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:

Golimumab (Simponi®)

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.

Simponi® (henceforth referred to as golimumab), a human immunoglobulin G1κ (IgG1κ) monoclonal antibody produced by murine hybridoma cell lines with recombinant deoxyribonucleic acid technology, binds with high affinity and specificity 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.

Golimumab, which is administered via SC injection, has been shown to be effective in inducing and maintaining clinical response and remission in patients with moderately to severely active UC.

Golimumab provides an effective option for the treatment of moderate to severe UC and has been demonstrated to be a cost-effective treatment, associated with an incremental cost-effectiveness ratio (ICER) of £27,322 in comparison with non-biologic standard of care (colectomy). Cost-effectiveness has also been demonstrated against the other licensed biologics; golimumab is a dominant intervention over adalimumab from a cost-effectiveness perspective and has been demonstrated cost-effective in comparison with infliximab.

The cost-effectiveness of golimumab is supported through the provision of a Patient Access Scheme (PAS) in which the list price of the 100mg dose is flat priced to that of the 50mg dose. There is no administrative burden to the NHS associated with the provision of this scheme.

MSD believes that the data and analyses presented herein demonstrate that golimumab is a clinically and cost-effective treatment for the treatment of UK patients with moderately to severely active UC.

1.2. The Technology

The key features of golimumab are presented in Table 1:

Table 1: Key features of golimumab

Approved name	Golimumab
Brand name	Simponi®
Marketing status	European Commission granted marketing authorisation valid throughout the European Union on 19th September 2013
Pharmacological action	Human immunoglobulin G1κ (IgG1κ) monoclonal antibody produced by murine hybridoma cell lines with recombinant DNA technology. Binds with high affinity and specificity to both soluble and transmembrane forms of TNF-α, neutralising the biological activity of TNF-α
Formulation	50mg solution for injection in pre-filled pen or syringe 100mg solution for injection in pre-filled pen
Dosing frequency	Induction dosing: 200mg at week 0, 100mg at week 2 Maintenance dosing: 50mg at week 6, and every 4 weeks thereafter For patients with body weight less than 80kg: • Golimumab should be given as an initial dose of 200mg, followed by 100mg at week 2, then 50mg every 4 weeks, thereafter, and For patients with body weight greater than or equal to 80kg: • Golimumab should be given as an initial dose of 200mg, followed by 100mg at week 2, then 100mg every 4 weeks, thereafter[1,2]
Average length of a course of treatment	Treatment may continue as long as adequate response is maintained. Available data suggest that clinical response is usually achieved within 12-14 weeks of treatment (after four doses). Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit within this time period[1,2]
Indications	*Ulcerative colitis:*

	Golimumab 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 *Rheumatoid arthritis:* Golimumab, in combination with MTX, is indicated for: • the treatment of moderate to severe, active rheumatoid arthritis in adults when the response to DMARD therapy including MTX has been inadequate • the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with MTX Golimumab, in combination with MTX, has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function *Psoriatic arthritis:* Golimumab, alone or in combination with MTX, is indicated for the treatment of active and progressive psoriatic arthritis in adult patients when the response to previous DMARD therapy has been inadequate. Golimumab has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease and to improve physical function *Ankylosing spondylitis:* Golimumab is indicated for the treatment of severe, active ankylosing spondylitis in adults who have responded inadequately to conventional therapy

6-MP, 6-mercaptopurine; AZA, azathioprine; DMARD, disease-modifying anti-rheumatic drug; DNA, deoxyribonucleic acid; MTX, methotrexate; TNF-α, tumour necrosis factor-alpha; UC, ulcerative colitis.

1.3. Clinical Effectiveness

The efficacy and safety of golimumab was evaluated in two randomised, double-blind, placebo-controlled clinical studies in adult patients with ulcerative colitis (UC).

1.3.1. PURSUIT-Induction

The PURSUIT-Induction study (henceforth referred to as PURSUIT-SC) comprised two parts; a Phase 2 dose-finding part to evaluate the dose-response relationship and to select SC golimumab induction regimens for continued development, and a Phase 3 dose-confirming part to evaluate the efficacy and safety of the selected SC golimumab induction regimens.

In Phase 2 enrolled participants were randomised (1:1:1:1) to receive SC injections of placebo or one of three golimumab induction regimens at weeks 0 and 2. Golimumab doses were 100mg at week 0/50mg at week 2, 200mg at week 0/100mg at week 2, or 400mg at week 0/200mg at week 2. The key outcome studied in Phase 2 was the median change from baseline in the Mayo

score, which were -1.0, -3.0, -2.0, and -3.0, in the groups given placebo, 100/50mg, 200/100mg, and 400/200mg golimumab, respectively, demonstrating a trend toward a dose-response relationship for golimumab. Based on the findings, the 200/100mg and 400/200mg SC induction regimens of golimumab were selected for continued development in the Phase 3 part.

In Phase 3, the primary endpoint was week 6 clinical response defined as a decrease from baseline in Mayo score of ≥30% and ≥3 points, with either a decrease from baseline in rectal bleeding sub-score of ≥1 or a rectal bleeding sub-score of 0 or 1. Secondary endpoints included week 6 clinical remission, mucosal healing, and Inflammatory Bowel Disease Questionnaire (IBDQ) score change. Rates of clinical response at week 6 were 51.0% and 54.9% among patients given 200/100mg and 400/200mg golimumab, respectively, versus 30.3% among those given placebo (both, $p \leq 0.0001$). Rates of clinical remission and mucosal healing and mean changes in IBDQ scores were significantly greater in both golimumab groups versus the placebo group ($p \leq 0.0014$, all comparisons). Rates of serious adverse events (SAEs) were 6.1% and 3.0%, and rates of serious infection were 1.8% and 0.5%, in the placebo and golimumab groups, respectively.

PURSUIT-SC demonstrated that treatment with SC golimumab induces clinical response, remission, and mucosal healing, and increases quality of life in larger percentages of patients with active UC than placebo.

1.3.2. PURSUIT-Maintenance

Patients achieving clinical response at week 6 of the induction trials (PURSUIT-SC, described above, and PURSUIT-IV, not described) were enrolled into the PURSUIT-Maintenance (PURSUIT-M) study. Patients who responded to induction therapy with golimumab (n=464) were assigned randomly to groups given placebo or injections of 50mg or 100mg golimumab every 4 weeks through week 52. Patients who responded to placebo in the induction study continued to receive placebo. Non-responders in the induction study received 100mg golimumab.

The primary endpoint was maintenance of clinical response through week 54 among golimumab-induction responders, assessed through the Mayo score at weeks 0, 30, and 54 and by partial Mayo score every 4 weeks to substantiate that patients had maintained clinical response at each visit (suspected loss of response was confirmed by endoscopy). Patients who maintained clinical response were considered to be in a state of continuous clinical response through week 54. Secondary endpoints included clinical remission, mucosal healing, sustained

clinical remission (at both weeks 30 and 54), and corticosteroid-free clinical remission at week 54 among patients receiving concomitant corticosteroids at baseline.

Clinical response was maintained through week 54 in 47.0% of patients receiving 50mg golimumab, 49.7% of patients receiving 100mg golimumab, and 31.2% of patients receiving placebo ($p=0.010$ and $p<0.001$, respectively). At weeks 30 and 54, a higher percentage of patients who received 100mg golimumab were in clinical remission and had mucosal healing (27.8% and 42.4%) than patients given placebo (15.6% and 26.6%; $p=0.004$ and $p=0.002$, respectively) or 50mg golimumab (23.2% and 41.7%, respectively). Percentages of SAEs were 7.7%, 8.4%, and 14.3% among patients given placebo, 50mg, or 100mg golimumab, respectively; percentages of serious infections were 1.9%, 3.2%, and 3.2%, respectively.

The maintenance study demonstrated that patients receiving golimumab (50mg or 100mg) were able to maintain clinical response through week 54. Furthermore, patients who received 100mg golimumab had clinical remission and mucosal healing at weeks 30 and 54. Safety was consistent with that reported for other TNF-α inhibitors and with that of golimumab in other approved indications.

1.4. Cost-Effectiveness

The basecase results for all comparisons are shown in Table 2 below. The results indicate that golimumab is a cost-effective treatment alternative, compared with standard non-biologic treatment (colectomy).

The incremental cost relative to colectomy over a 10 year time horizon is £15,101 and in combination with the incremental quality-adjusted life year (QALY) gain of 0.55, an ICER of £27,322 was obtained.

Golimumab is expected to result in a QALY gain of 0.05 when compared with adalimumab and has a reduced acquisition cost in UK clinical practice. Accordingly, golimumab is a dominating intervention over adalimumab from a cost-effectiveness perspective.

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)	15,576	16,329	11,171	23,554	0.50	0.51	-0.17	1.31	31,069	Smaller NMB, hence not cost-effective	32,129	Smaller NMB, hence not cost-effective
Infliximab 5mg/kg vs. Standard non-biologic treatment (colectomy)	27,297	28,615	19,158	41,109	0.70	0.72	-0.11	1.70	38,802	Smaller NMB, hence not cost-effective	39,767	Smaller NMB, hence not cost-effective
Golimumab 200/100/50(100)mg vs. Standard non-biologic treatment (colectomy)	15,101	15,611	11,670	21,567	0.55	0.56	-0.14	1.45	27,322	Greater NMB, hence cost-effective	27,994	Greater NMB, hence cost-effective
Infliximab 5mg/kg vs. Adalimumab 160/80/40mg	11,721	12,286	887	26,049	0.20	0.21	-0.01	0.55	57,980	Smaller NMB, hence not cost-effective	58,133	Smaller NMB, hence not cost-effective
Golimumab 200/100/50(100)mg vs. Adalimumab 160/80/40mg	-475	-718	-8,722	6,745	0.05	0.05	-0.09	0.23	Dominant	Greater NMB, hence cost-effective	Dominant	Greater NMB, hence cost-effective
Golimumab 200/100/50(100)mg vs. Infliximab 5mg/kg	-12,197	-13,004	-25,226	-2,315	-0.15	-0.16	-0.49	0.04	80,866	Greater NMB, hence cost-effective	80,318	Greater NMB, hence 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 substantially benefit from an on-going recommendation of golimumab for the treatment of moderately to severely active UC.

A network meta-analysis (NMA) provided evidence that golimumab was statistically significantly superior to adalimumab in maintenance therapy for clinical response and 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.

At £27,322, the ICER for golimumab falls under a £30,000 threshold, and thus golimumab can be considered a cost-effective treatment option for patients with moderately to severely active UC.

In conclusion, golimumab is a clinically and cost-effective treatment for the first-line biologic treatment of UC.

2. Description of Technology

2.1. Brand Name, Generic Name, and Therapeutic Class

Golimumab is a TNF-α inhibitor and part of the biologic disease-modifying anti-rheumatic drug (DMARD) class. It is available in either a 0.5ml pre-filled pen (auto-injector) or pre-filled syringe containing 50mg of golimumab, or a 1.0ml pre-filled pen (auto-injector) containing 100mg of golimumab.

2.2. Mechanism of Action

Golimumab is a human immunoglobulin G1κ (IgG1κ) monoclonal antibody produced by murine hybridoma cell line with recombinant deoxyribonucleic acid technology. Golimumab binds with high affinity and specificity to both soluble and transmembrane forms of TNF-α, thereby neutralising the biological activity of TNF-α.

2.3. Marketing Authorisation

The European Commission granted a marketing authorisation valid throughout the European Union for golimumab for the UC indication on 19th September 2013.

2.4. Indications

The approved indications for golimumab are as follows:

Ulcerative colitis:
Golimumab 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.

Rheumatoid arthritis:
Golimumab, in combination with methotrexate (MTX), is indicated for:

- the treatment of moderate to severe, active rheumatoid arthritis in adults when the response to DMARD therapy including MTX has been inadequate

- the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with MTX

Golimumab, in combination with MTX, has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.

Psoriatic arthritis:

Golimumab, alone or in combination with MTX, is indicated for the treatment of active and progressive psoriatic arthritis in adult patients when the response to previous DMARD therapy has been inadequate. Golimumab has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease and to improve physical function.

Ankylosing spondylitis:

Golimumab is indicated for the treatment of severe, active ankylosing spondylitis in adults who have responded inadequately to conventional therapy.

2.5. Costs

Table 3: Cost information for golimumab

Pharmaceutical formulation	50mg solution for injection in pre-filled pen or syringe 100mg solution for injection in pre-filled pen
Acquisition cost (excluding Value Added Tax [VAT])	50mg: £762.97 100mg: £1,525.94
Method of administration	Subcutaneous injection
Doses	50mg/100mg
Dosing frequency	Induction dosing: 200mg at week 0, 100mg at week 2 Maintenance dosing: 50mg at week 6, and every 4 weeks thereafter
Average length of a course of treatment	Treatment may continue as long as adequate response is maintained. Available data suggest that clinical response is usually achieved within 12-14 weeks of treatment (after four doses). Continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit within this time period[1,2]
Average cost of a course of treatment	Average cost in year 1: £11,444.55 Average cost in subsequent years: £9,918.61
Dose adjustments	For patients with body weight less than 80kg: • Golimumab should be given as an initial dose of 200mg, followed by 100mg at week 2, then 50mg every 4 weeks, thereafter, and For patients with body weight greater than or equal to 80kg: • Golimumab should be given as an initial dose of 200mg, followed by 100mg at week 2, then 100mg every 4 weeks, thereafter[1,2]

2.6. Additional Tests, Investigations, and Monitoring

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

Treatment with golimumab is contraindicated in patients with active tuberculosis (TB), other severe infections, moderate or severe heart failure (NYHA class III/IV), or hypersensitivity to the active substance or to any of the following excipients[1,2:]

- Sorbitol (E420)
- L-histidine
- L-histidine monohydrochloride monohydrate
- Polysorbate 80
- Water for injections

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 (although we are aware that there is some use in clinical practice). 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 intravenous (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[10,12].

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 golimumab was evaluated in two randomised, double-blind, placebo-controlled clinical studies in adult patients with UC.

5.1.1. PURSUIT-Induction[13]

PURSUIT-Induction; a Phase 2/3 multicentre, randomised, placebo-controlled, double-blind study to evaluate the efficacy and safety of golimumab induction therapy, administered subcutaneously, in subjects with moderately to severely active UC.

The PURSUIT-Induction (PURSUIT-SC) study was an adaptive, seamless Phase 2/3 trial comprising two parts: a Phase 2 dose-finding part to evaluate the dose-response relationship and to select SC golimumab induction regimens for continued development, and a Phase 3 dose-confirming part to evaluate the efficacy and safety of the selected SC golimumab induction regimens. In addition to this induction study which investigated SC regimens, an additional induction study investigated IV golimumab regimens (PURSUIT-IV, not described).

Study Participants

Inclusion Criteria

- Eligible patients had an established diagnosis of UC and moderate to severe disease activity, defined as a Mayo score of 6-12, with an endoscopic sub-score ≥2
- No minimum disease duration was pre-specified
- Patients had an inadequate response to, or had failed to tolerate, one or more of the following conventional therapies: oral 5-ASAs, oral corticosteroids, AZA, and/or 6-MP or were corticosteroid-dependent (i.e. an inability to taper corticosteroids without recurrence of UC symptoms)
- Patients treated concurrently with oral 5-ASAs or corticosteroids were to receive a stable dose for at least 2 weeks before baseline, and patients receiving AZA and/or 6-MP were to receive a stable dose for at least 4 weeks before baseline
- Patients were required to maintain stable doses of their concomitant UC medications during the study

Exclusion Criteria

- Patients with a history of, or at imminent risk of, colectomy; who required gastrointestinal surgery within 2 months before screening; had colitis limited to 20cm of the colon (patients with ulcerative proctitis often have rectal bleeding as the primary clinical manifestation of the disease, thus, the utility of the Mayo score in this patient population is less clear); or had a history of colonic mucosal dysplasia or adenomatous colonic polyps that were not removed, were ineligible
- Patients were excluded if their screening stool study was positive for enteric pathogens or *Clostridium difficile* toxin
- Earlier use of the following medications also precluded study participation: biologic TNF-α inhibitor(s), natalizumab, B-cell-depleting agents (rituximab), or T-cell-depleting agents (alemtuzumab, visilizumab) within 12 months of the first study agent injection (or continued B-cell or T-cell depletion >12 months after completing therapy with lymphocyte-depleting agents); oral corticosteroids at a dose >40mg prednisone or its equivalent per day; receipt of ciclosporin, tacrolimus, sirolimus, or mycophenolate mofetil within 8 weeks before the first study agent injection; or use of an investigational agent within five half-lives of that agent before the first study agent injection

Patient Enrolment

It was estimated that 176 patients would provide ≥80% probability of detecting a dose-response relationship in part one (Phase 2) of the study. The part two (Phase 3) sample size was based on statistical power considerations and the objective of providing the target study population for the subsequent 54 week PURSUIT-M study. Assuming week 6 clinical response rates of 45% for placebo (to reflect concerns around increasing clinical response rates in placebo groups of IBD studies), 55% for golimumab 200/100mg, and 65% for golimumab 400/200mg, ~150 patients per treatment group (total of 450 patients) in Phase 3 were necessary to provide 90% statistical power at a significance level of 0.05 (2-sided) for the primary endpoint of PURSUIT-SC. However, to provide a sufficient number of patients to adequately power PURSUIT-M, ~750 patients were required.

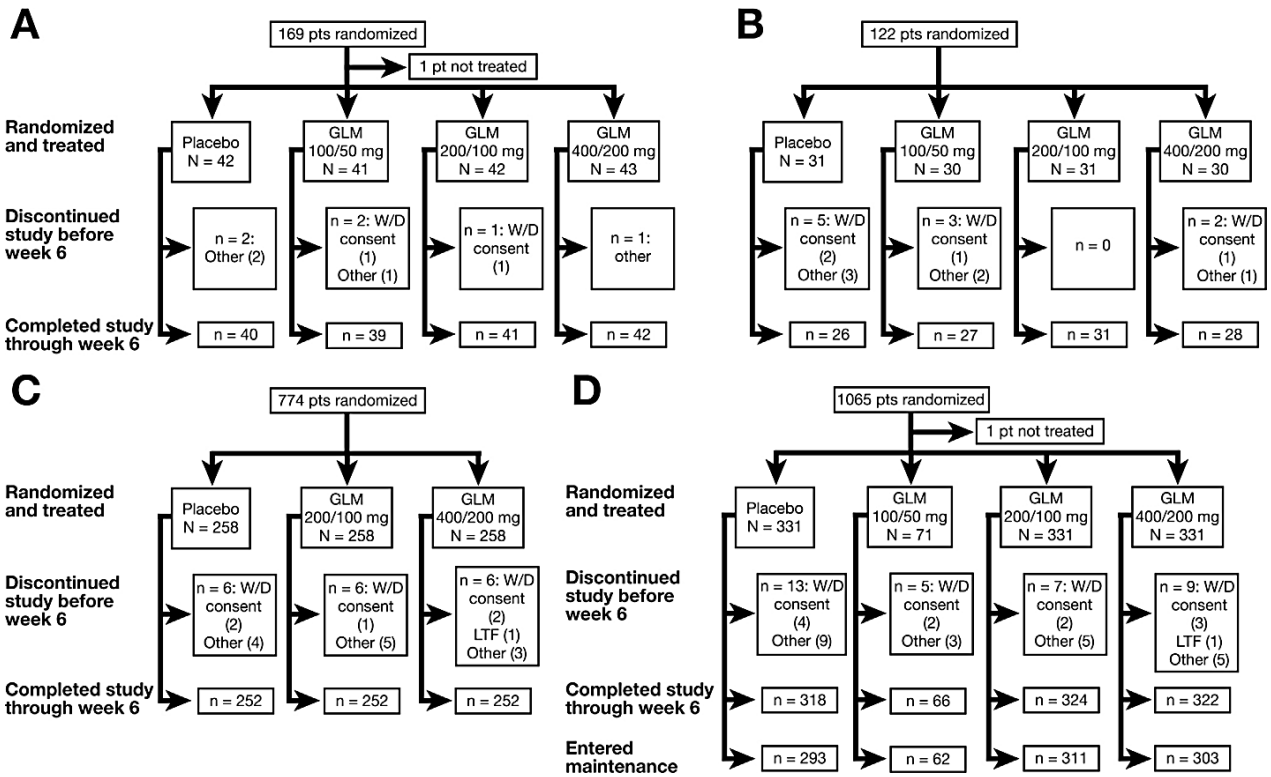
Allocation to treatment was performed using a central randomisation centre using an interactive voice-response system. Patients were allocated in Phase 2 using an adaptive randomisation procedure with investigative site as the stratification variable. After Phase 2, patients were allocated using a permuted block randomisation schema.

In Phase 2, 169 patients were randomised (1:1:1:1) to receive SC injections of placebo or one of three golimumab induction regimens at weeks 0 and 2 (Figure 1A). Golimumab doses were 100mg at week 0/50mg at week 2, 200mg at week 0/100mg at week 2, or 400mg at week 0/200mg at week 2. An additional 122 patients were enrolled while Phase 2 data were being analysed (Figure 1B); treatment regimens for this group were the same as those described for Phase 2. Data for this additional group are included in the overall safety and pharmacokinetic analyses.

After analysis of the dose-finding data, the 200/100mg and 400/200mg SC dosages were selected for continued evaluation in Phase 3. Overall, 774 patients were randomised in Phase 3 in a 1:1:1 ratio to receive SC injections of placebo, golimumab 200mg at week 0/100mg at week 2, or 400mg at week 0/200mg at week 2 (Figure 1C).

All treated patients (n=1064) (Figure 1D), irrespective of the study period in which they were enrolled, were eligible for subsequent participation in PURSUIT-M. Patients who did not enter the maintenance study were followed for safety monitoring through 16 weeks after the last administration of study agent.

Figure 1: Patient disposition through week 6



(A) Patients randomised in Phase 2; (B) Patients randomised while Phase 2 data were being analysed; (C) Patients randomised in Phase 3; (D) All randomised patients. The single patient randomised but never treated was assigned to the golimumab 100/50mg group. GLM, golimumab; W/D, withdrew.

Baseline Patient Characteristics

The randomised study population comprised 56% males, with a median age of 38 years. Patients had a median disease duration of 4.2 years. Approximately 40% of patients had a Mayo endoscopic sub-score of 3; extensive disease was observed in ~42% of patients. Concomitant baseline medications were 5-ASA (81.9%), corticosteroids (42.8%), and immunosuppressants (AZA, 6-MP, MTX [32.4%]).

Study Endpoints

To assess disease activity, Mayo scores were calculated at week 0 (baseline) and week 6. The Mayo score is the sum of four sub-scores (stool frequency, rectal bleeding, endoscopic findings, and a physician's global assessment).

The primary endpoint was clinical response at week 6 defined as a decrease from baseline in the Mayo score of ≥30% and ≥3 points, with either a decrease from baseline in the rectal bleeding sub-score of ≥1 or a rectal bleeding sub-score of 0 or 1.

The major secondary endpoints evaluated at week 6 were:

- Clinical remission (Mayo score ≤2 with no individual sub-score >1)
- Mucosal healing (Mayo endoscopy sub-score 0 or 1)
- Health-related quality of life (change from baseline in the IBDQ score [a 32-item questionnaire with a score ranging from 32 to 224; item responses range from 7 "not a problem at all" to 1 "a very severe problem"])

Blood samples were collected at baseline and weeks 2, 4, and 6 for serum trough golimumab concentration determinations using a validated electrochemiluminescent assay (lowest quantifiable concentration in a sample is 0.0391cg/ml), and at baseline and week 6 for the detection of antibodies to golimumab using a validated antigen-bridging immunoassay. Serum samples collected at baseline and weeks 2, 4, and 6 were also assessed for C-reactive protein (CRP) concentration. Adverse events, including injection-site reactions, and concomitant medication use were recorded throughout the study.

Study Results

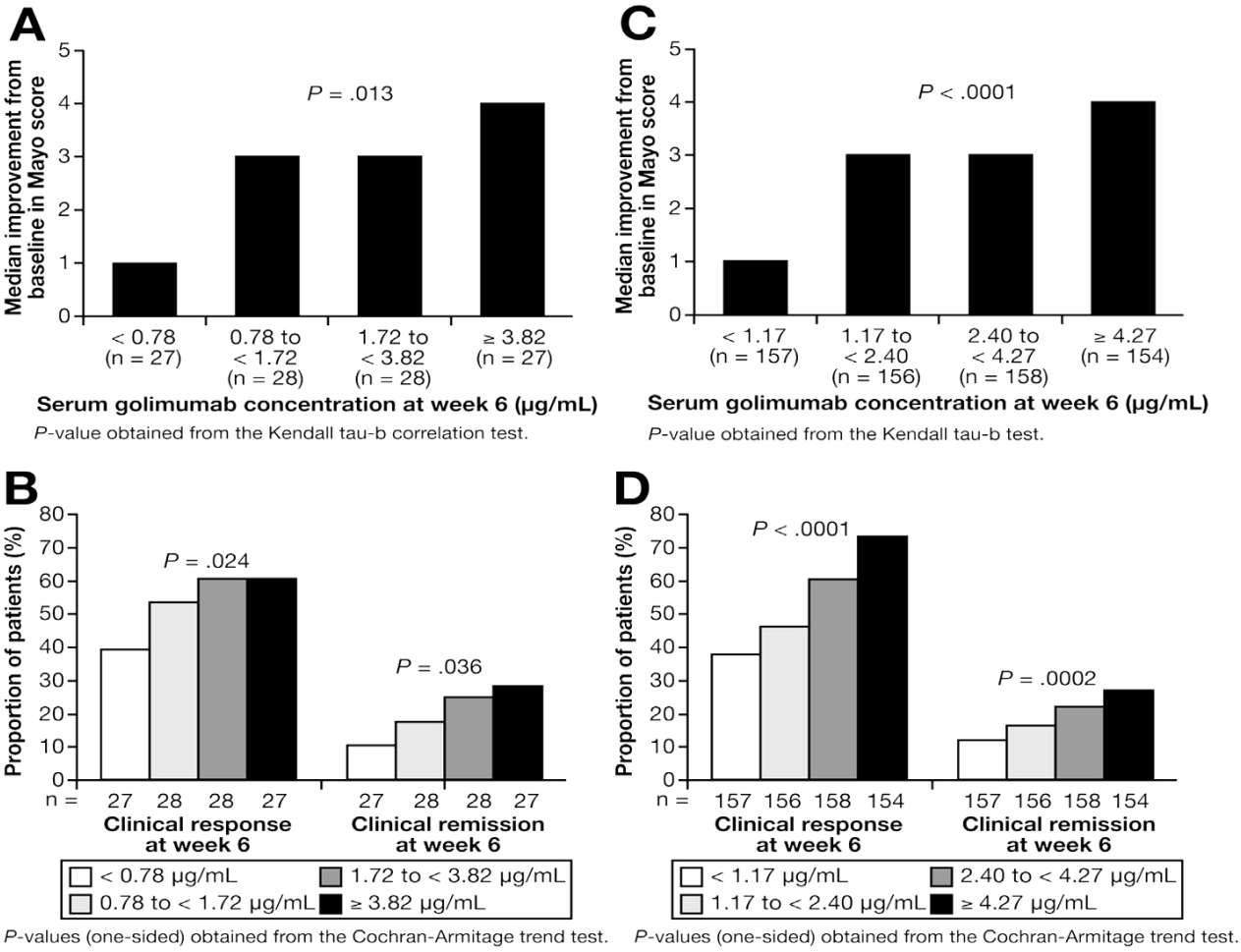
Phase 2 Efficacy Analyses

The dose-response of SC golimumab induction therapy was assessed based on the change in Mayo score from baseline to week 6. Baseline Mayo scores were similar among the placebo and golimumab groups. The median changes from baseline in the Mayo score were -1.0, -3.0, -2.0, and -3.0 for placebo and golimumab 100/50mg, 200/100mg, and 400/200mg, respectively, demonstrating a trend toward a dose-response relationship for golimumab. In addition, a numerically greater proportion of patients assigned to golimumab 400/200mg were in clinical response or remission, had mucosal healing, or had IBDQ scores superior to patients receiving placebo at week 6.

After golimumab administration, median serum golimumab concentrations were approximately dose-proportional at all pharmacokinetic sampling time points through week 6. Patients in the highest serum golimumab concentration quartiles had a greater improvement in median Mayo scores (Figure 2A and C) and greater rates of clinical response and clinical remission (Figure 2B and D) when compared with those in the lower quartiles at week 6, suggesting an exposure-response relationship.

Based on the pharmacokinetic and efficacy findings, the 200/100mg and 400/200mg SC induction regimens of golimumab were selected for continued development in the Phase 3 part.

Figure 2: Mayo score, clinical response, and clinical remission by serum golimumab concentration



Efficacy (A, C) Including median improvement from baseline in the Mayo score; (B, D) The proportions of patients in clinical response or clinical remission at week 6 by serum golimumab concentration among (A, B) Patients randomised in Phase 2; (C, D) All randomised patients. Patients who had all four Mayo sub-scores missing at week 6 were considered not to be in clinical response or clinical remission and had their last available Mayo sub-scores carried forward to impute the missing Mayo score at week 6. Patients who had a prohibited change in concomitant UC medication, an ostomy or colectomy, or discontinued study agent due to lack of therapeutic effect before week 6 were considered not to be in clinical response or clinical remission and had their baseline Mayo score carried forward to week 6. Serum samples collected at week 6 for one patient were excluded.

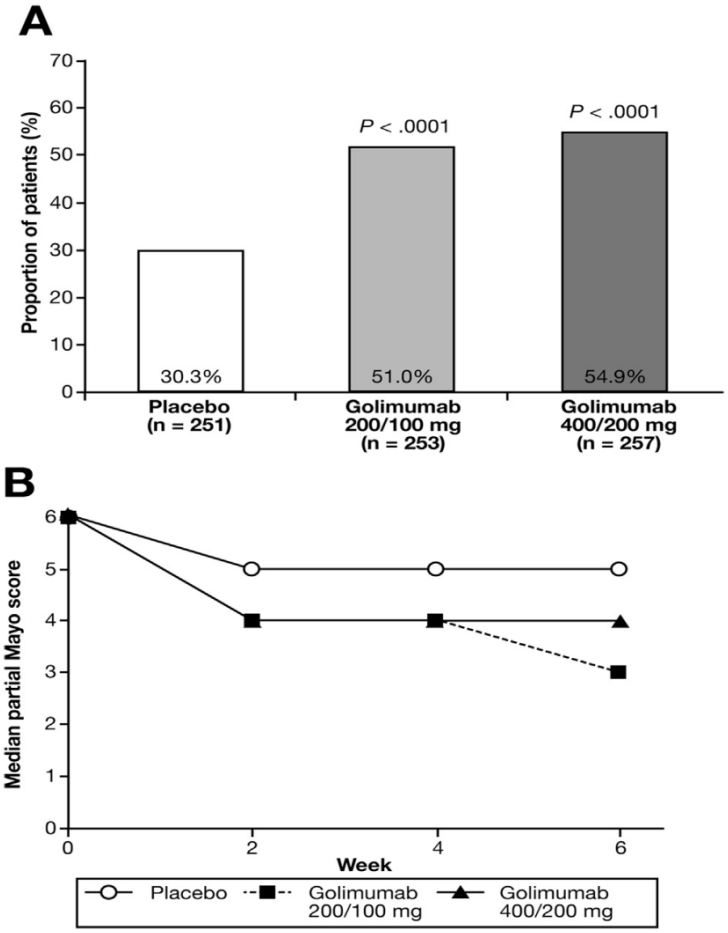
Phase 3 Efficacy Analyses

The primary efficacy analysis population comprised 761 patients (randomised in Phase 3), including 251 patients assigned to placebo, 253 patients to golimumab 200/100mg, and 257 patients to golimumab 400/200mg.

At week 6, significantly greater proportions of patients in the golimumab 200/100mg and 400/200mg groups (51.0% and 54.9%, respectively) were in clinical response than patients assigned to placebo (30.3%; p<0.0001 for both comparisons); the primary endpoint of PURSUIT-SC was therefore met (Figure 3A). In addition, greater median decreases in partial

Mayo scores (i.e. Mayo score excluding the endoscopy sub-score; values range from 0 to 9) with golimumab 200/100mg and golimumab 400/200mg compared with placebo were evident as early as week 2 (Figure 3B).

Figure 3: Clinical response and partial Mayo score at week 6



(A) Proportions of patients achieving clinical response (primary efficacy endpoint); (B) Median partial Mayo scores. Patients who had a prohibited change in concomitant UC medication, an ostomy or colectomy, or discontinued study agent due to lack of therapeutic effect before the week 6 visit were considered not to be in clinical response and had their baseline partial Mayo score carried forward from the time of the event onward.

The efficacy of both golimumab induction regimens was also demonstrated for the major secondary endpoints of clinical remission, mucosal healing, and improvement from baseline in the IBDQ score, all at week 6 (Table 4).

Table 4: Key efficacy outcomes at week 6

	Placebo (n=251)	Golimumab 200/100mg (n=253)	Golimumab 400/200mg (n=257)
Clinical remission [a]	6.4%	17.8% *	17.9% *
Mucosal healing [b]	28.7%	42.3% †	45.1% *
IBDQ change from baseline (mean ±SD)	14.8 ±31.25	27.0 ±33.72 *	26.9 ±34.28 *
Mayo score change from baseline (mean ±SD)	-1.6 ±2.53	-3.1 ±2.90 *	-3.1 ±2.95 *

* p≤0.001; † p=0.0014; a Defined as a Mayo score ≤2 points, with no individual sub-score >1; b Defined as 0 or 1 on the endoscopy sub-score of the Mayo score. IBDQ, Inflammatory Bowel Disease Questionnaire; SD, standard deviation.

The treatment effect of the selected golimumab dose regimens versus placebo across demographic subgroups (including study site geographic locations), UC disease characteristic subgroups, UC-related medication history subgroups, and baseline concomitant UC medication subgroups was generally consistent with that of the primary analysis population. Specifically, the treatment effect of golimumab dose regimens versus placebo across subgroups of patients receiving corticosteroids at baseline was also consistent with that of the primary analysis population.

Safety Analyses

Similar proportions of patients reported AEs through week 6 across groups (200/100mg, 37.5%; 400/200mg, 38.9%; and placebo, 38.2%). The most commonly observed AEs in golimumab- and placebo-treated patients were headache and nasopharyngitis. Overall, the incidences of SAEs (3.0% versus 6.1%), including serious infections (0.5% versus 1.8%), were also similar for golimumab- and placebo-treated patients, respectively. The most common SAE was the exacerbation of UC, reported by eight (1.1%) golimumab-treated and eight (2.4%) placebo-treated patients.

The only serious infection reported by more than one patient was pneumonia (one 200/100mg and one placebo patient). One patient (400/200mg) died from peritonitis and sepsis after surgical complications related to an ischiorectal abscess and subsequent bowel perforation after surgery; this patient was receiving concomitant prednisolone 20mg/day.

One patient (400/200mg) had a demyelinating disorder reported after the patient completed PURSUIT-SC and was subsequently randomised to placebo in the maintenance study. Two opportunistic infections were reported through week 6: oesophageal candidiasis (400/200mg)

and cytomegalovirus infection (placebo). Neither event was reported as serious. No patient developed active TB.

Few patients discontinued from the study due to an AE, including four (0.5%) golimumab-treated and three (0.9%) placebo-treated patients. The proportions of patients with injection-site reactions were low, occurring in 3.4% and 1.5% of golimumab- and placebo-treated patients, respectively. No difference was observed between the golimumab 200/100mg (3.3%) and 400/200mg (3.0%) groups. No delayed hypersensitivity or anaphylactic reactions were identified through week 6.

Summary

Golimumab 200/100mg and golimumab 400/200mg were both effective in inducing clinical response, remission, and mucosal healing, and improving health-related quality of life in patients with moderately to severely active UC. Clinical efficacy results were generally similar between the golimumab 200/100mg and golimumab 400/200mg groups.

5.1.2. PURSUIT-Maintenance[14]

PURSUIT-M; a Phase 3 multicentre, randomised, placebo-controlled, double-blind study to evaluate the efficacy and safety of golimumab maintenance therapy, administered subcutaneously, in subjects with moderately to severely active UC who achieved clinical response from previous induction therapy.

PURSUIT-M was a 54 week follow-on study in which enrolled participants had completed one of two golimumab induction studies: PURSUIT-IV (not described) or PURSUIT-SC (described in previous section). Note: serum golimumab concentration levels were tested and indicated that steady-state golimumab levels were comparable, regardless of which route of administration patients received in the induction studies.

Study Participants

Inclusion Criteria

- Patients eligible for PURSUIT-IV or PURSUIT-SC had an established diagnosis of UC with moderate to severe disease activity, defined as a Mayo score of 6-12, with an endoscopic sub-score ≥2

- Patients had an inadequate response to or had failed to tolerate one or more of the following conventional therapies: oral 5-ASAs, oral corticosteroids, immunosuppressives (AZA or 6-MP); or were corticosteroid-dependent (i.e. could not taper corticosteroids without recurrence of UC symptoms)
- Patients receiving 5-ASAs or immunosuppressives at baseline of PURSUIT-IV or PURSUIT-SC were required to have maintained stable doses throughout induction and maintenance
- Patients receiving corticosteroids at baseline of PURSUIT-IV or PURSUIT-SC had to have maintained doses throughout induction. After induction, patients in clinical response and receiving concomitant corticosteroids at baseline of PURSUIT-M were required to taper corticosteroids beginning at baseline (for doses of >20mg/day prednisone or equivalent: taper daily dose by 5mg/week; for dose of ≤20mg/day prednisone or equivalent: taper daily dose by 2.5mg/week)

Exclusion Criteria

- Patients with isolated proctitis were excluded from the induction studies (and therefore from the maintenance study)
- Patients were screened for TB before entry into one of the companion induction studies; those with active or previously identified latent disease were excluded - patients with newly-identified latent TB had to initiate appropriate treatment before being enrolled into and beginning treatment in this study (during the study, patients were evaluated routinely for signs and symptoms of active TB)

Patient Enrolment

The PURSUIT-M study was conducted at 251 sites in Eastern Europe (477 patients), North America (323 patients), Asia-Pacific and South Africa (237 patients), and Western Europe and Israel (191 patients). Overall, 1228 patients were enrolled from the induction studies, including 464 patients who were in clinical response to golimumab at week 6 of an induction study and were re-randomised and 764 patients who were enrolled but not re-randomised. Assuming a 35% clinical response rate for placebo and 55% for golimumab 100mg, ~128 patients in each randomised group (384 patients overall) provided an overall power of 90% for the primary endpoint at a 0.05 significance level based on a 2-sided chi-square test.

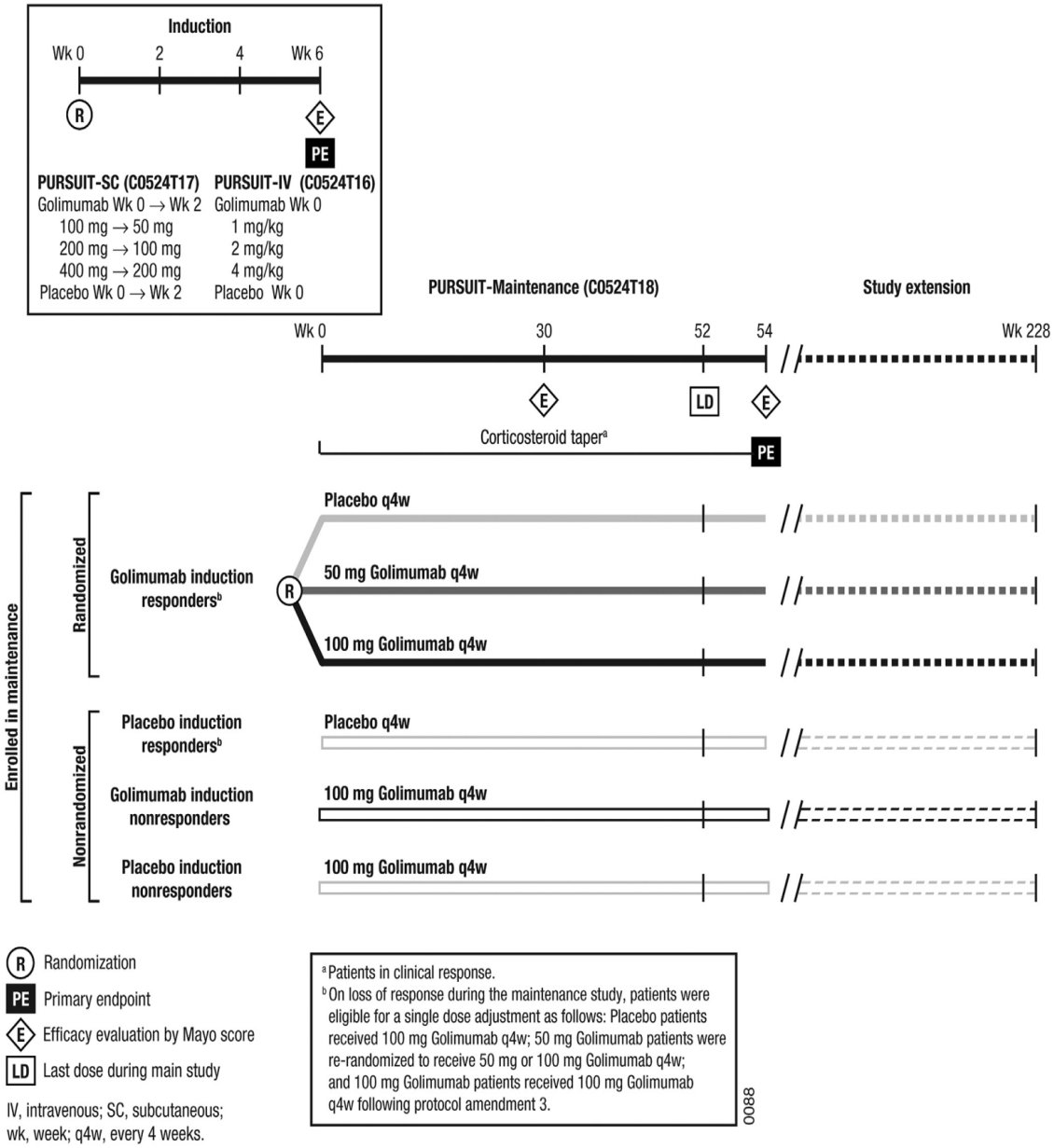
Patients who responded to golimumab induction therapy (n=464) were re-randomised at the baseline visit in a 1:1:1 ratio to receive SC placebo, golimumab 50mg, or golimumab 100mg

every 4 weeks through week 52 (Figure 4). Treatment allocation used an adaptive randomisation procedure based on three factors: (1) investigative site, (2) a four level cross-classification of clinical remission status and corticosteroid use at PURSUIT-M baseline, and (3) previous induction therapy (IV golimumab 1mg/kg, 2mg/kg, or 4mg/kg; SC golimumab 100/50mg, 200/100mg, or 400/200mg).

Placebo induction responders, and placebo or golimumab induction non-responders, were also eligible for PURSUIT-M but were not re-randomised (Figure 4). Placebo induction responders (n=129) received placebo every 4 weeks through week 52. Placebo- (n=230) or golimumab induction (n=405) non-responders received golimumab 100mg every 4 weeks through week 12; these patients were assessed at week 16 and were discontinued from the study if disease activity was not improved.

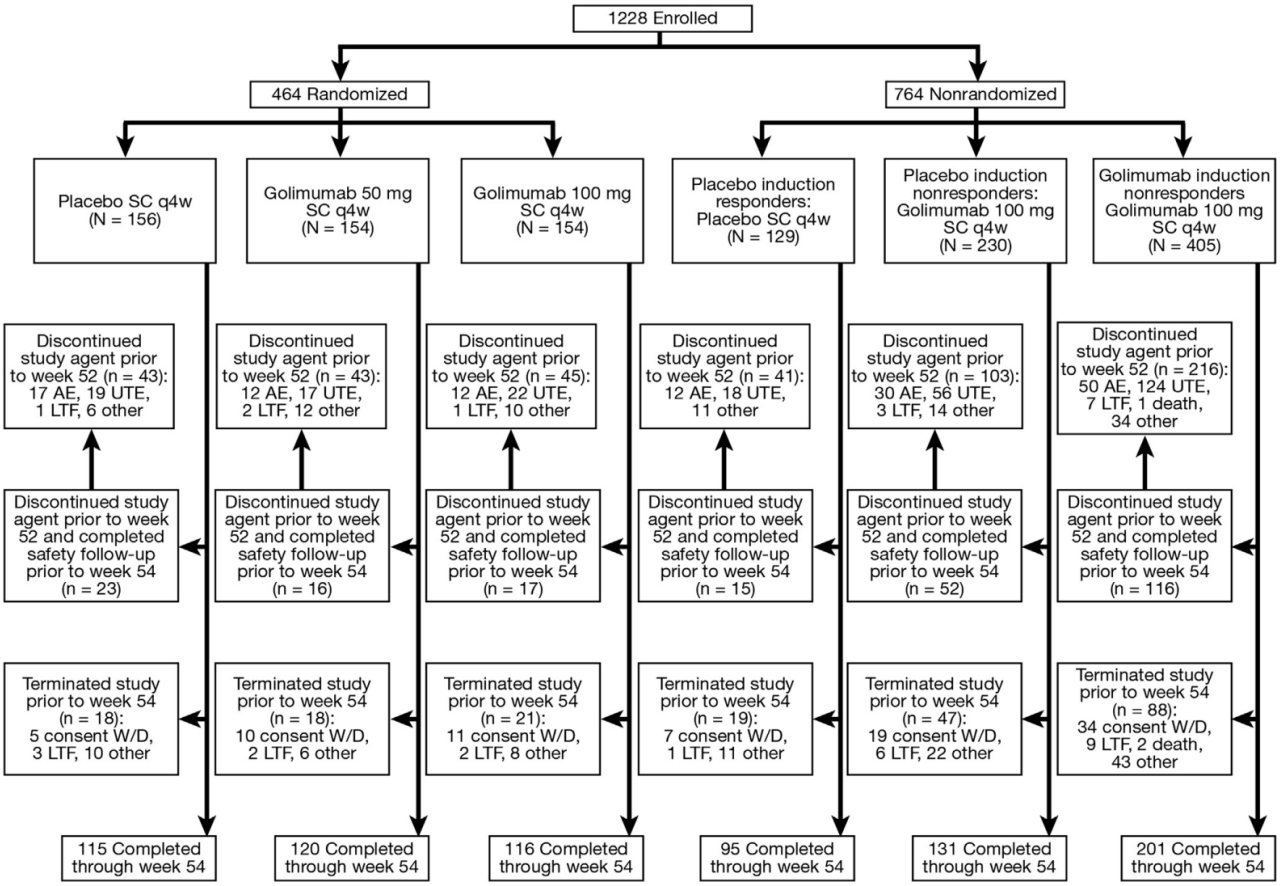
Induction therapy responders who subsequently lost clinical response could have their treatment modified as follows: placebo-treated patients received golimumab 100mg every 4 weeks, patients treated with golimumab 50mg were re-randomised to receive golimumab 50mg or 100mg every 4 weeks, and patients treated with golimumab 100mg initially were re-randomised to receive golimumab 100mg or 200mg every 4 weeks. After a protocol amendment, dose adjustment to 200mg every 4 weeks was discontinued; patients initially randomised to 100mg continued to receive 100mg, and patients who already had their dose increased to golimumab 200mg were decreased to golimumab 100mg.

Figure 4: Study design



Among re-randomised patients, 75.6% (351 of 464) of patients completed the study through week 54; more than 70.0% of patients completed the study in each group. Among non-randomised patients, 55.9% (427 of 764) of patients completed the study through week 54; 73.6% (95 of 129) of placebo induction responders, and 57.0% (131 of 230) and 49.6% (201 of 405) of placebo and golimumab induction non-responders, respectively, completed the study through week 54 (Figure 5).

Figure 5: Patient disposition through week 54



AE, adverse event; LTF, lost to follow-up evaluation; q4w, every 4 weeks; SC, subcutaneous; UTE, unsatisfactory therapeutic effect; W/D, withdrawn.

Patient Baseline Characteristics

Induction study baseline demographic characteristics and concomitant medication use were similar among re-randomised treatment groups at PURSUIT-M baseline. Almost half of the re-randomised patients were receiving corticosteroids, with ~35% receiving 20mg or more of prednisone equivalent/day. The median baseline (week 0 PURSUIT-M) dose of corticosteroids was 20mg prednisone or equivalent per day.

Approximately 30% of patients were receiving AZA/6-MP, and 80% were receiving 5-ASAs. Induction study baseline characteristics of the non-randomised patients were generally consistent with those of re-randomised patients at PURSUIT-M baseline. The proportion of males, the proportion of patients with severe disease, and median CRP concentrations were higher for golimumab induction non-responders (65.9%, 13.1%, and 6.3mg/l, respectively) than for re-randomised golimumab induction responders (51.9%, 6.7%, and 3.6mg/l, respectively).

Study Endpoints

The primary endpoint was maintenance of clinical response through week 54 among golimumab induction responders, assessed through the Mayo score at weeks 0, 30, and 54 and by partial Mayo score every 4 weeks to substantiate that patients had maintained clinical response at each visit (suspected loss of response was confirmed by endoscopy). Patients who maintained clinical response were considered to be in a state of continuous clinical response through week 54. Clinical response was defined as a decrease from baseline in Mayo score of ≥30% and ≥3 points, with either a decrease from baseline in rectal bleeding sub-score of ≥1 or a rectal bleeding sub-score of 0 or 1.

The analysis population for major secondary endpoints was golimumab-induction responders. Pre-specified major secondary endpoints were as follows:

- Clinical remission (Mayo score ≤2 with no individual sub-score >1 at both weeks 30 and 54)
- Mucosal healing (Mayo endoscopy sub-score 0 or 1 at both weeks 30 and 54)
- Clinical remission at both weeks 30 and 54 among patients who had clinical remission at PURSUIT-M baseline
- Corticosteroid-free clinical remission at week 54 among patients receiving concomitant corticosteroids at PURSUIT-M baseline

If the test for significance was positive for golimumab versus placebo for the primary endpoint, the significance of the major secondary endpoints was to be tested in a hierarchical order (as listed above).

Treatment failure rules were applied to all efficacy endpoints unless otherwise specified. Patients who had any of the following events were considered to be a treatment failure from the time of the event forward:

- Protocol-prohibited concomitant UC medication change(s)
- Colectomy (partial or total) or an ostomy
- Discontinued study agent because of a lack of therapeutic effect
- Dose adjustment before week 54

Patients experiencing a clinical flare (i.e. increased disease activity) at any time during the study were required to undergo sigmoidoscopy for calculation of the Mayo score and assessment for loss of clinical response (i.e. no longer in clinical response by Mayo score criteria). A clinical

flare was defined as either an increase from PURSUIT-M baseline in the partial Mayo score of 2 or more points with an absolute partial Mayo score of 4 or higher, or an absolute partial Mayo score of 7 or more points.

Serum samples were collected for determination of golimumab concentrations and identification of antibodies to golimumab using a validated antigen bridging immunoassay. Adverse events and concomitant medications were recorded through week 54.

Study Results

Primary Efficacy Analyses

Among the primary analysis population (n=456 [eight patients excluded from 464 re-randomised patients due to non-compliance with good clinical practice at three sites]), the proportion of patients who maintained a clinical response through week 54 was significantly greater in the 100mg and 50mg groups (49.7% and 47.0%, respectively) compared with the placebo maintenance group (31.2%; p<0.001 and p=0.010, respectively) (Figure 6A). The number needed to treat (NNT) for clinical response through week 54 was six and seven for the 100mg and 50mg golimumab groups, respectively.

The treatment effect of golimumab 100mg and 50mg was generally consistent across subgroups of patients, including study centre location. The inconsistency of efficacy results among induction baseline corticosteroid subgroups (none, <20mg/day, ≥20mg/day, ≥30mg/day, and ≥40mg/day) made it difficult to draw definitive conclusions regarding any corticosteroid carryover effects.

Major Secondary Analyses

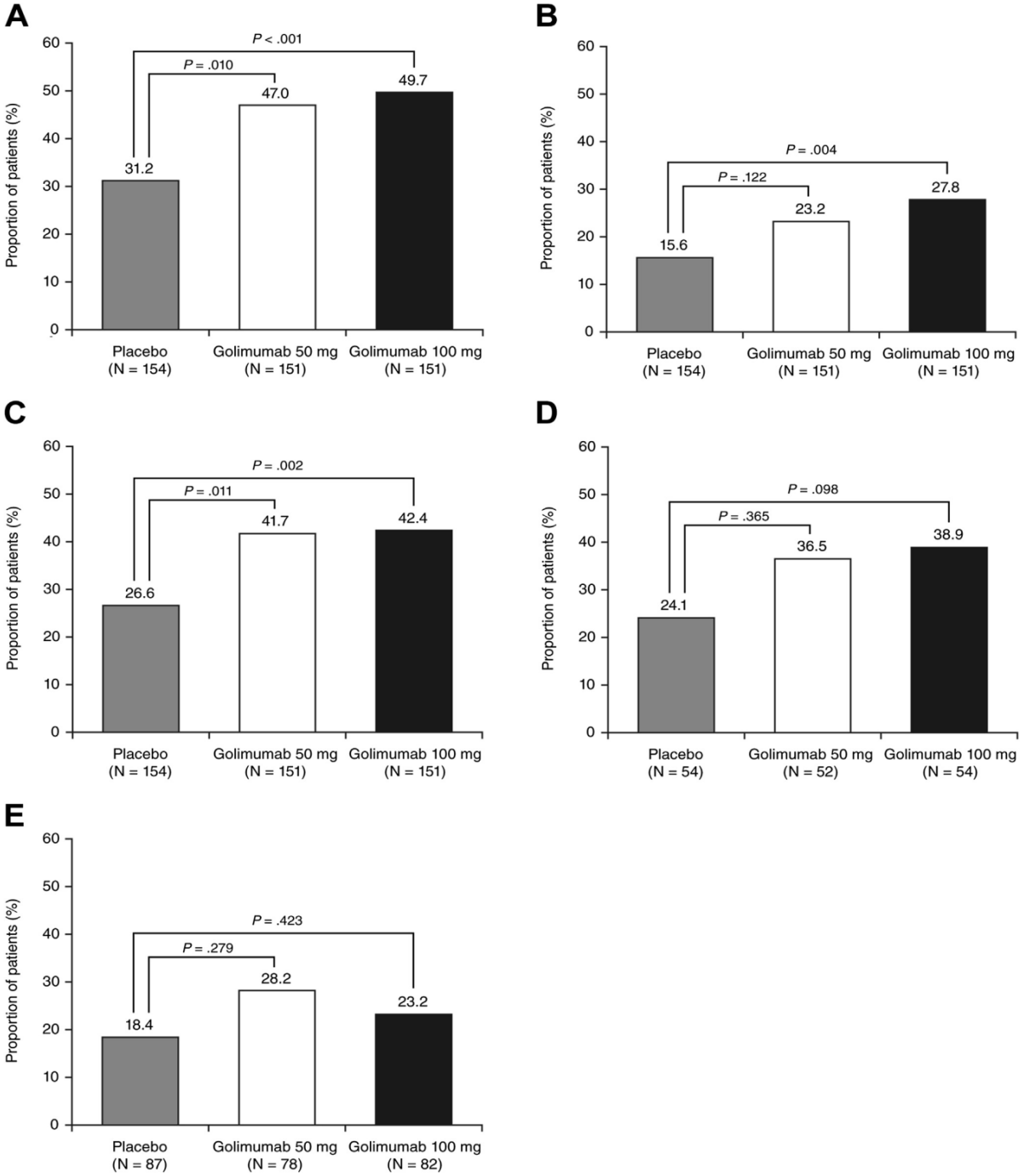
Among golimumab induction responders, the proportion of patients in clinical remission at both weeks 30 and 54 was significantly greater for golimumab 100mg (27.8%) compared with placebo (15.6%; p=0.004). The corresponding value for the golimumab 50mg group (23.2%) was greater than that for placebo; however, the difference was not statistically significant (Figure 6B). According to the pre-specified testing procedure, because the 50mg group did not test positive for this endpoint, statistical significance for the 50mg group for subsequent major secondary endpoints cannot be claimed as significant. The NNT for patients in remission at both weeks 30 and 54 was nine and 14 for the 100mg and 50mg golimumab groups, respectively. In a post-hoc logistic regression analysis, lower baseline Mayo score, lower baseline faecal

lactoferrin level, and higher baseline albumin level were associated with greater proportions of patients achieving clinical remission at both weeks 30 and 54.

The proportion of patients with mucosal healing at both weeks 30 and 54 was significantly greater for patients receiving golimumab 100mg (42.4%) or golimumab 50mg (41.7%) compared with placebo maintenance (26.6%; p=0.002 and p=0.011, respectively) (Figure 6C).

Approximately 35% (160 of 456) of patients were in clinical remission at the baseline visit of PURSUIT-M. Numerically greater proportions of patients who received 100mg or 50mg golimumab maintained clinical remission (38.9% and 36.5%, respectively) than those assigned to placebo (24.1%); however, the differences were not statistically significant (Figure 6D). Approximately 54% of patients were receiving concomitant corticosteroids at baseline, of whom the proportion in corticosteroid-free clinical remission at week 54 were 23.2%, 28.2%, and 18.4% in the 100mg, 50mg, and placebo groups, respectively (Figure 6E). The NNT for patients achieving corticosteroid-free clinical remission at week 54 was 21 and 11 for the 100mg and 50mg golimumab groups, respectively.

Figure 6: Proportion of golimumab-induction responders maintaining or achieving clinical response, clinical remission, mucosal healing, and corticosteroid-free remission at week 54



(A) Maintained clinical response through week 54; (B) Achieved clinical remission at both weeks 30 and 54; (C) Achieved mucosal healing at both weeks 30 and 54; (D) Maintained clinical remission among those who were in clinical remission at baseline; (E) Achieved corticosteroid-free clinical remission at week 54 among those who were receiving corticosteroids at baseline. (A-E) Patients who had a prohibited change in UC medication, an ostomy or colectomy, a dose adjustment, or discontinued study agent because of a lack of therapeutic effect before the week 54 visit were considered not to have a clinical response, be in clinical remission, be in corticosteroid-free clinical remission, or have mucosal healing. (A-D) Patients who had all four Mayo sub-scores missing at weeks 30 or 54 were considered not to be in clinical response or clinical remission. Patients who had a missing endoscopy sub-score at week 30 or 54 were considered not to have mucosal healing. (E) Patients who had a missing value in corticosteroid use at a time point had their last available value carried forward to that time point.

Additional Secondary Analyses

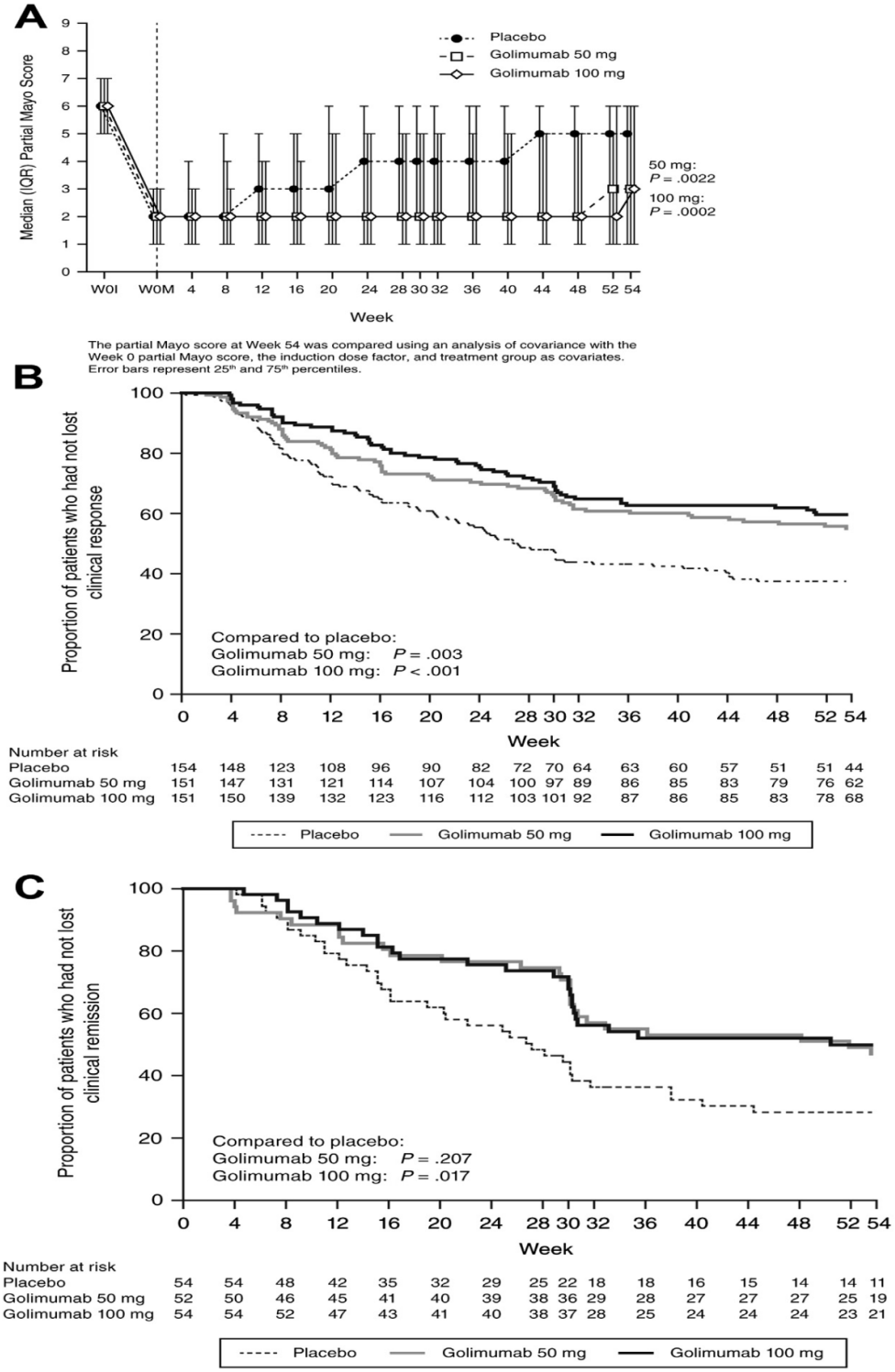
Reductions in median partial Mayo scores observed at baseline of PURSUIT-M among golimumab induction responders (i.e. decrease of 4 points from induction baseline) were maintained in the 100mg and 50mg groups through weeks 52 and 48, respectively (with small increases at weeks 54 and 52, respectively). The median partial Mayo score in the placebo group increased after week 8 and increased to a value approaching that at induction baseline at week 54 (nominal $p<0.001$ and $p=0.002$, respectively) (Figure 7A). In addition, time to loss of clinical response among golimumab induction responders was longer in the 100mg and 50mg groups (>54 weeks for both) compared with placebo (27 weeks; nominal $p<0.001$ and $p=0.003$, respectively) (Figure 7B).

Greater proportions of golimumab-treated patients achieved clinical remission at week 30 (nominal significance for both dose groups) and week 54 (nominally significant for the 100mg group only) compared with those in the placebo group. Among golimumab induction responders in clinical remission at week 0, a post-hoc analysis showed longer time to loss of clinical remission in patients who received golimumab 100mg (50 weeks) or 50mg (52 weeks) compared with placebo (27 weeks; nominal $p=0.017$ and $p=0.207$, respectively) (Figure 7C).

Among golimumab induction responders receiving corticosteroids at baseline, a greater proportion of patients in the 100mg group (30.5%; nominal $p=0.138$) and a greater proportion of patients in the 50mg group (38.5%; nominal $p=0.026$) maintained clinical response through week 54 and were corticosteroid-free at week 54 compared with the placebo group (20.7%).

At week 54, the proportions of patients with normal or inactive mucosal disease (i.e. an endoscopy sub-score equal to zero) were greater in the 100mg (21.9%) and 50mg (25.8%) groups compared with the placebo group (13.0%; nominal $p=0.033$ and $p=0.011$, respectively).

Figure 7: Partial Mayo score and time to loss of clinical response and clinical remission among golimumab-induction responders at week 54



A) Median (IQR) partial Mayo score through week 54; (B) Time to loss of clinical response, (C) time to loss of clinical remission among patients in clinical remission at baseline. IQR, interquartile range; W0I, week 0 of induction; W0M, week 0 of maintenance.

Safety Analyses

Among 464 randomised golimumab induction responders, 66.0%, 72.7%, and 73.4% of patients in the placebo, golimumab 50mg, and golimumab 100mg groups, respectively, reported one or more treatment-emergent AE(s). With adjustment for length of follow-up evaluation, the incidences of AEs per 100 patient-years were similar across treatment groups. Infections were reported in 28.2%, 39.0%, and 39.0%; SAEs were reported in 7.7%, 8.4%, and 14.3%; and serious infections were reported in 1.9%, 3.2%, and 3.2%, respectively. The proportion of patients who discontinued the study agent because of an AE through week 54 were 6.4%, 5.2%, and 9.1%, respectively. Injection-site reactions occurred in 1.9%, 1.9%, and 7.1%, respectively. No injection-site reaction was serious, and no anaphylactic reactions were reported. Similar types of AEs were observed among patients who had their golimumab dose increased, and no AEs of interest occurred in patients who received golimumab 200mg.

Adverse events observed for all treated patients were consistent with those observed for randomised patients. Overall, 63.9%, 72.7%, and 73.9% of patients who received placebo, golimumab 50mg, or golimumab 100mg experienced one or more AE(s). Through week 54, there were three deaths reported, all in the 100mg golimumab maintenance group. Causes of death were malnutrition and sepsis (golimumab 2mg/kg IV induction), cardiac failure in a patient with a history of thrombosis (golimumab 400/200mg SC induction), and disseminated TB in a patient who tested positive for latent TB on induction study entry (golimumab 200/100mg SC induction) and was receiving isoniazid at the time of the event.

Six deaths were reported after week 54: pneumonia and heart failure (placebo SC induction and maintenance); biventricular heart dysfunction in the presence of pronounced atherosclerosis and stenosis affecting the aorta, large arteries, and coronary arteries (golimumab SC 100/50mg induction, 50mg maintenance); myocardial infarction in a patient with a history of myocardial infarction (placebo SC induction, 100mg maintenance); gallbladder adenocarcinoma with liver metastasis (golimumab 2mg/kg IV induction, 100mg maintenance); sepsis (golimumab 2mg/kg IV induction, 100mg maintenance); and accidental nitrous oxide overdose (200/100mg SC induction, 100mg maintenance).

Tuberculosis was reported for four patients through week 54 (one placebo maintenance [golimumab 4mg/kg IV induction] and three golimumab 100mg maintenance [one each golimumab 400/200mg SC, 4mg/kg IV, and 200/100mg SC induction] -treated patients), including the fatal case described previously. Three patients had active TB and one patient was diagnosed with latent infection. Each of these patients was receiving concurrent corticosteroid

therapy at screening before entry into the preceding induction study; three of these patients remained on corticosteroids at the time of TB diagnosis. Another patient (golimumab 100mg maintenance [golimumab 200/100mg SC induction]) was diagnosed with a pleural effusion with a high adenosine deaminase concentration and subsequently was treated for suspicion of TB. Affected patients lived in endemic regions (e.g. Poland, India, and South Africa).

Two patients developed serious opportunistic infections: one patient with cytomegalovirus infection identified as antigenemia in the blood with negative polymerase chain reaction on colon biopsy ~3 months after the last golimumab dose (golimumab SC 200/100mg induction, placebo maintenance); and one patient with *Staphylococcus aureus* and *Nocardia* cultured from a brain abscess (golimumab SC 200/100mg induction, golimumab 100mg maintenance).

No association was observed between immunomodulator/corticosteroid use and infection development. Three malignancies were reported through week 54 in patients receiving golimumab 100mg maintenance; two of these (rectal cancer and thyroid cancer) presented with symptoms while the patients were receiving SC placebo induction and one (lung adenocarcinoma) occurred in a patient with a 40 year smoking history who received golimumab 200/100mg SC induction therapy. Breast cancer was reported in a patient who had received only placebo during induction and maintenance.

Summary

Maintenance therapy was evaluated in patients who had responded to induction therapy with golimumab. Significantly greater proportions of patients in the golimumab 50mg and 100mg groups maintained clinical response through week 54 compared with the placebo group. Maintenance efficacy of the 100mg dose was confirmed through secondary endpoints, where golimumab 100mg demonstrated significantly greater rates of clinical remission and mucosal healing at both weeks 30 and 54 than the placebo group.

5.2. Identification of Studies for Network Meta-Analysis

The objective for this submission is to assess the clinical and cost-effectiveness of golimumab 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 infliximab. In the absence of active-controlled studies evaluating golimumab 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 5). 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 5: 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 6. 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.

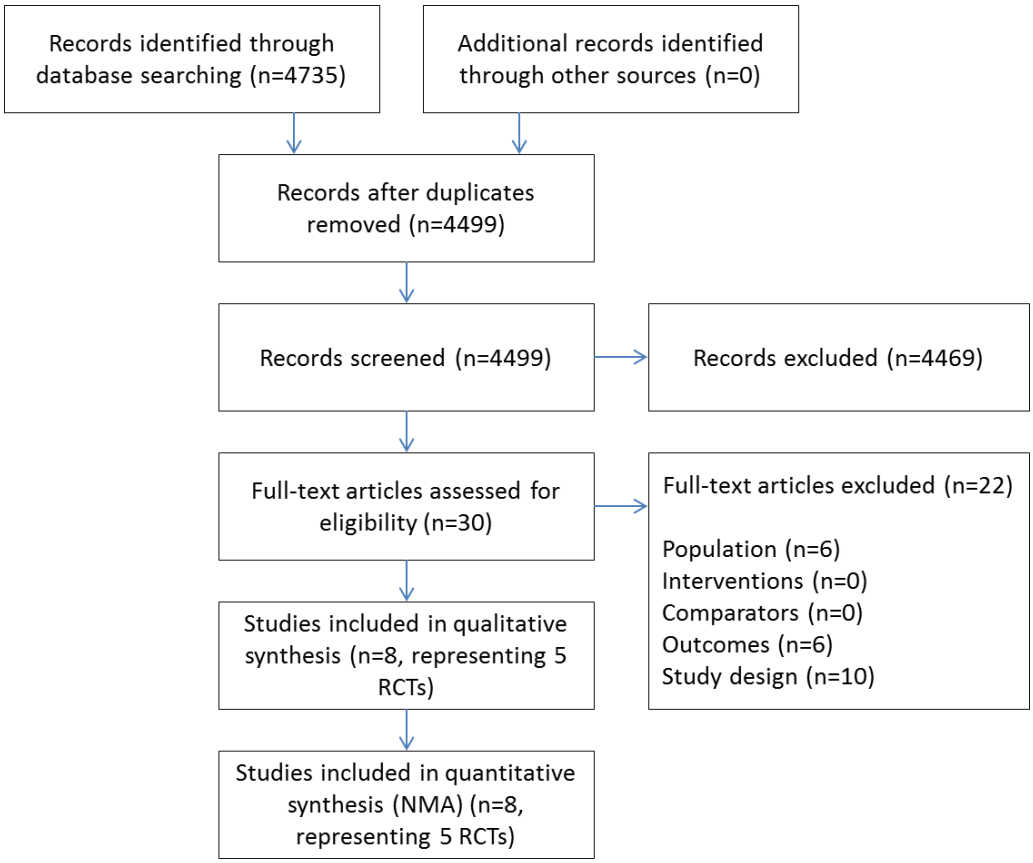
Table 6: Types of patients, interventions, controls, and outcomes considered

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 8. 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 8: 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 7), one assessed golimumab[13,14] (the respective phases of PURSUIT were considered as one study), two assessed infliximab (ACT 1 and ACT 2)[10,15,16], and two assessed adalimumab (ULTRA 1 and ULTRA 2)[17,18,19]. 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 8, with the justification for their exclusion.

Table 7: 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
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			
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			
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 8: Studies excluded after full-text screening

Study	Principal reason for exclusion
Colombel *et al.* 2011 [20]	Follow-up to Rutgeerts *et al.* 2005; no relevant data for current analysis
Gustavsson *et al.* 2010 [21]	Follow-up to Järnerot *et al.* 2005; no relevant data for current analysis
Oussalah *et al.* 2008 [22]	All patients have an inadequate clinical response to infliximab
Ferrante *et al.* 2007 [23]	Follow-up to Rutgeerts *et al.* 2005; no relevant data for current analysis
Reinisch *et al.* 2007 [24]	Follow-up to Rutgeerts *et al.* 2005; no relevant data for current analysis
Järnerot *et al.* 2005 [25]	Included only hospitalised patients with severe UC
Armuzzi *et al.* 2004 [26]	Not all patients were inadequate responders to conventional therapy
Ochsenkühn *et al.* 2004 [27]	Not all patients were inadequate responders to conventional therapy
Gornet *et al.* 2003 [28]	Not all patients had UC, outcomes not stratified by disease
Probert *et al.* 2003 [29]	Used different definition of remission and response than other trials
Sands *et al.* 2001 [30]	Outcomes only provided at 2 weeks
Jürgens *et al.* 2010 [31]	Non-randomised/observational study
Olsen *et al.* 2012 [32]	Non-randomised/observational study
Halpin *et al.* 2013 [33]	Non-randomised/observational study
Molander *et al.* 2012 [34]	Non-randomised/observational study
Rostholder *et al.* 2012 [35]	Non-randomised/observational study
Steenholdt *et al.* 2012 [36]	Non-randomised/observational study
Steenholdt *et al.* 2013 [37]	Non-randomised/observational study
Gies *et al.* 2010 [38]	Non-randomised/observational study
Italian Group *et al.* 2013 [39]	Non-randomised/observational study
Reinisch *et al.* 2013 [40]	Non-randomised/observational study
Suzuki *et al.* 2013 [41]	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 9: 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
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
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
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 10: Primary and secondary outcomes of RCTs eligible for inclusion in the NMA

Trial identifier	Primary outcome(s)	Definition	Secondary outcome(s)
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
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
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 11 to Table 17.

Primary Outcomes Data

Table 11: Primary outcomes data considered within the NMA - induction

Trial identifier	Interventions	Number of patients with outcome (n/N)		
		Remission	Response	Mucosal healing
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
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
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 12: Primary outcomes data considered within the NMA - maintenance

Trial identifier	Interventions	Number of patients with outcome (n/N)			
		Remission	Response	Mucosal healing	Colectomy
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
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 *
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 13: Primary outcomes data considered within the NMA - maintenance, sustained outcomes

Trial identifier	Interventions	Number of patients with outcome (n/N)	
		Sustained remission	Sustained response
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]
ACT 1	Placebo	8/121	17/121
	Infliximab 5mg/kg	24/121	47/121
	Infliximab 10mg/kg	25/122	45/122
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 14: 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
PURSUIT	Placebo	NR	11/330
	Golimumab 200/100mg	NR	7/331
	Golimumab 400/200mg	NR	6/332
ACT 1	Placebo	121/244 *	NR
	Infliximab 5mg/kg	169/242 *	NR
	Infliximab 10mg/kg	166/242 *	NR
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 15: 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
PURSUIT	Placebo	NR	14/389 [a]	NR	NR
	Golimumab 50mg	NR	22/289	NR	32/289
	Golimumab 100mg	NR	19/289	NR	28/289
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
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 16: 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 17: 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
PURSUIT	Placebo	10/156	12/156	3/156
	Golimumab 50mg	8/154	13/154	3/154
	Golimumab 100mg	14/154	22/154	11/154
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
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[42] was performed for all outcomes listed in Table 18. 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[42]. 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 13 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 9 and Figure 10, 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 9: Treatment network for the analyses of outcomes at the end of induction therapy

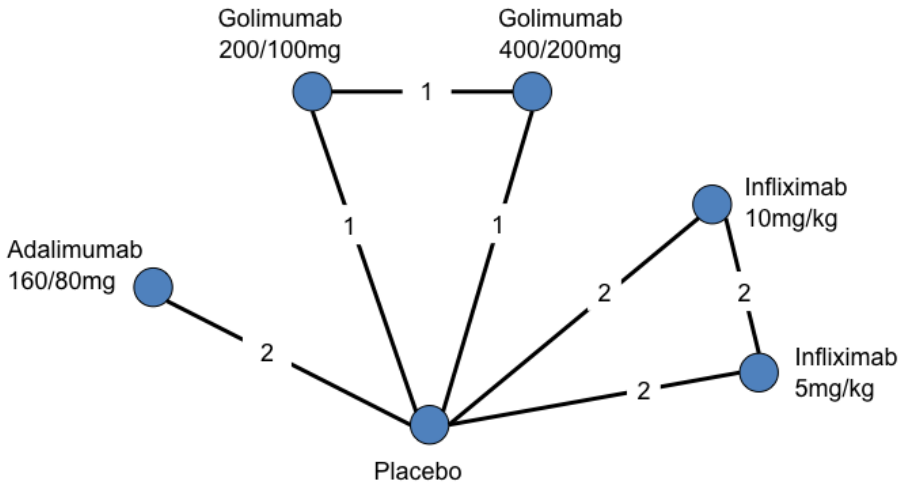
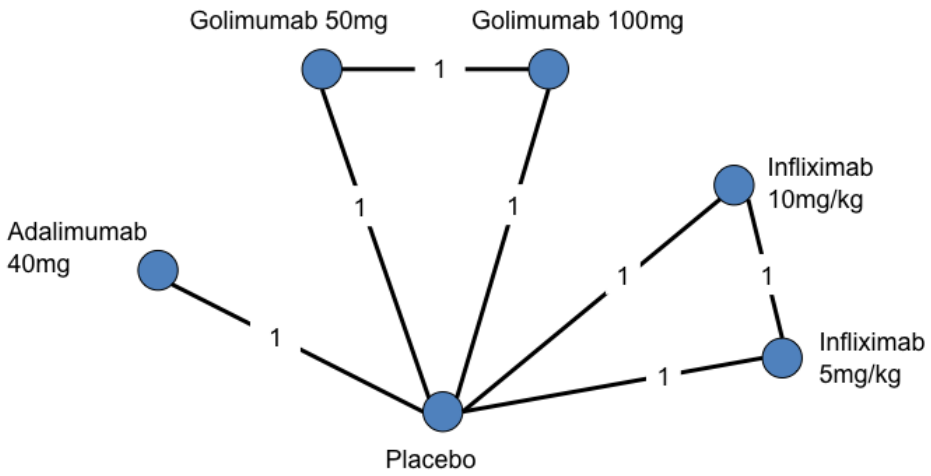


Figure 10: Treatment network for the analyses of outcomes at the end of maintenance therapy



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 18). Outcomes were reported at the end of induction therapy and/or at the end of maintenance therapy.

Table 18: 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 19 presents the relative efficacy between golimumab, infliximab, 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. There were no significant comparisons for golimumab against other TNF-α inhibitors.

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

Comparison	Clinical remission	Clinical response	Mucosal healing
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)**
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)**
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)
GOL 200/100 vs. GOL 400/200	0.90 (0.41 to 1.73)	0.85 (0.44 to 1.66)	0.89 (0.55 to 1.38)
GOL 200/100 vs. IFX 5	0.67 (0.29 to 1.38)	0.78 (0.51 to 1.10)	0.75 (0.55 to 1.02)
GOL 200/100 vs. IFX 10	0.82 (0.34 to 1.77)	0.80 (0.52 to 1.12)	0.76 (0.56 to 1.04)
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)
GOL 400/200 vs. IFX 5	0.72 (0.34 to 1.51)	0.83 (0.56 to 1.15)	0.80 (0.60 to 1.08)
GOL 400/200 vs. IFX 10	0.89 (0.40 to 1.93)	0.85 (0.57 to 1.19)	0.81 (0.60 to 1.11)
GOL 400/200 vs. ADA 160/80	1.35 (0.59 to 3.11)	1.14 (0.71 to 1.74)	1.17 (0.83 to 1.68)
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. 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. ADA 160/80	1.52 (0.69 to 3.46)	1.33 (0.91 to 2.01)	**1.45 (1.04 to 2.00)**

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 20 presents the relative efficacy estimates between golimumab, infliximab, 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.

Table 20: RRs and 95% CrIs for primary outcomes after maintenance therapy, between golimumab, adalimumab, and infliximab for clinical remission, clinical response, and mucosal healing

Comparison	Clinical remission	Clinical response	Mucosal healing
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)**
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)**
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)**
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. IFX 5	1.02 (0.58 to 1.80)	1.23 (0.86 to 1.80)	1.06 (0.72 to 1.62)
GOL 50 vs. IFX 10	1.03 (0.58 to 1.81)	1.26 (0.88 to 1.86)	1.03 (0.70 to 1.55)
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. IFX 5	1.20 (0.70 to 2.08)	1.31 (0.92 to 1.90)	1.10 (0.74 to 1.67)
GOL 100 vs. IFX 10	1.21 (0.71 to 2.10)	1.34 (0.95 to 1.96)	1.07 (0.72 to 1.60)
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)**
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. 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. ADA 40	1.25 (0.64 to 2.42)	1.45 (0.88 to 2.38)	1.63 (0.97 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 21 presents the relative efficacy estimates between infliximab and adalimumab for colectomy and Table 22 presents the relative efficacy estimates between golimumab, infliximab, 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 21: 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 22: RRs and 95% CrIs for primary outcomes after maintenance therapy, between golimumab, adalimumab, and infliximab for sustained clinical remission and sustained clinical response

Comparison	Sustained clinical remission	Sustained clinical response
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)**
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)**
ADA 160/80/40 vs. PBO	1.77 (0.81 to 4.02)	**1.83 (1.17 to 2.82)**
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. GOL 400/200/50	1.06 (0.57 to 1.98)	0.95 (0.72 to 1.25)
GOL 200/100/50 vs. GOL 400/200/100	0.96 (0.52 to 1.72)	0.89 (0.67 to 1.16)
GOL 200/100/50 vs. IFX 5	0.80 (0.27 to 2.35)	0.77 (0.46 to 1.31)
GOL 200/100/50 vs. IFX 10	0.77 (0.26 to 2.26)	0.82 (0.48 to 1.39)
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. GOL 200/100/50	1.06 (0.58 to 1.92)	1.06 (0.80 to 1.40)
GOL 200/100/100 vs. GOL 400/200/50	1.12 (0.61 to 2.07)	1.00 (0.76 to 1.32)
GOL 200/100/100 vs. GOL 400/200/100	1.01 (0.56 to 1.80)	0.94 (0.72 to 1.22)
GOL 200/100/100 vs. IFX 5	0.84 (0.29 to 2.46)	0.82 (0.49 to 1.39)
GOL 200/100/100 vs. IFX 10	0.82 (0.28 to 2.37)	0.86 (0.51 to 1.46)
GOL 200/100/100 vs. ADA 160/80/40	1.53 (0.51 to 4.72)	1.26 (0.73 to 2.16)
GOL 400/200/50 vs. GOL 200/100/50	0.94 (0.51 to 1.74)	1.06 (0.80 to 1.40)
GOL 400/200/50 vs. GOL 200/100/100	0.90 (0.48 to 1.63)	1.00 (0.76 to 1.31)
GOL 400/200/50 vs. GOL 400/200/100	0.90 (0.49 to 1.64)	0.94 (0.71 to 1.22)
GOL 400/200/50 vs. IFX 5	0.76 (0.25 to 2.23)	0.82 (0.49 to 1.38)
GOL 400/200/50 vs. IFX 10	0.73 (0.24 to 2.16)	0.86 (0.51 to 1.46)
GOL 400/200/50 vs. ADA 160/80/40	1.37 (0.44 to 4.29)	1.25 (0.73 to 2.15)
GOL 400/200/100 vs. GOL 200/100/50	1.05 (0.58 to 1.92)	1.13 (0.86 to 1.49)
GOL 400/200/100 vs. GOL 200/100/100	0.99 (0.56 to 1.78)	1.07 (0.82 to 1.39)
GOL 400/200/100 vs. GOL 400/200/100	1.11 (0.61 to 2.06)	1.07 (0.82 to 1.40)
GOL 400/200/100 vs. IFX 5	0.84 (0.29 to 2.44)	0.87 (0.53 to 1.46)
GOL 400/200/100 vs. IFX 10	0.81 (0.28 to 2.37)	0.92 (0.55 to 1.55)
GOL 400/200/100 vs. ADA 160/80/40	1.53 (0.50 to 4.71)	1.34 (0.79 to 2.28)
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 10 vs. ADA 160/80/40	1.89 (0.64 to 5.55)	1.46 (0.81 to 2.62)

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 23 presents the relative efficacy estimates between golimumab, infliximab, 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 23: RRs and 95% CrIs for secondary outcomes after maintenance therapy, between golimumab, adalimumab, and infliximab for UC-related hospitalisation, corticosteroid-free remission, and IBDQ response

Comparison	UC-related hospitalisation	Corticosteroid-free remission	IBDQ response
GOL 50 vs. PBO	--	**2.13 (1.13 to 4.10)**	--
GOL 100 vs. PBO	--	1.84 (0.94 to 3.60)	--
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)**
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)**
GOL 50 vs. GOL 100	--	1.17 (0.62 to 2.25)	--
GOL 50 vs. IFX 5	--	0.64 (0.24 to 1.60)	--
GOL 50 vs. IFX 10	--	0.62 (0.23 to 1.54)	--
GOL 50 vs. ADA 40	--	0.70 (0.21 to 2.16)	--
GOL 100 vs. IFX 5	--	0.55 (0.20 to 1.41)	--
GOL 100 vs. IFX 10	--	0.53 (0.20 to 1.36)	--
GOL 100 vs. ADA 40	--	0.60 (0.18 to 1.87)	--
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. 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. ADA 40	0.85 (0.50 to 1.46)	1.13 (0.35 to 3.65)	1.24 (0.86 to 1.80)

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 24 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 24: 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
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)
IFX 5 vs. PBO	--	--	--
IFX 10 vs. PBO	--	--	--
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)
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. IFX 5	--	--	--
GOL 50 vs. IFX 10	--	--	--
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. IFX 5	--	--	--
GOL 100 vs. IFX 10	--	--	--
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)
IFX 5 vs. IFX 10	--	--	--
IFX 5 vs. ADA 40	--	--	--
IFX 10 vs. ADA 40	--	--	--

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 25 presents the relative safety estimates between golimumab, infliximab, 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 golimumab, infliximab, adalimumab, and placebo. For injection-site reactions, golimumab 100mg and adalimumab were associated with a higher risk compared with placebo. Similar infusion-site reactions were observed with infliximab 5mg/kg and infliximab 10mg/kg. Golimumab 50mg was also 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 25: RRs and 95% CrIs for safety outcomes after maintenance therapy, between golimumab, adalimumab, and infliximab 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
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)**
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)
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)**
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. IFX 5	1.59 (0.49 to 4.93)	1.60 (0.69 to 3.51)	--
GOL 50 vs. IFX 10	1.18 (0.37 to 3.46)	1.55 (0.68 to 3.41)	--
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. IFX 5	2.78 (0.98 to 7.68)	**2.57 (1.27 to 5.08)**	--
GOL 100 vs. IFX 10	2.06 (0.76 to 5.38)	**2.50 (1.23 to 4.94)**	--
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)
IFX 5 vs. IFX 10	0.74 (0.35 to 1.54)	0.97 (0.63 to 1.51)	0.89 (0.52 to 1.50)
IFX 5 vs. ADA 40	0.76 (0.32 to 1.82)	0.70 (0.38 to 1.28)	--
IFX 10 vs. ADA 40	1.03 (0.45 to 2.34)	0.72 (0.39 to 1.32)	--

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. 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) (no data were available for golimumab). 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 corticosteroid-free remission, the RRs for golimumab were smaller than for infliximab and adalimumab, albeit not significantly. 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. 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 maintaining clinical response and mucosal healing when compared with adalimumab. The NMA also suggests similar efficacy profiles of golimumab and infliximab, and the safety profiles of golimumab, adalimumab, and infliximab were generally similar across outcomes. Therefore, golimumab provides an equally effective treatment option for patients with moderately to severely active UC who would prefer SC biologic treatment.

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

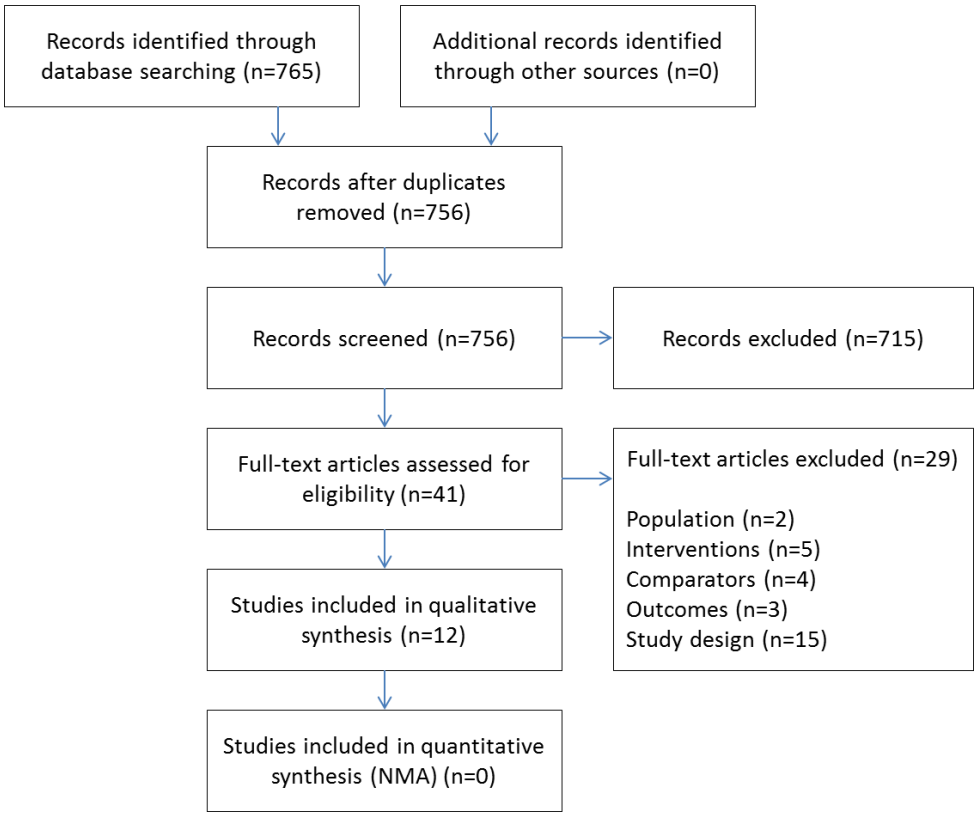
Searches were conducted in Embase®, PubMed®, and the National Health Service Economic Evaluation Database (NHSEED) (from inception to week 29, 2013) to identify published economic evaluations in UC to help inform the model structure and relevant parameters. The search strategies developed for each of 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 11).

Figure 11: Schematic of the publication selection process



NMA, network meta-analysis.

6.1.2. Description of Identified Studies

An overview of the 12 included 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 [43]	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 [44]	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 [45]	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 [46]	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 [47]	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 [48]	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 [49]	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 [50]	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 [51]	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 [52]	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 [53]	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 [54] *	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

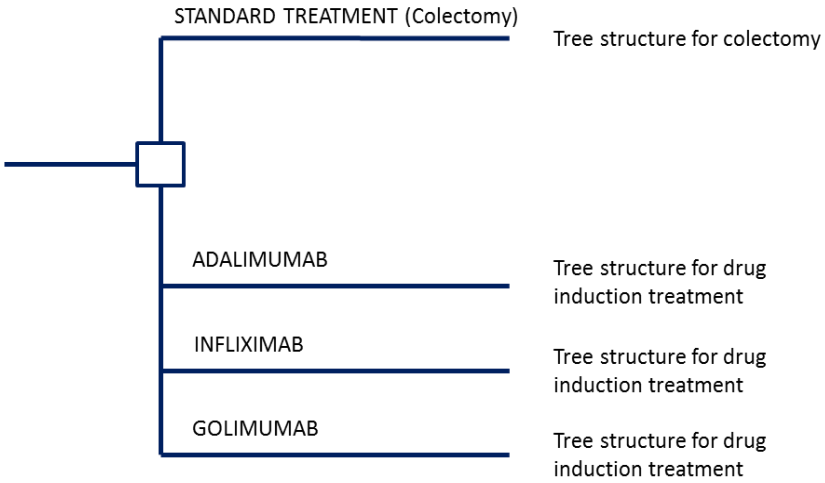
Golimumab is indicated for the treatment of moderately to severely active UC in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-MP or AZA, or who are intolerant to or have medical contraindications for such therapies. The target population in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

6.2.2. Model Structure

The model demonstrates the cost-effectiveness of golimumab 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 12.

Figure 12: 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:

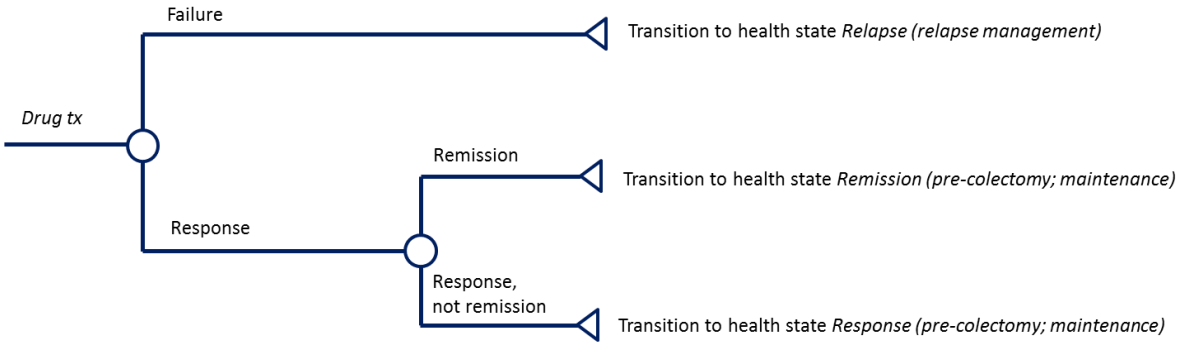
- Patients receiving a biologic (i.e. golimumab, infliximab, or adalimumab) as the initial treatment go through the following phases: drug induction treatment, drug maintenance treatment if a responder to induction treatment, relapse management, colectomy, and post-colectomy
- Patients receiving colectomy 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 13.

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

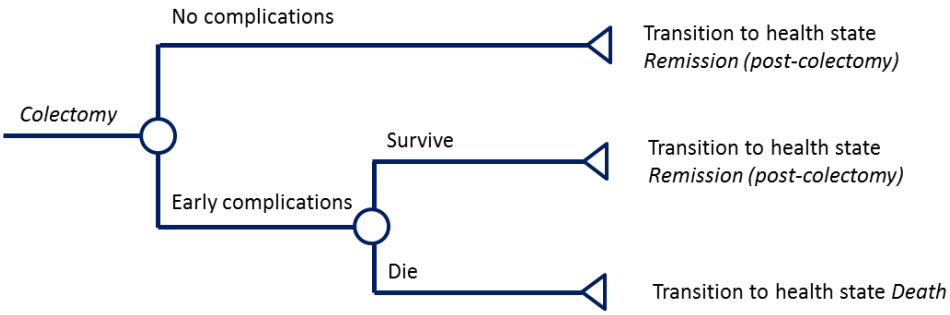


Colectomy as Induction Treatment

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 14.

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.

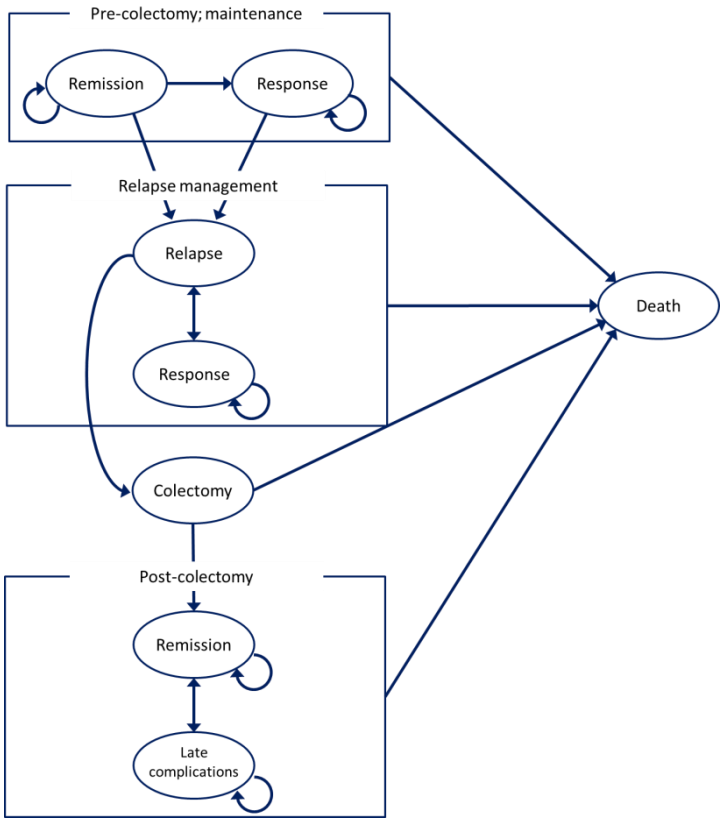
Figure 14: Tree structure reflecting outcomes with colectomy as treatment in model



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 15.

Figure 15: 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 16 and occur according to constant transition probabilities.

Figure 16: 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								

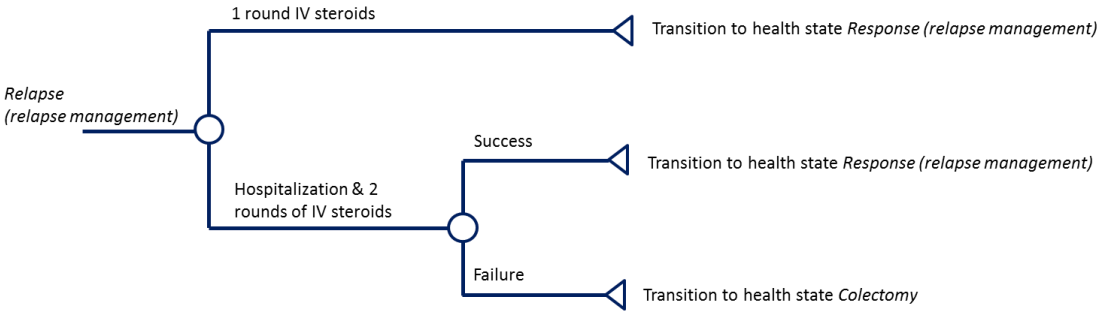
Patients who showed a response with biologic induction treatment but are not in remission start the Markov state-transition structure in the health state *Response (pre-colectomy; maintenance)*. Patients who experienced remission with induction treatment start the Markov state-transition structure in 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 17). Patients in the health state *Response (relapse management)* who relapse, transition back to *Relapse (relapse management)* and receive another course of IV steroids.

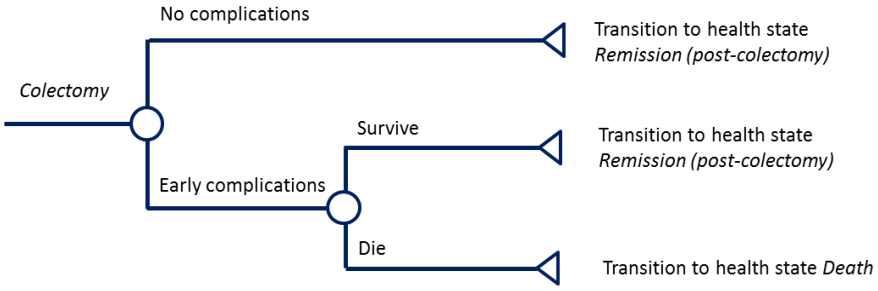
Figure 17: Possible transitions from health state relapse during relapse management phase



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 18.

Figure 18: 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

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 golimumab 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.

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 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.

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 SC injection. Some patients who experience a decrease in their response may benefit from an increase in dosing frequency to 40mg adalimumab every week (EW)[55]. 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			
Golimumab 200/100mg	2.12	1.01	3.95
Golimumab 400/200mg	2.47	1.19	4.65
Infliximab 5mg/kg	4.12	2.08	8.14
Infliximab 10mg/kg	3.81	1.95	7.59
Adalimumab 160/80mg	1.87	0.96	3.65
Induction remission			
Golimumab 200/100mg	2.99	1.32	6.28
Golimumab 400/200mg	3.32	1.56	7.23
Infliximab 5mg/kg	5.27	2.60	11.64
Infliximab 10mg/kg	3.90	1.88	8.56
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.*[56] 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 17, 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.*[22], Armuzzi *et al.*[26], Rostholder *et al.*[35]).

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.*[57]. 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.*[58]), 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)[59]: 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)[59] 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.*[60]. 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.*)[61]. A weighted average for male- and female-specific annual mortality (informed by the proportion of men [56%] and women [44%]) in the PURSUIT trial was applied. The average age of the population at the beginning of the initial treatment was set at 40 years, also informed by the PURSUIT trial.

6.3.9. Outcomes

Utility and cost estimates were assigned to the outcomes with the initial treatment (Figure 13 and Figure 14), and each of the eight health states of the Markov structure (Figure 15 and Figure 16). 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 PURSUIT trial. 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.* [62], Tsai *et al.* [43], HODaR [63] mild disease: 0.76 (se=0.014)
Relapse (relapse management) without hospitalisation	Woehl *et al.* [62], Tsai *et al.* [43], Punekar & Hawkins [49], Chaudhary & Fan [45], HODaR [63] moderate to severe: 0.42 (se=0.093)
Colectomy	Woehl *et al.* [62], HODaR [63] colectomy (ileostomy: 0.63 se=0.10, IPAA: 0.56 se=0.13, assumed 50% IPAA)
Remission (post-colectomy)	Woehl *et al.* [62], Punekar & Hawkins [49], Chaudhary & Fan [45]
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 13 and Figure 14. Outcomes accrued for each Markov cycle were calculated according to Sonnenberg & Beck[64], 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 PURSUIT study
- 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 PURSUIT trial where results for placebo and golimumab were combined.

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	0.80	0.014	0.77	0.83	PURSUIT induction phase
Remission with drug induction treatment	0.86	0.021	0.82	0.90	PURSUIT induction phase
Failure with drug induction treatment	0.70	0.007	0.69	0.71	PURSUIT induction phase
Health state: *Response (pre-colectomy; maintenance)*	0.80	0.014	0.77	0.83	PURSUIT maintenance phase
Health state: *Remission (pre-colectomy; maintenance)*	0.89	0.010	0.87	0.91	PURSUIT maintenance phase
Health state: *Response (relapse management)*	0.76	0.014	0.73	0.79	Woehl *et al.* [62], Tsai *et al.* [43], HODaR [63] mild disease
Health state: *Relapse (relapse management)* w/o hospitalisation	0.42	0.093	0.24	0.61	Woehl *et al.* [62], Tsai *et al.* [43], Punekar & Hawkins [49], Chaudhary & Fan [45], HODaR [63] moderate to severe
Health state: *Colectomy*	0.60	0.110	0.37	0.80	Woehl *et al.* [62], HODaR [63] 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.* [62], Punekar & Hawkins [49], Chaudhary & Fan [45]
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.*[65], Meagher *et al.*[66], Bullard *et al.*[67], Weinryb *et al.*[68], Michelassi *et al.*[69], Hahnloser *et al.* 2004[70], Hahnloser *et al.* 2007[71], Tulchinsky *et al.*[72], McCormick *et al.*[73]). 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.*[62], Chaudhary & Fan[45], Punekar & Hawkins[49]).

Arseneau *et al.*[74] 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, Table 34) 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 PURSUIT trial.

After induction treatment, the recommended dose of adalimumab is 40mg EOW via SC injection. Some patients who experience a decrease in their response may benefit from an increase in dosing frequency to 40mg adalimumab EW[55]. 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.

6.5.1. 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.

6.5.2. 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.*[57]. 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 20, Figure 21, and Figure 22 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 23 the development of utility among patients alive with the different intervention strategies is presented.

Figure 19: Distribution of health states over time with colectomy

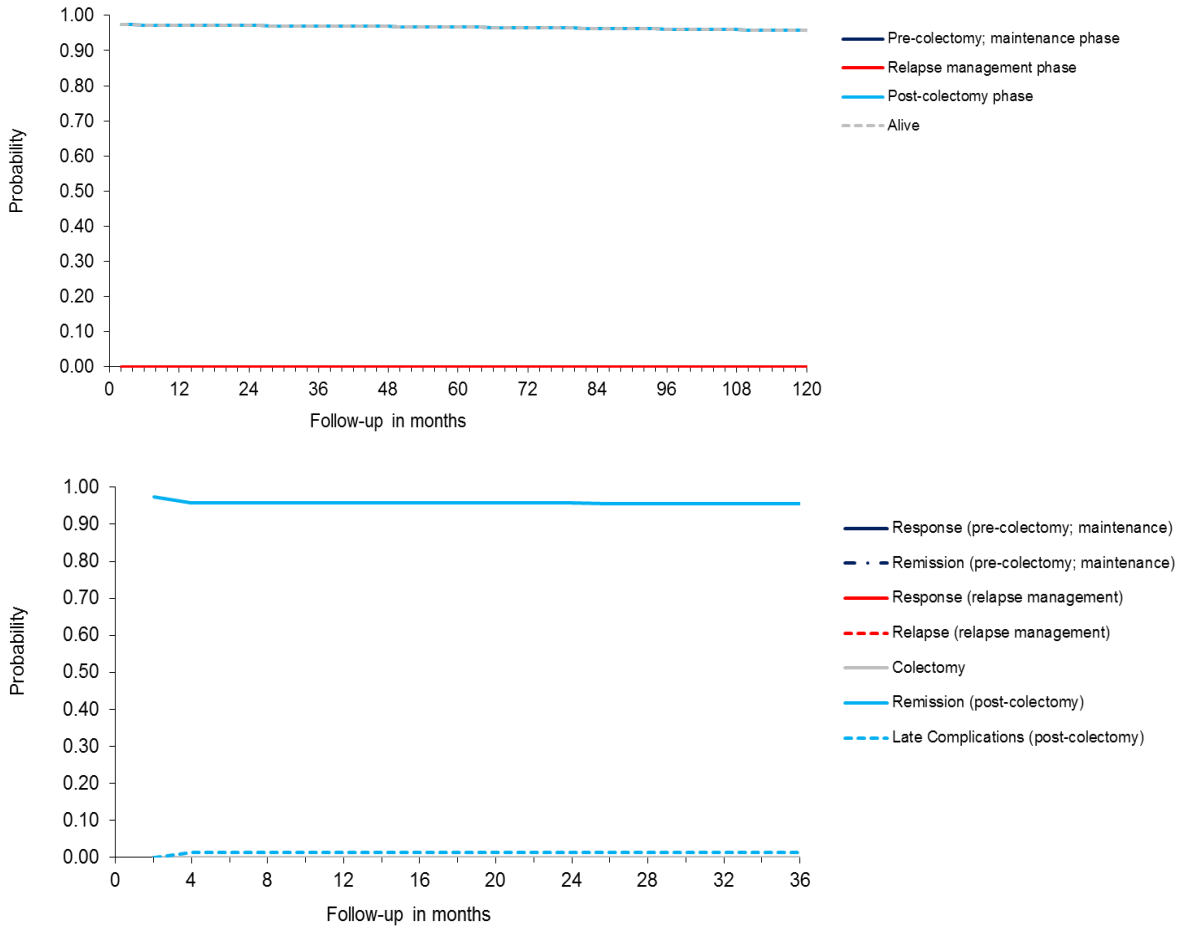


Figure 20: Distribution of health states over time with golimumab

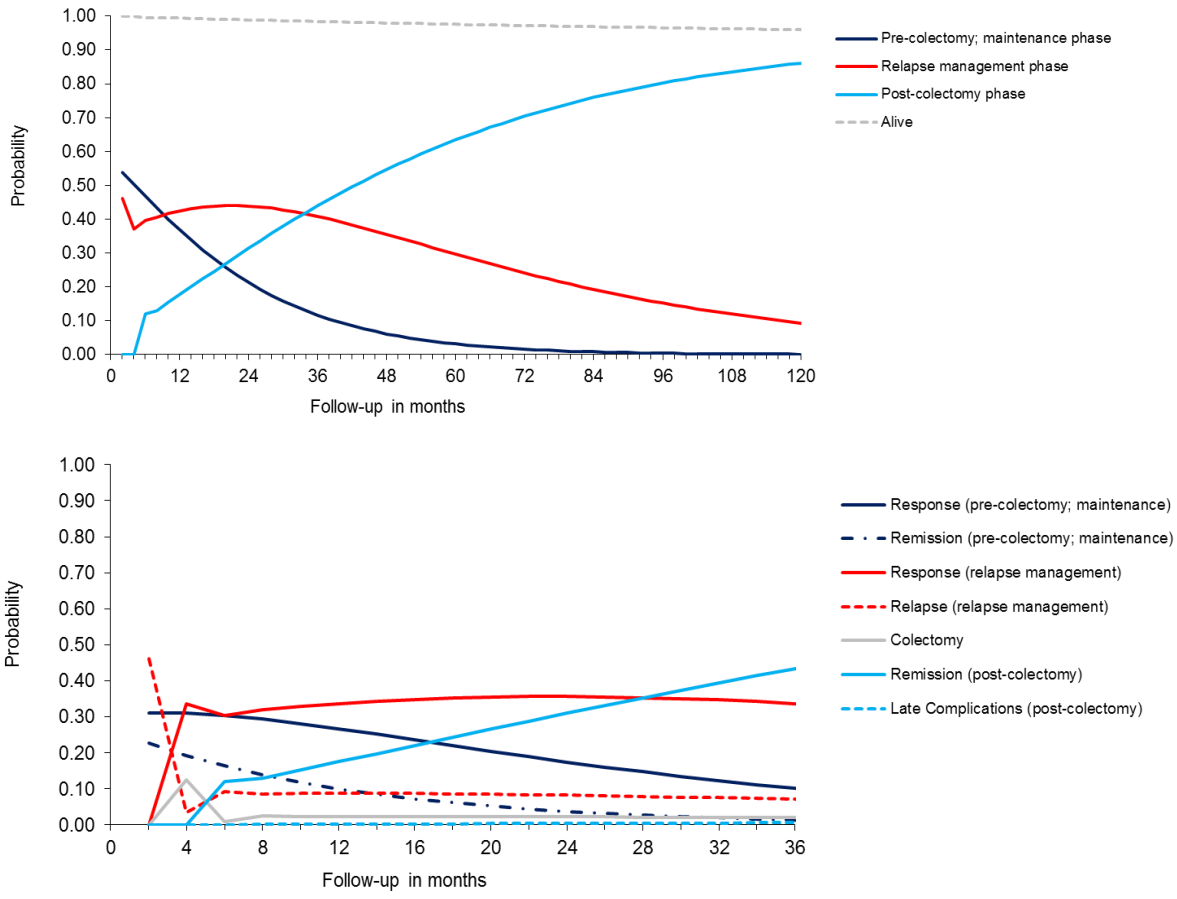


Figure 21: Distribution of health states over time with adalimumab

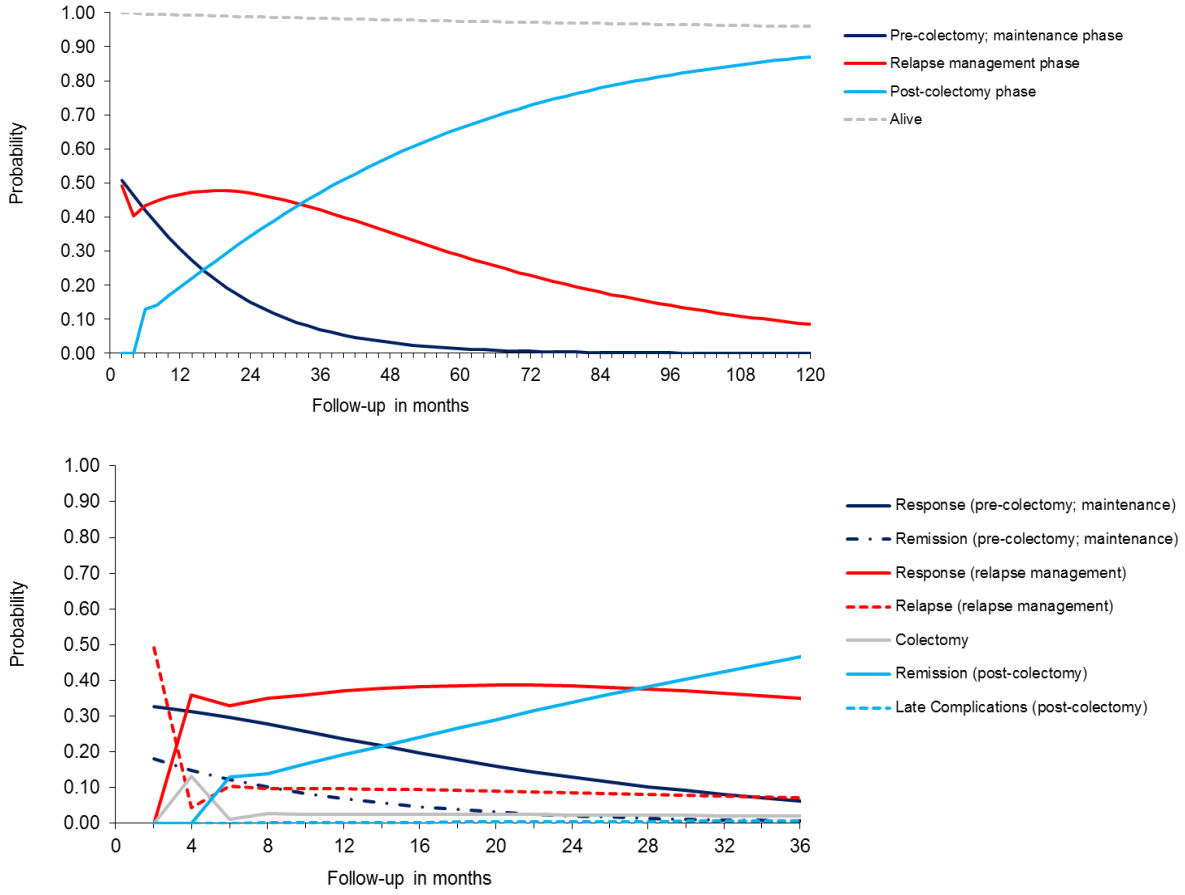


Figure 22: Distribution of health states over time with infliximab

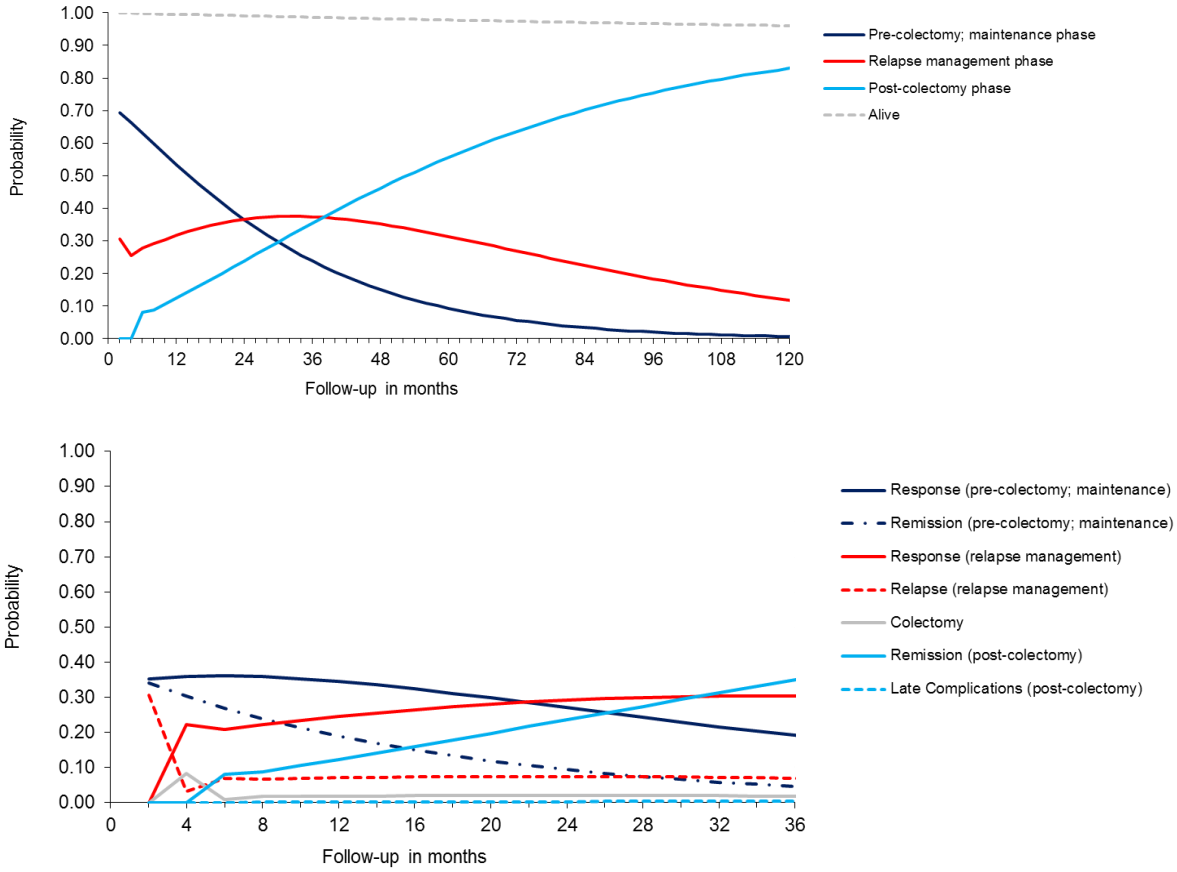
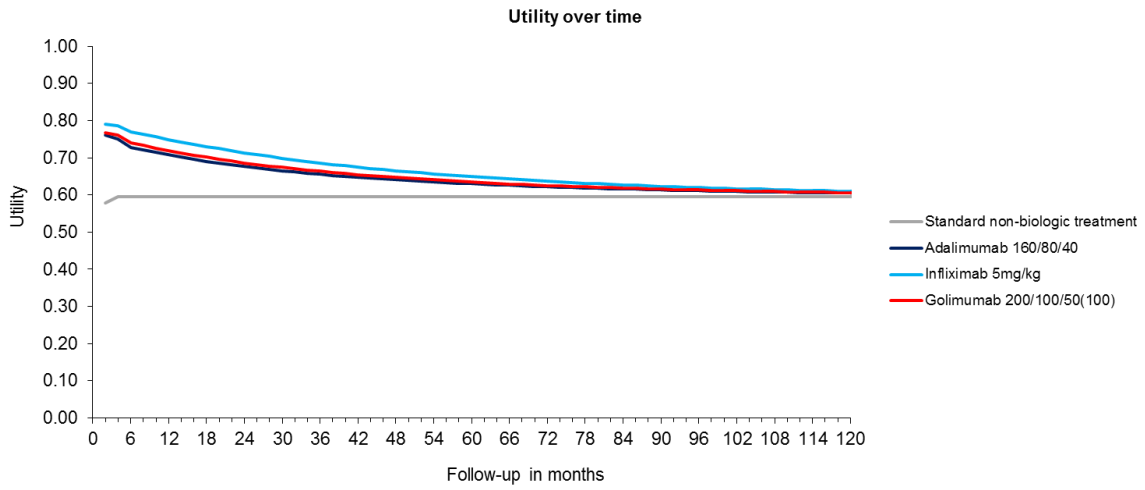


Figure 23: Development of utility over time (among patients alive)



6.6.2. Model Evaluations

A PAS has been submitted in support of this submission 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 Figure 24 to Figure 29, and in Table 41 and Table 42. 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 costs over a 10 year time horizon as presented in Figure 24 were obtained. The expected costs stratified by type of resource use are presented in Table 41.

Given the lower estimated total costs with golimumab under the PAS, the incremental cost relative to colectomy over a 10 year time horizon was reduced to £15,101 (from £21,011 without the PAS as shown in sensitivity analyses below). In combination with an incremental QALY estimate of 0.55, an ICER of £27,322 was obtained (Table 42).

Golimumab is expected to result in 0.05 more QALYs than adalimumab. The reduced acquisition cost of golimumab under the PAS implies that the total costs with golimumab are expected to be lower than with adalimumab (assuming 50% of the patients are on a 40mg EW schedule instead of the 40mg EOW schedule). Accordingly, golimumab is a dominating intervention over adalimumab from a cost-effectiveness perspective (Table 42).

The cost-effectiveness acceptability curves presented in Figure 29 illustrate the favourable cost-effectiveness of golimumab relative to colectomy, adalimumab, and infliximab for an acceptable WTP ratio when all four interventions are considered competing interventions. Overall, it can be concluded that golimumab under the PAS is a more cost-effective intervention than colectomy, or other biologic drugs for the treatment of moderately to severely active UC patients who have failed previous non-biologic drug treatment.

Figure 24: Development of costs over time by intervention

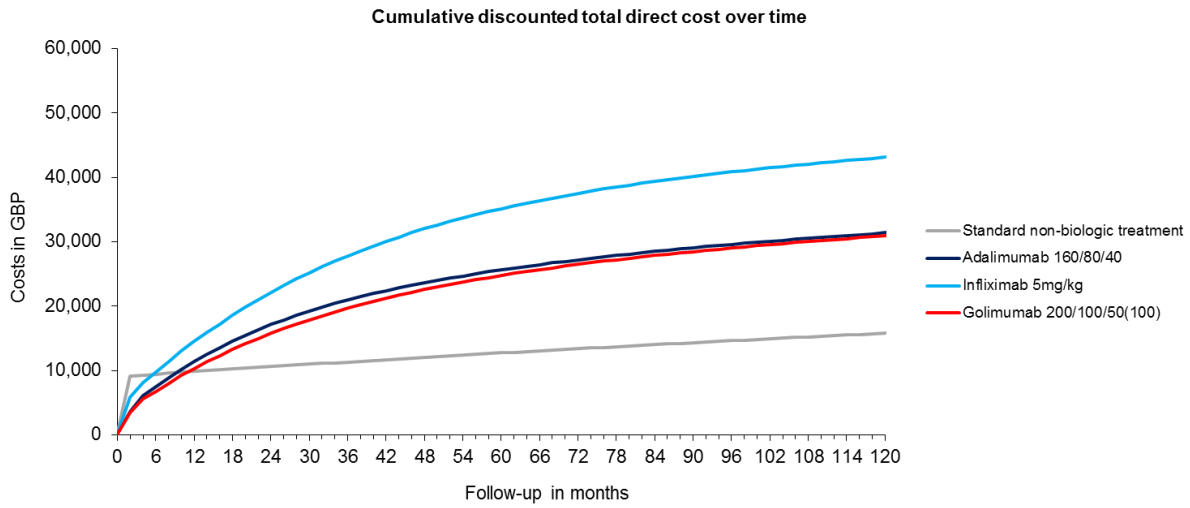


Table 41: Expected outcomes and costs for a 10 year time horizon

	Colectomy				Adalimumab 160/80/40mg				Infliximab 5mg/kg				Golimumab 200/100/50(100)mg			
	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	11.3	6.7	18.3	22.2	23.9	12.6	38.6	13.4	14.2	9.0	22.2
Time to colectomy (in months)	0.0	0.0	0.0	0.0	44.2	44.9	39.1	51.6	54.4	55.6	45.8	67.2	46.8	47.5	41.3	54.4
Duration of post-colectomy phase (in months)	114.0	114.0	112.1	115.4	71.1	70.5	64.0	76.0	61.3	60.2	49.1	69.6	68.7	68.0	61.3	74.0
Life years	9.66	9.66	9.50	9.78	9.76	9.77	9.67	9.84	9.79	9.79	9.70	9.85	9.77	9.77	9.67	9.84
Disc. life years	8.32	8.32	8.18	8.42	8.41	8.42	8.33	8.47	8.43	8.44	8.36	8.49	8.42	8.42	8.34	8.48
Discounted QALYs	4.95	4.98	3.16	6.59	5.45	5.49	4.42	6.44	5.65	5.70	4.74	6.50	5.50	5.54	4.49	6.45
Discounted drug acquisition and admin. cost	0	0	0	0	15,831	16,649	11,435	24,118	28,149	29,640	19,128	42,935	15,503	16,084	11,863	22,389
Discounted AE cost related to drug treatment	0	0	0	0	554	566	430	721	687	708	520	961	588	598	463	773
Disc. consultant visit cost	2,773	2,770	2,283	3,321	3,729	3,723	3,341	4,130	3,791	3,778	3,373	4,185	3,746	3,737	3,355	4,156
Discounted endoscopy cost	2,242	2,246	1,911	2,602	1,782	1,773	1,559	2,005	1,639	1,621	1,395	1,883	1,747	1,737	1,514	1,967
Discounted inpatient stay cost	0	0	0	0	916	908	833	980	911	890	759	988	910	902	827	977
Discounted colectomy cost	8,966	8,968	8,800	9,135	7,455	7,401	6,980	7,760	6,960	6,822	5,895	7,448	7,336	7,281	6,817	7,682
Discounted costs late complications	1,763	1,736	559	3,449	1,031	1,005	326	2,024	880	848	268	1,696	993	967	306	1,937
Discounted other UC cost	49	49	40	57	71	71	64	79	75	75	68	83	72	72	65	80
Discounted total direct cost	15,794	15,768	14,404	17,585	31,370	32,096	27,045	39,398	43,092	44,382	34,513	56,731	30,895	31,379	27,237	37,729
NMB at WTP of £30,000	132,650	133,596	80,497	180,022	132,115	132,514	105,411	153,682	126,458	126,568	107,651	138,209	134,130	134,715	107,539	155,681

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)	15,576	16,329	11,171	23,554	0.50	0.51	-0.17	1.31	31,069	Smaller NMB, hence not cost-effective	32,129	Smaller NMB, hence not cost-effective
Infliximab 5mg/kg vs. Standard non-biologic treatment (colectomy)	27,297	28,615	19,158	41,109	0.70	0.72	-0.11	1.70	38,802	Smaller NMB, hence not cost-effective	39,767	Smaller NMB, hence not cost-effective
Golimumab 200/100/50(100)mg vs. Standard non-biologic treatment (colectomy)	15,101	15,611	11,670	21,567	0.55	0.56	-0.14	1.45	27,322	Greater NMB, hence cost-effective	27,994	Greater NMB, hence cost-effective
Infliximab 5mg/kg vs. Adalimumab 160/80/40mg	11,721	12,286	887	26,049	0.20	0.21	-0.01	0.55	57,980	Smaller NMB, hence not cost-effective	58,133	Smaller NMB, hence not cost-effective
Golimumab 200/100/50(100)mg vs. Adalimumab 160/80/40mg	-475	-718	-8,722	6,745	0.05	0.05	-0.09	0.23	Dominant	Greater NMB, hence cost-effective	Dominant	Greater NMB, hence cost-effective
Golimumab 200/100/50(100)mg vs. Infliximab 5mg/kg	-12,197	-13,004	-25,226	-2,315	-0.15	-0.16	-0.49	0.04	80,866	Greater NMB, hence cost-effective	80,318	Greater NMB, hence 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 25: Results of one-way sensitivity analysis for golimumab relative to colectomy in terms of cost

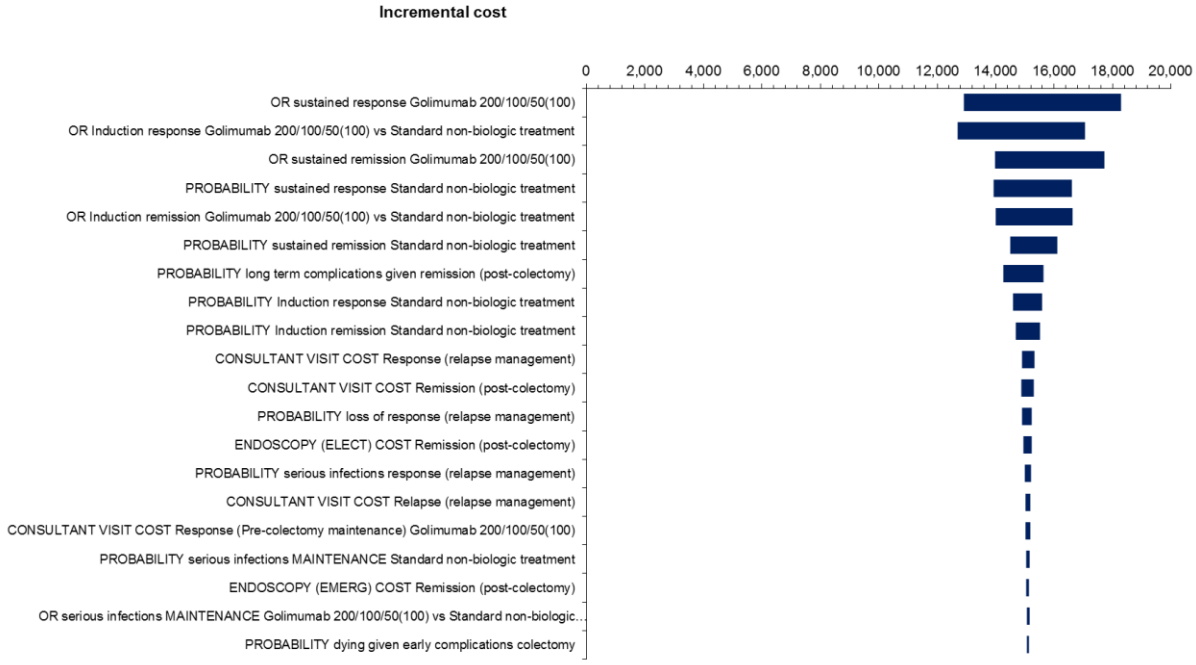


Figure 26: Results of one-way sensitivity analysis for golimumab relative to colectomy in terms of QALYs

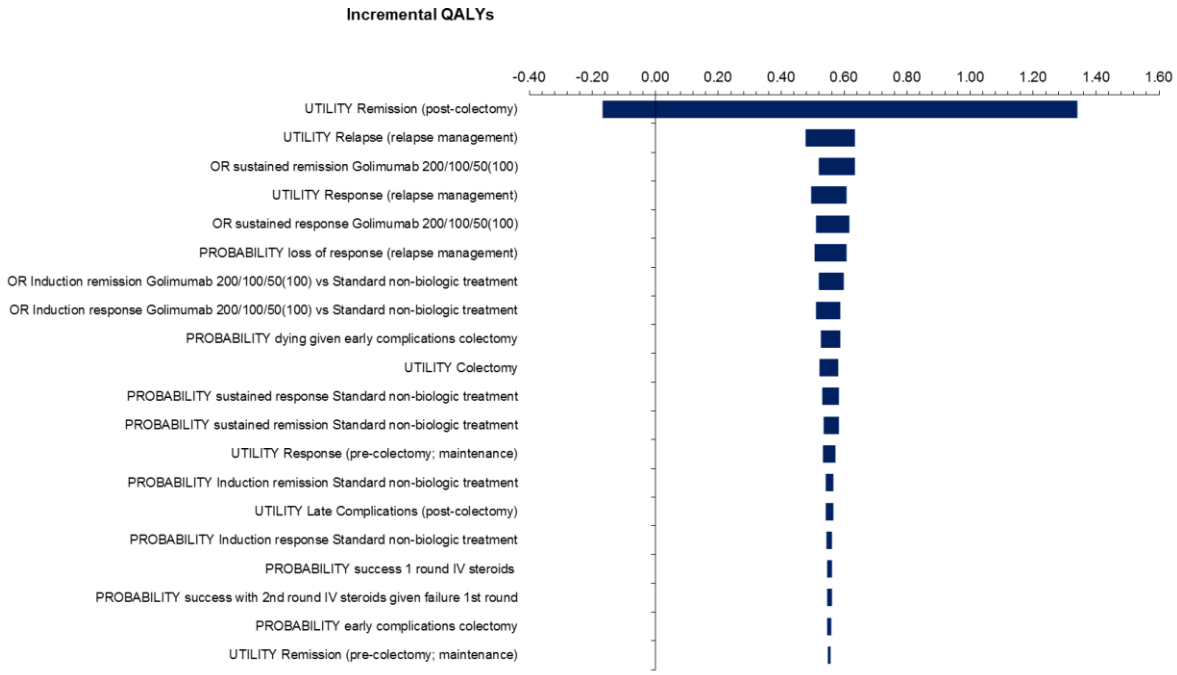


Figure 27: Results of one-way sensitivity analysis for golimumab relative to colectomy in terms of cost-effectiveness expressed as NMB with a WTP of £30,000

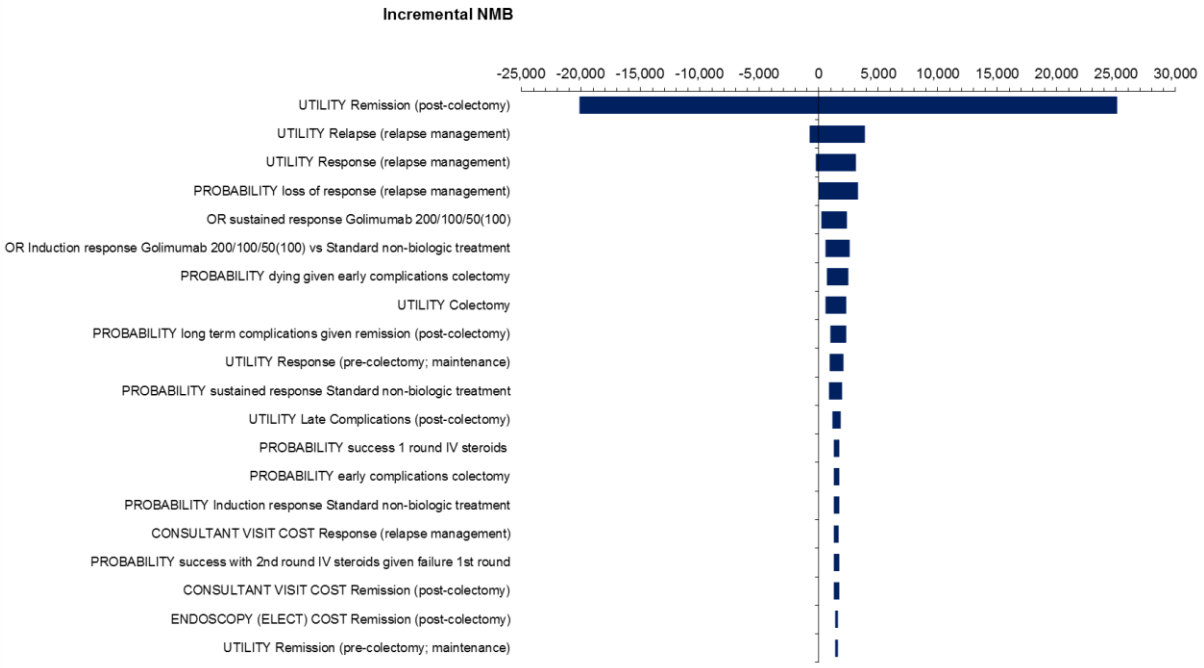


Figure 28: Cost-effectiveness plane

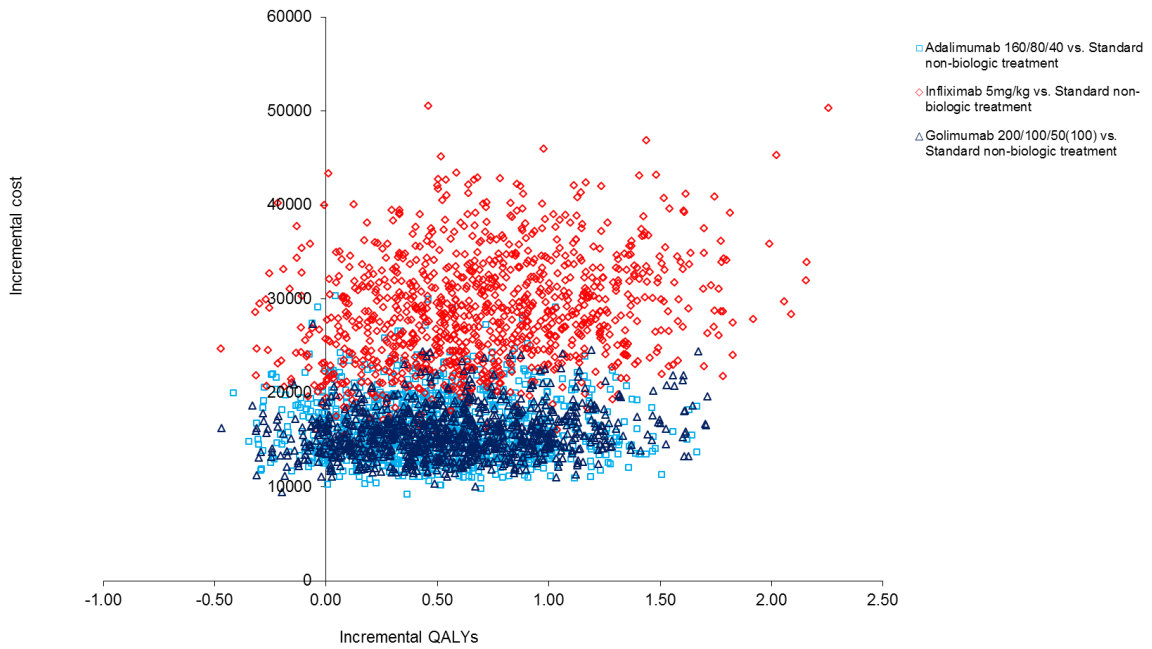
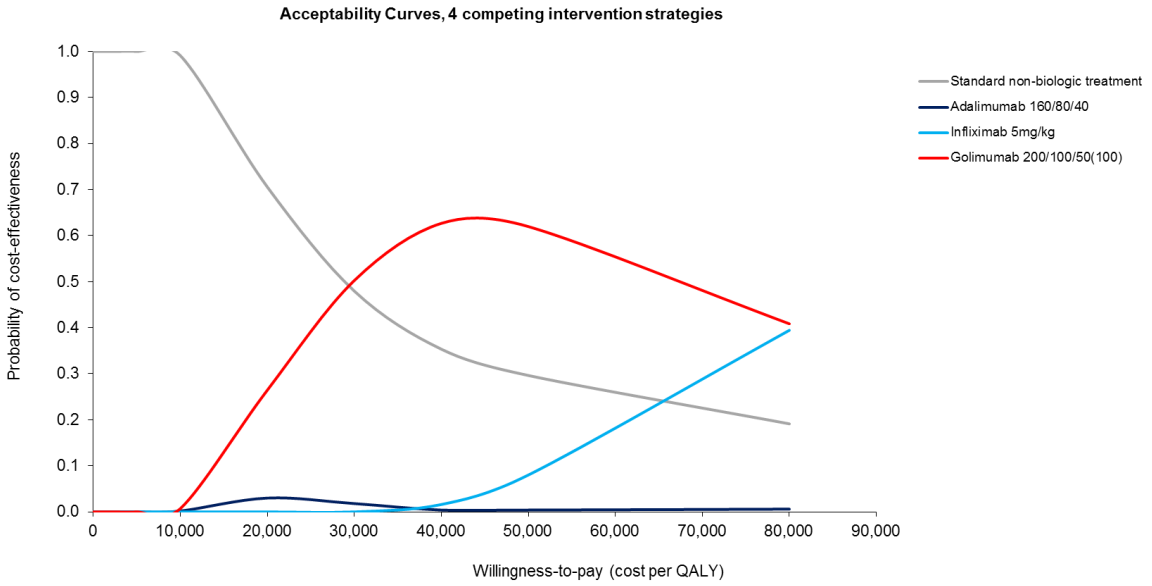


Figure 29: Cost-effectiveness acceptability curves for decision problem with four competing interventions



6.6.5. Sensitivity Analyses

The basecase analysis was re-run without the inclusion of the PAS for golimumab. In this analysis the 100mg dose was as per list price at £1525.94. The discounted QALYs over a 10 year time horizon were estimated to be 4.95 with colectomy and 5.50 with golimumab (Table 43). When the difference in total cost between golimumab and colectomy, i.e. £21,011, was expressed per unit QALY gained with golimumab relative to colectomy, an ICER of £38,017 was obtained (Table 44).

In Figure 30, Figure 31, and Figure 32 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 golimumab (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.

A comparison of golimumab with adalimumab resulted in an ICER of £105,877. The ICER for a comparison of adalimumab relative to colectomy was £31,059. In Figure 33 the joint uncertainty distribution of incremental costs and QALYs with the biologics relative to colectomy are presented. In Figure 34 the implications of model uncertainty in terms of decision uncertainty are presented with cost-effectiveness acceptability curves.

Table 43: Expected outcomes and costs for a 10 year time horizon (no PAS)

	Colectomy				Adalimumab 160/80/40mg				Infliximab 5mg/kg				Golimumab 200/100/50(100)mg			
	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	11.2	6.5	19.3	22.2	23.4	12.9	39.0	13.4	14.0	8.9	21.3
Time to colectomy (in months)	0.0	0.0	0.0	0.0	44.2	44.8	39.0	52.2	54.4	55.1	46.0	66.9	46.8	47.3	41.5	54.4
Duration of post-colectomy phase (in months)	114.0	114.0	112.2	115.5	71.1	70.5	63.5	76.3	61.3	60.6	49.6	69.4	68.7	68.2	61.2	73.8
Life years	9.66	9.66	9.51	9.79	9.76	9.76	9.67	9.84	9.79	9.79	9.71	9.85	9.77	9.77	9.68	9.85
Disc. life years	8.32	8.32	8.19	8.43	8.41	8.41	8.34	8.48	8.43	8.43	8.37	8.49	8.42	8.42	8.35	8.48
Discounted QALYs	4.95	4.98	3.08	6.63	5.45	5.48	4.38	6.46	5.65	5.68	4.67	6.54	5.50	5.53	4.46	6.48
Discounted drug acquisition and admin. cost	0	0	0	0	15,831	16,587	11,359	24,855	28,149	29,108	19,440	42,904	21,413	21,963	16,680	29,460
Discounted AE cost related to drug treatment	0	0	0	0	554	562	430	717	687	697	520	944	588	595	459	772
Disc. consultant visit cost	2,773	2,769	2,313	3,288	3,729	3,718	3,341	4,104	3,791	3,770	3,387	4,172	3,746	3,734	3,363	4,132
Discounted endoscopy cost	2,242	2,246	1,932	2,593	1,782	1,775	1,576	1,996	1,639	1,627	1,397	1,838	1,747	1,740	1,541	1,957
Discounted inpatient stay cost	0	0	0	0	916	908	840	979	911	894	756	990	910	903	827	975
Discounted colectomy cost	8,966	8,972	8,804	9,136	7,455	7,408	6,924	7,777	6,960	6,856	5,906	7,454	7,336	7,295	6,847	7,674
Discounted costs late complications	1,763	1,789	502	3,641	1,031	1,038	288	2,137	880	882	245	1,790	993	999	287	2,022
Discounted other UC cost	49	49	40	58	71	71	64	78	75	75	67	83	72	72	64	79
Discounted total direct cost	15,794	15,825	14,327	17,718	31,370	32,066	26,852	40,028	43,092	43,910	34,479	56,497	36,805	37,301	31,919	44,427
NMB at WTP of £30,000	132,650	133,426	78,011	181,161	132,115	132,306	104,436	153,861	126,458	126,535	105,526	139,752	128,220	128,524	101,770	149,849

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 (no PAS)

	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)	15,576	16,241	11,064	24,283	0.50	0.50	-0.19	1.29	31,069	Smaller NMB, hence not cost-effective	32,223	Smaller NMB, hence not cost-effective
Infliximab 5mg/kg vs. Standard non-biologic treatment (colectomy)	27,297	28,085	19,195	40,495	0.70	0.71	-0.10	1.67	38,802	Smaller NMB, hence not cost-effective	39,755	Smaller NMB, hence not cost-effective
Golimumab 200/100/50(100)mg vs. Standard non-biologic treatment (colectomy)	21,011	21,476	16,537	28,565	0.55	0.55	-0.17	1.42	38,017	Smaller NMB, hence not cost-effective	38,874	Smaller NMB, hence not cost-effective
Infliximab 5mg/kg vs. Adalimumab 160/80/40mg	11,721	11,844	-4	25,551	0.20	0.20	-0.01	0.54	57,980	Smaller NMB, hence not cost-effective	58,505	Smaller NMB, hence not cost-effective
Golimumab 200/100/50(100)mg vs. Adalimumab 160/80/40	5,435	5,235	-3,176	13,298	0.05	0.05	-0.10	0.21	105,877	Smaller NMB, hence not cost-effective	108,071	Smaller NMB, hence not cost-effective
Golimumab 200/100/50(100)mg vs. Infliximab 5mg/kg	-6,286	-6,609	-20,046	4,468	-0.15	-0.15	-0.46	0.05	41,678	Greater NMB, hence cost-effective	42,914	Greater NMB, hence 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 30: Results of one-way sensitivity analysis for golimumab relative to colectomy in terms of cost (no PAS)

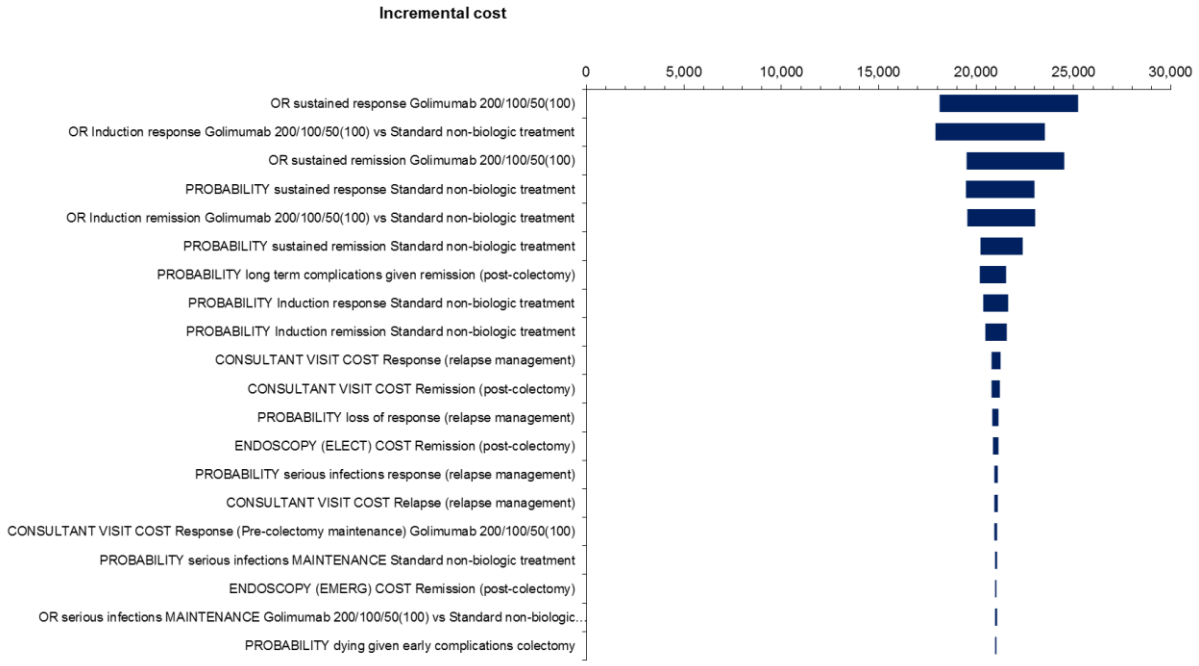


Figure 31: Results of one-way sensitivity analysis for golimumab relative to colectomy in terms of QALYs (no PAS)

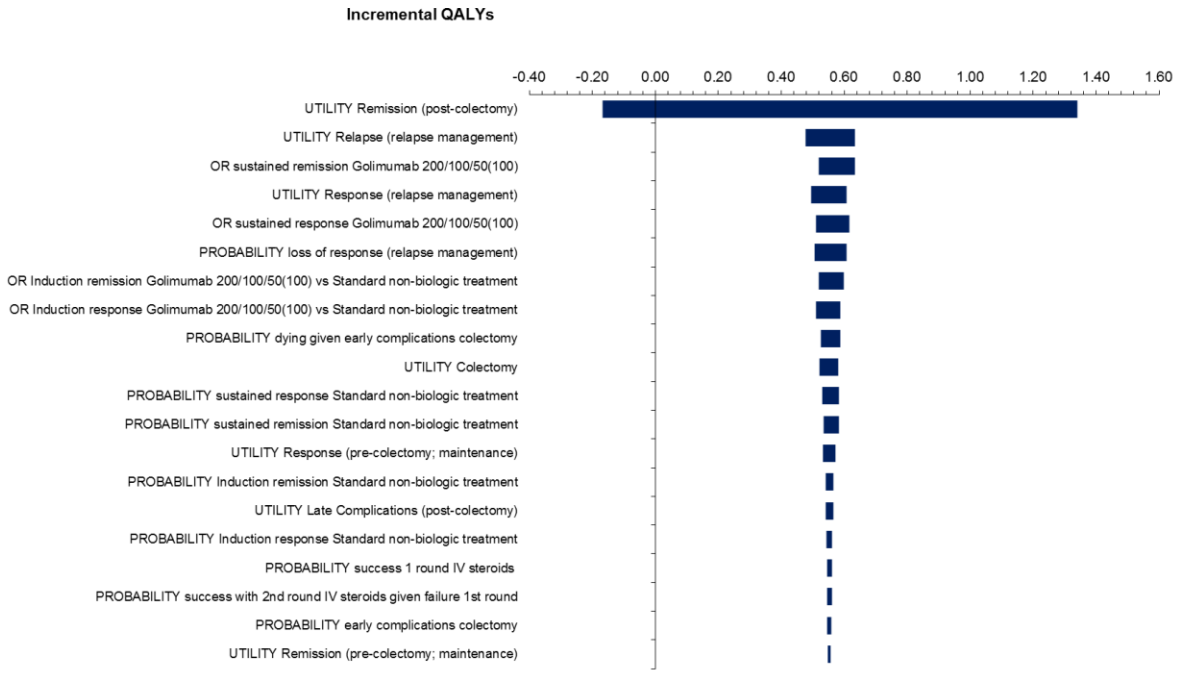


Figure 32: Results of one-way sensitivity analysis for golimumab relative to colectomy in terms of cost-effectiveness expressed as NMB with a WTP of £30,000 (no PAS)

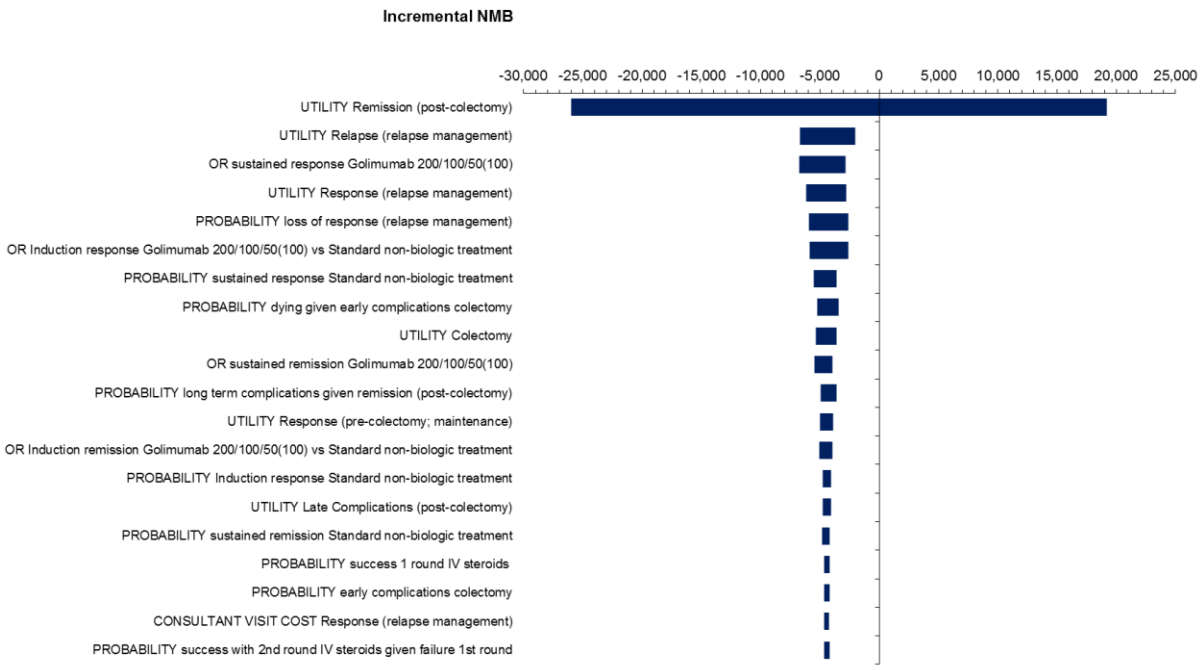


Figure 33: Cost-effectiveness plane (no PAS)

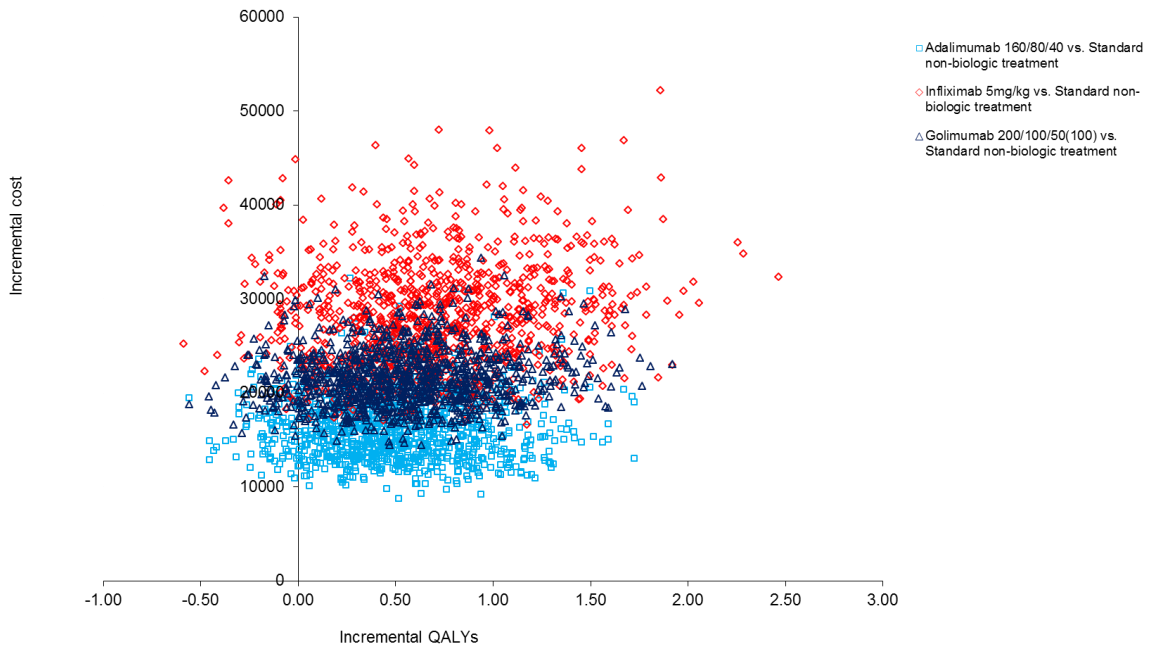
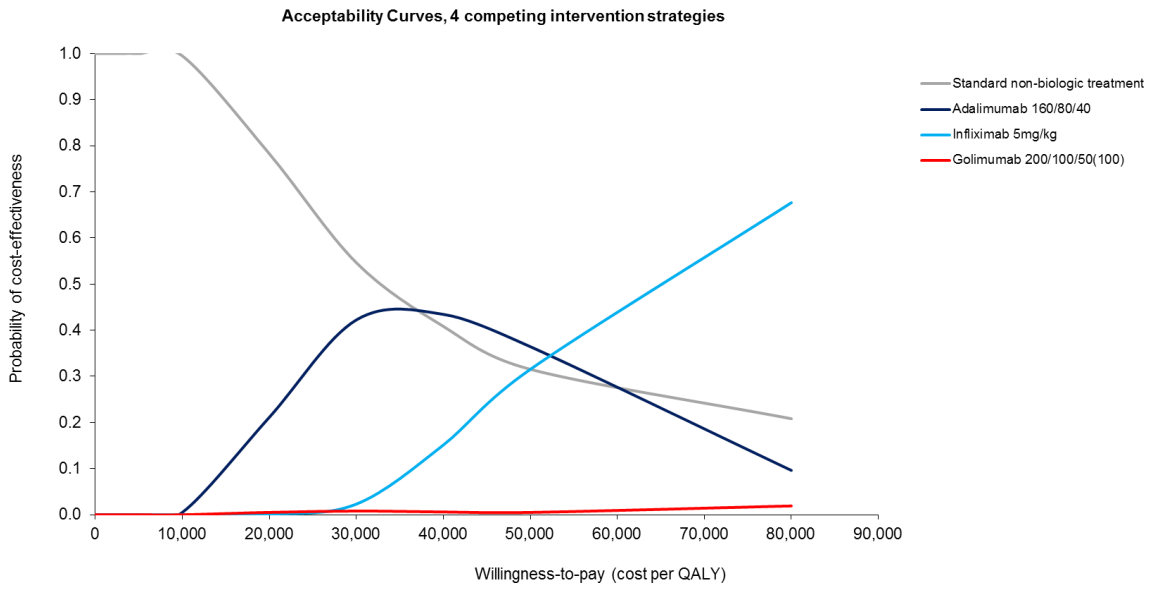


Figure 34: Cost-effectiveness acceptability curves for decision problem with four competing interventions (no PAS)



6.6.6. Additional 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.

Although the total direct costs with golimumab were £1,215 greater than with adalimumab, the 0.05 greater QALYs expected with golimumab resulted in an ICER of £23,667 (Table 46). This implies that golimumab remains a cost-effective intervention relative to adalimumab.

Figure 35: Development of costs over time (adalimumab 77% EOW/23% EW)

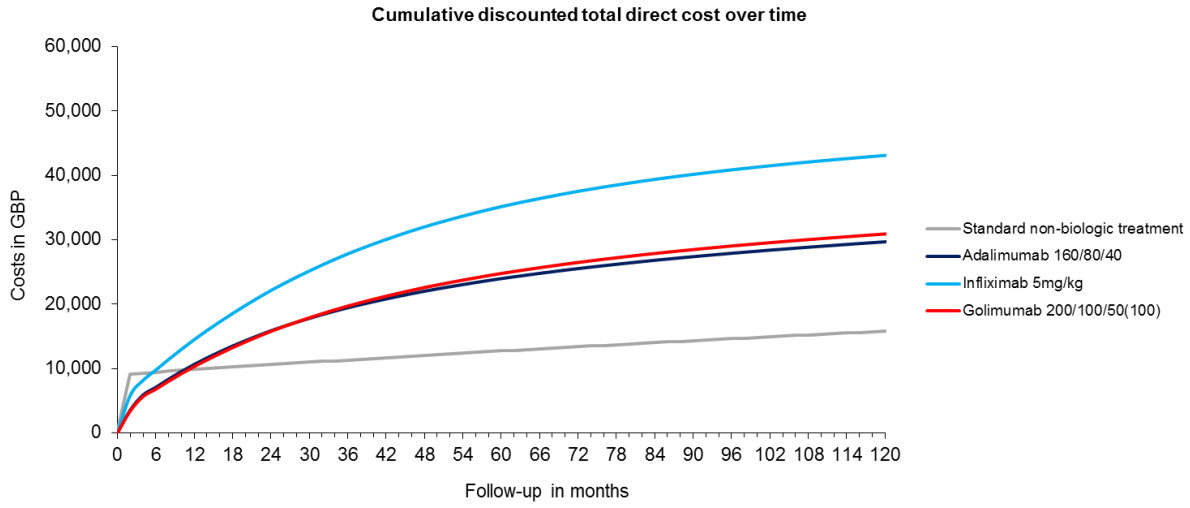


Table 45: Expected outcomes and costs for a 10 year time horizon (adalimumab 77% EOW/23% EW)

	Standard non-biologic treatment				Adalimumab 160/80/40mg				Infliximab 5mg/kg				Golimumab 200/100/50(100)mg			
	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	18.7	22.2	23.4	12.5	38.7	13.4	14.4	9.2	22.0
Time to colectomy (in months)	0.0	0.0	0.0	0.0	44.2	45.0	38.9	51.9	54.4	55.2	45.7	66.9	46.8	47.6	41.3	54.6
Duration of post-colectomy phase (in months)	114.0	114.0	112.2	115.5	71.1	70.4	63.7	76.0	61.3	60.6	49.3	69.7	68.7	67.9	61.2	74.0
Life years	9.66	9.66	9.51	9.79	9.76	9.77	9.67	9.84	9.79	9.79	9.70	9.86	9.77	9.77	9.68	9.85
Disc. life years	8.32	8.32	8.19	8.43	8.41	8.42	8.33	8.48	8.43	8.43	8.36	8.49	8.42	8.42	8.34	8.48
Disc. QALYs	4.95	4.99	3.14	6.63	5.45	5.49	4.44	6.49	5.65	5.69	4.69	6.54	5.50	5.54	4.49	6.48
Discounted drug acquisition and admin. cost	0	0	0	0	14,141	14,927	10,317	21,479	28,149	29,174	19,006	42,920	15,503	16,199	11,924	22,159
Discounted AE cost related to drug treatment	0	0	0	0	554	569	426	738	687	701	516	963	588	604	463	787
Disc. consultant visit cost	2,773	2,775	2,264	3,287	3,729	3,740	3,343	4,152	3,791	3,795	3,399	4,224	3,746	3,752	3,367	4,146
Discounted endoscopy cost	2,242	2,251	1,945	2,597	1,782	1,776	1,573	2,003	1,639	1,628	1,414	1,870	1,747	1,739	1,537	1,966
Disc. inpatient stay cost	0	0	0	0	916	908	830	984	911	892	752	987	910	901	824	972
Discounted colectomy cost	8,966	8,968	8,790	9,135	7,455	7,396	6,985	7,767	6,960	6,848	5,916	7,466	7,336	7,275	6,787	7,675
Disc. costs late complications	1,763	1,789	586	3,866	1,031	1,034	340	2,249	880	883	279	1,953	993	997	335	2,158
Discounted other UC cost	49	49	40	58	71	71	64	79	75	75	67	83	72	72	64	80
Discounted total direct cost	15,794	15,831	14,398	17,940	29,680	30,421	25,834	36,881	43,092	43,996	34,438	56,270	30,895	31,538	27,474	36,896
NMB at WTP of £30,000	132,650	133,861	79,919	180,961	133,805	134,334	107,340	157,693	126,458	126,797	106,396	139,841	134,130	134,729	107,178	157,618

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 46: 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)	13,886	14,590	10,289	20,868	0.50	0.50	-0.22	1.34	27,697	Greater NMB, hence cost-effective	29,057	Greater NMB, hence cost-effective
Infliximab 5mg/kg vs. Standard non-biologic treatment (colectomy)	27,297	28,164	18,710	40,058	0.70	0.70	-0.16	1.69	38,802	Smaller NMB, hence not cost-effective	40,043	Smaller NMB, hence not cost-effective
Golimumab 200/100/50(100)mg vs. Standard non-biologic treatment (colectomy)	15,101	15,706	11,532	21,409	0.55	0.55	-0.19	1.37	27,322	Greater NMB, hence cost-effective	28,428	Greater NMB, hence cost-effective
Infliximab 5mg/kg vs. Adalimumab 160/80/40mg	13,412	13,574	2,816	25,558	0.20	0.20	-0.01	0.55	66,342	Smaller NMB, hence not cost-effective	67,455	Smaller NMB, hence not cost-effective
Golimumab 200/100/50(100)mg vs. Adalimumab 160/80/40mg	1,215	1,116	-5,984	7,784	0.05	0.05	-0.11	0.23	23,667	Greater NMB, hence cost-effective	22,164	Greater NMB, hence cost-effective
Golimumab 200/100/50(100)mg vs. Infliximab 5mg/kg	-12,197	-12,458	-24,945	-3,017	-0.15	-0.15	-0.48	0.04	80,866	Greater NMB, hence cost-effective	82,576	Greater NMB, hence 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 36: Cost-effectiveness plane (adalimumab 77% EOW/23% EW)

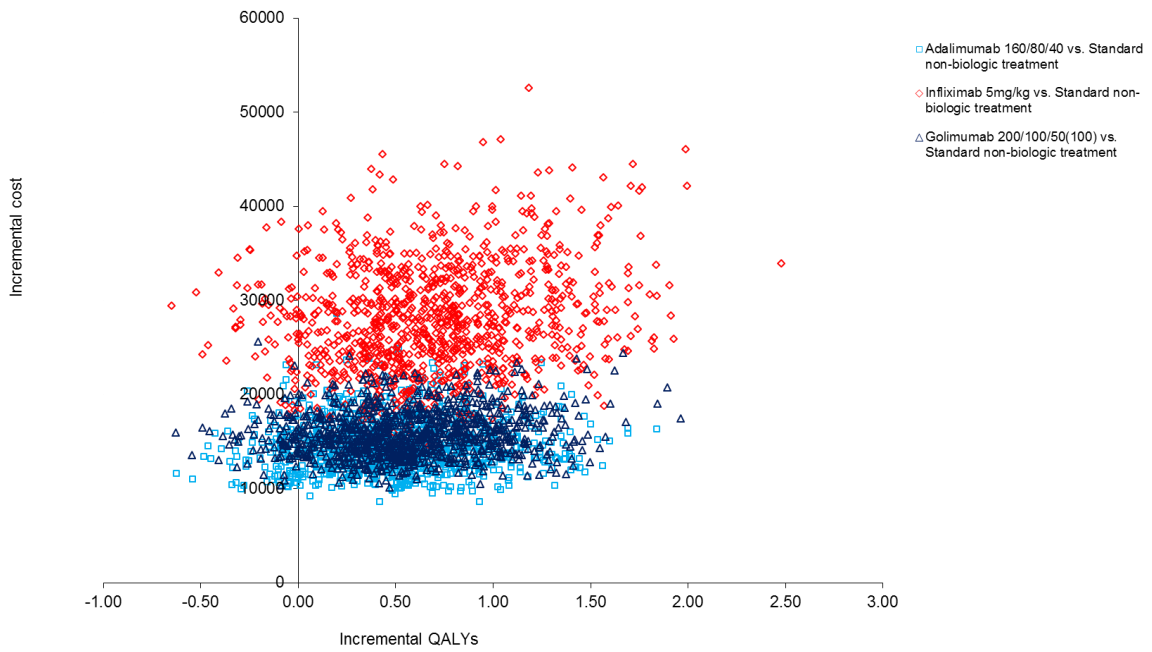
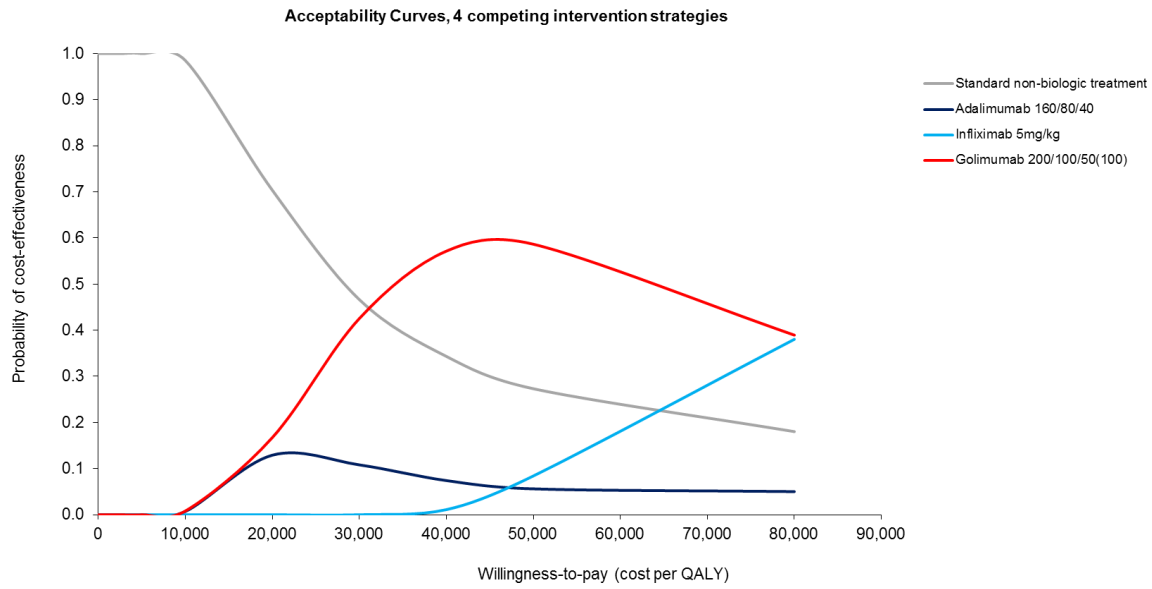


Figure 37: Cost-effectiveness acceptability curves for decision problem with four competing interventions (adalimumab 77% EOW/23% EW)



Additional one-way sensitivity analyses were performed to show the impact of varying selected parameters on ICERs (Table 47). 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 47: Incremental cost-effectiveness ratios for sensitivity analyses of the basecase

	Golimumab vs. standard non-biologic treatment (colectomy)	**Golimumab vs. adalimumab**	**Golimumab vs. infliximab**
Basecase	£27,322	Dominant	£80,866
Life time horizon instead of 10 year time horizon	£27,426	Dominant	£77,779
5-year time horizon instead of 10 year time horizon	£26,431	Dominant	£89,606
No successful relapse management phase following failure of biologics; automatic transition to colectomy after flare up	£55,875	Dominant	£74,290

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 48. 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 48: 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 it 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 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 Golimumab

Golimumab is self-administered by patients via a once every 4 weeks SC injection. The auto-injector has been specifically developed in response to patient needs and includes an ergonomically-designed barrel for ease of handling, a safety sleeve to avoid accidental firing, a large observation window, audible clicks for initiation and complete administration, and a needle which auto-injects and auto-retracts whilst remaining out of sight to patients.

Patients receiving golimumab for the treatment of UC require a 200mg dose at week 0 and a 100mg dose at week 2. A 100mg auto-injector has been developed which means that patients only need three injections in the induction setting, and one injection every 4 weeks thereafter. This is favourable when compared with adalimumab, where in the induction setting patients

require a total of six separate injections, followed by two to four injections in each subsequent 4 week period.

MSD provides a golimumab patient support programme, designed to encourage adherence to ensure that the efficacy demonstrated in the clinical trials translates into clinical practice. Patients receive reminders of when the next dose is due and the dose is delivered direct to the patients' home. The programme assists in managing treatment expectations, and provides simple and relevant information and timely, practical help so that patients can feel comfortable and confident with self-injection.

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