic; QALY, Quality-Adjusted Life Year; vs., versus.

Figure 20: Results of one-way sensitivity analysis for infliximab relative to colectomy in terms of cost

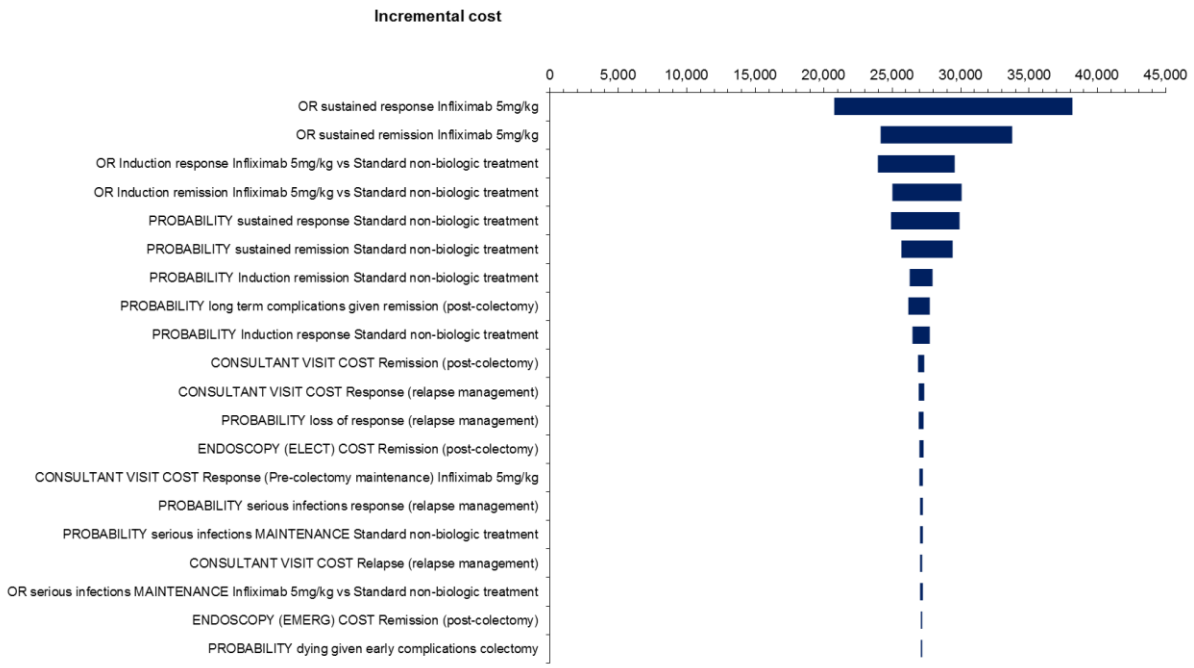


Figure 21: Results of one-way sensitivity analysis for infliximab relative to colectomy in terms of QALYs

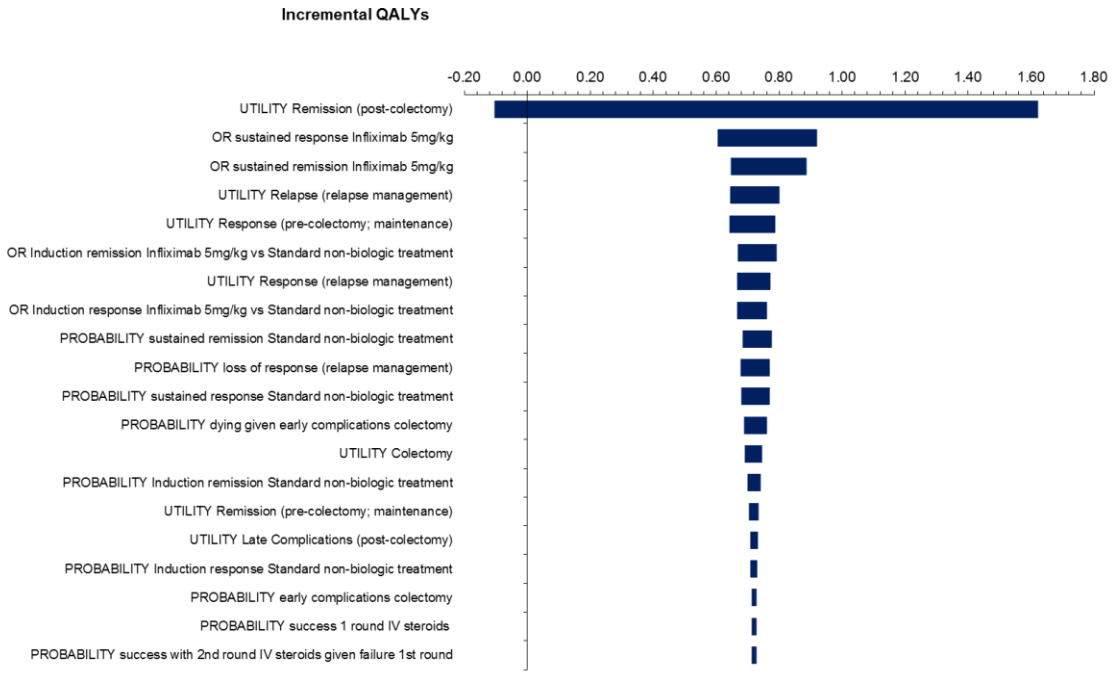


Figure 22: Results of one-way sensitivity analysis for infliximab relative to colectomy in terms of cost-effectiveness expressed as NMB with a WTP of £30,000

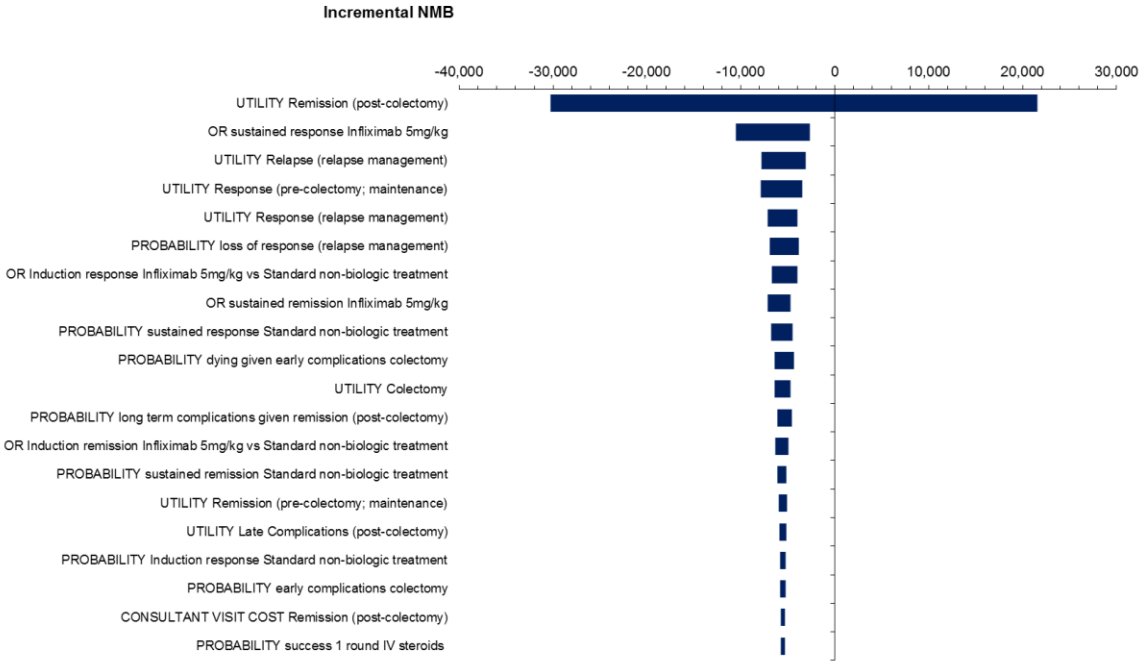


Figure 23: Cost-effectiveness plane

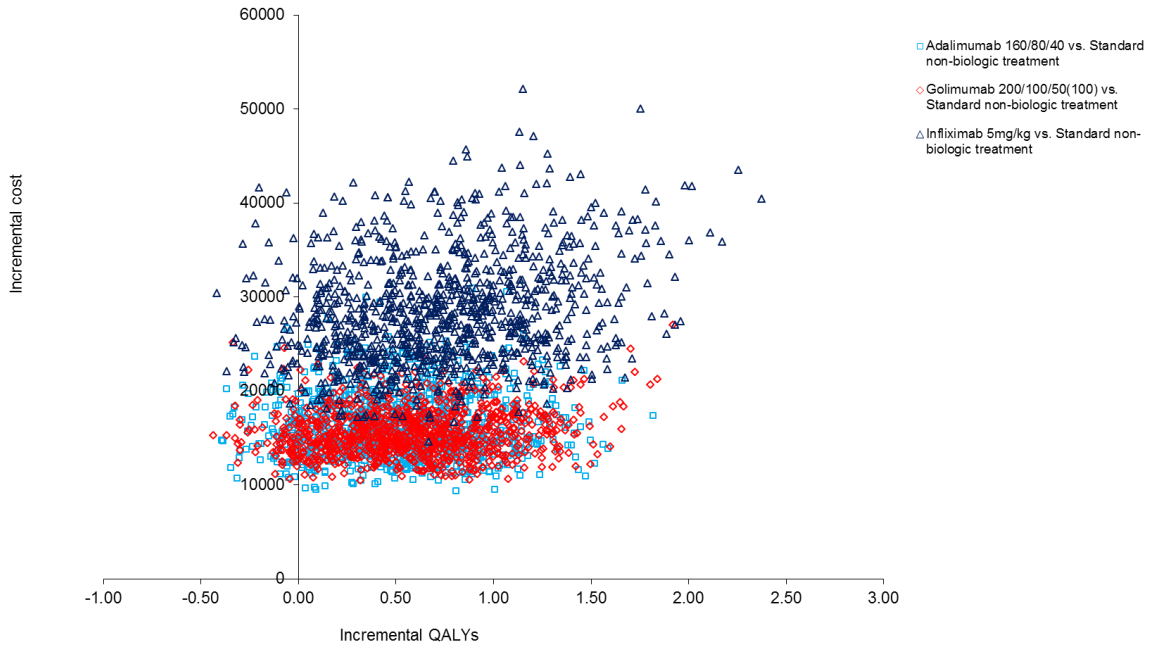
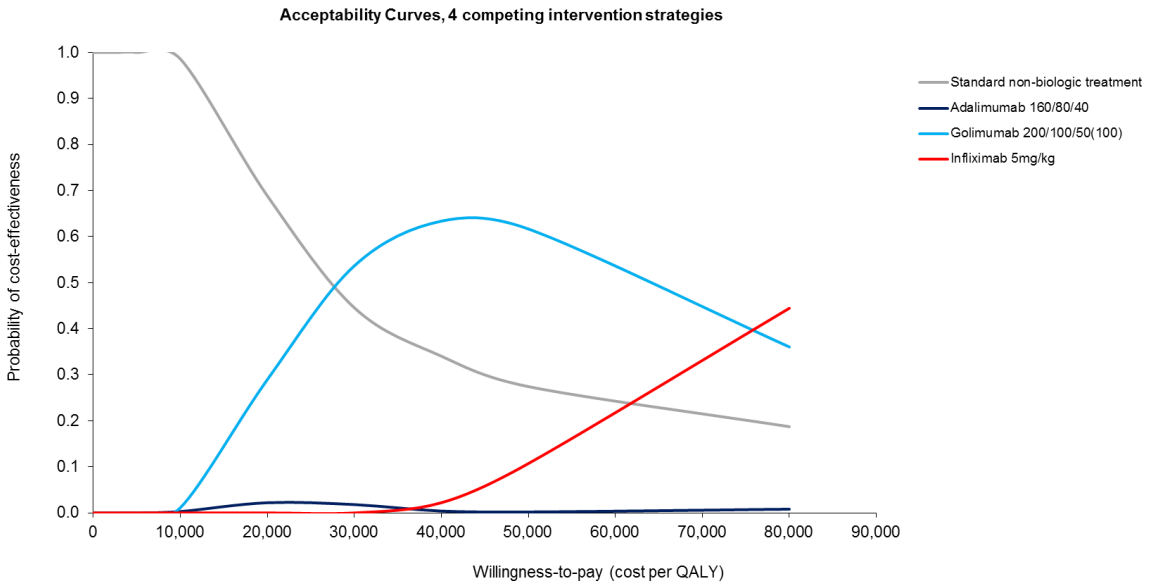


Figure 24: Cost-effectiveness acceptability curves for decision problem with four competing interventions



6.6.5. Sensitivity Analyses

In the basecase, it was assumed that 50% of patients treated with adalimumab receive a maintenance dose of 40mg EW and 50% receive 40mg EOW. This conservative assumption was applied as UK clinical experts advised that up to 80% of patients with moderately to severely active UC treated with adalimumab receive 40mg EW. In the ULTRA study ~23% of patients required dose escalation from 40mg EOW to 40mg EW, so an analysis was performed where 23% of patients treated with adalimumab had weekly maintenance dosing and the 77% of patients received 40mg adalimumab EOW.

This analysis includes the PAS for golimumab.

In Figure 25, Figure 26, and Figure 27, and in Table 43 and Table 44 the results of this scenario analysis are presented. In this analysis the ICER for infliximab versus standard non-biologic treatment (colectomy) was £37,682.

Figure 25: Development of costs over time (adalimumab 77% EOW/23% EW)

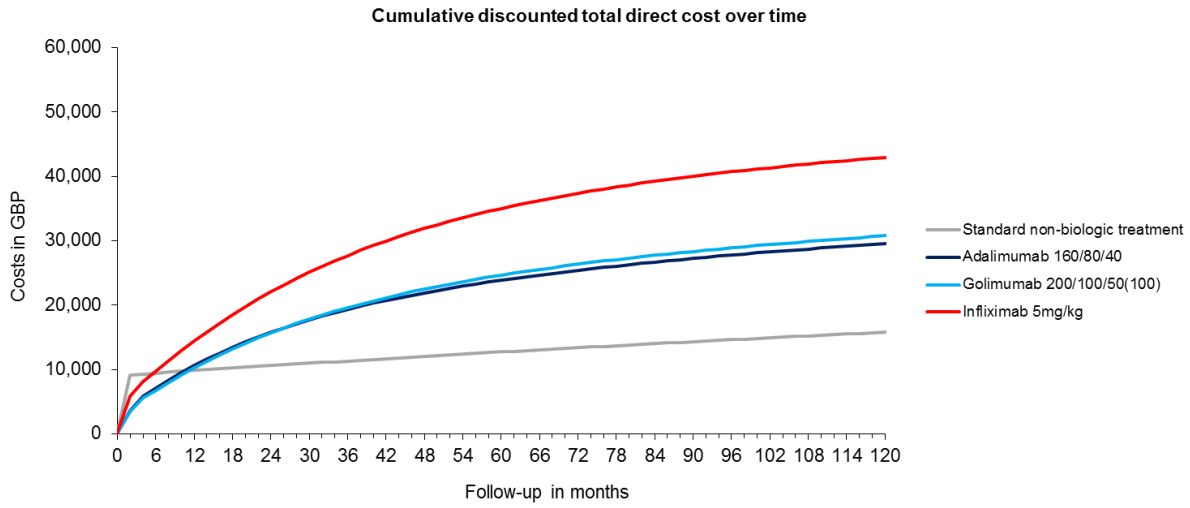


Table 43: Expected outcomes and costs for a 10 year time horizon (adalimumab 77% EOW/23% EW)

	Colectomy				Adalimumab 160/80/40mg				Golimumab 200/100/50(100)mg				Infliximab 5mg/kg			
	Det. value	Prob. value	95% CrI low	95% CrI high	Det. value	Prob. value	95% CrI low	95% CrI high	Det. value	Prob. value	95% CrI low	95% CrI high	Det. value	Prob. value	95% CrI low	95% CrI high
Duration of induction and maintenance treatment (pre-colectomy phase) (in months)	0.0	0.0	0.0	0.0	10.5	11.6	6.5	19.7	13.4	14.2	8.9	21.9	22.1	24.2	13.4	39.6
Time to colectomy (in months)	0.0	0.0	0.0	0.0	44.2	45.1	39.2	52.9	46.8	47.4	41.2	54.4	54.3	55.8	45.8	67.2
Duration of post-colectomy phase (in months)	113.9	113.9	112.0	115.4	71.1	70.2	62.8	76.0	68.6	68.0	61.4	74.3	61.3	59.9	48.9	69.6
Life years	9.65	9.66	9.49	9.78	9.76	9.76	9.66	9.83	9.76	9.76	9.66	9.84	9.78	9.78	9.69	9.85
Disc. life years	8.31	8.32	8.18	8.42	8.41	8.41	8.33	8.47	8.41	8.41	8.33	8.47	8.43	8.43	8.35	8.48
Discounted QALYs	4.94	4.95	3.13	6.60	5.45	5.48	4.38	6.45	5.51	5.52	4.47	6.48	5.66	5.70	4.74	6.53
Discounted drug acquisition and admin. cost	0	0	0	0	14,016	14,962	10,229	22,069	15,370	15,901	11,674	21,896	27,986	29,750	19,622	43,283
Discounted AE cost related to drug treatment	0	0	0	0	554	567	429	746	588	596	453	757	687	706	530	974
Disc. consultant visit cost	2,772	2,773	2,310	3,284	3,727	3,725	3,339	4,136	3,744	3,738	3,349	4,152	3,788	3,778	3,393	4,190
Discounted endoscopy cost	2,241	2,244	1,938	2,577	1,781	1,770	1,566	1,993	1,745	1,739	1,542	1,969	1,638	1,618	1,398	1,862
Discounted inpatient stay cost	0	0	0	0	916	906	828	977	910	901	825	973	911	886	753	984
Discounted colectomy cost	8,966	8,968	8,794	9,139	7,452	7,386	6,908	7,767	7,333	7,282	6,811	7,659	6,957	6,803	5,856	7,434
Discounted costs late complications	1,762	1,764	498	3,733	1,030	1,019	295	2,127	992	985	283	2,105	879	860	242	1,793
Discounted other UC cost	49	49	41	58	71	71	63	79	72	72	65	80	75	75	67	83
Discounted total direct cost	15,790	15,799	14,390	17,804	29,547	30,407	25,749	36,820	30,753	31,213	27,110	36,821	42,920	44,476	35,038	56,972
NMB at WTP of £30,000	132,554	132,639	79,513	180,339	134,081	133,889	105,514	156,732	134,486	134,493	107,062	157,462	127,023	126,517	107,047	139,021

Admin., administration; AE, adverse event; CrI, credible interval; Det., deterministic; Disc., discounted; NMB, net monetary benefit; Prob., probabilistic; QALY, Quality-Adjusted Life Year; UC, ulcerative colitis; WTP, willingness-to-pay.

Table 44: Pairwise comparisons; incremental costs, QALYs, and cost-effectiveness ratio for a 10 year time horizon (adalimumab 77% EOW/23% EW)

	Incremental discounted total direct cost				Incremental discounted QALYs				Incremental cost-effectiveness ratio			
	Det. value	Prob. value	95% CrI low	95% CrI high	Det. value	Prob. value	95% CrI low	95% CrI high	Det. value	Interpretation *	Prob. value	Interpretation *
Adalimumab 160/80/40mg vs. Standard non-biologic treatment (colectomy)	13,758	14,608	10,038	21,486	0.51	0.53	-0.20	1.31	27,002	Greater NMB, hence cost-effective	27,634	Greater NMB, hence cost-effective
Golimumab 200/100/50(100)mg vs. Standard non-biologic treatment (colectomy)	14,964	15,413	11,393	20,857	0.56	0.58	-0.17	1.40	26,569	Greater NMB, hence cost-effective	26,778	Greater NMB, hence cost-effective
Infliximab 5mg/kg vs. Standard non-biologic treatment (colectomy)	27,130	28,677	19,138	40,939	0.72	0.75	-0.14	1.77	37,682	Smaller NMB, hence not cost-effective	38,142	Smaller NMB, hence not cost-effective
Golimumab 200/100/50(100)mg vs. Adalimumab 160/80/40mg	1,206	806	-5,968	7,625	0.05	0.05	-0.12	0.25	22,467	Greater NMB, hence cost-effective	17,147	Greater NMB, hence cost-effective
Infliximab 5mg/kg vs. Adalimumab 160/80/40mg	13,373	14,070	3,104	27,053	0.21	0.22	0.00	0.60	63,537	Smaller NMB, hence not cost-effective	63,024	Smaller NMB, hence not cost-effective
Infliximab 5mg/kg vs. Golimumab 200/100/50(100)mg	12,166	13,264	2,868	26,166	0.16	0.18	-0.05	0.54	77,599	Smaller NMB, hence not cost-effective	75,258	Smaller NMB, hence not cost-effective

* Willingness-to-pay ratio of £30,000. CrI, credible interval; Det., deterministic; NMB, net monetary benefit; Prob., probabilistic; QALY, Quality-Adjusted Life Year; vs., versus.

Figure 26: Cost-effectiveness plane (adalimumab 77% EOW/23% EW)

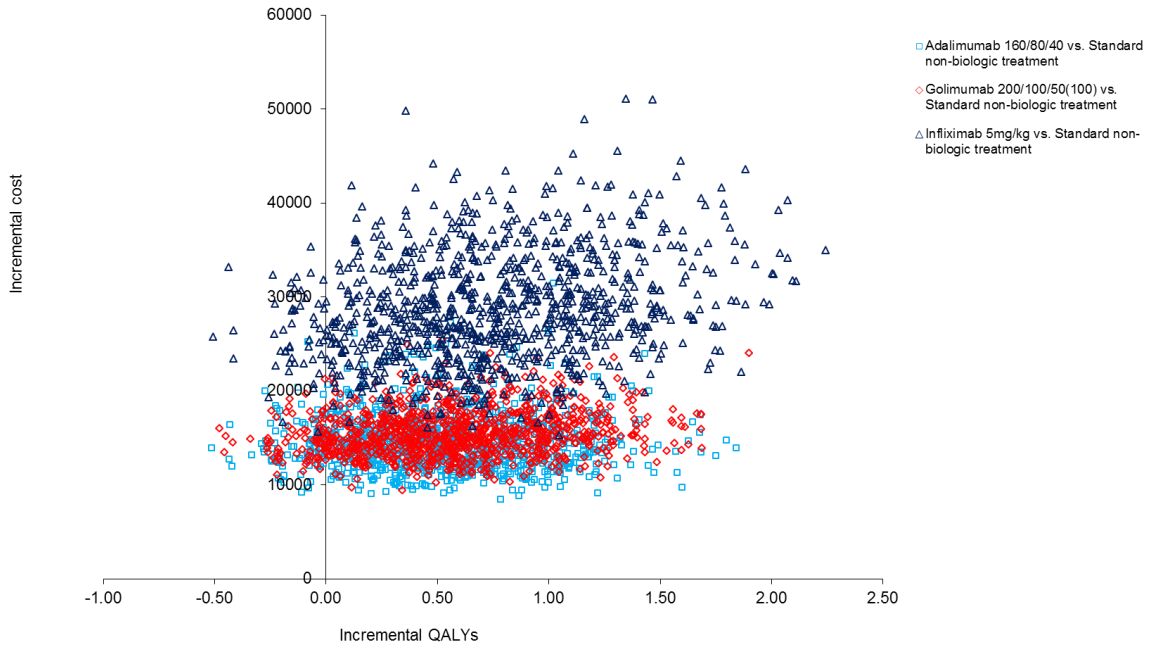
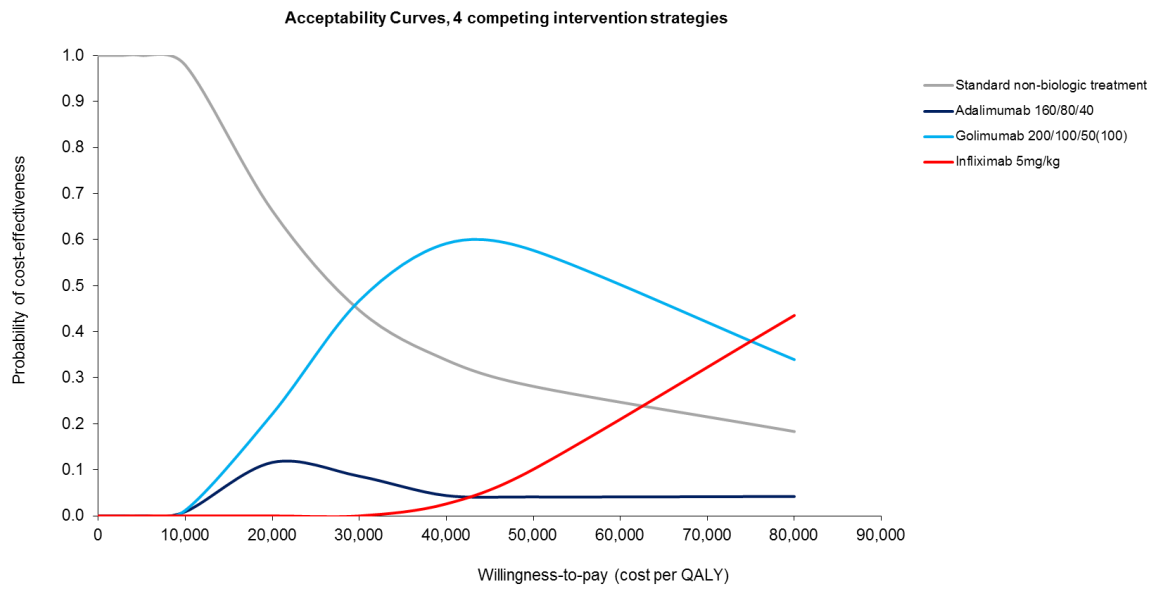


Figure 27: Cost-effectiveness acceptability curves for decision problem with four competing interventions (adalimumab 77% EOW/23% EW)



6.6.6. Additional Sensitivity Analyses

Additional one-way sensitivity analyses were performed to show the impact of varying selected parameters on ICERs (Table 45). In these analyses the PAS for golimumab was applied and it was assumed that 50% of maintenance treatment with adalimumab was EW with 50% EOW.

Table 45: Incremental cost-effectiveness ratios for sensitivity analyses of the basecase

	Infliximab vs. standard non-biologic treatment (colectomy)	**Infliximab vs. adalimumab**	**Infliximab vs. golimumab**
Basecase	£37,682	£55,507	£77,599
Life time horizon instead of 10 year time horizon	£37,296	£54,131	£74,763
5 year time horizon instead of 10 year time horizon	£38,054	£58,107	£86,182
No successful relapse management phase following failure of biologics; automatic transition to colectomy after flare	£60,816	£55,813	£71,556

Vs., versus.

6.7. Validation

Validation of the model structure and assumptions was conducted with three UK clinical experts: Dr Peter Irvine, Consultant Gastroenterologist - Guy's and St Thomas' Hospital and Hon. Senior Lecturer, King's College, London; Professor Chris Probert, Consultant Gastroenterologist - Royal Liverpool Hospital; and Dr Daniel R Gaya, Consultant Physician & Gastroenterologist - Glasgow Royal Infirmary.

Input was also sought from nine other UK consultant gastroenterologists as shown in Table 46. They each provided estimates of resource use required for the treatment of patients with UC at different stages of their treatment pathway which informed the modelling.

Table 46: UK clinical experts consulted on model inputs

Consultant gastroenterologist	Current NHS post
Dr Matt Johnson	Luton & Dunstable
Dr Anthony Shonde	King's Mill Hospital, Mansfield
Dr Paul Fortun	Royal Cornwall Hospital
Dr Tim Orchard	St Mary's Hospital, London
Dr Johan Rademaker	Conquest Hospital, East Sussex
Dr Sarah McCartney	University College London Hospitals
Dr Ian Shaw	Winfield Hospital, Gloucester
Dr Her Hsin Tsai	Hull and East Yorkshire
Dr Stuart Bloom	University College London Hospitals

NHS, National Health Service.

6.8. Interpretation of Economic Evidence

The primary strength of this analysis is that it is based on robust RCT evidence in the appropriate patient population. A second strength of the evaluation is that is based upon previous work in this area.

However, there are several limitations. A number of parameters such as health-related quality of life, long-term withdrawal rates, and resource use estimates were derived from literature and expert opinion and were based on non-randomised evidence. This adds significant uncertainty to the findings, but can be attributed only to the significant limitations in the available evidence.

Availability of long-term data for the use of biologics in the treatment of UC could enhance the robustness of the results by informing withdrawal rates and disease progression.

6.9. The Patient Experience with Infliximab

Infliximab is licensed for the treatment of both adult and paediatric patients (6 to 17 years) with UC. Despite a recommendation from NICE that infliximab use should be restricted to three doses for only those patients with acute, severely active UC, clinicians report successful maintenance treatment with infliximab whereby patients continue to receive infliximab (by IV infusion every 8 weeks) and remain in clinical response.

MSD offers an infliximab home care service where patients are able to receive maintenance infusions with infliximab in their own home. This offering not only provides convenience and comfort for the patient, but it can free up time and resource in hospital infusion suites.

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Available at http://www.ons.gov.uk/ons/rel/pop-estimate/population-estimates-for-uk--england-and-wales--scotland-and-northern-ireland/mid-2011-and-mid-2012/index.html. Accessed on 06/03/2014.

[5] MSD data on file.

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