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Abstract

Infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy (including a review of TA140 and TA262): clinical effectiveness systematic review and economic model

Rachel Archer,[1]* Paul Tappenden,[1] Shijie Ren,[1] Marrissa Martyn-St James,[1] Rebecca Harvey,[1] Hasan Basarir,[1] John Stevens,[1] Christopher Carroll,[1] Anna Cantrell,[1] Alan Lobo[2] and Sami Hoque[3]

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Background: Ulcerative colitis (UC) is the most common form of inflammatory bowel disease in the UK. UC can have a considerable impact on patients' quality of life. The burden for the NHS is substantial.

Objectives: To evaluate the clinical effectiveness and safety of interventions, to evaluate the incremental cost-effectiveness of all interventions and comparators (including medical and surgical options), to estimate the expected net budget impact of each intervention, and to identify key research priorities.

Data sources: Peer-reviewed publications, European Public Assessment Reports and manufacturers' submissions. The following databases were searched from inception to December 2013 for clinical effectiveness searches and from inception to January 2014 for cost-effectiveness searches for published and unpublished research evidence: MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature, The Cochrane Library including the Cochrane Systematic Reviews Database, Cochrane Controlled Trials Register, Database of Abstracts of Reviews of Effects, the Health Technology Assessment database and NHS Economic Evaluation Database; ISI Web of Science, including Science Citation Index, and the Conference Proceedings Citation Index-Science and Bioscience Information Service Previews. The US Food and Drug Administration website and the European Medicines Agency website were also searched, as were research registers, conference proceedings and key journals.

Review methods: A systematic review [including network meta-analysis (NMA)] was conducted to evaluate the clinical effectiveness and safety of named interventions. The health economic analysis included a review of published economic evaluations and the development of a de novo model.

Results: Ten randomised controlled trials were included in the systematic review. The trials suggest that adult patients receiving infliximab (IFX) [Remicade®, Merck Sharp & Dohme Ltd (MSD)], adalimumab (ADA) (Humira®, AbbVie) or golimumab (GOL) (Simponi®, MSD) were more likely to achieve clinical response and remission than those receiving placebo (PBO). Hospitalisation data were limited, but suggested more favourable outcomes for ADA- and IFX-treated patients. Data on the use of surgical intervention were

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sparse, with a potential benefit for intervention-treated patients. Data were available from one trial to support the use of IFX in paediatric patients. Safety issues identified included serious infections, malignancies and administration site reactions. Based on the NMA, in the induction phase, all biological treatments were associated with statistically significant beneficial effects relative to PBO, with the greatest effect associated with IFX. For patients in response following induction, all treatments except ADA and GOL 100 mg at 32–52 weeks were associated with beneficial effects when compared with PBO, although these were not significant. The greatest effects at 8–32 and 32–52 weeks were associated with 100 mg of GOL and 5 mg/kg of IFX, respectively. For patients in remission following induction, all treatments except ADA at 8–32 weeks and GOL 50 mg at 32–52 weeks were associated with beneficial effects when compared with PBO, although only the effect of ADA at 32–52 weeks was significant. The greatest effects were associated with GOL (at 8–32 weeks) and ADA (at 32–52 weeks). The economic analysis suggests that colectomy is expected to dominate drug therapies, but for some patients, colectomy may not be considered acceptable. In circumstances in which only drug options are considered, IFX and GOL are expected to be ruled out because of dominance, while the incremental cost-effectiveness ratio for ADA versus conventional treatment is approximately £50,300 per QALY gained.

Limitations: The health economic model is subject to several limitations: uncertainty associated with extrapolating trial data over a lifetime horizon, the model does not consider explicit sequential pathways of non-biological treatments, and evidence relating to complications of colectomy was identified through consideration of approaches used within previous models rather than a full systematic review.

Conclusions: Adult patients receiving IFX, ADA or GOL were more likely to achieve clinical response and remission than those receiving PBO. Further data are required to conclusively demonstrate the effect of interventions on hospitalisation and surgical outcomes. The economic analysis indicates that colectomy is expected to dominate medical treatments for moderate to severe UC.

Study registration: This study is registered as PROSPERO CRD42013006883.

Funding: The National Institute for Health Research Health Technology Assessment programme.

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List of abbreviations

5-ASA	5-aminosalicylate
6-MP	6-mercaptopurine
ACT	Active Ulcerative Colitis Trial
ADA	adalimumab
AE	adverse event
AS	ankylosing spondylitis
AZA	azathioprine
BIOSIS	Bioscience Information Service
BNF	*British National Formulary*
CCRT	Cochrane Central Register of Controlled Trials
CD	Crohn's disease
CDSR	Cochrane Database of Systematic Reviews
CEAC	cost-effectiveness acceptability curve
CHMP	Committee for Human Medicinal Products
CI	confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CrI	credible interval
CRP	C-reactive protein
CSR	clinical study report
DARE	Database of Abstracts of Reviews of Effects
ECCO	European Crohn's and Colitis Organisation
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EQ-5D	European Quality of Life-5 Dimensions
FDA	Food and Drug Administration
GOL	golimumab
HRQoL	health-related quality of life
HTA	Health Technology Assessment
i.v.	intravenous
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICER	incremental cost-effectiveness ratio
IFX	infliximab
IPAA	ileal pouch anal anastomosis
ITT	intention to treat
MeSH	medical subject heading
MSD	Merck Sharp & Dohme Ltd
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NMB	net monetary benefit
NYHA	New York Heart Association
OR	odds ratio
PAS	Patient Access Scheme
PBO	placebo
PLANET-AS	Programme evaLuating the Autoimmune disease iNvEstigational drug CT-P13 in ankylosing spondylitis patients
PLANET-RA	Programme evaLuating the Autoimmune disease iNvEstigational drug CT-P13 in rheumatoid arthritis patients
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	probabilistic sensitivity analysis
PSS	Personal Social Services

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PUCAI	Paediatric Ulcerative Colitis Activity Index
PURSUIT	Program of Ulcerative Colitis Research Studies Utilizing an Investigational Treatment
PY	patient-year
QALY	quality-adjusted life-year
RA	rheumatoid arthritis
RCT	randomised controlled trial
RR	risk ratio
SAE	serious adverse event
SCAI	Simple Colitis Activity Index
ScHARR	School of Health and Related Research
ScHARR-TAG	ScHARR Technology Assessment Group
SD	standard deviation
SDAI	Simplified Disease Activity Index
SF-36	Short Form questionnaire-36 items
SmPC	Summary of Product Characteristics
TB	tuberculosis
TNF-α	tumour necrosis factor alpha
TTO	time trade-off
UC	ulcerative colitis
UCSS	Ulcerative Colitis Symptom Score
ULTRA	Ulcerative colitis Long-Term Remission and maintenance with Adalimumab treatment of moderate to severe ulcerative colitis

Note

This monograph is based on the Technology Assessment Report produced for NICE. The full report contained a considerable number of data that were deemed commercial-in-confidence. The full report was used by the Appraisal Committee at NICE in their deliberations. The full report with each piece of commercial-in-confidence data removed and replaced by the statement 'commercial-in-confidence information (or data) removed' is available on the NICE website: www.nice.org.uk.

The present monograph presents as full a version of the report as is possible while retaining readability, but some sections, sentences, tables and figures have been removed. Readers should bear in mind that the discussion, conclusions and implications for practice and research are based on all the data considered in the original full NICE report.

Plain English summary

Ulcerative colitis (UC) is a form of inflammatory bowel disease. Patients with this disease experience symptoms including bloody diarrhoea, abdominal pain, weight loss and tiredness.

We reviewed the evidence for the use of infliximab [Remicade®, Merck Sharp & Dohme Ltd (MSD)], adalimumab (Humira®, AbbVie) and golimumab (Simponi®, MSD) for the treatment of patients with UC. The clinical trials included in the review suggested that adult patients receiving these drugs were more likely to achieve a treatment response than patients receiving placebo. More evidence is needed to determine whether or not these drugs reduce the need for hospitalisation or surgery in such patients.

We also assessed whether or not these therapies represent good value for money for the NHS. The analysis suggests that surgery may be more effective and less expensive than medical therapies. For patients that do not want to, or cannot, undergo surgery, the incremental cost-effectiveness ratios for these therapies are expected to be greater than £50,300 per quality-adjusted life-year gained.

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Scientific summary

Background

Ulcerative colitis (UC) is recognised as the most common form of inflammatory bowel disease in the UK. Peak incidence is between 15 and 25 years of age, with a potential second peak between 55 and 65 years. Inflammation in UC typically occurs in the colon and rectum. Symptoms include the development of bloody diarrhoea with or without mucus, abdominal pain, weight loss, fatigue and an urgent need to defecate. UC can have a substantial impact on the health-related quality of life (HRQoL) of patients owing to the young age of disease onset for some patients, the severity of symptoms and the likelihood of relapse. The burden of UC for the NHS is substantial.

Objectives

The aim of this assessment is to assess the clinical effectiveness and cost-effectiveness of infliximab (IFX) [Remicade®, Merck Sharp & Dohme Ltd (MSD)], adalimumab (ADA) (Humira®, AbbVie) and golimumab (GOL) (Simponi®, MSD) for the treatment of patients with moderately to severely active UC after the failure of conventional therapy.

The objectives of the assessment are:

- to evaluate the clinical effectiveness of each intervention
- to examine the effect of disease duration on the clinical effectiveness of each intervention (subject to the availability of evidence)
- to evaluate the adverse effect profile of each intervention
- to evaluate the incremental cost-effectiveness of each intervention compared (1) against each other and (2) against all comparators (including medical and surgical options)
- to estimate the expected net budget impact associated with implementing each intervention
- to identify key areas in which future research may be valuable.

Data sources

The following databases were searched from inception to December 2013 for clinical effectiveness searches and from inception to January 2014 for cost-effectiveness searches for published and unpublished research evidence: MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature, The Cochrane Library including the Cochrane Systematic Reviews Database, Cochrane Controlled Trials Register, Database of Abstracts of Reviews of Effects, the Health Technology Assessment (HTA) database and NHS Economic Evaluation Database; ISI Web of Science, including Science Citation Index, and the Conference Proceedings Citation Index-Science and Bioscience Information Service Previews. The US Food and Drug Administration website and the European Medicines Agency (EMA) website were also searched as were research registers, conference proceedings and key journals.

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Methods

A systematic review of the literature including network meta-analyses (NMAs) was conducted in order to evaluate the clinical effectiveness and safety of IFX, ADA and GOL in the treatment of moderately to severely active UC after the failure of conventional therapy. The protocol for this review is registered with PROSPERO (CRD42013006883). A review of the existing cost-effectiveness literature was also undertaken. A de novo health economic model was constructed by the Assessment Group in order to evaluate the cost-effectiveness of the interventions under assessment.

Results

Number and quality of studies

A total of 10 randomised controlled trials (RCTs) were identified in the clinical effectiveness systematic review. Five, three and two RCTs evaluated the use of IFX, ADA and GOL, respectively, in the treatment of moderately to severely active UC. Nine trials related to adults and one trial was conducted in a paediatric population. All of the adult RCTs (with the exception of one trial, UC-SUCCESS) were performed against placebo (PBO). No head-to-head RCTs were identified in which the interventions of interest were assessed against each other.

The risks of bias associated with included RCTs were assessed using the Cochrane risk-of-bias instrument. Only three RCTs could be considered as being at overall low risk of bias (as allocation concealment, blinded outcome assessment and completeness of outcome data were all judged as low risk). It should be noted that one of the maintenance trials [Program of Ulcerative Colitis Research Studies Utilizing an Investigational Treatment (PURSUIT)-Maintenance] rerandomised patients who had previously responded to GOL induction therapy in two previous trials; the extent of this potential bias on patient outcomes is unclear.

Summary of benefits and risks

The outcome measures specified in the final National Institute for Health and Care Excellence (NICE) scope were all addressed by the included trial evidence, with the exception of rates of relapse. Clinical response and remission data based on complete Mayo scores were well reported across trials. Evidence was identified to demonstrate that patients receiving IFX, ADA or GOL were more likely to achieve clinical response and remission at induction and maintenance time points than patients receiving PBO. Patients in the UC-SUCCESS trial who received combination treatment with IFX and azathioprine (AZA) experienced the most favourable rates of steroid-free remission when compared with IFX and AZA treatment groups. Seven RCTs performed on adult populations contributed data on clinical response and remission at induction or maintenance time points to NMAs.

Based on the NMA, in the induction phase all treatments were associated with statistically significant beneficial effects relative to PBO, with the greatest effect being associated with IFX. For patients classified as responders at the end of the induction phase, treatment effects were not statistically significant, although the greatest effect at 8–32 weeks was associated with 100 mg of GOL. At 32–52 weeks, only IFX and 50 mg of GOL were associated with beneficial effects on clinical response. For patients classified as being in remission at the end of the induction phase, all treatments except for ADA were associated with beneficial treatment effects relative to PBO, with the greatest effect being associated with 50 mg and 100 mg of GOL, although the effects were not statistically significant at 8–32 weeks. At 32–52 weeks, all treatments except 50 mg of GOL were associated with beneficial treatment effects relative to PBO, with the greatest effect being associated with ADA (the only treatment with statistically significant effect). ADA was associated with the highest probability of staying in remission and the smallest probability of moving from remission to response and from remission to no response.

Sensitivity analyses were conducted to assess the impact of including different studies and subgroups in the NMA. The sensitivity analyses conducted included replacing Ulcerative colitis Long-Term Remission and maintenance with ADA treatment of moderate to severe ulcerative colitis (ULTRA2) anti-tumour necrosis factor alpha (TNF-α)-naive data with ULTRA2 intention-to-treat (ITT) data (sensitivity analysis 1), including Suzuki *et al.* (Suzuki Y, Motoya S, Hanai H, Matsumoto T, Hibi T, Robinson A, *et al.* Efficacy and safety of ADA in Japanese patients with moderately to severely active ulcerative colitis. *Journal of Gastroenterology* 2014;**49**:283–94) (sensitivity analysis 2), and replacing ULTRA2 anti-TNF-α-naive data with ULTRA2 ITT data plus including Suzuki *et al.* (sensitivity analysis 3).

Available data on hospitalisation outcomes were very limited but suggested that outcomes may be more favourable for ADA-treated and IFX-treated patients compared with PBO (with no data available from GOL trials). Data on the use of surgical intervention were also very sparse, with a potential inconclusive benefit for intervention-treated patients compared with PBO. No trials reported whether or not surgical outcomes were elective or emergency in nature. However, more data are required to demonstrate the impact of interventions on hospitalisation and surgical intervention more conclusively. Data were available from a single trial to support the use of IFX in induction and maintenance treatment in a paediatric population.

The main safety issues highlighted in the RCT evidence appeared to be generally consistent with those previously discussed in the respective Summary of Product Characteristics (including serious infections, malignancies and administration site reactions). Deaths occurring during and after the study period were described in some trials evaluating GOL (PURSUIT-Maintenance) and IFX [Active Ulcerative Colitis Trials (ACTs)] of which infection or malignancy were most commonly implicated. This underlines the importance of monitoring and treating serious infections and malignancies in patients receiving immunosuppressive treatment.

Two biosimilars (Remsima®, Celltrion Healthcare, and Inflectra®, Hospira) to Remicade were considered as part of the evidence base for IFX within this assessment. The sponsor submission received from the manufacturers of Remsima and the European Public Assessment Reports for Remsima and Inflectra indicated that both biosimilars were approved by the EMA on the basis of reported similar pharmacokinetic and efficacy profiles to Remicade (demonstrated in ankylosing spondylitis and rheumatoid arthritis patients). No further trials of Remsima or Inflectra were identified over the course of this assessment.

Summary of cost-effectiveness evidence

The manufacturers of ADA, IFX and GOL submitted economic models to assess the cost-effectiveness of biological therapies versus conventional treatment. The MSD IFX submission model indicates that the estimated incremental cost-effectiveness ratio (ICER) for IFX versus standard non-biological treatment (colectomy) is £37,682 per quality-adjusted life-year (QALY) gained. The MSD GOL submission reports an estimated ICER of £27,322 per QALY gained. The AbbVie submission reports a base-case ICER of £34,590 per QALY gained. The Assessment Group identified several problems with these models. In particular, none of the models included all relevant treatment options specified in the final NICE scope and each model adopted a short time horizon (10 years). The Assessment Group does not consider that the cost-effectiveness evidence submitted by either manufacturer represents a sufficient basis for informing decision-making.

In order to address the problems identified within the manufacturers' submitted economic models, the Assessment Group developed a de novo cost-effectiveness model to assess IFX, ADA, GOL, conventional non-biological treatments and elective surgery within the moderate to severe UC population over a lifetime horizon. Underpinning the Assessment Group model is a series of NMAs that synthesise all relevant evidence relating to IFX, ADA, GOL and conventional non-biological therapies [5-aminosalicylates (5-ASAs), corticosteroids, immunosuppressants and surgery] in the induction and maintenance settings.

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The base-case analysis of the Assessment Group model suggests that colectomy is expected to produce 14.71 QALYs at a cost of approximately £56,300 over the patient's remaining lifetime. All medical options are expected to produce substantially fewer QALYs at a greater cost than colectomy; hence, colectomy is expected to dominate IFX, ADA, GOL and conventional non-biological treatments. For some patients, elective colectomy may not be considered an acceptable or preferable option. In circumstances whereby only drug options are considered acceptable, the Assessment Group model suggests that IFX and GOL are expected to be ruled out because of dominance, while the incremental cost-effectiveness of ADA versus conventional non-biological treatment is expected to be approximately £50,300 per QALY gained.

A separate economic analysis of IFX, conventional non-biological treatments and colectomy was undertaken within a paediatric population (mean age of 15 years). When colectomy is an acceptable treatment option, the economic analysis suggests that this option is expected to dominate IFX and conventional non-biological treatments. When colectomy is not an acceptable option, the economic analysis suggests that the incremental cost-effectiveness of IFX versus conventional treatments is approximately £68,000 per QALY gained. However, this analysis is based on adult efficacy evidence and, thus, it should be interpreted with some degree of caution.

A number of sensitivity analyses were undertaken using the Assessment Group model. These suggested that the results of the economic analysis are largely insensitive to changes in the model assumptions, except for scenarios in which the post-surgery utility value is altered. When utility scores from Swinburn *et al.* are used in the model (Swinburn P, Elwick H, Bean K, Curry A, Patel S, Bodger K, *et al.* The Impact of Surgery on Health Related Quality of Life in Ulcerative Colitis. Gut Conference: Digestive Disorders Federation Meeting, Liverpool; 2012) [rather than those reported by Woehl A, Hawthorne A, McEwan P. The relation between disease activity, quality of life and health utility in patients with ulcerative colitis. *Gut* 2008;**57**(Suppl. 1):A153], colectomy produces the lowest QALY gain and conventional management and GOL are ruled out as a consequence of extended dominance. Within this scenario, the incremental cost-effectiveness of ADA versus elective colectomy is estimated to be £79,714 per QALY gained, while the incremental cost-effectiveness of IFX versus ADA is estimated to be £178,982 per QALY gained. Although these results are very different from the Assessment Group's preferred base-case analysis, the economic conclusions that should be drawn from this sensitivity analysis are not.

Discussion

Strengths, limitations of the analyses and uncertainties

The systematic review was based on rigorous methods, with comprehensive searches for evidence, a good level of consistency between reviewers in study selection and double-checking of data extraction. Clinical response and remission data were well reported across included trials and study authors were consistent in their use of the complete Mayo score, which aided the comparison of trials. NMAs were performed to permit a comparison of the efficacy of interventions in terms of clinical response and remission.

The Assessment Group's economic analysis has a number of strengths:

- The treatment pathway represented within the model was based on considerable expert opinion from several leading UC experts.
- The Assessment Group model is underpinned by a complex NMA across all drug options, thereby synthesising relevant efficacy outcomes data within a single network of evidence.
- The model generally adheres to the NICE reference case and fully addresses the decision problem set out in the final NICE scope.
- When appropriate and possible, systematic search methods have been used to identify, select and use evidence to inform the model's parameters (efficacy, HRQoL and colectomy rates).
- The Assessment Group has undertaken extensive sensitivity analyses to examine the impact of alternative assumptions and sources of evidence on the robustness of the results of the model.

The Assessment Group model is also subject to a number of limitations:

- There is considerable uncertainty associated with Assessment Group's extrapolation of short-term trial data (maximum 54 weeks) to a lifetime horizon.
- The model does not consider an explicit sequential pathway of non-biological treatments. Instead, during any cycle, a proportion of patients are assumed to receive 5-ASAs, immunomodulators and steroids.
- Evidence relating to complications of colectomy was identified through consideration of approaches used within previous models rather than through a full systematic review; however, these assumptions were tested within the sensitivity analyses.

Key uncertainties in this assessment include:

- the optimal duration of intervention treatment in responding patients
- the maintenance of efficacy outcomes and safety of interventions beyond the limited study lengths available
- the maintenance of outcomes in responding patients following cessation of anti-TNF-α treatment.

Generalisability of the findings

The trials included in the clinical effectiveness systematic review typically excluded patients with ulcerative proctitis, patients with fulminant/acute severe disease, those with a history of or at imminent risk of bowel surgery, pregnant or lactating women, and patients with diseases of the central nervous system (e.g. demyelinating disease). Furthermore, patients with history of serious infection and/or immunodeficiency were also typically excluded, as were individuals with a history of malignancy or signs of dysplasia. Therefore, the effects of ADA, GOL or IFX in these UC populations have not specifically been investigated.

Study registration

This study is registered as PROSPERO CRD42013006883.

Funding

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Chapter 1 Background

Description of health problem

Ulcerative colitis (UC) is recognised as the most common form of inflammatory bowel disease (IBD) in the UK. The incidence of UC is approximately 10 per 100,000 population per year, while the prevalence of the disease is approximately 240 per 100,000 population.[1] This is typical for countries with a Westernised lifestyle.[2] Peak incidence is between 15 and 25 years of age, with a potential second peak between 55 and 65 years.[1] The majority (approximately 80%) of incident cases are reported to be of mild or moderate severity. An estimated 132,600 people in England and Wales have been diagnosed with UC,[1] which is distinct from Crohn's disease (CD) – the other principal form of IBD.[2]

Ulcerative colitis is a chronic disease of unknown cause. It is understood that pathogenesis may result from a change in the colonic environment of a genetically susceptible person and the condition is genetically heterogeneous, having a large number of implicated genes.[2,3] Genetic screening is therefore not currently indicated for UC;[2] however, appendectomy and smoking have been linked with a reduced risk and severity of UC.[2]

Inflammation in UC typically occurs in the colon and rectum. Disease may be limited to the rectum (proctitis), may be left sided or distal, or may be extensive (pancolitis).[3] Symptoms include the development of bloody diarrhoea with or without mucus, abdominal pain, weight loss, fatigue and an urgent need to defecate. Extraintestinal manifestations may occur in 10–30% of patients on the skin, eyes, mouth, joints or liver.[2,4] Symptoms may vary according to the degree and severity of bowel inflammation.[1,2] Acute severe exacerbations of UC are characterised by the development of systemic signs of disease (e.g. high temperature, tachycardia, anaemia, etc.) and require admission to hospital for urgent monitoring and treatment.[3]

Diagnosis of UC is made by medical history, endoscopy and biopsy following the exclusion of potential infectious causes by stool examination.[5] These techniques permit the evaluation of relevant histological features and enable the differentiation of UC from other conditions such as CD.[2] For example, inflammation is characteristically restricted to the mucosal layer of the colon.[2] Diagnostic investigations also enable a determination of disease severity and there is evidence to indicate that severity of disease may be associated with younger age at diagnosis.[6,7] Based on the findings of diagnostic investigations, appropriate treatment can then be identified.

Colectomy by definition removes the source of inflammation in UC and is therefore associated with the relief of UC symptoms but is associated with a range of complications.[2,8] Pharmacological treatments for UC do not offer the possibility of cure and the disease course follows a relapsing–remitting pattern. The aim of clinical management is to induce and maintain disease remission and to avoid potential complications and the necessity for surgical intervention.[9] Selection of the appropriate therapy to induce remission of UC is determined by a number of factors, including severity and extent of disease. Evidence on prognosis indicates that, in the first decade, remission occurs in most patients and the rate of colectomy after diagnosis is low.[10] Otherwise, reported rates of colectomy among patients with UC are in the region of approximately 5% and 20%[11,12] however this is an area of considerable uncertainty (some studies in selected populations have reported markedly higher colectomy rates, e.g. Gustavsson *et al.*[13]). A range of factors have been suggested as potentially influencing the risk of relapse, including age (and age at first relapse), sex, smoking status and number of previous relapses.[12]

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Impact of health problem

Significance for patients

Complications of UC, depending on the severity and duration of the disease and age at onset, include severe bleeding and toxic megacolon, extraintestinal manifestations and osteoporosis.[2] Dysplasia and bowel cancer may also develop. A meta-analysis by Jess *et al.*[14] demonstrated that UC is not associated with an increase in overall mortality. UC can have a substantial impact on the health-related quality of life (HRQoL) of patients on account of the young age of disease onset for some patients, the severity of symptoms and the likelihood of relapse.[8,15–17] The risk of relapse and disease flares is increased by poor adherence to medication regimens.[18,19] Relapse and flares can be unpredictable and require further treatment, thus affecting patients' HRQoL, their ability to perform daily activities (including work) and lead to increases in health-care costs.[8,19,20]

Significance for the NHS

The burden of UC for the NHS is substantial, particularly with respect to those patients who suffer from poor disease control. A study of the costs of IBD (UC and CD) to the NHS reported in 2004 found that, compared with quiescent cases of IBD, disease relapse was associated with a two- to threefold increase in costs for non-hospitalised cases and a 20-fold increase in costs for hospitalised cases.[21]

Measurement of disease

A range of clinical measures are available for the assessment of disease activity in UC.[22] Of most relevance to this assessment are the modified Truelove and Witts' criteria,[23] the Mayo score[24] and the Paediatric Ulcerative Colitis Activity Index (PUCAI).[25]

Truelove and Witts' severity index[23]

The Truelove and Witts' severity index describes the frequency of diarrhoea and whether or not systemic features of illness, such as high temperature, tachycardia and anaemia, are present or absent in patients (*Table 1*). When the disease is active, patients are categorised as having mild, moderate or severe disease.

TABLE 1 Features of the Truelove and Witts' severity index (adapted from Ha[26] and Cooney *et al.*[22])

Disease classification	Clinical features
Severe disease	Diarrhoea frequency > 6 stools per 24 hours with blood
	Temperature > 37.5 °C
	Tachycardia > 90 b.p.m.
	Anaemia (< 75% of normal value)
	Erythrocyte sedimentation rate > 30 mm per hour
Moderate disease	Values ranging between mild and severe
Mild disease	Diarrhoea < 4 stools per 24 hours, intermittently or non-bloody
	No fever
	No tachycardia
	Normal haemoglobin
	Erythrocyte sedimentation rate ≤ 30 mm per hour

b.p.m., beats per minute.

Mayo score

The Mayo score assesses patients' disease in relation to four components: (1) stool frequency; (2) rectal bleeding; (3) endoscopic findings; and (4) physician's global assessment[24] (*Table 2*). Full Mayo scores range from 0 to 12 points, with scoring increasing with disease severity. The partial Mayo score, which comprises the non-endoscopic elements of the full Mayo score (i.e. stool frequency, rectal bleeding and physician's global assessment), has been reported to have reasonable correlation with the full Mayo score (Spearman's correlation coefficient $\rho = 0.70$). Partial Mayo scores range from 0 to 9 points.[27]

Paediatric Ulcerative Colitis Activity Index

The PUCAI was developed with the aim of providing a non-invasive assessment instrument for use in paediatric practice and is based on measures of abdominal pain, rectal bleeding, stool consistency, stool frequency, nocturnal stools and activity level (*Table 3*). The tool has been described as showing good correlation with physician's global assessment (Pearson's $r = 0.91$; $p < 0.001$), full Mayo scores ($r = 0.95$; $p < 0.001$) and endoscopic subscores ($r = 0.77$; $p < 0.001$).[25]

TABLE 2 Features of the Mayo score (adapted from Ha[26] and Cooney *et al.*[22])

Mayo score features	
Stool frequency	
0	Normal stool frequency for patient
1	1–2 stools more than usual
2	3–4 stools more than usual
3	≥ 5 stools more than usual
Rectal bleeding	
0	No blood
1	Streaks of blood < 50% of time with stool
2	Obvious blood most of time with stool
3	Blood alone passed
Endoscopic findings[a]	
0	Normal/inactive disease
1	Mild disease (erythema, decreased vascular pattern, mild friability)
2	Moderate disease (marked erythema, lack of vascular pattern, friability, erosions)
3	Erosions
Physician's global assessment	
0	Normal
1	Mild
2	Moderate
3	Severe

a Not included in partial Mayo score assessments.

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TABLE 3 Features of the PUCAI (adapted from Ha[26])

Variable	Points scored
Abdominal pain	
Absent	0
Able to be ignored	5
Not able to be ignored	10
Rectal bleeding	
None	0
Small amount (< 50%) of stools	10
Small amount with most stools	20
Large amount (> 50%) of stools	30
Stool consistency	
Formed	0
Partially formed	5
Completely loose	10
Stool frequency (in 24 hours)	
0–2	0
3–5	5
6–8	10
≥ 9	15
Nocturnal stools	
Absent	0
Present	10
Activity level	
No limitations	0
Occasional limitations	5
Severe limitations	10

Current service provision

Clinical guidelines

As outlined in National Institute for Health and Care Excellence (NICE) Clinical Guideline 166,[1] conventional treatment options for moderately to severely active (non-systemic) UC include the use of oral or topical aminosalicylates, corticosteroids and/or immunosuppressants. Recommended conventional treatment options can vary according to the extent and location of colitis. Colectomy may be considered in the event of inadequate control of symptoms and/or poor HRQoL on conventional drug treatment.

Current NICE Technology Appraisal Guidance

Three NICE Technology Appraisals have previously been undertaken.[28–30] Infliximab (IFX) [Remicade®, Merck Sharp & Dohme Ltd (MSD)] was not previously recommended by NICE for the treatment of 'subacute' manifestations of moderately to severely active UC (NICE Technology Appraisal Guidance 140).[28] NICE Technology Appraisal 262 was terminated as no evidence submission was provided by the manufacturer.[29] NICE Technology Appraisal Guidance 163 recommended the use of IFX as an option for the treatment of

acute exacerbations of severely active UC only in patients for whom ciclosporin is contraindicated or clinically inappropriate.[30]

Current service cost

Cohen *et al.*[31] reports estimates of the direct and indirect costs of UC within the USA and Europe based on a systematic review of published cost studies. Cohen reports estimated annual per-patient direct medical costs of UC of between €8949 and €10,395 in Europe (2008 currency values). The study authors note that hospitalisations associated with UC accounted for 41–55% of direct medical costs. Indirect costs are also reported to be substantial, accounting for between 54% and 68% of total costs in Europe. The total economic burden of UC in Europe was estimated to be in the range of €12.5B to €29.1B.

Variation in services and uncertainty about best practice

The optimal treatment duration using IFX, adalimumab (ADA) (Humira®, AbbVie) and golimumab (GOL; Simponi®, MSD) is not yet known. The safety and efficacy of the readministration of interventions following an interruption of treatment has not been fully established. Furthermore, the maintenance of clinical remission following the withdrawal of biological treatment in responding patients is also unclear. There is no randomised controlled trial (RCT) evidence for the efficacy and safety of switching to a second biological intervention in patients who are primary or secondary non-responders, or in patients who are intolerant to a first biological intervention.

Current treatment pathway

There does not exist a universally agreed pathway for the second-line treatment of patients with moderate to severe UC. Treatments received by patients may be influenced by the severity of symptoms, the extent and location of inflammation, clinical advice and individual patient choice. Treatments may include a combination of aminosalicylates [5-aminosalicylates (5-ASAs) – sulfasalazine, mesalazine/mesalamine, balsalazide and olsalazine], corticosteroids (beclomethasone, budesonide, hydrocortisone or prednisolone), and thiopurines [6-mercaptopurine (6-MP) or azathioprine (AZA)], calcineurin inhibitors and surgical intervention (colectomy). The care of people with UC is usually shared between primary care and specialist gastroenterology units working in collaboration with specialist colorectal surgical units.[1] *Figure 1* presents a simplified pathway of the main types of treatments used for the management of patients with moderately to severely active UC 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 against, such therapies.

Induction and maintenance of response

Current medical treatments for UC are principally concerned with treating active disease to address symptoms of urgency, frequency of defecation and rectal bleeding to improve the patient's HRQoL and, thereafter, to maintain remission.[1] Treatment usually follows an escalation approach whereby additional drugs are added in order to induce and subsequently maintain response/remission. Initially, patients would most likely be treated using oral and topical 5-ASAs to induce a response. Most commonly, oral 5-ASA treatment involves high-dose oral mesalazine (usually 2.4–4.8 g/day depending on the particular product used). A dose of up to 2.4 g/day of mesalazine is used for maintenance. It is very likely that topical 5-ASAs (enemas or suppositories) would also be used during induction; the use of topical 5-ASAs is time-limited (usually a maximum of 4 weeks) and their efficacy is dependent on the extent of disease and severity of symptoms. If the patient does not respond or achieves but subsequently loses a response, or is contraindicated to or unable to tolerate 5-ASAs, treatment is likely to involve the use of oral corticosteroids and immunomodulators. Oral corticosteroids (most likely prednisolone) would be used as a short-term therapy with the intention of inducing a response; however, corticosteroids are not used as a maintenance treatment. Prednisolone is typically given at a dose of 40 mg/day, with the aim of the dose being tapered by 5 mg each week (8 weeks of treatment until the dose is zero). Treatment using immunomodulators, most commonly AZA and less commonly 6-MP, would be started at the same time as oral corticosteroids. These are indicated for maintenance rather than induction of response; hence patients may receive them on a long-term basis. Patients would likely remain on oral 5-ASA treatment continuously as they may

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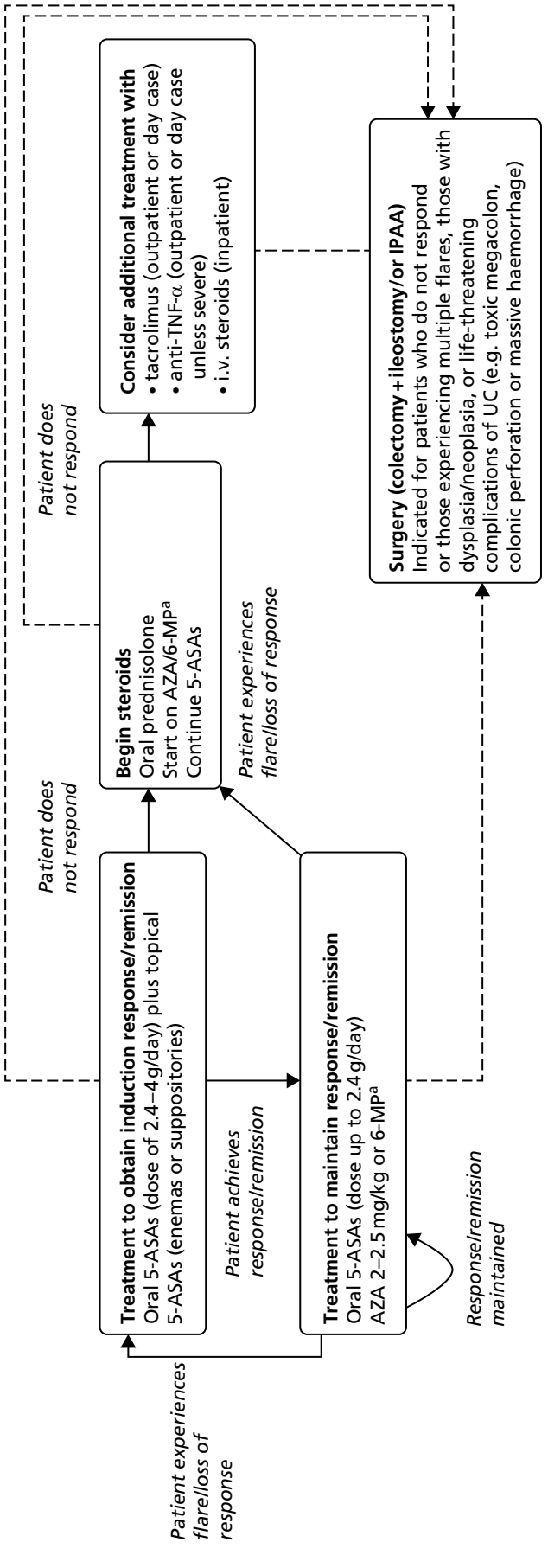

FIGURE 1 Treatment pathway for moderate to severe UC. Anti-TNF-α; anti-tumour necrosis factor alpha; IPAA, ileal pouch anal anastomosis; i.v. intravenous. a, steroids (oral prednisolone) are indicated for inducing response/remission. AZA and 6-MP are indicated as maintenance treatments in patients with two or more flares requiring systemic steroids, for whom it is not possible to taper steroids, or following acute severe attack. AZA and 6-MP would be started at the same time as oral prednisolone.

confer other benefits in avoiding cancer, although evidence is conflicting in this respect.[32] If the patient does not respond to corticosteroids, it is likely that the patient would be considered for treatment using tacrolimus, intravenous (i.v.) steroids or anti-tumour necrosis factor alpha (anti-TNF-α) therapy.

Surgery may be required in emergency scenarios (e.g. in cases of acute severe/fulminant UC) but within the moderately to severely active population, surgery is most likely to be elected by the individual patient. Emergency surgery may be required to ameliorate life-threatening complications of UC, such as toxic megacolon, colonic perforation and massive haemorrhage; it should be noted that surgery might also be used prophylactically to avoid the onset of these complications. More commonly, surgery is elective and is undertaken for severe disease characterised by prior treatment failures and/or frequent UC flares. In some cases, surgery may also be indicated owing to the increased risk of colorectal cancer associated with long-standing UC and may also be driven by the identification of pre-malignant dysplasia or malignant neoplasia. Colectomy is associated with post-operative morbidity and a risk of death. Among others, complications of surgery may include infertility, transient and chronic pouchitis, wound infections, wound dehiscence and small bowel obstruction.[1]

Patients with less severe disease may be managed either in primary or secondary care. For patients with left-sided or extensive UC, follow-up is likely to take place in an outpatient setting, with appointments every 3–12 months depending on the pattern of flares. Follow-up may be consultant-led or IBD nurse-led, but will usually involve a combination of both.

Description of technology under assessment

Interventions considered in the scope of this report

Three interventions are considered for the adult population (IFX, ADA and GOL). Only IFX is licensed for use in children and adolescents. Two biosimilars (Remsima®, Celltrion Healthcare, and Inflectra®, Hospira) are also considered as part of the evidence base for IFX. Interventions are assessed in line with licensed indications, as described in the respective Summary of Product Characteristics (SmPCs) for each intervention.[33–35] The interventions under assessment are licensed for the treatment of rheumatoid arthritis (RA), adult CD (IFX and ADA only), paediatric CD (IFX and ADA only), adult UC, paediatric UC (IFX only), ankylosing spondylitis (AS), psoriatic arthritis and psoriasis (IFX and ADA only).[33–35]

Mode of action

Infliximab, ADA and GOL are monoclonal antibodies that inhibit the activity of TNF-α, a key component in the inflammation process.

Marketing licence and administration method

Infliximab

Infliximab has a UK marketing authorisation for the treatment of moderately to severely active UC in adults who have had an inadequate response to conventional therapy including corticosteroids and mercaptopurine or AZA, or who are intolerant to, or have medical contraindications against, such therapies.[33] IFX also has a UK marketing authorisation for the treatment of severely active UC in children and adolescents aged 6 to 17 years, who have had an inadequate response to conventional therapy including corticosteroids and mercaptopurine or AZA, or who are intolerant to or have medical contraindications against such therapies.[33]

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Infliximab for the treatment of UC is administered by i.v. infusion at a dosage of 5 mg/kg followed by additional 5-mg/kg infusion doses at 2 and 6 weeks after the initial infusion, then every 8 weeks thereafter.[33] The SmPC states that other concomitant therapies (e.g. corticosteroids and immunosuppressants) should be optimised during IFX therapy.[33] IFX is typically administered intravenously over a 2-hour period as an outpatient or day-case appointment. As IFX treatment is associated with the development of acute infusion reactions, all patients receiving IFX are required to be observed, in a setting where emergency equipment is available, during the infusion for 1–2 hours post infusion for safety. Patients may receive pre-infusion treatment with, for example, an antihistamine, hydrocortisone and/or paracetamol. Contraindications to IFX treatment include a history of hypersensitivity to IFX or other murine proteins, the presence of tuberculosis (TB) or other severe infections such as sepsis, abscesses, and opportunistic infections, and moderate or severe heart failure. Furthermore, women of childbearing potential must use adequate contraception and continue use for at least 6 months after last receipt of IFX treatment.

Biosimilar versions of IFX (Remsima and Inflectra) are licensed for the same indications as Remicade. The therapeutic indications (including the wording of the licensed indication), dosage and method of administration for Remsima and Inflectra are identical to those for IFX (Remicade).

Adalimumab

Adalimumab has a UK marketing authorisation for the treatment of moderately to severely active UC in adults who have had an inadequate response to conventional therapy including corticosteroids and mercaptopurine or AZA, or who are intolerant to, or have medical contraindications against, such therapies.[34] ADA for the treatment of UC is administered subcutaneously according to an induction dose regimen of 160 mg at week 0 and 80 mg at week 2 followed by a recommended maintenance dosage of 40 mg every other week (increased to 40 mg every week if clinical response is insufficient).[34] Following physician advice, appropriate training and medical follow-up if required, patients may self-inject with ADA. The SmPC states that other concomitant therapies (e.g. corticosteroids and immunosuppressants) should be optimised during ADA therapy.[34] Contraindications to ADA treatment include hypersensitivity to the active substance, the presence of active TB or other severe infections such as sepsis and opportunistic infections, and moderate to severe heart failure [New York Heart Association (NYHA) class III/IV]. The administration of ADA during pregnancy is not recommended.

Golimumab

Golimumab has a UK marketing authorisation for the treatment of moderately to severely active UC in adults who have had an inadequate response to conventional therapy, including corticosteroids and mercaptopurine or AZA, or who are intolerant to, or have medical contraindications against, such therapies.[35]

Golimumab for the treatment of UC is administered subcutaneously according to body weight. Patients with body weight < 80 kg receive an initial dose of 200 mg, followed by 100 mg at week 2, then 50 mg every 4 weeks thereafter. Patients with body weight ≥ 80 kg receive an initial dose of 200 mg, followed by 100 mg at week 2, then 100 mg every 4 weeks thereafter.[35] Following physician advice and adequate training, patients may self-inject with GOL. Contraindications to GOL include hypersensitivity to the active substance, the presence of active TB or other severe infections such as sepsis, opportunistic infections, and moderate or severe heart failure (NYHA class III/IV). The use of GOL during pregnancy is not recommended.

Criteria for continuing treatment

The SmPC for each intervention describes the use of stopping rules for treatment in non-responders.[33–35]

The SmPC for IFX states that clinical response should typically be achieved within 14 weeks of treatment (i.e. three doses) and that continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within 14 weeks. The SmPC also indicates that, for paediatric patients, there is no evidence to support the further use of IFX in patients who do not respond within the first 8 weeks of treatment.

For ADA, the SmPC states that clinical response should be reached within 2–8 weeks of treatment and that treatment should not be continued in patients who fail to respond within this time frame.

The SmPC for GOL states that clinical response is expected to be achieved within 12–14 weeks of treatment (i.e. after four doses) and that continued therapy should be reconsidered in patients who do not experience therapeutic benefit within this time period.

The SmPCs for each intervention also refer to the requirement to monitor patients closely for infections and to discontinue treatment in patients who develop a serious infection or sepsis.

Current usage in the NHS

Infliximab is currently recommended by NICE as an option for the treatment of acute exacerbations of severely active UC, only in patients in whom ciclosporin is contraindicated or clinically inappropriate. ADA and GOL do not have recommendations from NICE for use in the treatment of UC. The Assessment Group has received clinical advice to suggest that IFX, and to a lesser degree ADA, are currently used for the treatment of moderate to severe UC in some larger centres in England and Wales.

Identification of important subgroups

The only subgroup pre-specified in the final NICE scope[36] relates to duration of disease.

Anticipated costs associated with interventions

Table 4 summarises the costs associated with the interventions based on their list prices.[37]

TABLE 4 Acquisition costs associated with IFX, ADA and GOL

Drug	Unit type and dose	Price per unit
IFX	Powder for reconstitution, 100-mg vial	£419.62
ADA	40-mg pre-filled pen or pre-filled syringe, 40-mg/0.8-ml vial	£352.14
GOL	50-mg pre-filled pen or pre-filled syringe	£762.97
	100-mg pre-filled pen	£1525.94

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Chapter 2 Definition of the decision problem

Decision problem

The aim of this assessment is to evaluate the clinical effectiveness and cost-effectiveness of IFX, ADA and GOL for the treatment of patients with moderately to severely active UC after the failure of conventional therapy.

Interventions

Three interventions are considered within this assessment: IFX (Remicade), ADA (Humira) and GOL (Simponi). These interventions are described in detail in *Chapter 1, Description of technology under assessment*. Biosimilar versions of IFX (Remsima and Inflectra) are also licensed for the same indications and are considered as part of the evidence base for IFX within this assessment report.

Populations (including subgroups)

The assessment considers the following two populations:

1. Adults aged ≥ 18 years with moderately to severely active UC who have had an inadequate response to conventional therapy including corticosteroids and mercaptopurine or AZA, or who are intolerant to, or have medical contraindications against, such therapies.
   As referred to in the final NICE scope,[36] severity of disease in adults would be defined according to the modified Truelove and Witts' severity index (as described in NICE Clinical Guideline 166).[1]
   The following interventions are indicated for use in adults:

   i. ADA
   ii. IFX
   iii. GOL.

2. Children and adolescents aged 6–17 years (inclusive) with severely active UC, who have had an inadequate response to conventional therapy including corticosteroids and mercaptopurine or AZA, or who are intolerant to, or have medical contraindications against, such therapies.
   As described in NICE Clinical Guideline 166,[1] severity of UC in children and adolescents was to be assessed using the PUCAI.[25]
   The following intervention is indicated for use in children and adolescents:

   i. IFX.

The final NICE scope[36] highlighted duration of disease as a potential subgroup of interest; this is examined according to the availability of evidence.

Populations outside of the scope of the appraisal

The following groups were considered to be beyond the scope of the appraisal and, therefore, are not considered in this assessment report:

- children with mildly or moderately active UC (as defined by the PUCAI measure)
- adults with mildly active UC (as defined by the modified Truelove and Witts' criteria)
- adults and children with acute severe (systemic) UC.

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Relevant comparators

The interventions are compared against each other. Other relevant comparators include standard clinical management options, which (as described in the final NICE scope[36]) could include a combination of aminosalicylates (sulfasalazine, mesalazine, balsalazide or olsalazine), corticosteroids (beclomethasone, budesonide, hydrocortisone or prednisolone), thiopurines (mercaptopurine or AZA), calcineurin inhibitors or elective surgical intervention.

Emergency surgical intervention is not considered as a comparator in this assessment as acute severe UC was stated in the final scope as being beyond the remit of the appraisal.

Outcomes

The outcome measures to be considered included:

- mortality
- measures of disease activity
- rates of and duration of response, relapse and remission
- rates of hospitalisation
- rates of surgical intervention (both elective and emergency)
- time to surgical intervention (both elective and emergency)
- adverse events (AEs) of treatment (including leakage and infections following surgery)
- HRQoL.

Following discussions during the NICE appraisal scoping process, data relating to mucosal healing were not considered eligible for this assessment.

Overall aims and objectives of assessment

This assessment addresses the question 'what is the clinical effectiveness and cost-effectiveness of IFX, ADA and GOL for the treatment of patients with moderately to severely active UC after the failure of conventional therapy as compared against each other and standard clinical management?'.

More specifically, the objectives of the assessment are:

1. to evaluate the clinical effectiveness of each intervention
2. to examine the effect of disease duration on the clinical effectiveness of each intervention (subject to the availability of evidence)
3. to evaluate the adverse effect profile of each intervention
4. to evaluate the incremental cost-effectiveness of each intervention compared (1) against each other and (2) against all comparators (including medical and surgical options)
5. to estimate the expected net budget impact associated with implementing each intervention
6. to identify key areas in which future research may be valuable.

Chapter 3 Assessment of clinical effectiveness

A systematic review of the literature including network meta-analyses (NMAs) was conducted in order to evaluate the clinical effectiveness and safety of IFX, ADA and GOL in the treatment of moderately to severely active UC after the failure of conventional therapy.

The systematic review of clinical effectiveness was undertaken in accordance with the general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[38]

Methods for reviewing clinical effectiveness

The protocol for this review is registered with PROSPERO (CRD42013006883).[39]

This report contains reference to confidential information provided as part of the NICE appraisal process. This information has been removed from the report and the results, discussions and conclusions of the report do not include the confidential information. These sections are clearly marked in the report.

Identification of studies

A comprehensive search was undertaken to systematically identify literature relating to the clinical effectiveness and safety of IFX, ADA and GOL for treating moderately to severely active UC after the failure of conventional therapy. The search strategy comprised the following main elements:

- searching of electronic databases
- hand-searching bibliographies of retrieved papers, key journals and conference proceedings
- contact with experts in the field.

The following electronic databases were searched from inception for published trials and systematic reviews:

- MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations: via Ovid – 1946 to December 2013.
- EMBASE: via Ovid – 1974 to December 2013.
- Cochrane Library: via Wiley Interscience
    - Cochrane Database of Systematic Reviews (CDSR) – 1996 to December 2013
    - Database of Abstracts of Reviews of Effects (DARE) – 1995 to December 2013
    - Cochrane Central Register of Controlled Trials (CCRT) – 1995 to December 2013
    - Cochrane Methodology Register – 1904 to December 2013
    - Health Technology Assessment (HTA) database – 1995 to December 2013.
- Cumulative Index to Nursing and Allied Health Literature (CINAHL): via EBSCO*host* – 1982 to December 2013.
- Web of Science Citation Index: via Web of Knowledge – 1900 to December 2013.
- Conference Proceedings Citation Index: via Web of Knowledge – 1990 to December 2013.
- Bioscience Information Service (BIOSIS) Previews: via Web of Knowledge – 1969 to December 2013.

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The MEDLINE search strategy is presented in *Appendix 1*. The search strategy combined free text and medical subject headings (MeSHs) or thesaurus terms relating to UC, with free text and MeSHs or thesaurus terms relating to IFX, ADA or GOL combined with highly sensitive filters to retrieve RCTs and systematic reviews. Search terms for IFX biosimilars were also included. The search strategy was translated across all databases. No date or language restrictions were applied. Literature searches were conducted during December 2013. References were collected in a bibliographic management database and duplicates were removed.

Searches were undertaken to identify unpublished studies (nearing or at completion) relevant to the decision problem within the following research registers:

- ClinicalTrials.gov (searched December 2013)
- UK Clinical Research Network Portfolio database (searched December 2013)
- World Health Organization International Clinical Trials Registry Platform (searched March 2014).

Proceedings of the following conferences were searched from 2009 to 2014 (when possible) for recent research:

- Congress of Crohn's and Colitis Conference, European Crohn's and Colitis Organisation (ECCO)
- Digestive Disease Week
- Gut (British Society of Gastroenterology).

Key journals were identified using the PubMed PubReMiner facility and electronic tables of contents were searched from March 2013 to February 2014 for the following journals:

- *Inflammatory Bowel Diseases*
- *Alimentary Pharmacology & Therapeutics*
- *Gastroenterology*
- *Journal of Crohn's and Colitis*
- *American Journal of Gastroenterology*.

Citation searches were performed on included studies in Web of Science in March 2014.

Manufacturers' submissions received by NICE, as well as any relevant systematic reviews, were also hand-searched in order to identify any further potentially relevant clinical trials.

Inclusion and exclusion criteria

Inclusion and exclusion criteria were based on the final NICE scope[36] and were applied as described below.

Study selection

The selection of eligible articles was undertaken using a two-stage process. First, in order to assess agreement in the sifting approach between systematic reviewers, a check for consistency was conducted in the early stages of the sifting process. The reviewers (RA and MMSJ) double-sifted a total of 940 titles and abstracts. Kappa statistics of 0.888 and 1.000 were obtained, indicating very high strength of agreement.

All remaining titles and abstracts were examined for inclusion by one reviewer (either RJA or MMSJ sifted 50% of total citations at title and abstract level). Any citations that clearly did not meet the inclusion criteria (e.g. animal studies, studies unrelated to UC) were excluded. During the second stage of the sifting process, full-text articles were examined for inclusion by one reviewer (RJA or MMSJ). Any uncertainty in the eligibility of potentially relevant full-text articles was resolved through discussion. Trials retrieved for full-paper screening which were subsequently excluded were tabulated (see *Appendix 2*) together with justification for their exclusion.

Inclusion criteria

Studies were included in the review if they met the inclusion criteria outlined below.

Interventions

Any of the following interventions were included:

i. For adults (defined by the Assessment Group as aged ≥ 18 years):

- ADA
- IFX
- GOL.

ii. For children and adolescents aged 6–17 years (inclusive):

- IFX.

Biosimilar versions of IFX (Remsima and Inflectra) are also licensed for the same indications as Remicade and have been considered as part of the evidence base for IFX within this assessment.

Studies in which the interventions were assessed in line with licensed indications were included in the systematic review.

Populations

i. Adults aged ≥ 18 years with moderately to severely active (non-systemic) UC (defined as patients with moderately active disease according to the modified Truelove and Witts' criteria[23]) whose disease has responded inadequately to conventional therapy including corticosteroids and mercaptopurine or AZA, or who are intolerant of, or have medical contraindications to, such therapies.
ii. Children and adolescents aged 6–17 years with severely active (non-systemic) UC (as classified by the PUCAI measure[25]) whose disease has responded inadequately to conventional therapy including corticosteroids and mercaptopurine or AZA, or who are intolerant to, or have medical contraindications to, such therapies.

Comparators

Relevant comparators included in the final NICE scope were (1) interventions as defined in the protocol for this assessment (i.e. IFX, ADA or GOL compared with each other) and (2) standard clinical management, which may include a combination of aminosalicylates (sulfasalazine, mesalazine/mesalamine, balsalazide or olsalazine), corticosteroids (beclomethasone, budesonide, hydrocortisone or prednisolone), thiopurines (mercaptopurine or AZA), calcineurin inhibitors or elective surgical intervention.

It should be noted that although calcineurin inhibitors (tacrolimus and ciclosporin) were included as potential comparators in the final NICE scope, these options were excluded from the assessment for two reasons:

1. They are treatments typically reserved for patients with acute severe disease. This differs to the population within the final NICE scope. Studies were specifically excluded if they related to these patients (see *Exclusion criteria*).
2. There are no direct data comparing biologicals versus calcineurin inhibitors for the population under investigation. Altogether, there are very limited data on the efficacy of either ciclosporin or tacrolimus in this indication.

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Outcomes

Eligible outcomes for consideration were:

- mortality
- measures of disease activity
- rates of and duration of response, relapse and remission
- rates of hospitalisation
- rates of surgical intervention (both elective and emergency)
- time to surgical intervention (both elective and emergency)
- AEs of treatment (including leakage and infections following surgery)
- HRQoL.

Following discussions during the NICE appraisal scoping process, data relating to mucosal healing were not considered eligible for this assessment.

Study design

Randomised controlled trials were eligible for inclusion in the systematic review of clinical effectiveness. Long-term extension studies associated with included RCTs were also included in the review.

Studies published as abstracts or conference presentations were eligible for inclusion only if sufficient details were presented to allow an assessment of the trial methodology and results to be undertaken.

Exclusion criteria

The following types of studies were excluded from the review:

- Studies that included adults with mildly active UC (as defined by the modified Truelove and Witts' criteria[23]), for which no separate data were reported for patients with moderate to severe UC.
- Studies that included children with mildly or moderately active UC (as defined by the PUCAI measure[25]).
- Studies that included adults with (acute) severely active UC as defined by the modified Truelove and Witts' criteria[23] (representing patients who are systemically ill and are, therefore, beyond the remit of this appraisal).
- Studies that included adults, adolescents or children with acute severe UC, whose disease is systemic as shown by tachycardia, fever, anaemia or a raised erythrocyte sedimentation rate (representing patients who are excluded as they are outside the remit of this appraisal).
- Studies that included patients with acute severe UC previously hospitalised and treated with i.v. steroids (representing patients in a potentially life-threatening medical emergency and excluded as they are outside the remit of this appraisal).
- Studies that included patients with IBD other than UC (e.g. CD) for which data were not reported separately for UC patients.
- Studies that interventions were not administered in accordance with licensed indications.
- Systematic reviews and clinical guidelines (selected systematic reviews identified by the clinical effectiveness searches were used as sources of references).
- Studies that were published only in languages other than English.
- Studies based on animal models.
- Pre-clinical and biological studies.
- Narrative reviews, editorials and commentaries.
- Reports published as abstracts or conference presentations only, for which insufficient details were reported to allow an assessment of study quality or results.

Data abstraction strategy

Data relevant to the decision problem were extracted by one reviewer (RA or MMSJ). Data were extracted without blinding to authors or journal. A data extraction form was developed and piloted on two included trials before slight revisions and final use on all included trials. Data relating to study arms in which the intervention treatments were administered in line with their licensed indications were extracted; data

relating to the unlicensed use of the interventions were not extracted. All extracted data were double-checked by a second reviewer (MMSJ or CC). The safety data extracted were informed by the SmPCs for each product [available from www.medicines.org.uk/emc/ (accessed 26 May 2014)].[33–35] The key safety issues included such items as the number of patients experiencing infections, number of patients experiencing serious infections, number of patients experiencing malignancy and the occurrences of infusion-related or injection site reactions (as appropriate to the mode of administration for each intervention). Study results that were presented only in graphical format were digitised and estimated using Engauge software version 4.1 [http://sourceforge.net/projects/digitizer/files/Engauge%20Digitizer/digitizer-4.1/ (accessed April 2014)]. When multiple publications of the same study were identified, data extraction was undertaken on all relevant associated publications and findings were presented together with reference to their published source.

Critical appraisal strategy

The methodological quality of each included study was assessed by one reviewer (RJA or MMSJ). The quality of included studies was assessed using the Cochrane Risk of Bias Tool.[40] This tool addresses specific domains, namely sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective outcome reporting. RCTs were classified as being at 'high risk' of attrition bias where drop-out in any treatment arm was $\geq 10\%$.[41] The Assessment Group requested the trial protocols for all included trials from the manufacturers of the products included in this appraisal. These were received for some trials and were used alongside clinical study reports (CSRs) provided by the manufacturer for some trials and outcomes listed in ClinicalTrials.gov records in order to inform the selective reporting domain of the Cochrane Risk of Bias Tool. All quality assessment findings were double-checked by a second reviewer (RJA or MMSJ).

Methods of data synthesis

The extracted data were presented for each study, both in structured tables and as a narrative description.

Methods for the estimation of efficacy using network meta-analysis

Network meta-analysis methods are described in full on page 69.

Supplementary meta-analyses

When considered appropriate, secondary outcomes of interest were analysed using classical meta-analysis methods. Meta-analysis was undertaken using Cochrane Review Manager software (version 5.2; The Cochrane Collaboration, Copenhagen, Denmark). Outcomes reported as continuous data were estimated using a mean difference with 95% confidence intervals (CIs). Dichotomous outcomes were estimated as risk ratios (RRs) with associated 95% CIs. When RCTs reported AEs in sufficient detail, these were analysed as dichotomous data. Clinical heterogeneity across RCTs (the degree to which RCTs appear different in terms of participants, intervention type and duration and outcome type) was considered prior to data pooling. Random-effects models were applied and effect estimates, estimated in Review Manager as *z*-values, were considered statistically significant at a cut-off point of $p < 0.05$.

Results

Quantity of research available

The searches described in *Identification of studies* yielded 7774 potentially relevant citations (7602 from searches of electronic databases after removal of duplicates), three from hand-searching of key journals, one from sponsor submissions and 168 from trial register searches). Of these records, 7546 were excluded at the title and abstract stage. Full texts of 228 studies were obtained for scrutiny and of these, 181 citations were excluded (it was not possible to obtain nine studies and hence these were excluded; see *Appendix 2*).

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No additional eligible trials that were completed or nearing completion were identified through the trial register searches. Trial NCT01551290 [a study of IFX vs. placebo (PBO) in Chinese subjects by Xian-Janssen Pharmaceutical Ltd[42]] was stated to be ongoing with an estimated completion date of November 2014. Trial NCT01863771 (a study of GOL maintenance treatment vs. PBO in Japanese patients by Janssen Pharmaceutical[43]) was recruiting as of February 2014. As such, neither trial was judged to be completed or nearing completion.

A total of 47 citations relating to 10 RCTs were included in the review.[44–52] The search process is summarised in the form of a PRISMA diagram in *Figure 2*.

European Public Assessment Reports (EPARs) were available for all included interventions; however, associated Food and Drug Administration (FDA) reports for interventions could not be identified from the FDA website (www.fda.gov/drugs/).

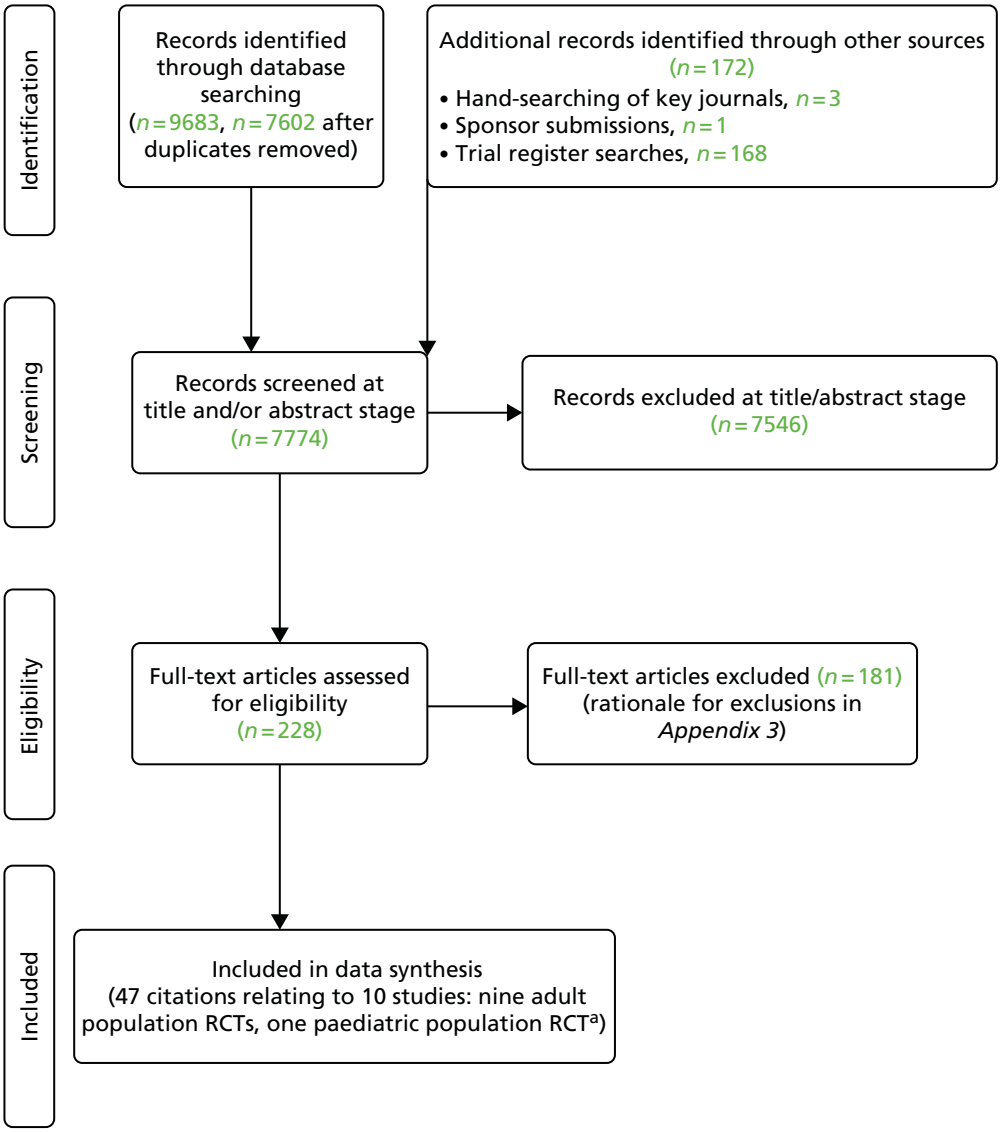

FIGURE 2 Flow diagram of study inclusion (adapted from PRISMA).[53] a, Not including sponsor submissions and European Public Assessment Reports.

Summary of study and population characteristics of included trials

Study characteristics

The available comparisons between licensed doses of interventions and PBO are tabulated within the adult population RCTs in *Table 5*. The trial design characteristics of the included trials are outlined in *Tables 6* and *7*. The outcome measures pre-specified in the final NICE scope[36] and protocol were all addressed by the included trial evidence, with the exception of rates of relapse. As stated in *Methods for reviewing clinical effectiveness*, data relating to mucosal healing were not eligible for this assessment.

Population: adults aged ≥ 18 years with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who are intolerant to, or have medical contraindications against, such therapies

A total of nine relevant RCTs were identified which were performed in adult populations. Four RCTs evaluated the use of IFX [Active Ulcerative Colitis Trial (ACT)1,[49] ACT2,[49] Probert *et al.*[50] and UC-SUCCESS[51]], three RCTs were of ADA [Ulcerative colitis Long-Term Remission and maintenance with Adalimumab treatment of moderate to severe ulcerative colitis (ULTRA)1,[44] ULTRA2,[45] and Suzuki *et al.*, 2014[46]] and two RCTs were of GOL [Program of Ulcerative Colitis Research Studies Utilizing an Investigational Treatment (PURSUIT)-SC,[47] PURSUIT-Maintenance[48]]. Four of these RCTs (ACT1,[49] ACT2,[49] ULTRA1,[44] and ULTRA2[45]) had long-term open-label extension studies associated with them (ACT1 and ACT2 extension studies,[55] ULTRA3[54]) that were also included as part of the evidence for these interventions. All of the included RCTs for adults were undertaken against a comparator of PBO, with the exception of UC-SUCCESS[51] which assessed the use of IFX against active comparators of AZA and combination IFX/AZA. No head-to-head RCTs comparing interventions of interest against each other were identified for adults. All RCTs were Phase III (if stated), with the exception of Suzuki *et al.*[46] (Phase II/III) and PURSUIT-SC[47] (Phase II/III). If stated, all included adult population trials were powered for the primary end points of clinical remission (ULTRA1,[44] ULTRA2,[45] Probert *et al.*,[50] UC-SUCCESS[51]) or clinical response (ACT1,[49] ACT2,[49] PURSUIT-SC,[47] PURSUIT-Maintenance[48]). Where the geographical location(s) of study sites were reported, all trials were multicentre, international studies, with the exception of Probert *et al.*,[50] which was performed in the UK and Germany, and Suzuki *et al.*,[46] which was conducted exclusively in Japan. All trials were at least partly industry funded.

TABLE 5 Licensed dose comparisons for included adult population RCTs

Trial	Licensed treatment comparisons
ULTRA1[44]	PBO; 160 mg/80 mg of ADA (licensed induction dose)
ULTRA2[45]	PBO; 160 mg of ADA at week 0, 80 mg at week 2 and then 40 mg every other week (licensed maintenance dose) beginning at week 4
Suzuki *et al.*[46]	PBO; 160 mg/80 mg of ADA (licensed induction dose)
PURSUIT-SC[47]	PBO; 200 mg/100 mg of GOL (licensed induction dose)
PURSUIT-Maintenance[48]	PBO; 50 mg of GOL; 100 mg of GOL (licensed maintenance doses)
ACT1[49]	PBO; 5 mg/kg of IFX
ACT2[49]	PBO; 5 mg/kg of IFX
Probert *et al.*[50]	PBO; 5 mg/kg of IFX
UC-SUCCESS[51]	No PBO; 5 mg/kg of IFX; AZA; IFX5 mg/kg/AZA

ACT1, Active Ulcerative Colitis Trial 1; ACT2, Active Ulcerative Colitis Trial 2; PURSUIT, Program of Ulcerative Colitis Research Studies Utilizing an Investigational Treatment; ULTRA, Ulcerative colitis Long-Term Remission and maintenance with Adalimumab treatment of moderate to severe ulcerative colitis.

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TABLE 6 Trial design characteristics of included clinical effectiveness studies in adults

Trial identifier (NCT number), primary publication details	Trial design	Inclusion/exclusion criteria	Geographical location of study sites	Treatment groups and numbers randomised	Open label escape allowance	Primary outcome	Assessment of induction	Assessment of maintenance	Study sponsor
ADA									
ULTRA1 (NCT00385736, M06–826), Reinisch *et al.*, 2011[44]	Multicentre, randomised, double-blind, PBO-controlled trial. Phase III	Inclusion: adult ambulatory patients, moderately to severely active UC, Mayo score of 6–12 points with endoscopy subscore of 2–3, despite concurrent and stable treatment with oral CSs and/or immunomodulators. Concurrent therapy not required if failed to respond/could not tolerate previous CS/immunomodulator treatment. Exclusion: ulcerative proctitis, previous receipt of anti-TNF agent or biological agent, receipt of i.v. CSs within 14 days prior to screening/during screening; receipt of ciclosporin, tacrolimus, mycophenolate mofetil, or methotrexate within 60 days of baseline	USA, Puerto Rico, Canada, Western Europe, and Eastern Europe. 94 study centres: (USA, 34; Puerto Rico, 3; Canada, 5; Western Europe, 32; and Eastern Europe, 20)	Original study protocol: ADA 160 mg/80 mg s.c. = 93 randomised, PBO s.c. = 93 randomised Protocol amended to include ADA 80 mg/40 mg group ADA 160 mg/80 mg s.c. = 130 randomised ADA 80 mg/40 mg s.c. = 130 randomised PBO s.c. = 130 randomised ADA 160 mg/80 mg group received ADA 160 mg at week 0, ADA 80 mg at week 2, ADA 40 mg at weeks 4 and 6 ADA 80 mg/40 mg group received ADA 80 mg at week 0, ADA 40 mg at week 2 and ADA 40 mg at weeks 4 and 6 PBO group received same number of s.c. injections as patients in ADA treatment groups	No	Clinical remission (Mayo score of ≤2 with no individual subscore of >1) at week 8 assessed in the ITT-A3 (amendment) population	Week 8. Included in NMA? Yes	NA. Included in NMA? No (8-week study)	Abbott

Trial identifier (NCT number), primary publication details	Trial design	Inclusion/exclusion criteria	Geographical location of study sites	Treatment groups and numbers randomised	Open label escape allowance	Primary outcome	Assessment of induction	Assessment of maintenance	Study sponsor
ULTRA2 (NCT00408629, M06–827), Sandborn *et al.*, 2012[45]	Multicentre, randomised, double-blind, PBO-controlled trial. Phase III	Inclusion: adults with moderately to severely active UC for ≥ 3 months and Mayo score of 6–12 points (endoscopy subscore of ≥ 2), despite concurrent therapy with steroids and/or AZA or 6-MP. Exclusion: previous treatment with ADA; receipt of i.v. CSs, i.v. CSs within 2 weeks of screening; receipt of ciclosporin, tacrolimus, or mycophenolate mofetil within 1 month of baseline; or receipt of any investigational agent within 30 days/five half-lives before baseline	North America, Europe, Australia, New Zealand and Israel. 103 study centres	PBO $n = 260$ (14 excluded owing to site non-compliance) ADA 160 mg/80 mg/ 40 mg $n = 258$ (10 excluded owing to site non-compliance) Patients received ADA s.c. 160 mg at week 0, 80 mg at week 2 and 40 mg EOW from week 4 or matching PBO and followed through week 52	Yes. Patients with inadequate response permitted to switch to open-label ADA (40 mg EOW) from week 12. Patients with inadequate response at two visits on open-label ADA 40 mg EOW permitted to escalate to 40 mg EW. Data handled using non-responder imputation methods	Proportion of patients achieving clinical remission at week 8 and proportion of patients achieving clinical remission at week 52	Week 8 included in NMA? Yes	Weeks 32 and 52 included in NMA? Yes	Abbott
ULTRA3 (M10–223), Reinisch *et al.*, 2013[54]	Long-term, single-arm, open-label extension study including patients from ULTRA1 and ULTRA2 (currently ongoing)	Inclusion: patients in both studies who completed the 52-week visit had the option of enrolling in the extension study (M10–223). Exclusion: patients not responding to weekly ADA from Study M06–826 or M06–827	See ULTRA1 and ULTRA2	Patients continued to receive open-label ADA (EOW or EW dosing permitted). ADA 40 mg EOW or EW ($n = 588$)	Yes. Patients who had inadequate response or responded and then experienced disease flare eligible for ADA dose increase to 40 mg EW (no earlier than the week 12 visit) or the week 2 visit if already receiving open-label ADA	NR	NA	Evaluation of ADA maintenance regimens	Abbott

continued

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TABLE 6 Trial design characteristics of included clinical effectiveness studies in adults (*continued*)

Trial identifier (NCT number), primary publication details	Trial design	Inclusion/exclusion criteria	Geographical location of study sites	Treatment groups and numbers randomised	Open label escape allowance	Primary outcome	Assessment of induction	Assessment of maintenance	Study sponsor
Suzuki *et al.*, 2014 (NCT00853099, M10–447), Suzuki *et al.*, 2014[46]	Multicentre, randomised, double-blind, PBO-controlled trial. Phase II/III	Inclusion: Japanese patients ≥ 15 years, moderately to severely active UC, Mayo score of 6–12 points with endoscopy subscore of ≥ 2 despite concurrent treatment with stable doses of oral CSs and/or immunomodulators. Patients previously treated with CSs or immunomodulators during past 5 years and had failed to respond or who could not tolerate treatment eligible. Exclusion: patients with prior treatment with anti-TNF therapies or other biologicals, discontinuation of oral CSs ≤ 2 weeks before baseline; receipt of CS injection, ciclosporin, tacrolimus, or mycophenolate mofetil ≤ 4 weeks before baseline	Japan. 65 study centres	PBO $n = 96$ ADA 160 mg/80 mg = 90 randomised ADA 80 mg/40 mg = 87 randomised Patients received s.c. ADA 160 mg at week, 80 mg at week 2 and 40 mg EOW from week 4, or ADA 80 mg at week 0, 40 mg at week 2 and 40 mg EOW from week 4 or PBO	Yes. Patients with inadequate response to study drug or flare at or after week 8 permitted to enter rescue arm with 4 weeks of blinded ADA (either 160 mg initially and 80 mg 2 weeks later for PBO group, or 40 mg initially and 2 weeks later for patients in either ADA group) followed by open-label ADA 40 mg EOW (with option to escalate to 80 mg EOW if inadequate response/ flare ≥ 8 weeks later. Data handled using non-responder imputation	NR	Week 8. Included in NMA? Sensitivity analysis only (on basis of exclusively Japanese population and population eligibility age patients ≥ 15 years)	Weeks 32 and 52. Included in NMA? Sensitivity analysis only (on basis of exclusively Japanese population and population eligibility age patients ≥ 15 years)	Abbott

Trial identifier (NCT number), primary publication details	Trial design	Inclusion/exclusion criteria	Geographical location of study sites	Treatment groups and numbers randomised	Open label escape allowance	Primary outcome	Assessment of induction	Assessment of maintenance	Study sponsor
GOL									
PURSUIT-SC (NCT00487539) (programme of UC Research Studies Utilising an Investigational Treatment – Subcutaneous), Sandborn *et al.*, 2014[47]	Multicentre, randomised, double-blind, PBO-controlled trial. Integrated Phase II and Phase III trial	Inclusion: patients with moderate to severe UC, Mayo score of 6–12 points, with endoscopic subscore of ≥ 2, inadequate response to/failed to tolerate one or more of following: oral 5-ASA, oral CSs, AZA, and/or 6-MP; or CS dependent. Exclusion: patients with colitis limited to 20 cm of colon; patients with earlier use of: biological anti-TNF agent(s) natalizumab or other agents targeting alpha-4 integrin, B-cell depleting agents (rituximab), or T-cell depleting agents (alemtuzumab, visilizumab) within 12 months of first study drug dose (or continued B- or T-cell depletion > 12 months after completing treatment with lymphocyte-depleting agents); oral CSs at dose > 40 mg prednisone or equivalent per day; receipt of ciclosporin, tacrolimus, sirolimus, or mycophenolate mofetil within 8 weeks before first study agent infection	Eastern Europe, North America, Asia Pacific, South Africa, Western Europe, Israel. 217 sites (Eastern Europe 400 patients, North America 278 patients, Asia Pacific and South Africa 204 patients, and Western Europe and Israel 183 patients)	Phase II PBO = 42 plus 31 enrolled while Phase II data being analysed. Phase II GOL 200 mg/100 mg = 42 plus 31 enrolled while Phase II data being analysed. Phase III PBO = 258. Phase III GOL 200 mg/100 mg = 258. Patients received s.c. GOL or PBO at weeks 0 and 2	No	Phase III primary end point was clinical response at week 6	Week 6. Included in NMA? Yes	NA. Included in NMA? No (6-week study)	Janssen Research & Development

continued

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TABLE 6 Trial design characteristics of included clinical effectiveness studies in adults (*continued*)

Trial identifier (NCT number), primary publication details	Trial design	Inclusion/exclusion criteria	Geographical location of study sites	Treatment groups and numbers randomised	Open label escape allowance	Primary outcome	Assessment of induction	Assessment of maintenance	Study sponsor
PURSUIT-Maintenance (NCT00488631), Sandborn *et al.*, 2014[48]	Randomised-withdrawal, PBO-controlled, double-blind multicentre trial. Patients who responded to GOL induction therapy ($n = 464$) randomised at baseline visit in 1 : 1 : 1 ratio to SC PBO, GOL 50 mg or GOL 100 mg. Phase III	Inclusion: patients had completed one of two GOL induction studies (PURSUIT-SC or PURSUIT-IV). Patients eligible for induction studies had moderate to severe UC and Mayo score of 6–12 points with endoscopic subscore of ≥ 2. Patients had inadequate response to/had failed to tolerate one or more of following: oral 5-ASA, oral CSs, immunosuppressives (AZA or 6-MP) or were CS-dependent. Exclusion: patients with isolated proctitis excluded from induction studies	Eastern Europe, North America, Asia Pacific and South Africa, and Western Europe and Israel. 251 sites across Eastern Europe (477 patients), North America (323 patients), Asia Pacific and South Africa (237 patients), and Western Europe and Israel (191 patients)	PBO randomised = 156 GOL 50 mg = 154 randomised GOL 100 mg = 154 randomised Randomised patients received s.c. PBO, GOL 50 mg or GOL 100 mg every 4 weeks through week 52 (efficacy analysis population). PBO-induction responders and PBO- or GOL-induction non-responders eligible but not randomised. PBO induction responders received PBO every 4 weeks through week 52. GOL-induction or PBO-induction non-responders received GOL 100 mg every 4 weeks through week 12, assessed at week 16 and discontinued from study if disease activity unimproved. Non-randomised patients included in demographic, pharmacokinetic and safety summaries only	Yes. Induction responders who lost clinical response permitted to modify treatment. PBO group to GOL 100 mg every 4 weeks, GOL 50 mg rerandomised to GOL 50 mg or GOL 100 mg every 4 weeks and GOL 100 mg rerandomised to GOL 100 mg or GOL 200 mg (GOL 200 mg dose subsequently discontinued and patients on GOL 200 mg decreased to GOL 100 mg). Proportions of subjects who underwent dose adjustments were 33.8% in the GOL 50 mg group, 28.5% in the GOL 100 mg group and 48.7% in the PBO group	Clinical response maintained through week 54 among GOL induction responders	NA. Included in NMA? No (maintenance trial only)	Weeks 30 and 54. Included in NMA? Yes	Janssen Research & Development

Trial identifier (NCT number), primary publication details	Trial design	Inclusion/exclusion criteria	Geographical location of study sites	Treatment groups and numbers randomised	Open label escape allowance	Primary outcome	Assessment of induction	Assessment of maintenance	Study sponsor
IFX									
ACT1 (NCT00096655), Rutgeerts *et al.*, 2005[49]	Multicentre, randomised, double-blind, PBO-controlled trial. Phase III	Active UC with Mayo score of 6–12 points and moderate to severe active disease on sigmoidoscopy despite concurrent treatment with CSs alone or in combination with AZA or 6-MP included. Patients with diagnosis of indeterminate colitis, CD or clinical findings suggestive of CD; positive tuberculin skin tests; previously exposed to IFX or any other anti-TNF agent excluded	62 sites. Geographical locations NR	PBO:121 randomised IFX 5 mg/kg:121 randomised IFX 10 mg/kg:121 randomised Received agent at weeks 0, 2, 6, 14, 22, 30, 38 and 46	No	Clinical response at week 8	Week 8. Included in NMA? Yes	Weeks 30 and 54. Included in NMA? Yes	Schering-Plough
ACT2 (NCT00036439), Rutgeerts *et al.*, 2005[49]	Multicentre, randomised, double-blind, PBO-controlled trial. Phase III	Patients needed only have failed 5-ASA as a minimum. Active UC with a Mayo score of 6–12 points and endoscopy subscore of 2–3. Concurrent treatment with at least oral CSs, immunosuppressants or 5-ASAs. Patients could enrol if they failed to tolerate or respond to CSs, AZA, 6-MP or 5-ASA	55 sites. Geographical locations NR	PBO:123 randomised IFX 5 mg/kg:121 randomised IFX 10 mg/kg:120 randomised Received agent at weeks 0, 2, 6, 14, 22, 30, 38 and 46: Received agent at weeks 0, 2, 6, 14, 22, 30, 38 and 46	No	Clinical response at week 8	Week 8. Included in NMA? Yes	Week 30. Included in NMA? Yes	Schering-Plough

continued

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TABLE 6 Trial design characteristics of included clinical effectiveness studies in adults (*continued*)

Trial identifier (NCT number), primary publication details	Trial design	Inclusion/exclusion criteria	Geographical location of study sites	Treatment groups and numbers randomised	Open label escape allowance	Primary outcome	Assessment of induction	Assessment of maintenance	Study sponsor
ACT1 and ACT2 extension studies, Reinisch *et al.*, 2012[55]	Long-terms extension studies (open label) of ACT Phase III trials. Study design identical for ACT1 and ACT2 extension studies	Inclusion: patient eligibility described for ACT studies. Patients who (in opinion of investigator) could benefit from continued treatment eligible to enter extension study after completing main study treatment and assessments through weeks 46 and 54 (ACT1) or weeks 22 and 30 (ACT2). Exclusion: patients who received experimental medication to treat UC after completion of main study ineligible	See ACT1 and ACT2	229 randomised patients in IFX group entering extension studies. Participating patients continued to receive blinded treatment to which they had been randomised. Sites unblinded to treatment after week 54 ACT1 and extension week 24 in ACT2 analyses completed (and PBO patients discontinued at this point and not included in analyses)	Yes. Patients receiving IFX 10 mg/kg permitted to lower dose to 5 mg/kg. Patients losing response while receiving IFX 5 mg/kg permitted to raise dose to 10 mg/kg	NR	NA	Evaluation of long-term IFX maintenance to week 152	As for ACT1 and ACT2
Probert *et al.*, 2003 (NCT number NR), Probert *et al.*, 2003[50]	Multicentre, randomised, double-blind, PBO-controlled trial. Phase NR	Inclusion: patients with UCSS of ≥ 6 and a sigmoidoscopy score of ≥ 2 on Baron scale, failed to respond to conventional treatment with glucocorticoids. Exclusion: patients who had received ciclosporin, any therapeutic agent used to directly reduce TNF, or any investigational drug within 3 months of enrolment, as well as those who had recently commenced treatment (within the last 3 months) with 6-MP or AZA	UK and Germany. Four study centres	PBO = 20 randomised IFX 5 mg/kg = 23 Patients received i.v. IFX 5 mg/kg or PBO at week 0 and second identical infusion at week 2. At week 6, all patients with continued active UC offered open-label IFX 10 mg/kg	Yes, from week 6 only (all patients with continued active UC offered open-label IFX 10 mg/kg)	Clinical remission at week 6	Week 6 (clinical remission only; no clinical response data available for week 6). Included in NMA? No (excluded from NMA as definition of clinical remission inconsistent with other trials (i.e. total Mayo score of ≤ 2 points but does not specify no individual subscore of > 1 as in other trials)	NA. Included in NMA? No (no maintenance time points)	Schering-Plough and BMBF Competence Network (Germany)

Trial identifier (NCT number), primary publication details	Trial design	Inclusion/exclusion criteria	Geographical location of study sites	Treatment groups and numbers randomised	Open label escape allowance	Primary outcome	Assessment of induction	Assessment of maintenance	Study sponsor
UC-SUCCESS (NCT00537316), Panacionne *et al.*, 2014[51]	Multicentre, randomised, double-blind (double-dummy), PBO-controlled trial. Phase III	Inclusion: patients with moderate to severe UC defined as Mayo scores of 6–8 and 9–12 points, respectively. Patients responded inadequately to course of CSs ± mesalamine within past 12 weeks. Patients required to be either AZA-naïve or free from AZA treatment for at least 3 months before enrolment. Prohibited medications at study entry included methotrexate and calcineurin inhibitors (tacrolimus, ciclosporin)	62 study centre. Geographical locations NR	AZA = 80 randomised IFX = 79 randomised IFX/AZA = 80 randomised Patients received i.v. IFX 5 mg/kg at weeks 0, 2, 6 and 14 + oral once daily PBO capsules, or oral AZA 2.5 mg/kg daily + PBO i.v. on IFX schedule or combination therapy with both drugs	Yes. Non-responders to AZA at week 8 had IFX rescue infusions at weeks 8, 10 and 14 while continuing AZA. Non-responders considered treatment failures	CS-free remission at week 16	Week 8. Included in NMA? No (borderline inclusion and partial Mayo response only at week 8)	16 weeks. Included in NMA? No (16 weeks of treatment only)	Schering-Plough

ACT1, Active Ulcerative Colitis Trial 1; ACT2, Active Ulcerative Colitis Trial 2; CS, corticosteroid; EOW, every other week; EW, every week; ITT-A3, intention to treat-amendment 3; NA, not applicable; NCT, National Clinical Trial; NR, not reported; PURSUIT, Program of Ulcerative Colitis Research Studies Utilizing an Investigational Treatment; s.c., subcutaneous; TNF, tumour necrosis factor; UCSS, Ulcerative Colitis Symptom Score; ULTRA, Ulcerative colitis Long-Term Remission and maintenance with Adalimumab treatment of moderate to severe ulcerative colitis.

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TABLE 7 Trial design characteristics of included paediatric population clinical effectiveness studies

Trial identifier (NCT number), primary publication details	Trial design	Inclusion/exclusion criteria	Geographical location of study sites	Treatment groups and numbers randomised	Open label escape allowance?	Primary outcome	Assessment of induction	Assessment of maintenance	Study sponsor
IFX									
Hyams (NCT00336492, C0168T72), Hyams *et al.*, 2012[52]	Randomised, Multicentre, open-label study. Phase III	Inclusion: patients aged 6–17 years old, with moderately to severely active UC, Mayo score of 6–12 points and endoscopy subscore of ≥ 2), failed to respond to adequate treatment/ experienced medical complications/adverse effects from 5-ASAs immunomodulators (6-MP/AZA) or oral/i.v. CSs. Exclusion: patients with acute severe extensive UC and those who previously used other investigational drugs or any TNF antagonist	USA, the Netherlands, Canada and Belgium. 23 study centres	All patients received induction regimen of IFX 5 mg/kg at weeks 0, 2 and 6.45 patients who achieved clinical response at week 8 (primary endpoint) randomised to receive: IFX 5 mg/kg q8w = 22. IFX 5 mg/kg q12w = 23	Yes. Patients losing response during maintenance eligible to increase IFX dose and/or frequency to set regimens. IFX 5 mg/kg q8w group to 10 mg/kg q8w. IFX 5 mg/kg q12w group to 10 mg/kg q8w, with those losing response between 8 and 12 weeks after previous infusion to 5 mg/kg q8w	Clinical response at week 8	All patients received induction with IFX 5 mg/kg at week 0, 2 and 6 and clinical response and clinical remission assessed at week 8 (no PBO control for induction)	Week 54 (no PBO control for maintenance)	Janssen Research & Development

CS, corticosteroid; NCT, National Clinical Trial; q8w, every 8 weeks; q12w, every 12 weeks.

Eight trials included time points for the assessment of the use of interventions in achieving induction of clinical response or remission, of which four assessed IFX (ACT1,[49] ACT2,[49] Probert *et al.*[50] and UC-SUCCESS[51]), three assessed ADA (ULTRA1,[44] ULTRA2[45] and Suzuki *et al.*[46]) and one assessed GOL (PURSUIT-SC[47]). Six trials reported outcomes at time points for the evaluation of the use of interventions in the maintenance of clinical response or remission, consisting of three IFX trials (ACT1,[49] ACT2[49] and UC-SUCCESS[51]), two ADA trials (ULTRA2[45] and Suzuki *et al.*[46]) and one GOL trial (PURSUIT-Maintenance[48]).

None of the included RCTs applied Truelove and Witts' disease severity criteria[23] in their eligibility criteria (as referred to in the final NICE scope for this appraisal[36] and as specified in the protocol). All included trials applied the Mayo score [except Probert *et al.*[50] for which the score was specified simply as Ulcerative Colitis Symptom Score (UCSS)] to classify the disease severity of potential participants (note: the UCSS was confirmed to be equivalent to Mayo score by Professor C Probert, University of Liverpool, 2014, personal communication). The included trials required a Mayo score of 6–12 points (with evidence of endoscopic disease) for participant eligibility. Mayo scores of 6–12 points were described in the included trial literature as moderate to severe disease and were also subsequently confirmed following clinical advice as representing moderate to severe disease (note: ad-hoc searches were performed to attempt to identify evidence relating to the relationship between the Truelove and Witts' and Mayo disease severity indices; however, no evidence published in full text in English could be identified). Included trials required a varying range of prior use of conventional therapy for eligibility, as described in *Tables 6* and *7*. The UC-SUCCESS trial,[51] which specified patients to be either AZA-naive or free from AZA treatment for at least 3 months before enrolment, was a borderline inclusion in the clinical effectiveness systematic review because the wording of the population in the scope and the licensed indications required prior use of AZA or 6-MP. However, as the trial reported the use of a stated (albeit low) proportion of prior immunosuppressant use, this trial was included in the clinical effectiveness systematic review for completeness. However, this trial was not eligible for subsequent inclusion in meta-analyses or NMAs. Suzuki *et al.*[46] included Japanese patients aged ≥ 15 years (ADA is not licensed in the paediatric population), but the mean ages of participants across treatment arms at baseline was 41.3–42.5 years.

The Core Outcome Measures in Effectiveness Trials (COMET) initiative,[56] which promotes the use of core outcome sets in clinical trials, referenced the work by Cooney *et al.*[22] in classifying the use of outcome measures in UC clinical trials. Although acknowledging the very broad range of available disease severity/activity measures available, all adult population trials included in the assessment were consistent in their utilisation of the Mayo score as a measure of clinical response and/or remission. The included trial by Probert *et al.*[50] applied the UCSS in the evaluation of clinical remission at induction. This score is equivalent to the full Mayo score: the components of the UCSS are consistent with the elements assessed within the Mayo score (i.e. stool frequency, rectal bleeding, sigmoidoscopic appearance and physician's global assessment) and also is referenced using the citation quoted for the Mayo score.[24] None of the included studies utilised the modified Truelove and Witts' criteria[23] (as referred to in the NICE appraisal scope[36] and as specified in the assessment protocol) in their outcome assessments.

As recommended in the Committee for Human Medicinal Products (CHMP) guideline[57] on the development of new medicinal products for the treatment of UC patients with confirmed UC were eligible for the included trials. Severity of disease was defined by clinical and endoscopic evaluation, as recommended in the CHMP guideline. Although the interventions of interest in this assessment were developed for the treatment of patients not responding/intolerant to previous immunomodulatory therapy, the Assessment Group did not consider that adequate definitions of inadequate response/intolerance were included in trials, as recommended by the CHMP guideline. The guideline recommended that, for refractory populations, a minimum duration and dose of previous baseline medication should be defined, but this was not the case in the included trials. In addition, intolerance was not defined by minimum criteria of severity in the trials. In terms of study duration, it was recommended that induction studies should be 8–12 weeks, but could be shorter based on the pharmacodynamic properties of the study drug. All induction trials assessed efficacy at 8 weeks, with the exception of the PURSUIT-SC GOL trial,[47] which was a 6-week study. All maintenance studies were at least 1 year in length, as recommended in the CHMP guideline.

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Adalimumab

ULTRA1[44] was a multicentre Phase III RCT in adults undertaken across the USA, Puerto Rico, Canada, Western Europe, and Eastern Europe. In the original protocol, 186 participants were randomised and in the amended protocol 390 were randomised (130 per group including PBO). Length of treatment was 12 weeks in the original protocol and 8 weeks in the amendment, and outcomes were reported at week 8. ULTRA2[45] was a multicentre Phase III RCT in adults undertaken across North America, Europe, Australia, New Zealand and Israel. A total of 518 patients entered the study, of which 258 were randomised to 160 mg/80 mg/40 mg of ADA and 260 were randomised to PBO. Outcomes were reported at week 8 and week 52. Suzuki *et al.*[46] was a 52-week Phase II/III trial in Japanese adults in which 274 participants were randomised to three treatment groups, including PBO. Outcomes were reported at 8 weeks and 52 weeks. The two induction ADA groups (one licenced dose and the other unlicensed) were combined as one active treatment group for outcomes at 52 weeks. ULTRA3[54] was the 156-week open-label extension study to ULTRA1[44] and ULTRA2.[45]

Golimumab

PURSUIT-SC[47] was a Phase II/III multicentre RCT in adults reporting outcomes at week 6. The trial was performed across 217 sites (Eastern Europe, 400 patients; North America, 278 patients; Asia Pacific and South Africa, 204 patients; and Western Europe and Israel, 183 patients). This was a dose-ranging study with 169 patients randomised to four groups, including PBO. PURSUIT-Maintenance[48] was a Phase III RCT in adults across 251 sites (Eastern Europe, 477 patients; North America, 323 patients; Asia Pacific and South Africa, 237 patients; and Western Europe and Israel, 191 patients). Out of the 1228 patients who enrolled in PURSUIT, 464 were randomised to receive PBO ($n = 156$), 50 mg of GOL ($n = 154$) or 100 mg of GOL ($n = 154$). A total of 764 patients were not randomised: 129 were PBO non-responders, 230 were PBO induction non-responders and 405 were GOL induction non-responders.

Infliximab

ACT1[49] was a multicentre Phase III RCT conducted across 62 sites. A total of 364 adult patients were randomly assigned to licensed and unlicensed induction doses or PBO. ACT2 was a multicentre Phase III RCT across 55 sites. A total of 364 adult patients were randomly assigned to licensed and unlicensed maintenance doses or PBO. Probert *et al.*[50] was a RCT undertaken across four centres in the UK and Germany; 43 adult participants were randomised to IFX or PBO and outcomes assessed at week 6. UC-SUCCESS[51] was a multicentre RCT undertaken in adults. A total of 239 participants were randomised to IFX, AZA or combination therapy (with no PBO group included). Outcomes were assessed at weeks 8 and 16.

Population: children and adolescents aged 6–17 years (inclusive) with severely active ulcerative colitis who have had an inadequate response to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who are intolerant to, or have medical contraindications against, such therapies

A single Phase III open-label RCT was identified for the paediatric population (T72[52]) which evaluated the use of IFX in maintenance therapy. All patients received the licensed IFX induction regimen before being randomised to one of two IFX maintenance regimens. Outcomes were reported at week 30 and week 54. No PBO-controlled or head-to-head RCTs were identified for children and young people. The absence of a PBO or non-IFX control group in the included RCT made it difficult to consider the effectiveness of IFX in paediatric patients compared with conventional UC therapies. This industry-funded trial had the primary end point of clinical response and was conducted in the USA, the Netherlands, Canada and Belgium. Eligible patients were 6–17 years of age with moderately to severely active UC and a Mayo score of 6–12 points with endoscopic evidence of disease. Therefore, although IFX is licensed in this age group with severe disease only (as reflected in the scope population), this trial was included in consideration of limited paediatric RCT evidence.

Quality of included evidence

All of the included trials were considered to be at low risk of selection bias as all trials reported an appropriate method for generating the randomisation sequence. Likewise, the majority of trials reported adequate information that allocation was concealed and were considered to be at low risk of bias for this domain. This was with the exception of two trials in which there was no information reported to make a judgement. These trials were therefore classified as being at unclear risk of bias.[46,52] Eight out of the 10 trials (see *Figure 3*) were considered to be at low risk of performance bias because there was reporting to indicate that participants and personnel were blinded to participants' treatment allocation. Two trials were considered at unclear risk of bias for this domain; one because there was no clear statement in the trial report[52] and one because the treatment regimen differed for non-responders at week 8 in AZA arm which could break the blinding.[51] Blinding of the outcome assessment was reported by five trials,[44,45,47,48,50] all of which were considered at low risk of bias for this domain. The remaining five trials included no statement in the trial report and were considered at unclear risk for this domain (ACT1,[49] ACT2,[49] Hyams *et al.*,[52] UC-SUCCESS,[51] Suzuki *et al.*[46]).

All included trials were reported according to the intention-to-treat (ITT) principle. However, for two trials (ACT1[49] and ACT2[49]), although ITT was reported, > 50% of patients in the PBO group and > 30% of patients in IFX groups did not complete the trial. Similarly, in another IFX trial,[52] the numbers of patients withdrawing from the study were unbalanced across groups with > 50% of patients withdrawing from the every 12-week dose group. In the UC-SUCCESS trial,[51] there was also a high level of attrition and an imbalance between treatment groups (AZA, 34%; IFX, 18%; IFX/AZA, 21%). In one of the ADA trials (ULTRA2[45]), although ITT analysis was undertaken, there was a high level of attrition and an imbalance between treatment groups (PBO, 44.2%; ADA, 36.4%). In the GOL maintenance trial (PURSUIT-Maintenance[48]), withdrawal of > 10% was evident across all treatment groups. These trials were all considered to be at high risk of bias for this domain. Of note, the trial of ADA reported by Suzuki *et al.*[46] was considered at low risk of attrition bias for the induction phase (*Figures 3* and *4*). A high risk of attrition bias was evident for the maintenance phase (> 10% withdrawing). The maintenance active treatment group comprised participants receiving both licensed and unlicensed doses of ADA during induction (data not used in this report). Details of the numbers of participants withdrawing and reasons for withdrawal by trial are presented in *Appendix 3*. The extent of reporting of the reasons for withdrawals was variable between studies.

Selective outcome reporting was assessed based on ClinicalTrials.gov records, trial protocols and CSRs when provided by the manufacturers. Adequate data were available across ClinicalTrials.gov records and CSRs (available for some trials only) to compare outcomes with those reported in the associated peer-review publications for all included trials with the exception of Probert *et al.*[50] Stated primary outcomes were compared between published reports and trial protocols (for those RCTs for which trial protocols were provided by manufacturers). With the exception of Probert *et al.*[50] and Suzuki *et al.*,[46] all included RCTs were considered to be of at low risk of bias for this domain. Probert *et al.*[50] and Suzuki *et al.*,[46] were judged as being at unclear risk of selective reporting bias.

Population characteristics

The baseline characteristics of participants in the included RCTs are presented in *Tables 8* and *9*. In addition to comparator arm data, only data relating to licensed doses of interventions are presented.

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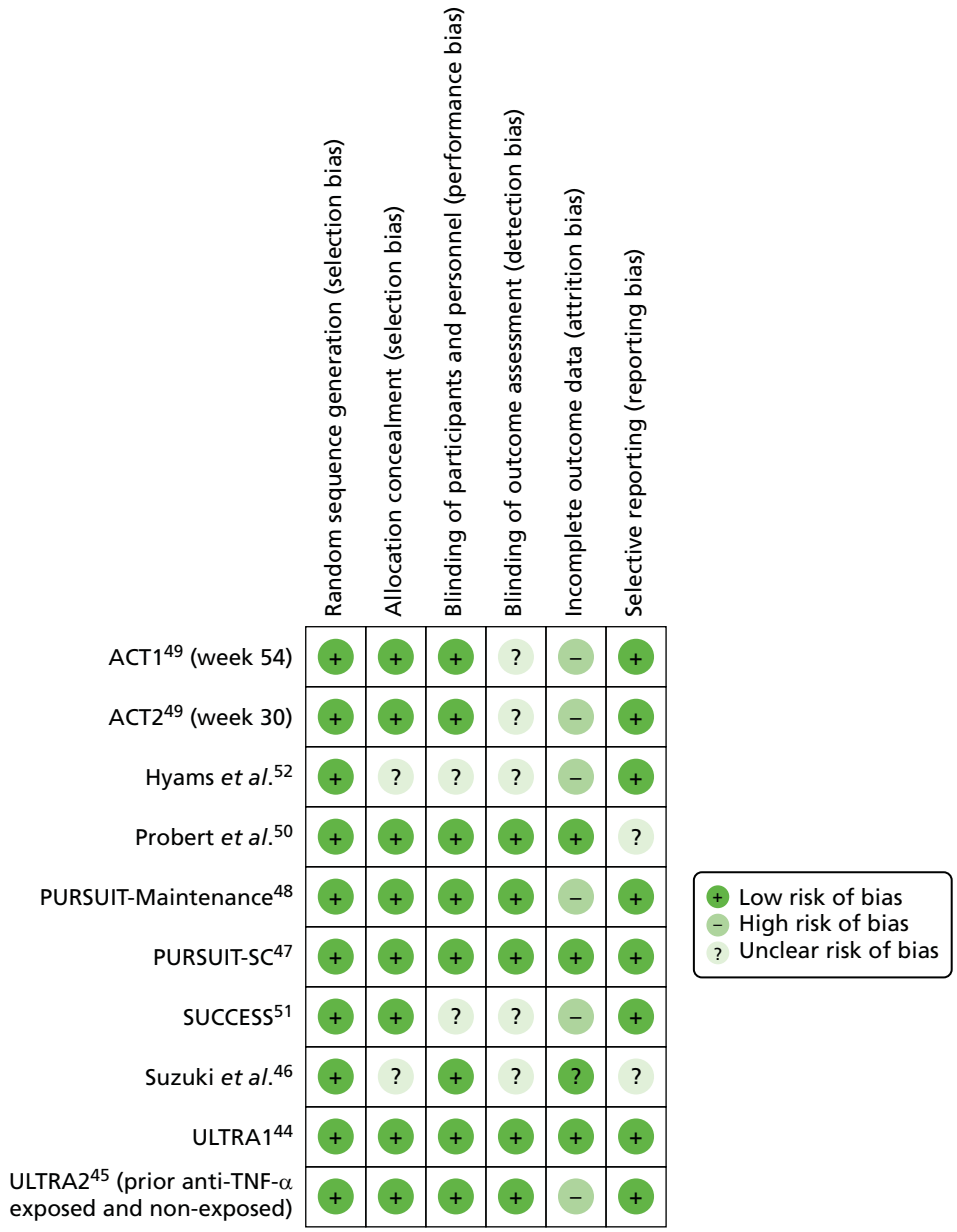

FIGURE 3 Risk-of-bias summary: review authors' judgements about each risk-of-bias item for each included study.

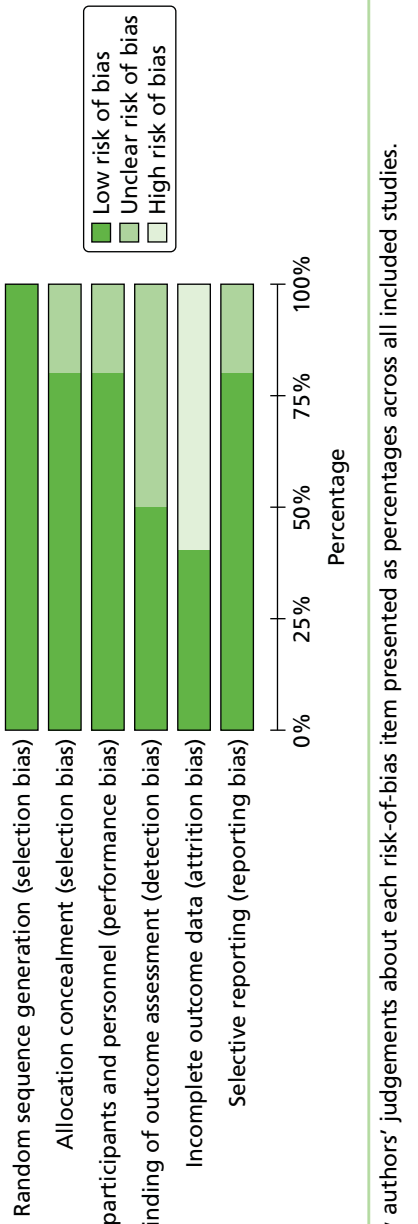

FIGURE 4 Risk-of-bias graph: review authors' judgements about each risk-of-bias item presented as percentages across all included studies.

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TABLE 8 Population characteristics of included clinical effectiveness studies in adults

Trial identifier (NCT number), primary publication details	Age, mean years (SD)	Male participants (%)	Ethnicity, Caucasian (%)	Disease extent/location and disease duration, mean years (SD)	Disease severity at baseline: Mayo score, mean (SD)	CRP at baseline, mean mg/dl	Medications at baseline	Weight kg, mean (SD)	Smoking status
ADA									
ULTRA1[44]	Mean NR, median (range) PBO = 37 (18–72), ADA 160 mg/ 80 mg = 37 (18–75)	PBO = 63.1% ADA 160 mg/ 80 mg = 63.8%	NR	PBO = extensive colitis, 73/130 (56.2%); left-sided colitis, 42/130 (32.3%); other,15/130 (11.5%), duration median (range) 5.35 (0.3–34.1) ADA 160 mg/80 mg = extensive colitis, 60/130 (46.2%); left-sided colitis, 61/130 (46.9%); other, 9/130 (6.9%), duration median (range) 6.06 (0.2–34.4)	PBO = 8.7 (1.56) ADA 160 mg/ 80 mg = 8.8 (1.61)	Mean NR, median (range) PBO = 0.32, ADA 160 mg/ 80 mg = 0.33	PBO = CS, 55/130 (41.5%); IMM, 18/130 (13.8%); CS + IMM, 34/130 (26.1%); no CS or IMM, 23/130 (17.7%); aminosalicylates, 98/130 (75.4%) ADA 160 mg/80 mg = CS, 48/130 (36.9%); IMM, 28/130 (21.5%); CS + IMM, 23/130 (17.7%); no CS or IMM, 31/130 (23.8%); aminosalicylates, 105/130 (80.8%) Dosages of concomitant UC medication(s) stable throughout study	PBO = 78.7 (17.4) ADA 160 mg/ 80 mg = 75.5 (14.2)	NR

Trial identifier (NCT number), primary publication details	Age, mean years (SD)	Male participants (%)	Ethnicity, Caucasian (%)	Disease extent/location and disease duration, mean years (SD)	Disease severity at baseline: Mayo score, mean (SD)	CRP at baseline, mean mg/dl	Medications at baseline	Weight kg, mean (SD)	Smoking status
ULTRA2[45]	PBO = 41.3 (13.22) ADA 160 mg/ 80 mg/40 mg = 39.6 (12.47)	PBO = 152/246 (61.8%) ADA 160 mg/ 80 mg/40 mg = 142/248 (57.3%)	NR	PBO = pancolitis, 120/248 (48.8%); descending colon, 96/246 (39.0%); other, 30/246 (12.2%), duration 8.5 (7.37) ADA 160 mg/80 mg/ 40 mg = pancolitis, 120/ 248 (48.4%); descending colon, 96/248 (38.7%); other, 32/248 (12.9%), duration 8.1 (7.09)	PBO = 8.9 (1.75) ADA 160 mg/ 80 mg/40 mg = 8.9 (1.50)	PBO = 1.3 ADA 160 mg/ 80 mg/40 mg = 1.5	PBO = CSs 140/246 (56.9%); AZA/6-MP 80/246 (32.5%); aminosalicylates 155/246 (63.0%); AZA/6-MP and/or steroids 175/246 (71.1%); AZA/6-MP and steroids 45/246 (18.3%) (41.1%) ADA 160 mg/80 mg/ 40 mg = CSs150/248 (60.5%); AZA/6-MP 93/248 (37.5%); aminosalicylates 146/248 (58.9%); AZA/6-MP and/or steroids 193/248 (77.8%); AZA/6-MP and steroids 50/248 (20.2%) Prior anti-TNF-α treatment PBO = 101/246 (41.1) ADA 160 mg/80 mg/ 40 mg = 98/248 (39.1) Concomitant UC medications held stable except steroids, which could be tapered after week 8 at discretion of investigator for patients with satisfactory clinical response	PBO = 77.1 (17.31) ADA 160 mg/ 80 mg/40 mg = 75.3 (17.71)	NR

continued

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TABLE 8 Population characteristics of included clinical effectiveness studies in adults (*continued*)

Trial identifier (NCT number), primary publication details	Age, mean years (SD)	Male participants (%)	Ethnicity, Caucasian (%)	Disease extent/location and disease duration, mean years (SD)	Disease severity at baseline: Mayo score, mean (SD)	CRP at baseline, mean mg/dl	Medications at baseline	Weight kg, mean (SD)	Smoking status
Suzuki *et al.*, 2014[46]	PBO = 41.3 (13.6) ADA 160 mg/ 80 mg/40 mg = 42.5 (14.6)	PBO = 70/96 (72.9%) ADA 160 mg/ 80 mg/40 mg = 61/90 (67.8%)	Exclusively Japanese	PBO = pancolitis, 59/96 (61.5%); descending colon, 35/96 (36.5); other, 2/96 (2.1%); duration 7.8 (6.6) ADA 160 mg/80 mg/ 40 mg = pancolitis, 63/90 (70.0%); descending colon, 27/90 (30.0); other 0/96 (0%); duration 7.8 (7.1)	PBO = 8.5 (1.6) ADA 160/80/ 40 mg = 8.6 (1.4)	Mean NR Median (range) PBO = 0.34 (0.05–8.72) ADA 160 mg/ 80 mg/40 mg = 0.22 (0.05–6.28)	PBO = 5-ASAs, 89/96 (92.7%); IMMs (AZA, 6-MP), 52/96 (54.2%); systemic CSs, 58/97 (60.4%) ADA 160 mg/80 mg/ 40 mg = 5-ASAs, 83/90 (92.2%); IMMs (AZA, 6-MP), 41/90 (45.6%); systemic CSs, 57/90 (63.3%) Changes in doses of UC concomitant medications not permitted during study (other than CSs). After 8 weeks, patient responders permitted to taper CS dose	PBO = 60.8 (14.1) ADA 160 mg/ 80 mg/40 mg = 60.1 (12.3)	Tobacco non-smoker PBO = 55/96 (57.3%) ADA 160 mg/ 80 mg/40 mg = 50/90 (55.6%)

Trial identifier (NCT number), primary publication details	Age, mean years (SD)	Male participants (%)	Ethnicity, Caucasian (%)	Disease extent/location and disease duration, mean years (SD)	Disease severity at baseline: Mayo score, mean (SD)	CRP at baseline, mean mg/dl	Medications at baseline	Weight kg, mean (SD)	Smoking status
GOL									
PURSUIT-SC (all randomised patients), Sandborn *et al.*, 2014[47]	PBO = 39.0 (13.04) GOL 200 mg/100 mg = 40.0 (13.54)	PBO = 175/331 (52.9%) GOL 200 mg/100 mg = 180/331 (54.4%)	PBO = 263/331 (79.5%) GOL 200 mg/100 mg = 271/331 (81.9%)	PBO = *n* = 330, limited to left side of colon, 188/330 (57.0); extensive = 142/330 (43.0); duration 6.0 (6.65) GOL 200 mg/100 mg = *n* = 331, limited to left side of colon, 193/331 (58.3); extensive = 138/331 (41.7), duration 6.4 (6.17)	PBO = 8.3 (1.50) GOL 200 mg/100 mg = 8.6 (1.53)	PBO = 1.1 GOL 200 mg/100 mg = 1.1	PBO = patients receiving any UC medication (%) = 310/331 (93.7), CS (excluding budesonide) = 134/331 (40.5), ≥ 20 mg/d PEq = 78/331 (23.6), < 20 mg/d PEq = 56/331 (16.9), budesonide = 8/331 (2.4), immunomodulatory drugs = 106/331 (32.0), 6-MP/AZA = 102/331 (30.8), MTX = 4/331 (1.2), aminosalicylates = 276/331 (83.4) GOL 200 mg/100 mg = patients receiving any UC medication (%) = 302/331 (91.2), CS (excluding budesonide) = 142/331 (42.9), ≥ 20 mg/d PEq = 85/331 (25.7), < 20 mg/d PEq = 57/331 (17.2), budesonide = 6/331 (1.8), immunomodulatory drugs = 105/331 (31.7), 6-MP/AZA = 100/331 (30.2), MTX = 5/331 (1.5), aminosalicylates = 270/331 (81.6) Patients maintained stable doses of concomitant UC treatments during study	NR	NR

continued

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TABLE 8 Population characteristics of included clinical effectiveness studies in adults (*continued*)

Trial identifier (NCT number), primary publication details	Age, mean years (SD)	Male participants (%)	Ethnicity, Caucasian (%)	Disease extent/location and disease duration, mean years (SD)	Disease severity at baseline: Mayo score, mean (SD)	CRP at baseline, mean mg/dl	Medications at baseline	Weight kg, mean (SD)	Smoking status
PURSUIT-Maintenance (randomised patients), Sandborn *et al.*, 2014[48]	PBO = 40.2 (14.05) GOL 50 mg = 41.4 (13.84) GOL 100 mg = 39.1 (13.11)	PBO = 75/156 (48.1%) GOL 50 mg = 77/154 (50.0%) GOL 100 mg = 89/154 (57.8%)	PBO = 137/156 (87.8%) GOL 50 mg = 138/154 (89.6%) GOL 100 mg = 130/154 (84.4%)	Disease extent/location NR PBO = mean 6.9 (6.96), median 4.2 (IQR NR) GOL 50 mg = mean 6.8 (6.93), median 4.5 (IQR NR) GOL 100 mg = mean 7.2 (7.04), median 4.8 (IQR NR)	PBO = 8.3 (1.37) GOL 50 mg = 8.1 (1.38) GOL 100 mg = 8.5 (1.34)	PBO = 1.0 GOL 50 mg = 0.9 GOL 100 mg = 0.9	PBO = Any UC medication = 148 (94.9), CS = 83 (53.2) (excluding budesonide), ≥ 20 mg/day PEq = 59 (37.8), < 20 mg/day PEq = 24 (15.4), budesonide = 5 (3.2), immunomodulatory drugs = 52 (33.3), 6-MP/AZA = 51 (32.7), MTX = 1 (0.6), 5-ASA = 125 (80.1) GOL 50 mg = any UC medication = 144 (93.5), CS = 77 (50.0), ≥ 20 mg/day PEq = 52 (33.8), < 20 mg/day PEq = 25 (16.2), budesonide 6 (3.9), immunomodulatory drugs = 47 (30.5), 6-MP/AZA = 45 (29.2), MTX = 2 (1.3), 5-ASA = 128 (83.1) GOL 100 mg = Any UC medication = 143 (92.9), CS = 79 (51.3), ≥ 20 mg/day PEq = 55 (35.7), < 20 mg/day PEq = 24 (15.6), budesonide = 4 (2.6), immunomodulatory drugs = 48 (31.2), 6-MP/AZA = 48 (31.2), MTX = 0,	NR	NR

Trial identifier (NCT number), primary publication details	Age, mean years (SD)	Male participants (%)	Ethnicity, Caucasian (%)	Disease extent/location and disease duration, mean years (SD)	Disease severity at baseline: Mayo score, mean (SD)	CRP at baseline, mean mg/dl	Medications at baseline	Weight kg, mean (SD)	Smoking status
							5-ASA = 119 (77.3) Patients receiving 5-ASAs/ immunosuppressants at baseline of induction studies required to have held stable doses during induction and maintenance. After induction, patients in clinical response receiving concomitant CSs at baseline of PURSUIT-Maintenance required to taper CSs		
IFX									
ACT1 Rutgeerts *et al.*, 2005[49]	PBO = 41.4 (13.7) IFX 5 mg/kg = 42.4 (14.3)	PBO = 72/121 (59.5%) IFX 5 mg/kg = 78/121 (64.5%)	PBO = 111/121 (91.7%) IFX 5 mg/kg = 116/121 (95.9%)	PBO = left side, 66/120 (55.0%); extensive, 54/120 (45.0%); duration, 6.2 (5.9) IFX 5 mg/kg = left side, 63/121 (52.9%); extensive, 56/119 (47.1%); duration, 5.9 (5.4)	PBO = 8.4 (1.8) IFX 5 mg/kg = 8.5 (1.7)	PBO = 1.7 (2.7) IFX 5 mg/kg = 1.4 (1.9)	PBO = CS, 79 (65.3%); ≥ 20 mg/day, 54 (44.6%); 5-ASA, 85 (70.2%); IMM, 53 (43.8%); AZA, 36 (29.8%); MP, 17 (14.0%). CS-refractory disease, 38 (31.4%) IFX 5 mg/kg = CS, 70 (57.9%); ≥ 20 mg/day, 45 (37.2%); 5-ASA, 82 (67.8%); IMM, 66 (54.5%); AZA, 45 (37.2%); MP, 21 (17.4%). CS-refractory disease, 36 (29.8%) Doses of concomitant medications kept stable apart from CS, tapered by 5 mg/week after week 8 until dose of 20 mg/day reached, thereafter dose reduced by 2.5 mg/week until discontinuation	PBO = 76.8 (16.2) IFX 5 mg/kg = 80.0 (17.8)	Current smoker PBO = 7/121 (5.8%) IFX 5 mg/kg = 2/121 (1.7%)

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TABLE 8 Population characteristics of included clinical effectiveness studies in adults (*continued*)

Trial identifier (NCT number), primary publication details	Age, mean years (SD)	Male participants (%)	Ethnicity, Caucasian (%)	Disease extent/location and disease duration, mean years (SD)	Disease severity at baseline: Mayo score, mean (SD)	CRP at baseline, mean mg/dl	Medications at baseline	Weight kg, mean (SD)	Smoking status
ACT2 Rutgeerts *et al.*, 2005[49]	PBO = 39.3 (13.5) IFX 5 mg/kg = 40.5 (13.1)	PBO = 71/123 (57.7%) IFX 5 mg/kg = 76/121 (62.8%)	PBO = 117/123 (95.1%) IFX 5 mg/kg = 116/121 (95.9%)	PBO = left side, 70/120 (58.3%); extensive, 50/120 (41.7%); duration, 6.5 (6.7) IFX 5 mg/kg = left side, 70/118 (59.3%); extensive, 48/118 (40.7%); duration, 6.7 (5.3)	PBO = 8.5 (1.5) IFX 5 mg/kg = 8.3 (1.5)	PBO = 1.6 (2.9) IFX 5 mg/kg = 1.3 (2.3)	PBO = CS, 60 (48.8%); ≥ 20 mg/day, 43 (35.0%); 5-ASA, 89 (72.4%); IMM, 54 (43.9%); AZA, 35 (28.5%); MP, 19 (15.4). CS-refractory disease, 36 (29.3) IFX 5 mg/kg = CS, 60 (49.6%), ≥ 20 mg/day, 40 (33.1%), 5-ASA, 92 (76.0%), IMM, 52 (43.0%), AZA, 41 (33.9%), MP, 11 (9.1). CS-refractory disease, 35 (28.9) Doses of concomitant medications kept stable apart from CS, tapered by 5 mg/week after week 8 until dose of 20 mg/day reached, thereafter dose reduced by 2.5 mg/week until discontinuation	PBO = 76.1 (17.4) IFX 5 mg/kg = 78.4 (17.8)	Current smoker PBO = 6/123 (4.9%) IFX 5 mg/kg = 8/121 (6.6%)

Trial identifier (NCT number), primary publication details	Age, mean years (SD)	Male participants (%)	Ethnicity, Caucasian (%)	Disease extent/location and disease duration, mean years (SD)	Disease severity at baseline: Mayo score, mean (SD)	CRP at baseline, mean mg/dl	Medications at baseline	Weight kg, mean (SD)	Smoking status
Probert *et al.*, 2003[50]	Mean NR Median (IQR) PBO = 40 (29–43.5) IFX 5 mg/kg = 41 (35.5–50.5)	NR	NR	PBO = extensive UC, 13/20, left-side, 3/20, distal colitis, 4/20; median (IQR) duration 59 (35–96) months IFX 5 mg/kg = extensive UC, 14/23, left-side 5/23, distal colitis 4/23; median (IQR) duration 75 (39–141) months	Mean (SD) UC severity score PBO = 8.5 (2) IFX 5 mg/kg = 8 (2) Mean (SD) Baron score PBO = 2.4 (0.5) IFX 5 mg/kg = 2 (0.5)	PBO = 12 (10) IFX 5 mg/kg = 9 (9)	PBO = AZA use, 7/20 (35%); prednisolone equivalent (mg/day), mean 28 (7 SD), median 30 (IQR 25–30); duration of steroid treatment (days), median 28 (IQR 14–45) 28 (11.5–42) IFX 5 mg/kg = AZA use, 6/23 (26%); prednisolone equivalent (mg/day), mean 32 (11 SD), median 30 (IQR 30–30); duration of steroid treatment (days), median 28 (IQR 11.5–42) Doses of 5-ASA and AZA/6-MP kept stable during study. Glucocorticoids kept stable during screening then permitted to be changed 'according to clinical demands', with goal of reducing daily dose by 5 mg prednisolone equivalent per week	Mean NR Median (IQR) PBO = 72 (60–8 as reported) IFX 5 mg/kg = 66 (61–78)	NR

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TABLE 8 Population characteristics of included clinical effectiveness studies in adults (*continued*)

Trial identifier (NCT number), primary publication details	Age, mean years (SD)	Male participants (%)	Ethnicity, Caucasian (%)	Disease extent/location and disease duration, mean years (SD)	Disease severity at baseline: Mayo score, mean (SD)	CRP at baseline, mean mg/dl	Medications at baseline	Weight kg, mean (SD)	Smoking status
UC-SUCCESS Panaccione *et al.*, 2014[51]	AZA = 40.7 (13.2) IFX 5 mg/kg = 38.5 (12.7) IFX 5 mg/kg + AZA = 38.0 (12.2)	AZA = 33/79 (41%) IFX 5 mg/kg = 42/78 (54%) IFX 5 mg/kg + AZA = 48/80 (60%)	NR	Disease extent/duration NR Disease duration AZA = 6.6 (7.8) IFX 5 mg/kg = 6.3 (6.5) IFX 5 mg/kg + AZA = 5.2 (5.1)	AZA = 8.5 (1.4) IFX 5 mg/kg = 8.1 (1.4) IFX 5 mg/kg + AZA = 8.6 (1.3)	NR	AZA = CS use, 27/79 (34.2%); prior immunomodulatory therapy, 8/79 (10%) IFX 5 mg/kg = CS use, 31/78 (39.7%); prior immunomodulatory therapy, 8/78 (10.3%) IFX 5 mg/kg + AZA = CS use, 38/80 (47.5%); prior immunomodulatory therapy, 8/80 (10.0%) Baseline concomitant treatments kept stable during study. Patients receiving CSs at baseline tapered to 0 mg by week 14 unless medically contraindicated	NR	NR

CRP, C-reactive protein; CS, corticosteroid; IMM, immunomodulator; IQR, interquartile range; MTX, methotrexate; MP, mercaptopurine; NR, not reported; PEq, prednisone equivalent; SD, standard deviation.

TABLE 9 Population characteristics of included paediatric population clinical effectiveness studies

Trial identifier (NCT number), primary publication details	Age, mean years (SD)	Male participants (%)	Ethnicity, Caucasian (%)	Disease extent/location and disease duration, mean years (SD)	Disease severity at baseline: Mayo score, mean (SD)	CRP at baseline, mean mg/dl	Medications at baseline	Weight kg, mean (SD)	Smoking status
Hyams *et al.*, 2012[52] (NCT0033649, C0168T72)	Mean NR Median (IQR) Maintenance IFX 5 mg/kg every 8 weeks = 15.0 (12.0–16.0) Maintenance IFX 5 mg/kg every 12 weeks = 15.0 (12.0–16.0)	Maintenance IFX 5 mg/kg every 8 weeks = 10/22 (45.5%) Maintenance IFX 5 mg/kg every 12 weeks = 10/23 (43.5%)	Maintenance IFX 5 mg/kg every 8 weeks = 20/22 (90.9%) Maintenance IFX 5 mg/kg every 12 weeks = 19/23 (82.6%)	Maintenance IFX 5 mg/kg every 8 weeks = left side of colon, 6/22 (27.3%); extensive, 16/22 (72.7%); duration median (IQR) 1.8 (0.6–2.4) Maintenance IFX 5 mg/kg every 12 weeks = left side of colon, 4/23 (17.4%); extensive, 19/23 (82.6%); duration median (IQR) 1.1 (0.6–1.9)	Mean NR Median (IQR) Maintenance IFX 5 mg/kg every 8 weeks = 7.5 (7.0–9.0); median PUCAI (IQR) 50.0 (35.0–55.0) Maintenance IFX 5 mg/kg every 12 weeks = 8.0 (7.0–10.0); median PUCAI (IQR) 57.5 (50.0–65.0)	Mean NR Median (IQR) Maintenance IFX 5 mg/kg every 8 weeks = 0.3 (0.3–1.5) Maintenance IFX 5 mg/kg every 12 weeks = 0.3 (0.3–2.2)	Maintenance IFX 5 mg/kg every 8 weeks = at least 1 concomitant medication, 22/22 (100%); CSs (parenteral or oral), 14/22 (63.6%); ≤ 1 mg/kg prednisone-equivalent, 10/22 (45.5%); ≤ 1 mg/kg prednisone-equivalent, 4/22 (18.2%); CSs (budesonide), 1/22 (4.5%); CSs (rectal), 2/22 (9.1%); immunomodulatory agents, 11/22 (50.0%); 6-MP/AZA, 10/22 (45.5%); MTX,1/22 (4.5%); aminosalicylates, 10/22 (45.5%); antibiotics, 0/22 (0%) Maintenance IFX 5 mg/kg every 12 weeks = at least 1 concomitant medication, 23/23 (100%); CSs (parenteral or oral), 14/23 (60.9%); ≤ 1 mg/kg prednisone-equivalent, 10/23 (43.5%); > 1 mg/kg prednisone-equivalent, 4/23 (17.4%); CSs (budesonide), 0/23 (0%); CSs (rectal),1/23 (4.3%); immunomodulatory agents, 13/23 (56.5%); 6-MP/AZA, 11/23 (47.8%); MTX, 2/23 (8.7%); aminosalicylates, 12/23 (52.2%); antibiotics, 0/23 (0%) UC therapies to remain stable, CS could be tapered if clinically indicated	Maintenance IFX 5 mg/kg every 8 weeks = 51.54 (18.294) [median 50.40 (range 26.2 to 91.6, IQR 36.10–61.50)] Maintenance IFX 5 mg/kg every 12 weeks = 52.80 (16.855) [median 52.30 (range 24.5–86.4, IQR 40.30–68.60)]	NR

CRP, C-reactive protein; CS, corticosteroid; IQR, interquartile range; NCT, National Clinical Trial; NR, not reported; SD, standard deviation.

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Population: adults aged ≥ 18 years with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who are intolerant to, or have medical contraindications against, such therapies

Mean and median reported ages of participants were considered consistent across included adult population trials, ranging from 37 to 42.5 years. Mayo scores at baseline were also consistent across trials and spanned from 8.1 to 8.9. Average proportions of male participants ranged from 41% to 73% and the majority of included patients (when reported) were Caucasian in ethnicity (79.5–95.9%), with the exception of the Suzuki *et al.*[46] study, which included exclusively Japanese patients. Mean and median disease duration of participants ranged from 59 months (4.9 years) to 8.5 years. Conventional UC medications at baseline were variable between the included trials. In none of the included studies had all participants previously been trialled on corticosteroids and AZA or 6-MP, as required by the wording used in the final NICE scope[36] population and the wording of the European Medicines Agency (EMA) licensing for IFX, ADA and GOL. Although it is noted that AZA and 6-MP may be used more typically in clinical practice as maintenance therapies owing to their longer initiation of effect, it is debatable whether or not the included trial populations would represent patients who had failed or were intolerant to previous conventional therapies. All trials related to anti-TNF-α-naive populations, with the exception of ULTRA2[45] (which permitted the inclusion of anti-TNF-α experienced patients) and PURSUIT-Maintenance[48] (in which patients responding to prior GOL induction therapy were randomised to GOL maintenance regimens or PBO). Data at induction were reported according to anti-TNF-α experience. Data relating to patients who were anti-TNF-α-naive for maintenance time points were requested and received from the manufacturer of ADA (AbbVie). Weight and smoking status were both relatively poorly reported across included studies.

Population: children and adolescents aged 6–17 years (inclusive) with severely active ulcerative colitis who have had an inadequate response to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who are intolerant to, or have medical contraindications against, such therapies

The included trial population[52] averaged 15 years of age in both treatment groups, was 43.5–45.5% male and mostly Caucasian in ethnic origin (82.6–90.9%) with average disease duration of 1.1–1.8 years. Patients had a median Mayo score of 7.5 to 8.0 points and a median PUCAI score of 50–57.5 points, for which a PUCAI of score of ≥ 65 would indicate severe disease (and, therefore, were a mixture of patients with moderate and severe disease, while IFX is licensed in paediatric patients with severe disease only). Participants were required to have had prior use of at least one conventional therapy (with 61% to 64% receiving corticosteroids, 50% to 57% immunosuppressants and 46% to 52% aminosalicylates at baseline).

Assessment of effectiveness

Population: adults aged ≥ 18 years with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who are intolerant to, or have medical contraindications against, such therapies

Rates of and duration of response, relapse and remission

Clinical response and remission data were well reported across the included trials for the adult population. It was assumed by the Assessment Group that the numbers of patients who were reported in the trial publications as being in clinical response also included those patients who were in clinical remission. Data relating to transitions of patients between no response, response and remission categories at maintenance time points were requested and received from the manufacturers (MSD and AbbVie). The induction trial data (as reported in the trial publications) and maintenance transition data (received from the manufacturers) from eligible trials were analysed using NMA methods (see page 69). Definitions of clinical response and clinical remission used in the included trials are presented in *Table 10*.

TABLE 10 Definitions of clinical response and remission in adult population RCTs included in the clinical effectiveness systematic review

Trial	Definition of clinical response	Definition of clinical remission	Measurement time points
ACT1[49]	Decrease from baseline in total Mayo score of ≥ 3 points and ≥ 30%, with accompanying decrease in subscore for rectal bleeding of ≥ 1 point or absolute rectal bleeding subscore of 0 or 1	Total Mayo score of ≤ 2 points, with no individual subscore of > 1	Clinical response and remission assessed at weeks 8, 30 and 54
ACT2[49]	As above	As above	Clinical response and remission assessed at weeks 8 and 30
Probert *et al.*, 2003[50]	No definition of response, mean UC 'severity score' and improvement reported only	UCSS (i.e. Mayo score). Clinical remission = UCSS ≤ 2	Outcomes reported at week 2 and 6
UC-SUCCESS[51]	Decrease in total Mayo score of ≥ 3 points and ≥ 30% decrease from baseline Mayo score	CS-free remission = total Mayo score of ≤ 2 points, with no individual subscore of > 1 point without the use of CSs	Mayo scores assessed at weeks 0, 8 (partial Mayo) and 16
ULTRA1[44]	Decrease in Mayo score of ≥ 3 points and ≥ 30% from baseline plus decrease in subscore for rectal bleeding of ≥ 1 point or absolute rectal bleeding subscore of 0 or 1	Mayo score of ≤ 2 points, with no individual subscore of > 1	Mayo scores recorded at weeks 0 and 8
ULTRA2[45]	Decrease from baseline in total Mayo score of ≥ 3 points and ≥ 30% plus decrease in subscore for rectal bleeding of ≥ 1 point or absolute rectal bleeding subscore of 0 or 1	Total Mayo score of ≤ 2 points, with no individual subscore of > 1	Clinical response and remission measured at weeks 8, 32 and 52/early termination
Suzuki *et al.*, 2014[46]	Decrease from baseline in total Mayo score of ≥ 3 points and ≥ 30%, with accompanying decrease in subscore for rectal bleeding of ≥ 1 point or absolute rectal bleeding subscore of ≤ 1	Total Mayo score of ≤ 2 points, with no individual subscore of > 1	Clinical response and remission assessed at weeks 8, 32 and 52
PURSUIT-SC[47]	Decrease from baseline in Mayo score of ≥ 3 points and ≥ 30% plus decrease in subscore for rectal bleeding of ≥ 1 point or absolute rectal bleeding subscore of 0 or 1	Mayo score of ≤ 2 points, with no individual subscore of > 1	Mayo scores recorded at weeks 0 and 6
PURSUIT-Maintenance[48]	Decrease from baseline value (observed in preceding induction study) in Mayo score of ≥ 3 points and ≥ 30% plus decrease in subscore for rectal bleeding of ≥ 1 point or absolute rectal bleeding subscore of 0 or 1	Mayo score of ≤ 2 points, with no individual subscore of > 1	Mayo scores calculated at weeks 0, 30 and 54

CS, corticosteroid.

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Adalimumab Four ADA trials presented clinical response and remission data (ULTRA1,[44] ULTRA2,[45] ULTRA3[54] and Suzuki *et al.*[46]).

At week 8, more patients in the ADA 160 mg/80 mg induction treatment arm of ULTRA1[44] achieved clinical response (54.6% vs. 44.6%; *p*-value not reported) and twice as many reached clinical remission (18.5% vs. 9.2%; $p = 0.031$) than PBO patients.[44] Subgroup analyses demonstrated that patients with a Mayo score of ≥ 10 points at baseline of ULTRA1 were less likely to achieve remission at week 8 than patients with lower baseline Mayo scores.[44] Baseline C-reactive protein (CRP) levels > 10 mg/l and baseline weight of ≥ 82 kg were also linked with lower remission rates in ULTRA1.[44] When baseline prior UC medications were considered, the treatment effect of 160 mg/80 mg of ADA compared with PBO was most pronounced in patients who had received immunomodulator treatment (i.e. AZA/6-MP) at baseline without corticosteroids, and patients who had received no prior aminosalicylates.[44] Clinical response rates at week 8 in the PBO group, when stratified by geographical region, appeared to be higher in Canada and Eastern Europe (than in USA/Puerto Rico and Western Europe) although reasons for this are unclear.[44]

In ULTRA2,[45] patients in the ADA 160 mg/80 mg induction group were more likely to achieve clinical response (50.4% vs. 34.6%; $p < 0.005$) and clinical remission (16.5% vs. 9.3%; $p < 0.05$) at week 8 than in the PBO group.[45] Similarly, among patients who had received no prior anti-TNF-α treatment, greater proportions of patients in the ADA 160 mg/80 mg induction group reached clinical response (59.3% vs. 38.6%; $p < 0.005$) and clinical remission (21.3% vs. 11.0%; $p < 0.05$) at week 8 than PBO-treated patients.[45] Patients receiving ADA as maintenance therapy in ULTRA2[45] were also more likely at week 52 to be in clinical response (30.2% vs. 18.3%; $p < 0.05$) or clinical remission (17.3% vs. 8.5%; $p < 0.005$) than subjects in the PBO group.[45] Anti-TNF-α-naive ADA-treated patients were also more likely to achieve clinical response (36.7% vs. 24.1%; $p = 0.019$) or remission (22.0% vs. 12.4%; $p = 0.029$) at week 52 than those in the PBO group.[45] Patients in the ADA group were more likely to achieve sustained response (ITT 21.8%, anti-TNF-α-naive 26.7%; both $p < 0.05$ vs. PBO) and sustained remission (ITT 8.1%, anti-TNF-α-naive 10.7%; both $p < 0.05$) than PBO group subjects (sustained response: ITT 11.4%, anti-TNF-α-naive 16.6%; sustained remission ITT 2.4%, anti-TNF-α-naive 3.4%).[58] At week 52 of ULTRA2, corticosteroid-free remission was achieved by more ADA group patients versus PBO (both $p < 0.05$).[59] A post-hoc analysis of ULTRA2[45] data at week 52, which included patients from the PBO arm who switched to ADA, demonstrated that mean days in clinical response (134.58 vs. 94.55; $p < 0.001$) and mean days in clinical remission were also greater for ADA-treated patients (85.32 vs. 52.87; $p < 0.001$).[60] For patients with no prior anti-TNF-α use, stool frequency and rectal bleeding Mayo subscores of ≤ 1 point at week 8 were most likely to be achieved in patients receiving ADA than PBO (both $p < 0.05$).[45] At week 52, the proportions of patients who had discontinued corticosteroid use and achieved sustained clinical remission at both weeks 32 and 52 (among patients with baseline corticosteroid use) were 10.0% and 1.2% in the ADA (no prior anti-TNF-α use) and PBO groups, respectively ($p = 0.014$).[45] At week 52, for patients with no prior anti-TNF-α use, 20.3% of the ADA group and 6.2% of the PBO group were in corticosteroid-free clinical remission ($p < 0.05$).[59]

The open-label extension study ULTRA3[54] presented the 4-year efficacy and safety results of 588 patients from ULTRA1[44] and ULTRA2[45] who were followed. Of the 588 patients who entered the ULTRA3[54] extension study, 52.2% (307/588) were in remission at entry according to partial Mayo scores. Partial Mayo scores were calculated at each study visit and at week 156, 46.4% (273/588) of patients had achieved clinical remission.

Patients who received ADA for induction in the Suzuki *et al.*[46] trial were more likely to be in clinical response (50% vs. 35%; $p < 0.05$) by week 8 but not in clinical remission (10% vs. 11%; *p*-value not reported) than PBO group patients.[46] At week 8, a statistically significant greater proportion of patients in the ADA arm reached a subscore of ≤ 1 for physician's global assessment domain than in the PBO arm ($p \leq 0.05$); differences in the other Mayo subscores were not statistically significant.[46] Within the Suzuki *et al.*[46] trial, greater proportions of ADA maintenance-treated patients were in clinical response than PBO group patients (31% vs. 18%; $p < 0.05$) and clinical remission (23% vs. 7%; $p < 0.01$) through week 52.

At week 52, a greater proportion of subjects in the ADA group versus PBO experienced subscores of ≤ 1 point for physician's global assessment and stool frequency subscore (both $p \leq 0.05$).[46] The proportions of patients in steroid-free clinical remission at week 52 were 14.2% and 6.9% in the ADA and PBO arms, respectively (*p*-value not reported).[46]

Golimumab In the PURSUIT-SC induction trial,[47] clinical response and remission data were reported for both Phase II and Phase III. By week 6, in the Phase II analyses (plus additional Phase II randomised patients), more patients receiving GOL were in clinical response (46.5% vs. 37.7%; *p*-value not reported) and remission (18.3% vs. 10.1%; *p*-value not reported) than the PBO group. Similarly, more GOL-treated patients achieved clinical response (51.0% vs. 30.3%; $p < 0.0001$) and remission (17.8% vs. 6.4%; $p < 0.0001$) than PBO-treated patients by week 6 in the Phase III analyses.

In the PURSUIT-Maintenance study,[48] proportions of patients maintaining clinical response (47.0% vs. 31.3%; $p = 0.010$) and in clinical remission [33.1% (50 mg of GOL; $p = 0.068$), 33.8% (100 mg of GOL, $p = 0.011$) vs. 22.1%] through week 54 were larger for the GOL groups than PBO. PURSUIT-Maintenance patients who maintained clinical response and were corticosteroid-free among those who receiving corticosteroids at maintenance baseline were 38.5% in the 50 mg of GOL group ($p = 0.026$), 30.5% in the 100 mg of GOL group ($p = 0.138$) and 20.7% in the PBO group.

Infliximab By week 8 of the ACT1 trial,[49] more patients treated with 5 mg/kg of IFX were in clinical response (69.4% vs. 37.2%; $p < 0.001$) and remission (38.8% vs. 14.9%; $p < 0.001$) than those who received PBO. At week 54, more IFX group patients were in clinical response (45.5% vs. 19.8%; $p < 0.001$) and remission (34.7% vs. 16.5%; $p = 0.001$) than PBO-treated subjects.[49] Patients who sustained clinical response at weeks 8, 30 and 54 were 38.8% in the IFX group and 14.0% in the PBO group ($p < 0.001$).[49] Proportions of patients who sustained clinical remission at weeks 8, 30 and 54 were 19.8% and 6.6% in the IFX and PBO treatment arms, respectively ($p = 0.002$).[49] Of the 5 mg/kg of IFX group, 25.7% were in clinical remission and had discontinued corticosteroids at week 54, compared with 8.9% in the PBO group ($p = 0.006$).[49]

In ACT2,[49] more patients in the 5 mg/kg of IFX group were in clinical response (64.5% vs. 29.3%; $p < 0.001$) and remission (33.9% vs. 5.7%; $p < 0.001$) at week 8 compared with PBO. By week 30, more 5 mg/kg of IFX-treated patients were in clinical response (47.1% vs. 26.0%; $p < 0.001$) and remission (25.6% vs. 10.6%; $p = 0.003$) than PBO.[49] The proportions of patients who sustained clinical response (41.3% vs. 15.4%; $p < 0.001$) and clinical remission (14.9% vs. 2.4%; $p < 0.001$) at weeks 8 and 30 were also higher in the 5 mg/kg of IFX group than patients receiving PBO.[49]

No statistically significant differences were observed between the IFX and PBO treatment groups through week 6 of the Probert *et al.*[50] trial in terms of clinical remission (as defined by a UCSS of ≤ 2) (39% vs. 30%; $p = 0.76$). Remission rates among patients receiving AZA were 67% for IFX and 33% for PBO groups ($p = 0.89$).[50]

A greater proportion of patients in the UC-SUCCESS study[51] who received combination treatment with IFX plus AZA were in steroid-free clinical remission at week 16 (39.74%) than in the IFX monotherapy (22.08%, *p* vs. IFX = 0.017) and AZA monotherapy (23.68%, *p* vs. IFX = 0.813; *p* vs. IFX/AZA = 0.032) groups.[51]

No included trials reported data on rates or duration of relapse.

Data relating to clinical response and remission are summarised in *Table 11*.

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TABLE 11 Summarised clinical response and remission data from RCTs in adults

Study name	Treatment arm	Time point	Rates of and duration of response	Rates of and duration of remission
ULTRA1[44]	PBO	Week 8	Clinical response: 58/130 (44.6%) (*p*-value NR)	Clinical remission: ITT-A3 protocol: 12/130 (9.2%)
ULTRA1[44]	160 mg/80 mg of ADA	Week 8	Clinical response: 71/130 (54.6%)	Clinical remission: ITT-A3 protocol: 24/130 (18.5%), *p*-value vs. PBO = 0.031
ULTRA2[45]	PBO	Week 52	Patients with response: 45/246 (18.3%)	Patients with remission: 21/246 (8.5%)
			No prior anti-TNF-α: clinical response 35/145 (24.1%) Prior anti-TNF-α clinical response 10/101 (9.9%)	No prior anti-TNF-α: clinical remission 18/145 (12.4%) Prior anti-TNF-α clinical remission 3/101 (3.0%)
ULTRA2[45]	160 mg/80 mg of ADA	Week 52	Patients with response: 75/248 (30.2%)	Patients with remission: 42/248 (17.3%)
			No prior anti-TNF-α: clinical response 55/150 (36.7%) Prior anti-TNF-α clinical response 20/98 (20.4%)	No prior anti-TNF-α: clinical remission 33/150 (22.0%) prior anti-TNF-α clinical remission 10/98 (10.2%)
Suzuki *et al.*[46]	PBO	Week 8	Full Mayo score response: 34/96 (35%)	Full Mayo score remission: 11/96 (11%)
Suzuki *et al.*[46]	160 mg/80 mg of ADA	Week 8	Full Mayo score response: 45/90 (50%): *p*-value vs. PBO ≤ 0.05	Full Mayo score remission: 9/90 (10%)
Suzuki *et al.*[46]	PBO	Week 52	Full Mayo score response: 17/96 (18%)	Full Mayo score remission: 7/96 (7%)
Suzuki *et al.*[46]	ADA 80 mg/40 mg or ADA 160 mg/80 mg to week 8 then ADA 40 mg EOW	Week 52	Full Mayo score response: 55/177 (31%); *p*-value vs. PBO, ≤ 0.05	Full Mayo score remission: 41/177 (23%); *p*-value vs. PBO, ≤ 0.01
PURSUIT-SC[47]	Phase III PBO	Week 6	Phase III. PBO. Proportion with clinical response: 76/251 (30.3%)	Phase III. Clinical remission: 16/251 (6.4%)
PURSUIT-SC[47]	Phase III GOL 200 mg/ 100 mg phase III	Week 6	Phase III. GOL 200 mg/ 100 mg. Proportion with clinical response: 129/253 (51.0%) ($p < 0.0001$)	Phase III. Clinical remission: GOL 200/100, 45/253 (17.8) ($p < 0.0001$)
PURSUIT-Maintenance[48]	PBO	Week 54	Proportion of patients maintaining clinical response: 31.2%, $n = 154$	Clinical remission: 34/154 (22.1%)
PURSUIT-Maintenance[48]	50 mg of GOL	Week 54	Proportion of patients maintaining clinical response: 47.0%, $n = 151$ ($p = 0.010$)	Clinical remission: 50/151 (33.1%) ($p = 0.068$)
PURSUIT-Maintenance[48]	100 mg of GOL	Week 54	Proportion of patients maintaining clinical response: 49.7%, $n = 151$ ($p < 0.001$)	Clinical remission: 51/151 (33.8%) ($p = 0.011$)

TABLE 11 Summarised clinical response and remission data from RCTs in adults (*continued*)

Study name	Treatment arm	Time point	Rates of and duration of response	Rates of and duration of remission
UC-SUCCESS[51]	AZA	Week 16	Data not available	Patients in steroid-free remission: 18/76 (23.68%); *p*-value between IFX, 0.813; IFX/AZA, 0.032
UC-SUCCESS[51]	IFX 5 mg/kg	Week 16	Data not available	Patients in steroid-free remission at: 17/77 (22.08%); *p*-value between IFX/AZA, 0.017
UC-SUCCESS[51]	IFX/AZA	Week 16	Data not available	Patients in steroid-free remission: 31/78 (39.74%)
Probert *et al.*[50]	PBO	Week 6	Data not available	Patients with UCSS of < 2: 6/20 (30%). 95% CI for difference with IFX –19% to 34%; $p = 0.76$ When remission rates of patients with total disease in each of the two groups were compared, no significant difference was found ($p = 0.9$)
Probert *et al.*[50]	5 mg/kg of IFX	Week 6	Data not available	Patients with UCSS of < 2: 9/23 (39%)
ACT1[49]	PBO	Week 8	Proportion of patients with clinical response: 45/121 (37.2%)	Proportion of patients in clinical remission: 14.9% (18/121)
ACT1[49]	5 mg/kg of IFX	Week 8	Proportion of patients with clinical response: 84/121 (69.4%) ($p < 0.001$)	Proportion of patients in clinical remission: 38.8% (47/121) ($p < 0.001$)
ACT1[49]	PBO	Week 54	Proportion of patients with clinical response: 24/121 (19.8%)	Proportion of patients in clinical remission: 16.5% (20/121)
ACT1[49]	5 mg/kg of IFX	Week 54	Proportion of patients with clinical response: 55/121 (45.5%) ($p < 0.001$)	Proportion of patients in clinical remission: 34.7% (42/121) ($p = 0.001$)
ACT2[49]	PBO	Week 8	Proportion of patients with clinical response: 36/123 (29.3%)	Proportion of patients in clinical remission: 5.7% (7/123)
ACT2[49]	5 mg/kg of IFX	Week 8	Proportion of patients with clinical response: 78/121 (64.5%) ($p < 0.001$)	Proportion of patients in clinical remission: 33.9% (41/121) ($p < 0.001$)
ACT2[49]	PBO	Week 30	Proportion of patients with clinical response: 32/123 (26.0%)	Proportion of patients in clinical remission: 10.6% (13/123)
ACT2[49]	5 mg/kg of IFX	Week 30	Proportion of patients with clinical response: 57/121 (47.1%) ($p < 0.001$)	Proportion of patients in clinical remission: 25.6% (31/121) ($p = 0.003$)

EOW, every other week; ITT-A3, intention to treat-amendment 3.

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Consideration was given to whether or not it would be appropriate to conduct meta-analysis using the response and remission outcomes within the trials included in the clinical effectiveness review. It was acknowledged that the ADA trials differed from the IFX and GOL trials in the method of estimation of Mayo scores, in that the IFX and GOL trials were based on the average Mayo scores over a consecutive 3-day diary period and the ADA trials included scores based on the worst entry over a consecutive 3-day diary period. However, clinical advisors to the Assessment Group did not expect that this difference would preclude a synthesis of the evidence. It was further noted by the Assessment Group that there may be potential issues in the consistency of measurement of Mayo scores and levels of PBO response according to physician experience and geographical location. The comparability of the trial data set in terms of prior UC treatment was improved by the requesting and receipt from the manufacturer of ADA of anti-TNF-α-naive maintenance data from ULTRA2.[45] It should also be noted that the PURSUIT-Maintenance trial[48] rerandomised patients who had previously responded to GOL induction therapy in two previous trials; the extent of this potential bias on patient outcomes is unclear.

Clinical response and remission at induction and maintenance in eligible adult population trials were analysed using NMAs. The results of these analyses are presented on page 72. For the sake of brevity, all secondary efficacy and safety outcomes data are presented in *Appendices 4* and *5*.

Measures of disease activity

Adalimumab At week 8 of the ULTRA1 trial,[44] median changes in CRP from baseline were greater in the ADA 160 mg/80 mg group than PBO (–0.77 mg/l vs.–0.09 mg/l). Patients receiving ADA 160 mg/80 mg in ULTRA1[44] were also more likely to achieve scores of ≤ 1 point for the Mayo rectal bleeding ($p = 0.038$) and physician global assessment ($p = 0.035$) subscores.[44] Statistically significant changes from baseline in haemoglobin and red blood cells (both $p < 0.001$), total protein and albumin levels (both $p < 0.01$) were observed in the ADA group versus PBO in ULTRA1.[61]

In ULTRA2,[45] greater proportions of patients receiving ADA achieved Mayo subscores of ≤ 1 point at week 8 than PBO, although only stool frequency and rectal bleeding were statistically significant at the 5% level. Significantly more ADA group patients who had not previously received anti-TNF-α treatment reached a rectal bleeding score of ≤ 1 than PBO ($p < 0.001$).[45]

Golimumab At week 6 in the Phase II and Phase III components of PURSUIT-SC,[47] mean changes from baseline in Mayo score were –2.6 [standard deviation (SD) 2.73] points and –1.8 (SD 2.96) points (Phase II; $p = 0.219$), followed by –3.1 (SD 2.90) points and –1.6 (SD 2.53) points (Phase III; $p < 0.0001$) in the GOL 200 mg/100 mg and PBO arms. Mean changes in CRP concentration (mg/l) at week 6 (Phase III) were –3.35 (GOL 200 mg/100 mg) and +1.59 (PBO) ($p < 0.0001$).

Infliximab In ACT1,[49] the proportion of patients at week 8 who were not refractory to corticosteroid therapy was higher in the IFX group than PBO (66.7 vs. 37.9%; $p < 0.001$).[49] Proportions of patients not refractory to corticosteroids at week 8 of the ACT2 study[49] were 64.8% for 5 mg/kg of IFX and 26.4% for PBO ($p < 0.001$).[49] As of week 152 of the extension studies, 20 patients remained, of whom 18 (90.0%) had no or mild disease.

Mean improvements in UCSS at week 6 of the Probert *et al.*[50] study were 4 (SD 3) for both PBO and IFX groups. The mean reduction in daily dose of glucocorticoid was equivalent to 19 mg (SD 15 mg) and 14 mg prednisolone (SD 12 mg) in the IFX and PBO groups, respectively ($p = 0.037$).[50] No statistically significant changes in CRP levels were observed between IFX and PBO arm patients.[50]

At week 8 of the UC-SUCCESS trial,[51] 65.79% and 36.84% of the AZA arm, 88.31% and 49.35% of the IFX arm and 85.90% and 52.56% of the IFX/AZA combination arm achieved partial Mayo score decreases of ≥ 1 point and ≥ 2 points respectively.[51] Week 8 mean changes from baseline in partial Mayo scores were –2.81 (SD 2.46) points, –3.52 (SD 2.25) points and –4.01 (SD 2.04) points for AZA, IFX and

combination IFX/AZA.[51] Mean changes in total Mayo score from baseline at week 16 were –3.00 (baseline 8.50) points for AZA (p vs. IFX/AZA = 0.001), –4.27 (baseline 8.08) points for IFX (p vs. IFX/AZA = 0.001), and –5.28 (baseline 8.54) points for combination IFX/AZA.[51]

Mortality

Reported deaths for the included trials are presented in *Appendix 4*.

Adalimumab No deaths occurred in the ULTRA1[44] or ULTRA2[45] ADA trials. Deaths were not reported in Suzuki *et al.*[46]

Golimumab One death occurred in PURSUIT-SC[47] in the unlicensed 400 mg/200 mg of GOL induction treatment arm in a patient receiving concomitant 20 mg of prednisolone with a case of peritonitis and sepsis after surgical complications related to an ischiorectal abscess and subsequent bowel perforation after surgery. In PURSUIT-Maintenance,[48] no deaths occurred through week 54 in the PBO arm but one death (from pneumonia and heart failure) occurred after week 54 in a patient who had received PBO induction and maintenance. No deaths were observed in the 50 mg of GOL group of PURSUIT-Maintenance; however, one death was reported after week 54 (in a patient who received 100 mg/50 mg of GOL induction and 50 mg of GOL maintenance) owing to heart dysfunction in the presence of pronounced atherosclerosis and stenosis affecting the aorta, large arteries and coronary arteries. Three deaths were reported through week 54 of PURSUIT-Maintenance in the 100 mg of GOL treatment arm due to malnutrition and sepsis (patient receiving 2 mg/kg of i.v. GOL induction); cardiac failure with history of thrombosis (patient receiving 400 mg/200 mg of GOL, subcutaneous induction); and disseminated TB in patient who tested positive for latent TB on induction study entry and was receiving isoniazid at time of event (receiving 200 mg/100 mg of GOL, subcutaneous induction). Four deaths were reported after week 54 for the 100 mg of GOL group in PURSUIT-Maintenance, including one case of myocardial infarction in a patient with history of myocardial infarction (PBO, subcutaneous induction and 100 mg of GOL maintenance), two deaths due to gallbladder adenocarcinoma with liver metastasis and due to sepsis (patients receiving 2 mg/kg of i.v. GOL induction) and 100 mg of GOL maintenance) and one death due to accidental nitrous oxide overdose (in a patient receiving 200 mg/100 mg of GOL, subcutaneous induction and 100 mg of GOL maintenance).

Infliximab The only reported deaths in any of the included IFX trials occurred in patients recruited into the ACT studies.[49] No deaths occurred through week 54 in ACT1 and ACT2. After week 54, two patients died in the PBO arm of ACT1 (due to suicide and cerebrovascular accident). After 54 weeks, four patients died who received IFX in the ACT studies (no dose information available), histoplasmosis 4 weeks after last infusion, listeria encephalitis 3 years after last infusion, prostate cancer 3.5 years after last infusion, and natural causes 10 months after last infusion.

Rates of hospitalisation

A total of four included trials reported hospitalisation data for the adult population (ULTRA1[44] and ULTRA2[45] for ADA, ACT1[49] and ACT2[49] for IFX, no trials for GOL).

Adalimumab In ULTRA1,[44] all reported hospitalisation outcome measure data were lower in the 160 mg/80 mg of ADA group than PBO at week 8, indicating more favourable outcomes for the intervention group, including physician visits ($p = 0.559$), emergency room visits (p-value not reported), hospital admissions (p-value not reported) and days in hospital ($p = 0.297$). None of these differences were statistically significant.[62] Similarly, for the ULTRA2 trial,[45] hospitalisation-related outcome data were also slightly lower for the ADA group than PBO at week 52, although this was only statistically significant for physician visits (physician visits, $p = 0.035$; emergency room visit, $p = 0.847$; hospital admissions, $p = 0.418$; and days in hospital, $p = 0.467$).[62] A range of hospitalisation-related measures were also reported for ULTRA1 and ULTRA2 data combined. The all-cause hospitalisation incidence rate was lower for ADA than PBO ($p = 0.047$), as was the UC-related hospitalisation incidence rate ($p = 0.002$), with a relative risk for UC-related hospitalisation of 0.48 for ADA versus PBO ($p < 0.001$).[63]

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Golimumab No included trials reported hospitalisation data for GOL.

Infliximab In the ACT1 and ACT2 trials,[49] hospitalisations through week 54 were reported to be lower for the 5 mg/kg of IFX group than PBO (ACT1, $p = 0.061$; ACT2, $p = 0.009$).[64]

Rates of surgical intervention (both elective and emergency)

Six included trials in the adult population included information on rates of surgical intervention (ULTRA1[44] and ULTRA2[45] for ADA, PURSUIT-Maintenance[48] for GOL, and ACT1,[49] ACT2[49] and Probert *et al.*[50] for IFX). No trials reported whether surgical outcomes were elective or emergency in nature.

Adalimumab In ULTRA1,[44] colectomies to week 8 were lower in the 160 mg/80 mg of ADA group than PBO (1.4% vs. 3.6%; *p*-value not reported; elective or emergency not reported). Colectomy rates were very slightly lower through week 52 of ULTRA2[45] in the ADA group (4%) vs. PBO (4.9%) (*p*-value not reported; elective or emergency not reported).[63,65]

Golimumab Limited data were available for GOL, which indicated that only 2–3% of GOL induction responders rerandomised to 50 mg or 100 mg of GOL in PURSUIT-Maintenance[48] received colectomy at the end of maintenance.[66]

Infliximab Colectomy and ostomy rates through week 54 of ACT1[49] were both slightly lower in the 5 mg/kg of IFX group (5.8% and 2.5%, respectively) than in the PBO group (7.4% and 4.1% respectively) (*p*-values not reported).[64] One patient in each case from the PBO arm was reported as having the outcomes of colectomy and an ostomy (0.7% and 0.7%) through week 54 of ACT2, while no patients in the 5 mg/kg IFX group underwent colectomy or ostomy.[64] Limited details were available from the Probert *et al.*[50] trial to the effect that a single patient in the PBO arm received a colectomy during the intervention period.

Meta-analysis

Colectomy rates during induction were reported by one trial (ULTRA1[44]). The between-group difference was not statistically significant [RR = 0.63 (random effects), 95% CI 0.21 to 1.86; $p = 0.40$; *Figure 5*).

Colectomy rates during maintenance were reported by one trial evaluating the licensed maintenance dose of ADA comprising a mixed sample of anti-TNF-α exposed and naive participants (ULTRA2,[45] 517 participants). The between-group difference was not significant [RR = 0.83 (random effects), 95% CI 0.36 to 1.88; $p = 0.65$). Two trials evaluating the licensed maintenance dose of IFX reported maintenance outcomes at 30 weeks (ACT2[49]) and 54 weeks (ACT1[49]). The pooled effect across these trials (486 participants) was not significant [RR = 0.73 (random effects), 95% CI 0.29 to 1.81; $p = 0.49$]. The forest plot for these analyses (random effects) is presented in *Figure 6*.

Ostomy rates during maintenance in adults were reported by two trials evaluating the licensed maintenance dose of IFX at 30 weeks (ACT2[49]) and 54 weeks (ACT1[49]). The pooled effect across these trials (486 participants) was not significant [RR = 0.55 (random effects), 95% CI 0.15 to 1.98; $p = 0.36$]. The forest plot for these analyses is presented in *Figure 7*.

Time to surgical intervention (both elective and emergency)

Very limited data were reported from the included trials in the adult population for the outcome of time to surgical intervention. Sandborn *et al.*[67] combined data from the ACT1 and ACT2 IFX trials[49] and reported that the cumulative incidence of colectomy through 54 weeks was higher for the PBO group (17%) than for the combined IFX group (10%) ($p = 0.02$) and calculated a hazard ratio of 0.59, indicating a 41% reduction in the risk of colectomy for the combined licensed and unlicensed IFX groups versus PBO.

Study or subgroup	Monoclonal antibody Events	Total	PBO Events	Total	Weight	RR M–H, random, 95% CI
ADA						
ULTRA1[44]	5	130	8	130	100.0%	0.63 (0.21 to 1.86)
Subtotal (95% CI)		**130**		**130**	**100.0%**	**0.63 (0.21 to 1.86)**
Total events	5		8			
Heterogeneity: not applicable						
Test for overall effect: $z = 0.84$ ($p = 0.40$)						
Test for subgroup differences: not applicable						

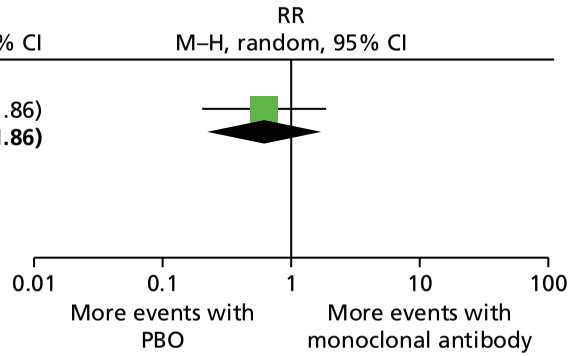

FIGURE 5 Forest plot of comparison: colectomy – adults. Outcome: colectomy – induction-licensed dose. M–H, Mantel–Haenszel.

Study or subgroup	Monoclonal antibody Events	Total	PBO Events	Total	Weight	RR M–H, random, 95% CI
ADA						
ULTRA2[45] (prior anti-TNF-α exposed and non-exposed)	10	248	12	246	100.0%	0.83 (0.36 to 1.88)
Subtotal (95% CI)		**248**		**246**	**100.0%**	**0.83 (0.36 to 1.88)**
Total events	10		12			
Heterogeneity: not applicable						
Test for overall effect: $z = 0.45$ ($p = 0.65$)						
IFX						
ACT1[49] (week 54)	7	121	9	121	91.8%	0.78 (0.30 to 2.02)
ACT2[49] (week 30)	0	121	1	123	8.2%	0.34 (0.01 to 8.24)
Subtotal (95% CI)		**242**		**244**	**100.0%**	**0.73 (0.29 to 1.81)**
Total events	7		10			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.24$, df = 1 ($p = 0.62$); $I^2 = 0\%$						
Test for overall effect: $z = 0.68$ ($p = 0.49$)						
Test for subgroup differences: $\chi^2 = 0.04$, df = 1 ($p = 0.84$); $I^2 = 0\%$						

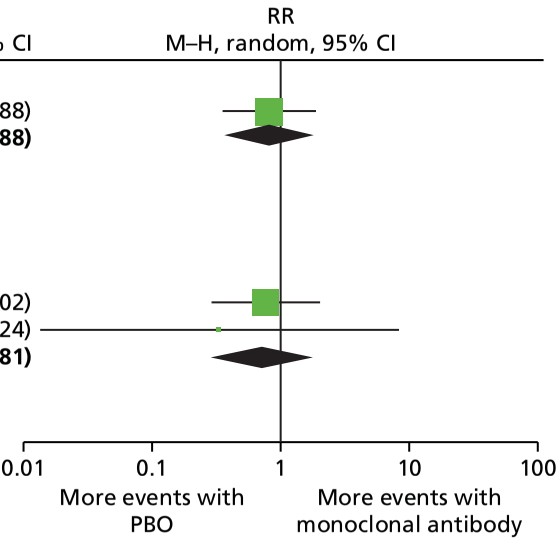

FIGURE 6 Forest plot of comparison: colectomy – adults. Outcome: colectomy – maintenance-licensed dose. df, degrees of freedom; M–H, Mantel–Haenszel.

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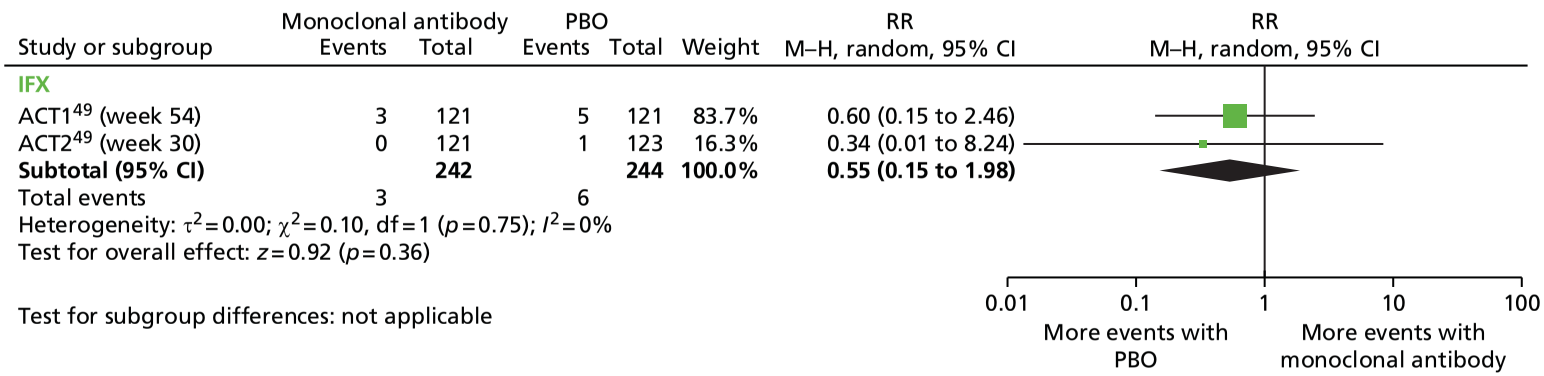

FIGURE 7 Forest plot of comparison: ostomy – adults. Outcome: ostomy – maintenance-licensed dose. df, degrees of freedom; M–H, Mantel–Haenszel.

Health-related quality of life

Health-related quality-of-life data were available from nine included trials in the adult population (ULTRA1,[44] ULTRA2[45] and ULTRA3 for ADA, PURSUIT-SC[47] and PURSUIT-Maintenance[48] for GOL, and ACT1,[49] ACT2,[49] UC-SUCCESS[51] and Probert *et al.*[50] for IFX, see *Appendix 6*). Data related to HRQoL were measured using Inflammatory Bowel Disease Questionnaire (IBDQ), Short Form questionnaire-36 items (SF-36) and the European Quality of Life-5 Dimensions (EQ-5D) [note: total IBDQ scores can range from 32 (very poor) to 224 (perfect HRQoL)].

Adalimumab

In ULTRA1,[44] the changes from baseline scores to week 8 in IBDQ were very similar for the 160 mg/80 mg of ADA and PBO groups (153 vs. 152; *p*-value not reported). Furthermore, the difference between IBDQ mean responses at week 8 in the 160 mg/80 mg of ADA and PBO groups was not statistically significant (70 vs. 75; $p = 0.532$). Changes from baseline in SF-36 mental and physical component summary scores were also similar at week 8 in the ADA and PBO group (46 vs. 44). ULTRA2[45] week 52 IBDQ scores were higher in the 160 mg/80 mg of ADA group than PBO, indicating more favourable HRQoL in the ADA group (27 vs. 19; $p < 0.05$). A greater proportion of patients experienced an increase in IBDQ of ≥ 16 points from baseline by week 52 in the ADA group than PBO (26.2% vs. 16.3%; $p < 0.05$).

Golimumab

In both Phase II and Phase III of the PURSUIT-SC[47] GOL trial, patients in the 200 mg/100 mg of GOL induction arms reported a greater change in IBDQ from baseline to week 6 than the patients of PBO groups [Phase II, mean 24.9 vs. 14.8 (*p*-value NS); Phase III mean 27.0 vs. 14.8; $p < 0.0001$]. Greater proportions of patients in each GOL group were also described as achieving 'any improvement' to 'clinically meaningful improvement' in IBDQ (51.1% vs. 35.2%; $p < 0.001$), physical component summary (41.0% vs. 31.6%; $p = 0.01$) and mental component summary scores (42.7% vs. 28.5%; $p < 0.001$) at week 6.

Infliximab

In the ACT1 trial,[49] changes from baseline in SF-36 physical and mental component summary scores to week 8 were larger for the 5 mg/kg of IFX group than the PBO group (both $p < 0.05$). Statistically significant improvements in IBDQ and SF-36 components were evident in the 5 mg/kg of IFX treatment arm compared with PBO to week 8 for ACT1 and ACT2 trials combined. The greatest changes from baseline to week 16 in both IBDQ and SF-36 physical function were observed in the IFX/AZA combination treatment arm ($p < 0.05$ vs. AZA, $p < 0.05$ vs. IFX for both outcomes). Improvements in IBDQ and EQ-5D from baseline to week 6 in Probert *et al.*[50] were larger in the IFX group than PBO (*p*-value not reported).

Adverse events of treatment (including leakage and infections following surgery)

The included trials report data relating to AEs associated with the interventions under assessment only (i.e. IFX, ADA and GOL) and do not report safety outcomes (e.g. leakage and infections) post surgery. However, although the clinical effectiveness systematic review does not take these factors into account, these factors are relevant to the economic analysis (see *Chapter 4*). *p*-values are provided when available; however, the statistical significance of observed differences in safety outcomes was poorly reported across the included trials.

Discontinuations due to adverse events

Adalimumab

Discontinuations due to AEs at week 8 in ULTRA1[44] were 5.4% in both 160 mg/80 mg of ADA and PBO groups.[44] Withdrawals due to AEs were slightly lower for ADA than PBO by week 52 of ULTRA2,[45] at 23 out of 257 (8.9%) for 160 mg/80 mg of ADA and 34 out of 260 (13.1%) for PBO.[45] More AEs leading to discontinuation occurred in the Suzuki *et al.*[46] trial in the 40 mg of ADA every other week group versus PBO [$n = 22$ vs. $n = 6$; 22.4/100 patient-years (PYs) vs. 13.4/100 PYs].

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Golimumab

Numbers of patients who discontinued study agent through week 6 because of at least one AE were relatively low across both 200 mg/100 mg of GOL induction (1/331, 0.3%) and PBO (3/330, 0.9%) groups for PURSUIT-SC.[47] Through week 54 of PURSUIT-Maintenance,[48] 8/154 (5.2%) of the 50 mg of GOL, 14/154 (9.1%) of the 100 mg of GOL and 10/156 (6.4%) of the PBO groups had discontinued study agent owing to at least one AE.[48]

Infliximab

Through week 54 of ACT1[49] the number of patients with AEs leading to study drug discontinuation was 10 out of 121 (8.3%) and 11 out of 121 (9.1%) for the 5 mg/kg of IFX and PBO groups, respectively. Through week 30 of ACT2,[49] discontinuations due to AEs occurred in 2 out of 121 (1.7%) and 12 out of 123 (9.8%) for 5 mg/kg of IFX and PBO arm patients, respectively. Through week 8 of UC-SUCCESS[51] AEs leading to discontinuation were highest for AZA (6/79, 8%), compared with 2/78 (3%) for IFX and 3/80 (4%) for combination IFX and AZA.[51]

Number of patients experiencing one or more adverse event

Adalimumab

In ULTRA1,[44] patients reporting at least one treatment emergent AE were 112 out of 223 (50.2%) and 108 out of 223 (48.4%) for the 160 mg/80 mg of ADA induction and PBO groups, respectively.[44] At week 52 of ULTRA2,[44] the proportions of patients reporting any AE were similar between groups; 213 out of 257 (82.9%) for the 160 mg/80 mg of ADA arm and 218 out of 260 (83.8%) of the PBO arm. At week 52 in the Suzuki *et al.*[46] study, fewer AEs occurred (in terms of events per 100 PYs) in the 40 mg of ADA every other week group than in the PBO group (547.9/100 PYs vs. 609.4/100 PYs).

Golimumab

By week 6 of PURSUIT-SC,[47] the proportions of patients with at least one AE were similar for 200 mg/100 mg of GOL induction (124/331, 37.5%) and PBO (126/330, 38.2%).[46] Patients reporting one or more AEs through week 54 of PURSUIT-Maintenance[48] were 112 out of 154 (72.7%) in the 50 mg of GOL arm, 113 out of 154 (73.4%) in the 100 mg of GOL arm and 103 out of 156 (66.0%) in the PBO treatment arm.

Infliximab

The proportions of patients through week 54 of ACT1[49] reporting at least one AE were 106 out of 121 (87.6%) and 103 out of 121 (85.1%) for 5 mg/kg of IFX and PBO respectively. At week 30 of ACT2,[49] these values were 99 out of 121 (81.8%) and 90 out of 123 (73.2%) for 5 mg/kg of IFX and PBO, respectively. Through week 8 of UC-SUCCESS,[51] patients reporting one or more AE were higher in the AZA group (41/79, 52%) than IFX (26/78, 33%) or combination IFX/AZA (30/80, 38%).

Number of patients experiencing one or more serious adverse event

Definitions of serious adverse events (SAEs) were poorly reported across included RCTs.

Adalimumab

At week 8 in ULTRA1,[44] the proportions of patients reporting one or more SAEs were exactly equivalent, at 5.4% (12/223) in the 160 mg/80 mg of ADA group and 5.4% (12/223) in the PBO group.[44] Proportions of ULTRA2[45] patients reporting any SAEs were also roughly equivalent, with 12.1% (31/257) and 12.3% (32/260) in the 160 mg/80 mg of ADA and PBO groups, respectively.[45] At week 52 of the Suzuki *et al.*[46] study, a similar number of events per 100 PYs were classed as serious in the 40 mg of ADA every other week group than in the PBO group (33.6/100 PYs vs. 31.3/100 PYs).[46]

Golimumab

By week 6 of PURSUIT-SC,[47] the proportion of patients reporting at least one SAE was lower in the 200 mg/100 mg of GOL treatment arm (9/331, 2.7%) than the PBO group (20/330, 6.1%).[47] More patients

in the 100 mg of GOL group reported one or more SAE (22/154, 14.3%) than patients in the 50 mg of GOL (13/154, 8.4%) or PBO (12/156, 7.7%) groups by week 54 of PURSUIT-Maintenance.[48]

Infliximab

Proportions of patients through week 54 of ACT1[49] who reported SAEs were similar for 5 mg/kg of IFX (26/121, 21.5%) and PBO (31/121, 25.6%) groups.[49] At week 30 of ACT2,[49] slightly fewer patients reported SAEs in the 5 mg/kg of IFX group [13/121 (10.7%)] than the PBO group [24/123 (19.5%)].[49] SAEs were more frequently reported by week 8 of UC-SUCCESS[51] among patients receiving AZA (6/79, 8%) than IFX (0/78) or combination IFX and AZA (3/80, 4%).

Infections

Adalimumab

The occurrence of infections at week 8 of ULTRA1[44] was very similar for the 160 mg/80 mg of ADA group (32/223, 14.3%) and the PBO group (35/223, 15.7%).[44] This was also the case at week 52 of ULTRA2,[45] with 45.1% (116/257) and 39.6% (103/260) of patients reporting infections within the 160 mg/80 mg of ADA and PBO groups, respectively.[45] At week 8 of Suzuki *et al.*,[46] infections occurred in 18.9% (17/90) and 15.6% (15/96) of the 160 mg/80 mg of ADA and PBO groups.[46]

Golimumab

At week 6 of PURSUIT-SC,[47] 12.1% (40/330) of PBO group patients reported at least one infection, of which 7.0% required treatment (23/330); these values were similar to those in the 200 mg/100 mg of GOL induction group (39/331, 11.8%; 15/331, 4.5%).[47] Infections at week 54 of PURSUIT-Maintenance[48] were more common in the 50 mg of GOL (60/154, 39.0%; requiring treatment 39/154, 25.3%) and 100 mg of GOL (60/154, 39.0%; requiring treatment 44/154, 28.6%) maintenance groups than PBO (44/156, 28.2%; requiring treatment 24/156, 15.4%).[47]

Infliximab

Through week 54 of ACT1,[49] infections were slightly more common among patients receiving 5 mg/kg of IFX (53/121, 43.8%; requiring treatment 39/121, 32.2%) than PBO (47/121, 38.8%; requiring treatment 25/121, 20.7%).[49] At week 30 of ACT2,[49] infections had occurred in 18 out of 121 (14.9%, requiring treatment 17/121, 14.2%) and 29 out of 123 (23.6%; requiring treatment 15/123, 12.2%) of patients receiving IFX and PBO respectively.[49] Through week 54 of the ACT1 and ACT2 extension studies, infections occurred in 94 out of 242 (39%) of 5 mg/kg IFX and 80 out of 244 (33%) of PBO group patients.[67]

Serious infections

Adalimumab

Reported serious infections were low through week 8 of ULTRA1[44] in both PBO (3/223, 1.3%, one pneumonia, one sepsis, one staphylococcal wound infection) and 160 mg/80 mg of ADA treatment arms (0/223), and remained similarly comparable between treatment arms through week 52 of ULTRA2[45] (160 mg/80 mg of ADA 4/257, 1.6% vs. PBO 5/260, 1.9%). Serious infections were reported at week 52 of ULTRA3 at a rate of 3.4 events per 100 PYs for patients receiving ADA.[62] No serious infections were reported at week 8 of the Suzuki *et al.*[46] trial in the PBO arm, while three cases occurred by week 8 in the 160 mg/80 mg of ADA group (3/90, 3.3%).

Golimumab

The proportion of patients reporting one or more serious infections were slightly higher at week 6 of PURSUIT-SC[47] in the PBO treatment arm (6/330, 1.8%) than 200 mg/100 mg of GOL induction (1/331, 0.3%, one pneumonia).[47] By week 54 of PURSUIT-Maintenance,[48] the occurrence of serious infections was marginally higher in the 50 mg of GOL (5/154, 3.2%) and 100 mg of GOL (5/154, 3.2%) maintenance groups than PBO (3/156, 1.9%).

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Infliximab

The proportion of patients with serious infections through week 54 of the ACT1[49] trial was similar between treatment arms (5 mg/kg of IFX 3/121, 2.5%; PBO 5/121, 4.1%). Numbers of patients with serious infections through week 30 of ACT2[49] were similar for 5 mg/kg of IFX (2/121, 1.7%) and PBO (1/123, 0.8%).[49] Through week 54 of the ACT1 and ACT2 extension studies, serious infections occurred in 7/242 (2.89%) of 5 mg/kg of IFX and 6/244 (2.46%) of PBO group patients.[67]

Serious infections occurred in very low numbers through week 8 of the UC-SUCCESS[51] trial (AZA 1/79, 1%; IFX 1/78, 1%; combination IFX/AZA 0/80, 0%).

Meta-analysis

Serious infections associated with the licensed induction dose of ADA in were reported by two trials, one in Western populations (ULTRA1,[44] 446 participants) and one in Japanese populations (Suzuki *et al.*,[46] 186 participants). The between-group difference in both trials was not significant [RR = 0.14 (random effects) 95% CI 0.01 to 2.75; $p = 0.20$; RR = 7.46 (random effects) 95% CI 0.39 to 142.47; $p = 0.18$ respectively]. The forest plot for this analysis (random effects) is presented in *Figure 8*. Serious infections associated with the licensed induction of GOL in adults were reported by one trial (PURSUIT-SC,[47] 661 participants). The between-group difference was not significant [RR = 0.17 (random effects), 95% CI 0.02 to 1.37; $p = 0.10$].

Serious infections associated with the licensed maintenance dose of ADA were reported by one trial comprising a mixed sample of anti-TNF-α exposed and naive participants (ULTRA2,[45] 517 participants). The between-group difference was not significant [RR = 0.81 (random effects) 95% CI 0.22 to 2.98; $p = 0.75$]. Serious infections associated with maintenance dose of 50 mg or 100 mg of GOL in adults were reported by one trial (PURSUIT-Maintenance[48]). The between-group difference for 50 mg of GOL compared with PBO (312 participants) was not significant [RR = 1.67 (random effects) 95% CI 0.41 to 6.85; $p = 0.48$]. The between-group difference for 100 mg of GOL compared with PBO (310 participants) was also not significant [RR = 1.69 (random effects) 95% CI 0.41 to 6.94; $p = 0.47$]. Two trials evaluating the licensed maintenance dose of IFX reported maintenance outcomes at 30 weeks (ACT2[49]) and 54 weeks (ACT1[49]). The pooled effect across these trials (486 participants) was not significant [RR = 0.82 (random effects) 95% CI 0.24 to 2.77; $p = 0.77$]. The forest plot for these analyses is presented in *Figure 9*.

Reactivation of tuberculosis

Adalimumab

No data relating to the reactivation of TB were reported for ULTRA1[44] or ULTRA2.[45] Reactivation of TB occurred in a single patient (equating to < 0.1 events/100 PYs) by week 52 of ULTRA3.[62] No events occurred in the PBO arm of the Suzuki *et al.*[46] study through week 8, while for the 40 mg of ADA every other week group, a single event of reactivation of TB was described (1.0 events/100 PYs).[46]

Golimumab

No cases of reactivation of TB were reported in the PURSUIT-SC trial.[47] In the PBO maintenance group of PURSUIT-Maintenance,[48] one event of reactivation occurred (in a patient who had received unlicensed 4 mg/kg of GOL i.v. induction).[47] No cases were reported for patients receiving 50 mg of GOL maintenance treatment. However, three cases occurred in the 100 mg of GOL maintenance group (one patient each had received induction regimens of 400 mg/200 mg of GOL, subcutaneous; 4 mg/kg i.v.; or 200 mg/100 mg subcutaneous) (including one fatal case: 200 mg/100 mg of GOL, subcutaneous).[47]

Infliximab

No cases of reactivation of TB were reported in the ACT1,[49] ACT2,[49] Probert *et al.*[50] or UC-SUCCESS[51] studies.

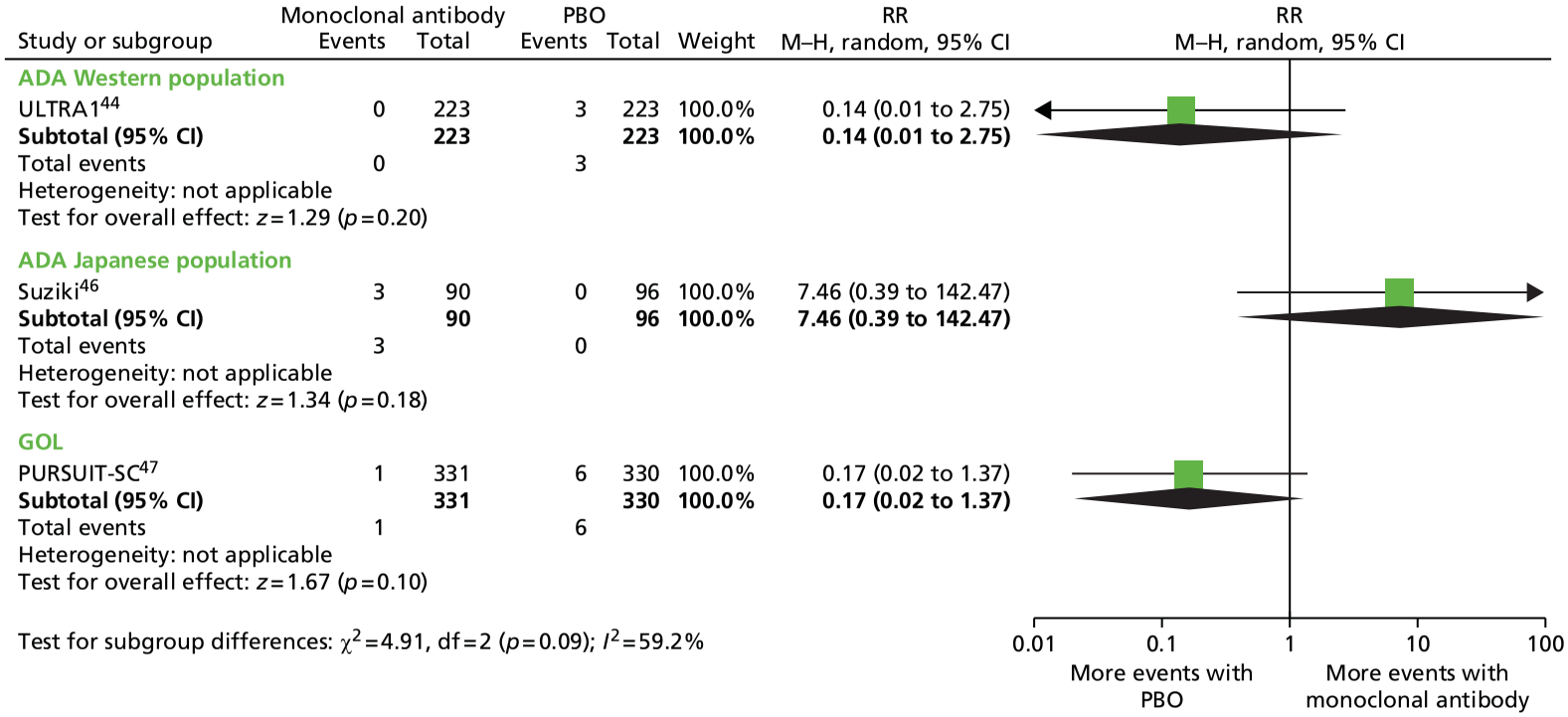

FIGURE 8 Forest plot of comparison: serious infections – adults. Outcome: serious infections – induction-licensed dose. df, degrees of freedom; M–H, Mantel–Haenszel.

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Study or subgroup	Monoclonal antibody Events	Total	PBO Events	Total	Weight	RR M–H, random, 95% CI
ADA						
ULTRA2[45] (prior anti-TNF-α exposed and non-exposed)	4	257	5	260	100.0%	0.81 (0.22 to 2.98)
Subtotal (95% CI)		**257**		**260**	**100.0%**	**0.81 (0.22 to 2.98)**
Total events	4		5			
Heterogeneity: not applicable						
Test for overall effect: $z = 0.32$ ($p = 0.75$)						
50 mg of GOL						
PURSUIT-Maintenance[48]	5	156	3	156	100.0%	1.67 (0.41 to 6.85)
Subtotal (95% CI)		**156**		**156**	**100.0%**	**1.67 (0.41 to 6.85)**
Total events	5		3			
Heterogeneity: not applicable						
Test for overall effect: $z = 0.71$ ($p = 0.48$)						
100 mg of GOL						
PURSUIT-Maintenance[48]	5	154	3	156	100.0%	1.69 (0.41 to 6.94)
Subtotal (95% CI)		**154**		**156**	**100.0%**	**1.69 (0.41 to 6.94)**
Total events	5		3			
Heterogeneity: not applicable						
Test for overall effect: $z = 0.73$ ($p = 0.47$)						
IFX						
ACT1[49] (week 54)	3	121	5	156	74.2%	0.60 (0.15 to 2.46)
ACT2[49] (week 30)	2	121	1	**156**	25.8%	2.03 (0.19 to 22.13)
Subtotal (95% CI)		**242**			**100.0%**	**0.82 (0.24 to 2.77)**
Total events	5		6			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.75$, df = 1 ($p = 0.39$); $I^2 = 0\%$						
Test for overall effect: $z = 0.32$ ($p = 0.75$)						
Test for subgroup differences: $\chi^2 = 1.11$, df = 3 ($p = 0.77$); $I^2 = 0\%$						

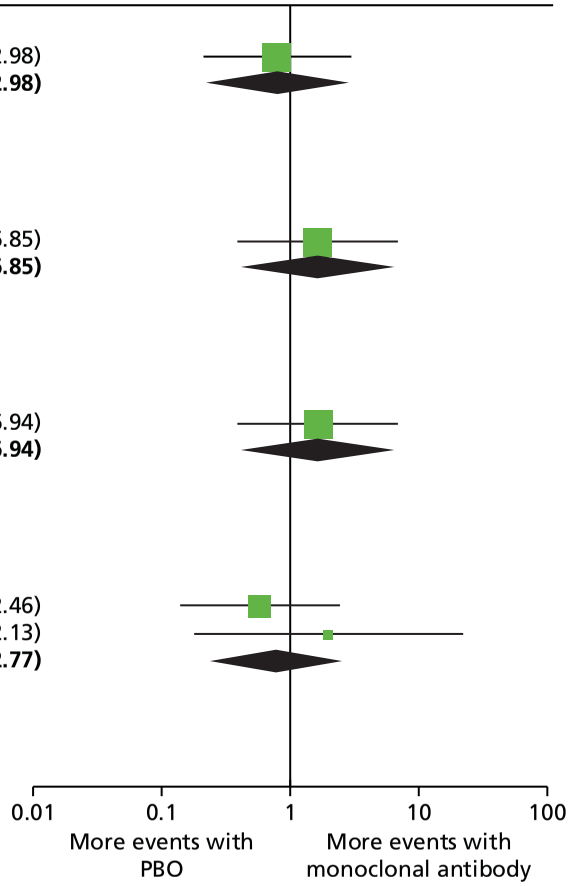

FIGURE 9 Forest plot of comparison: serious infections – adults. Outcome: serious infections – maintenance-licensed dose. df, degrees of freedom; M–H, Mantel–Haenszel.

Reactivation of hepatitis B

Adalimumab
No incidents of reactivation of hepatitis B were reported in any of the included ADA trials.

Golimumab
No cases were described in the included GOL studies.

Infliximab
No events were reported in the included IFX studies.

Administration reactions (injection site reactions/infusion reactions/serious allergic reactions)

Injection site reactions

Adalimumab
Injection site reactions were slightly more frequent at week 8 of ULTRA1[44] among patients receiving 160 mg/80 mg of ADA (13/223, 5.8%) than PBO (7/223, 3.1%).[44] Injection site reactions were also more frequent in the 160 mg/80 mg of ADA group at week 52 of ULTRA2[45] (31/257, 12.1%) than for PBO (10/260, 3.8%).[45] Patients receiving ADA through week 52 of ULTRA3 experienced injection site reactions at a rate of 10.5 per 100 PYs.[62] Injection site reactions were more frequent through week 8 of the Suzuki *et al.*[46] trial in the 160 mg/80 mg of ADA group (7/90, 7.8%) than for PBO (2/96, 2.1%).[46]

No serious allergic reactions were described as having occurred in the included ADA trials.

Golimumab
At week 6 of the PURSUIT-SC[47] trial, injection site reactions were more common in patients receiving 200/100 mg of GOL induction (11/331, 3.3%) than PBO (5/330, 1.5%).[47] The number of patients reporting one or more injection site reactions through week 54 of PURSUIT-Maintenance[48] was higher in the 100 mg of GOL maintenance treatment arm (11/154, 7.1%) than 50 mg of GOL (3/154, 1.9%) and PBO (3/156, 1.9%).[47,48]

No serious allergic reactions were reported.

Meta-analysis
Injection site reactions associated with the licensed induction dose of ADA in were reported by two trials, one in Western populations (ULTRA1,[44] 446 participants) and one in Japanese populations (Suzuki *et al.*,[46] 186 participants). The between-group difference in both trials was not significant [RR = 1.86 (random effects), 95% CI 0.76 to 4.57; $p = 0.18$; RR = 3.73 (random effects) 95% CI 0.80 to 17.50; $p = 0.09$ respectively]. The forest plot for this analysis (random effects) is presented in *Figure 10*. Injection site reactions associated with the licensed induction dose of GOL in adults were reported by one trial (PURSUIT-SC,[47] 661 participants). The between-group difference was not significant [RR = 2.19 (random effects), 95% CI 0.77 to 6.24; $p = 0.14$].

Injection site reactions associated with maintenance doses of ADA were reported by one trial comprising a mixed sample of anti-TNF-α-exposed and -naive participants (ULTRA2,[45] 517 participants). The between-group difference was significant in favour of PBO (fewer events) [RR = 3.14 (random effects) 95% CI 1.57 to 6.26; $p = 0.001$]. The forest plot for this analysis is presented in *Figure 11*. Injection site reactions associated with maintenance dose of 50 mg or 100 mg of GOL in adults were reported by one trial (PURSUIT-Maintenance[48]). The between-group difference for 50 mg of GOL compared with PBO (312 participants) was not significant [RR = 1.00 (random effects), 95% CI 0.20 to 4.88; $p = 1.00$]. The between-group difference for 100 mg of GOL compared with PBO (310 participants) was significant in favour of PBO (fewer events) [RR = 3.71 (random effects), 95% CI 1.06 to 13.06; $p = 0.04$].

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Study or subgroup	Monoclonal antibody Events	Total	PBO Events	Total	Weight	RR M–H, random, 95% CI
ADA Western population						
ULTRA1[44]	13	223	7	223	100.0%	1.86 (0.76 to 4.57)
Subtotal (95% CI)		**223**		**223**	**100.0%**	**1.86 (0.76 to 4.57)**
Total events	13		7			
Heterogeneity: not applicable						
Test for overall effect: $z=1.35$ ($p=0.18$)						
ADA Japanese population						
Suziki[46]	7	90	2	96	100.0%	3.73 (0.80 to 17.50)
Subtotal (95% CI)		**90**		**96**	**100.0%**	**3.73 (0.80 to 17.50)**
Total events	7		2			
Heterogeneity: not applicable						
Test for overall effect: $z=1.67$ ($p=0.09$)						
GOL						
PURSUIT-SC[47]	11	331	5	330	100.0%	2.19 (0.77 to 6.24)
Subtotal (95% CI)		**331**		**330**	**100.0%**	**2.19 (0.77 to 6.24)**
Total events	11		5			
Heterogeneity: not applicable						
Test for overall effect: $z=1.47$ ($p=0.14$)						
Test for subgroup differences: $\chi^2=0.59$, df=2 ($p=0.75$); $I^2=0\%$						

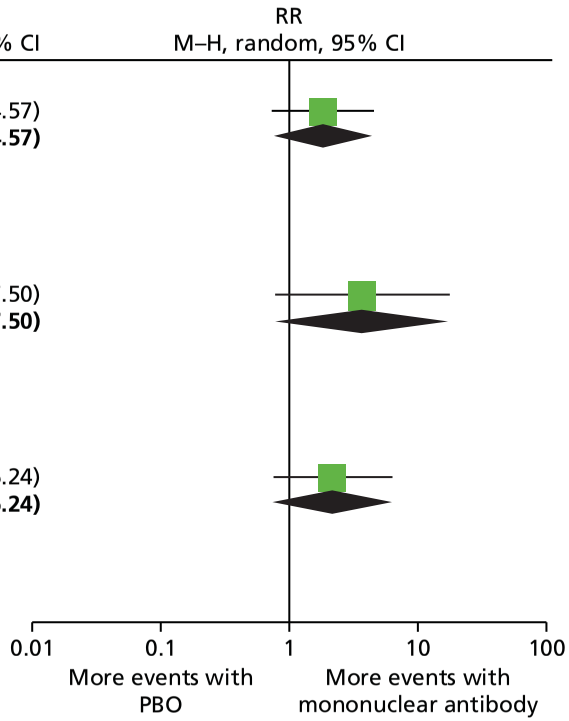

FIGURE 10 Forest plot of comparison: injection site reactions – adults. Outcome: injection site reactions (ADA and GOL only) – induction-licensed dose. df, degrees of freedom; M–H, Mantel–Haenszel.

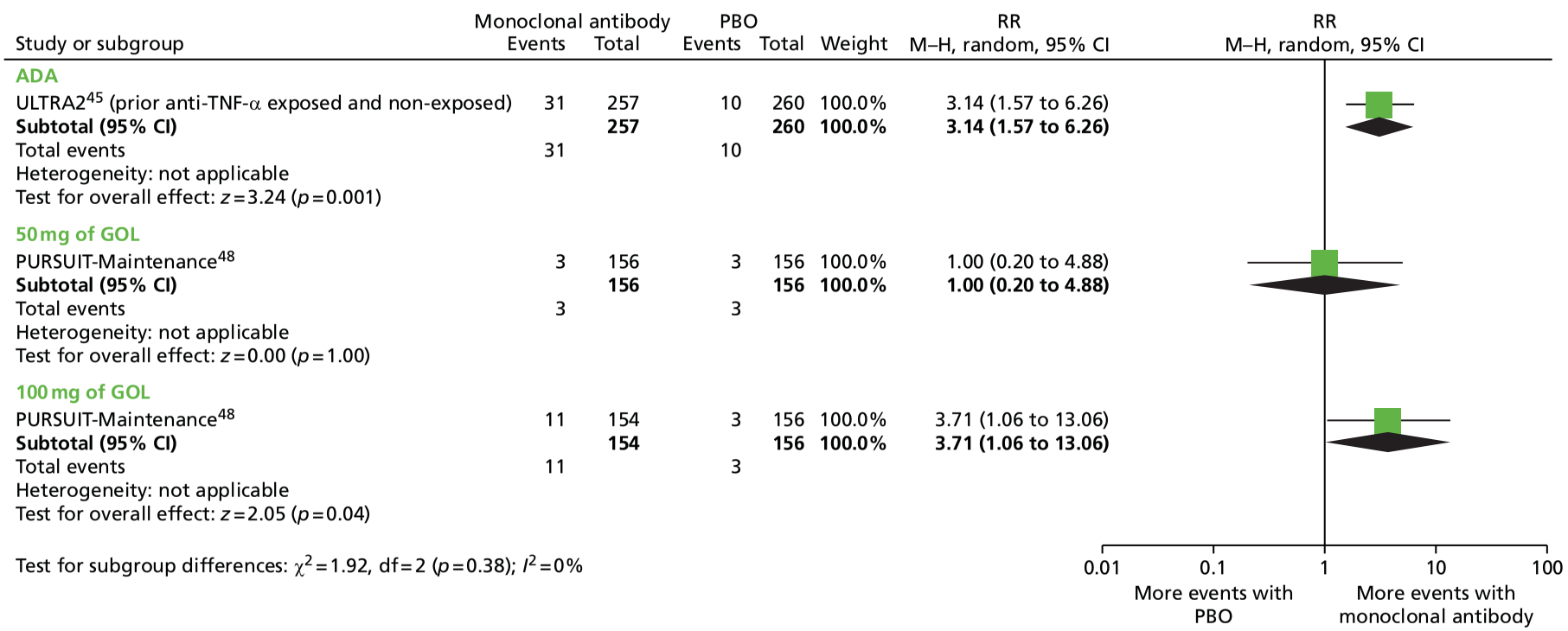

FIGURE 11 Forest plot of comparison: injection site reactions – adults. Outcome: injection site reactions (ADA and GOL only) – maintenance-licensed dose. df, degrees of freedom; M–H, Mantel–Haenszel.

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Infusion reactions

Infliximab

Acute infusion reactions occurred in similar numbers of patients in both treatment arms through week 54 of ACT1[49] (5 mg/kg of IFX 12/121, 9.9%; PBO 13/121, 10.7%).[49] Infusion reactions were slightly higher in ACT2[49] patients receiving 5 mg/kg of IFX (14/121, 11.6%) than PBO (10/123, 8.1%).[49]

Infusion reactions were rare through week 8 of UC-SUCCESS (AZA 1/79, 1%; IFX 0/78, 0%; combination IFX/AZA 0/80, 0%).[51] Possible delayed hypersensitivity reactions occurred in 2/242 (1%) of the 5 mg/kg of IFX group and 2/242 (1%) of the PBO group through week 54 of the ACT1 and ACT2 extension studies.[67]

No serious allergic reactions were reported.

Heart failure

Adalimumab

Heart failure did not occur in any patients in either 160 mg/80 mg of ADA induction or PBO arms by week 8 of ULTRA1.[44] Only one case of heart failure was reported through week 52 of ULTRA2,[45] which was in a patient receiving 160 mg/80 mg of ADA for induction (1/257, 0.4%).[45] Heart failure was reported at a rate of 0.2 events per 100 PYs for 40 mg of ADA every other week/every week at week 52 of ULTRA3.[62] Through week 8 of the Suzuki *et al.*[46] trial, no cases of heart failure were reported.

Golimumab

No cases of heart failure were reported for either the 200 mg/100 mg of GOL induction or PBO treatment arms through week 6 of PURSUIT-SC[47] or for the GOL maintenance or PBO groups in PURSUIT-Maintenance.[47,48]

Infliximab

No cases of heart failure were reported in the ACT1,[49] ACT2[49] and ACT2 extension studies, Probert *et al.*[50] and UC-SUCCESS[51] trials.

Malignancies and lymphoproliferative disorders

Adalimumab

Malignancies were reported at low levels through week 8 of ULTRA1,[44] with 2 out of 223 events (0.9%, one basal cell carcinoma, one breast cancer) in the PBO group and no cases in the 160 mg/80 mg of ADA group.[44] Two cases of malignancy were reported through week 52 of ULTRA2,[45] both of which were in patients receiving 160 mg/80 mg of ADA.[45] Through week 52 of ULTRA3, events (excluding lymphoma) occurred in the 40 mg of ADA maintenance arm at a rate of 1.0 events per 100 PYs and at a rate of 230.1 events per 100 PYs for lymphoma.[62] One case of malignancy (1/90, 1.1%) was described in the 160 mg/80 mg of ADA group at week 8 of the Suzuki *et al.*[46] trial.

Golimumab

No cases of malignancy were reported for either the 200 mg/100 mg of GOL induction or PBO treatment arms through week 6 of PURSUIT-SC.[47] Although one malignancy (1/156, 0.6%) was described by week 54 of PURSUIT-Maintenance[48] in the PBO arm, four cases each were observed in the 50 mg of GOL (4/154, 2.6%) and 100 mg of GOL (4/154, 2.6%) maintenance groups.[47,48]

Infliximab

Two cases of malignancy were reported through week 54 of ACT1[49] in patients receiving 5 mg/kg of IFX.[67] One case of basal cell carcinoma was reported in the PBO arm and one case of rectal adenocarcinoma was described in the 5 mg/kg of IFX arm of ACT2[49] through week 30. No malignancies were described in the UC-SUCCESS trial.[51]

Hepatobiliary events/liver enzyme changes

Adalimumab

No cases were described in ULTRA1[44] or ULTRA2.[45] Hepatobiliary events were reported at a rate of 0.5 events per 100 PYs in the 40 mg of ADA maintenance arm through week 52 of ULTRA2.[62] By week 8 of the Suzuki *et al.*[46] trial, events occurred in 1 out of 90 (1.1%) of 160 mg/80 mg of ADA and 1 out of 96 (1.0%) of PBO group patients.[46]

Golimumab

No cases were reported for either the 200 mg/100 mg of GOL induction or PBO treatment arms through week 6 of PURSUIT-SC[47] or the GOL maintenance or PBO groups of PURSUIT-Maintenance.[47,48]

Infliximab

No cases of hepatobiliary events were reported in the ACT1 and ACT2 trials.[49] The occurrence of hepatobiliary events was higher in the AZA treatment arm (13/79, 16%) than the IFX (3/78, 4%) and combination IFX/AZA (5/80, 6%) treatment groups through week 8 of UC-SUCCESS.[51]

Autoimmune processes (e.g. lupus-like syndrome)

Adalimumab

It was stated that no events of lupus-like syndrome occurred in the 160 mg/80 mg of ADA or PBO treatment arms by week 8 of ULTRA1.[44] One case of lupus-like syndrome (1/257, 0.4%) was reported in a patient receiving 160 mg/80 mg of ADA through week 52 of ULTRA2.[45] No cases were reported through week 8 of the Suzuki *et al.*[46] trial.

Golimumab

No cases of autoimmune processes were reported for either the 200 mg/100 mg of GOL induction or PBO treatment arms through week 6 of PURSUIT-SC[47] or the GOL maintenance or PBO groups of PURSUIT-Maintenance.[47,48]

Infliximab

One patient receiving 5 mg/kg of IFX reported experiencing a lupus-like reaction by week 30 of ACT2.[49] No cases of autoimmune processes were described in the UC-SUCCESS trial.[51]

Neurological events

Adalimumab

No cases of demyelinating disease occurred in the 160 mg/80 mg of ADA or PBO treatment arms by week 8 of ULTRA1[44] or by week 52 of ULTRA2.[45] No cases of neurological events were reported through week 8 of the Suzuki *et al.*[46] trial.

Golimumab

No cases were reported for either the 200 mg/100 mg of GOL induction or PBO treatment arms through week 6 of PURSUIT-SC[47] or the GOL maintenance or PBO groups of PURSUIT-Maintenance.[48]

Infliximab

One patient receiving 5 mg/kg of IFX reported having optic neuritis through week 54 of ACT1. One patient receiving 5 mg/kg of IFX also experienced optic neuritis by week 30 of ACT2.[49,67] No neurological events were described in the UC-SUCCESS trial.[51]

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Haematological reactions

Adalimumab

No haematological reactions were described in ULTRA1.[44] One haematological reaction was reported in 5 out of 257 (1.9%) patients receiving 160 mg/80 mg of ADA by week 52 of ULTRA2.[45] Haematological reactions occurred in 1 out of 90 (1.1%) and 1 out of 96 (1.0%) patients receiving 160 mg/80 mg of ADA and PBO, respectively, by week 8 of the Suzuki *et al.*[46] study.

Golimumab

No haematological reactions were reported for either the 200 mg/100 mg of GOL induction or PBO treatment arms through week 6 of PURSUIT-SC[47] or the GOL maintenance or PBO groups of PURSUIT-Maintenance.[47,48]

Infliximab

No haematological reactions were described in ACT1,[49] ACT2,[49] Probert *et al.*[50] or UC-SUCCESS.[51]

Population: children and adolescents aged 6–17 years (inclusive) with severely active ulcerative colitis who have had an inadequate response to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who are intolerant to, or have medical contraindications against, such therapies

Rates of and duration of response, relapse and remission

Table 12 presents the definitions of clinical response and remission in the included paediatric population RCT.

All enrolled patients received induction therapy with 5 mg/kg of IFX. At week 8, clinical response was reached by 44 out of 60 patients (73.3%), while 24 out of 60 (40.0%) of patients achieved clinical remission.

The PUCAI remission rates were evaluated at weeks 30 and 54. A greater proportion of patients in the 5 mg/kg of IFX every 8 weeks treatment group achieved PUCAI remission at week 30 (40.0% vs. 19.0%; *p*-values not reported) and week 54 (38.1% vs. 18.2%, *p*-values not reported) than the 5 mg/kg of IFX every 12 weeks group. At week 54, PUCAI remission without the use of corticosteroids was reported for 38.5% of the every 8 weeks group and 0% of the every 12 weeks group.[52]

The absence of a PBO or non-IFX control group limits the comparative evaluation of the efficacy of IFX in induction and maintenance of clinical response and remission in paediatric patients. A briefing document[68] by Centocor Ltd to the FDA Gastrointestinal Drugs Committee was produced in June 2011 and considered the evidence available from the Hyams *et al.* 2012/T72 study[52] and compared this with the ACT1 and ACT2 trials[49] of IFX previously conducted in the adult UC population. The briefing document considered efficacy to be similar between T72 and the ACT1 and ACT2 studies during (1) induction (with clinical response and Mayo remission at week 8 induced in 73.3% and 40.0% of paediatric patients and 66.9% and 36.4% of pooled 5 mg/kg adult patients from ACT1 and ACT2, respectively) and (2) maintenance (with PUCAI remission at week 54 in 38.1% of paediatric subjects in the every 8 weeks group and 34.7% at week 54 of ACT1) (with reported good correlation of 0.75–0.88 between PUCAI and Mayo scores described at baseline and week 8).

TABLE 12 Definitions of clinical response and remission in included paediatric population RCT

Trial	Definition of clinical response	Definition of clinical remission	Measurement time points
Hyams *et al.*, 2012[52]	Decrease in Mayo score of ≥ 3 points and ≥ 30%, with accompanying decrease in subscore for rectal bleeding of ≥ 1 point or absolute rectal bleeding subscore of 0 or 1	Mayo score of ≤ 2 points, with no individual subscore of > 1. PUCAI clinical remission = score of < 10	Mayo scores assessed at weeks 0, 8 and 54. Endoscopy at week 54 optional

Measures of disease activity

At week 8 of the Hyams *et al.*[52] study, the median reductions in partial Mayo scores were 4 points for both the 5 mg/kg of IFX every 8 weeks group and 5 mg/kg of IFX every 12 weeks group.[52] By week 30, the median reduction in partial Mayo score was approximately 3 points for the every 8 weeks group and 1 point for the every 12 weeks group.[52]

Mortality

No deaths were reported in the Hyams *et al.*[52] trial.

Rates of hospitalisation

No hospitalisation-related outcome data were reported in Hyams *et al.*[52]

Rates of surgical intervention (both elective and emergency)

One of 22 patients (4.5%) in the 5 mg/kg of IFX every 8 weeks group required colectomy through week 54 in the Hyams *et al.*[52] trial as compared with 2 out of 23 (8.7%) patients in the 5 mg/kg of IFX every 12 weeks treatment arm.

Colectomy rates during maintenance in children were reported by one trial evaluating the licensed dose of IFX every 8 weeks or every 12 weeks (Hyams *et al.*,[52] 45 participants). The between-group at week 54 was not significant [RR = 0.52 (random effects), 95% CI 0.05 to 5.36; $p = 0.59$; *Figure 12*].

Time to surgical intervention (both elective and emergency)

No data were reported in the paediatric population for the outcome of time to surgical intervention.

Health-related quality of life

No HRQoL data were included in the Hyams *et al.*[52] trial.

Adverse events of treatment (including leakage and infections following surgery)

Discontinuations due to adverse events Through week 54 of the Hyams *et al.*[52] trial, discontinuations due to at least one AE were higher in the 5 mg/kg of IFX every 12 weeks group than the every 8 weeks frequency group (6/23, 26.1% vs. 3/22, 13.6%).[52]

Number of patients experiencing one or more adverse event All patients in both treatment arms of the Hyams *et al.*[52] study reported at least one AE (22/22, 100% vs. 23/23, 100%).[52]

Number of patients experiencing one or more serious adverse event The numbers of patients reporting at least one SAE were similar between the 5 mg/kg of IFX every 12 weeks (5/23, 21.7%) and every 8 weeks (4/22, 18.2%) treatment arms.[52]

Infections The occurrence of infections was comparable between 5 mg/kg of IFX every 8 weeks (13/22, 59.1%) and every 12 weeks (14/23, 60.9%) treatment groups.[52]

Serious infections No cases of serious infection were reported in the Hyams *et al.*[52] trial.

Reactivation of tuberculosis No cases were reported.

Reactivation of hepatitis B No cases were reported.

Administration reactions (injection site reactions/infusion reactions/serious allergic reactions) The number of patients experiencing infusion reactions were similar between treatment groups in the Hyams *et al.*[52] study (4/22, 18.2% vs. 3/23, 13.0%).

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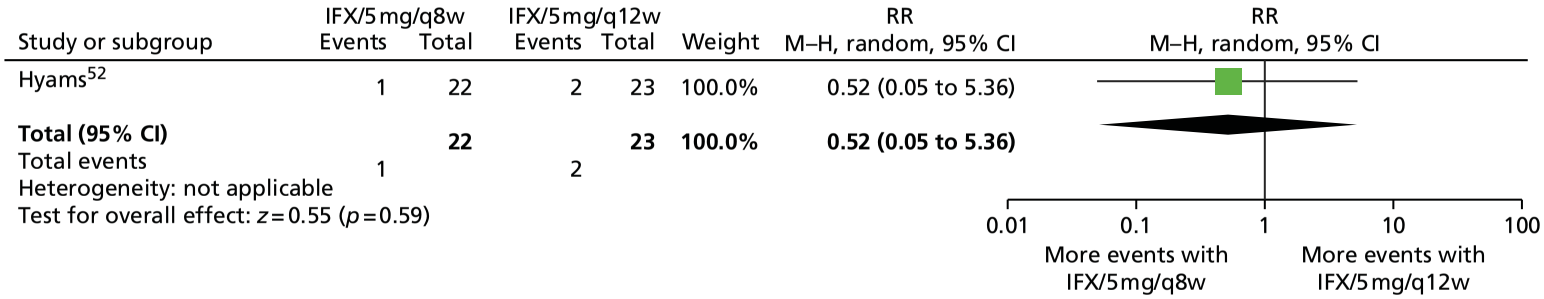

FIGURE 12 Forest plot of comparison: colectomy – children. Outcome: IFX maintenance. M–H, Mantel–Haenszel; q8w, every 8 weeks; q12w, every 12 weeks.

Subgroups

As stated in the assessment protocol, the only pre-specified subgroup of interest was duration of disease. However, clinical data reported according to disease duration were very limited. The only studies to evaluate the effect of disease duration on outcomes were ULTRA2[45] and PURSUIT-Maintenance.[47,48]

For ULTRA2,[45] the odds ratios (ORs) for the proportion of patients in clinical remission at week 8 for ADA versus PBO were very similar for patients with disease duration of ≤ 2 years (OR 1.91, 95% CI 0.4 to 8.8; $p = 0.40$) and those with disease duration of > 2 years (OR 1.92, 95% CI 1.1 to 3.4; $p = 0.03$). However, at week 52, the OR for clinical remission was considerably higher for patients with disease duration > 2 years (OR 3.59, 95% CI 1.9 to 6.9; $p < 0.001$) than for patients with a shorter disease duration of ≤ 2 years (OR 0.22, 95% CI 0.04 to 1.1; $p = 0.05$).

PURSUIT-Maintenance[48] reported the ORs for comparing the proportion of patients in clinical response in the GOL maintenance group versus the PBO group for GOL-induction responders. The OR for proportion of patients in clinical response through week 54 for 50 mg of GOL versus PBO treatment arms was slightly higher among patients with longer disease duration (> 5 to ≤ 15 years; OR 2.3, 95% CI 1.0 to 5.4; $p = 0.056$) than those with shorter duration of disease (≤ 5 years; OR 1.4, 95% CI 0.9 to 2.7; $p = 0.533$). Similarly, OR for 100 mg of GOL versus PBO groups was also reported to be greater among those with a disease duration of > 5 to ≤ 15 years (OR 2.2, 95% CI 1.0 to 4.9; $p = 0.068$) than for patients with disease duration of ≤ 5 years (OR 1.6, 95% CI 0.8 to 3.1; $p = 0.128$). However, it was noted that the 95% CIs for these observations overlapped between estimates.

Methods for network meta-analysis

The trials identified in the systematic review formed a connected network such that each trial had at least one treatment in common with at least one other trial. Treatment effects were estimated using NMAs of clinical response and remission as defined by the complete Mayo score.

Selection of evidence contributing to the network meta-analysis

For RCTs to be eligible for inclusion in the NMA they were required to have information about clinical response and/or clinical remission data for either an induction (6–8 weeks) or maintenance (approximately 30 weeks or 52–54 weeks) time point. It should be noted that two adult population RCTs evaluating the use of IFX as an induction treatment (Probert *et al.*,[50] and UC-SUCCESS[51]) were excluded from the adult population NMA. These studies were excluded for other reasons, as described in the table of trial characteristics (see *Table 6*). The base-case analyses utilised data from the anti-TNF-α-naive population rather than the ITT population in ULTRA2[45] in order to increase comparability of the dataset. The induction base case also incorporated both Phase II (plus additional analysed patients from Phase II) and Phase III data from PURSUIT-SC.[47] The effect of using the ITT (mixed anti-TNF-α experienced) population from ULTRA2[45] was explored in a sensitivity analysis. As the Suzuki *et al.*[46] trial was conducted in exclusively Japanese patients, this trial was not included in the base case; however, the addition of this trial to the network was explored in a sensitivity analysis. Therefore, three sensitivity analyses were performed for both induction and maintenance phases to assess the robustness of replacing ULTRA2 anti-TNF-α-naive data with ULTRA2 ITT data (sensitivity analysis 1), including Suzuki *et al.*[46] (sensitivity analysis 2), and replacing ULTRA2 anti-TNF-α-naive data with ULTRA2 ITT data plus including Suzuki *et al.*[46] (sensitivity analysis 3).

Clinical response and remission data were defined as outlined in *Table 10* and were taken from two different sources. First, data relating to clinical response and remission for the use of interventions as induction treatment were extracted directly from the published RCT reports. Second, data relating to clinical response and remission for the use of interventions as maintenance treatments conditional on outcomes at previous timepoints were requested and received from the manufacturers of the products under assessment (MSD and AbbVie).

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Statistical model for the network meta-analysis

Clinical response/remission can be considered as ordered categorical data with three mutually exclusive categories: (1) no response; (2) response; and (3) remission. The model for the data assumed that the treatment effect was the same irrespective of the category. Data available at 6 weeks and 8 weeks were combined, as were data available at 30 weeks and 32 weeks, and 52 weeks and 54 weeks. The likelihood function for the data is described as follows. Let r_{ikj} represent the number of patients in arm k of trial i in the mutually exclusive category $j = 1, 2, \ldots J$. The responses r_{ikj} will follow a multinomial distribution such that:

$$r_{ikj=1,\ldots,J} \sim \text{Multinomial}(p_{ikj=1,\ldots,J},\ n_{ik}),\ \sum_{j=1}^{J} p_{ikj=1,\ldots,J} = 1. \quad (1)$$

The parameters in the model are the probabilities, p_{ikj}, that a patient in arm k of trial i has a response equivalent to category j.

We used a probit link function to map the probabilities, p_{ikj}, onto the real line such that:

$$\theta_{ikj} = \Phi^{-1}(p_{ikj}) = \mu_{ij} + \delta_{i,bk} I_{k \neq 1} \quad (2)$$

so that:

$$p_{ikj} = \Phi(\mu_{ij} + \delta_{i,bk} I_{k \neq 1}). \quad (3)$$

In this model, the effect of treatment was to change the probit score of the control arm by $\delta_{i,bk}$ SDs.

The study-specific treatment effects, $\delta_{i,bk} I_{k \neq 1}$, were assumed to arise from a common population distribution with mean treatment effect relative to the reference treatment, which in this analysis was PBO, such that:

$$\delta_{i,1k} \sim N(d_{t_{i1},t_{ik}}, \tau^2). \quad (4)$$

We further assumed that there is an underlying continuous latent variable that has been categorised by specifying cut-off points z_{ij}, which corresponds to the point at which an individual moves from one category to the next in trial i. The model is rewritten as:

$$p_{ikj} = \Phi(\mu_i + z_{ij} + \delta_{i,bk} I_{k \neq 1}). \quad (5)$$

The z_{ij} can be treated as fixed, which would assume that these points are the same in each trial and each treatment. Alternatively, they can be treated as random in which they are assumed to vary according to the trial but that within a trial they are the same such that:

$$z_{ic} \sim N(\nu_c, \sigma_z^2). \quad (6)$$

We used a model in which the z_{ij} were treated as being random because this resulted in a much better fit of the model to the data. Further details of the model are presented in Dias *et al.*[69]

The model was completed by giving the parameters prior distributions. When there are sufficient sample data, we can use conventional reference prior distributions and these will have little influence on the posterior results.

The reference prior distributions used in the analyses were:

- trial-specific baselines, $\mu_i \sim N(0, 1000)$
- treatment effects relative to reference treatment, $d_{1t} \sim N(0, 1000)$
- between-study SD of treatment effects, $\tau \sim U(0,2)$
- population cut-off points, $\upsilon_{c_j} = \upsilon_{c_{j-1}} + \upsilon_c^{'},\ \upsilon_c^{'} \sim U(0,5)$
- between-study SD of cut-off points, $\sigma_z^2 \sim U(0,2)$.

In both the induction and maintenance phases, there were relatively few studies to allow Bayesian updating of the implausibly vague prior distribution for the between-study SD. Without Bayesian updating, a reference prior distribution that does not represent genuine prior belief will have a significant impact on the results and give posterior distributions that are unlikely to represent genuine posterior beliefs. To allow for this, we used a weakly informative prior distribution (a half-normal distribution) for the between study SD such that $\tau \sim HN\ (0,0.32^2)$.

To estimate the absolute probabilities of being in each category for each treatment, we combined the treatment effects with an estimate of the PBO 'No response' category (baseline model). We used a Binomial likelihood function for the number of patients, r_{ik1} in each study who were classified as having 'no response' when treated with PBO for the baseline model such that:

$$r_{ik1} \sim \text{Binomial}(n_{ik}, p_{ik1}). \tag{7}$$

We used a probit link function such that:

$$\Phi^{-1}(p_{ik1}) = \mu_i^{'}. \tag{8}$$

We assumed that the study-specific baselines arose from population of effects such that:

$$\mu_i^{'} \sim N(\mu_b, \tau_b^2). \tag{9}$$

The model was completed by giving the parameters prior distributions such that:

- population baseline effect, $\mu_b \sim N(0, 1000)$
- between-study SD of the baseline effects, $\tau_b \sim U(0, 2)$.

Again, in both the induction and maintenance phase there were relatively few studies providing data so a weakly informative prior distribution was used for the between-study SD such that:

$$\tau \sim HN(0,\ 0.32^2). \tag{10}$$

All analyses were conducted in the freely available software package OpenBUGS version 3.2.3.[69,70] For the baseline and relative treatment effects models, we used a burn-in of 50,000 iterations of the Markov chain and retained a further 10,000 iterations to estimate parameters. In addition, the NMAs exhibited moderate correlation between successive iterations of the Markov chains so the chains were thinned by retaining every tenth sample.

The total residual deviance was used to formally assess whether or not the statistical model provided a reasonable representation of the sample data. The total residual deviance is the mean of the deviance under the current model minus the deviance for the saturated model, so that each data point should contribute about one to the deviance.

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Results of network meta-analyses

A summary of the data used in the NMA is provided in *Appendix 7*. As described earlier, three sensitivity analyses were undertaken to assess the robustness of replacing ULTRA2[45] anti-TNF-α-naive data with ULTRA2[45] ITT data (sensitivity analysis 1), including Suzuki *et al.*[46] (sensitivity analysis 2), and replacing ULTRA2 anti-TNF-α-naive data with ULTRA2[45] ITT data and including Suzuki *et al.*[46] (sensitivity analysis 3). The results presented in *Base case: induction phase* to *Sensitivity analysis 3: maintenance phase 32–52 weeks* were derived using weakly informative prior distributions (a half-normal distribution) for the between-study SD such that $\tau \sim HN(0, 0.32^2)$. Results using vague reference prior distributions [$\tau \sim U(0,2)$] are presented in *Appendix 8*.

Base case: induction phase

A NMA was used to compare the effects of ADA, GOL and IFX relative to PBO on clinical response in the induction phase. Data were available from five studies comparing two treatments.[44,45,47,49] *Figure 13* presents the network of evidence for the base-case induction phase.

Figure 14 presents the effects of each treatment relative to PBO on the probit scale for the base-case induction phase. *Figure 15* presents the probabilities of treatment rankings for this analysis. The model fitted the data reasonably well, with the total residual deviance, 18.16, being close to the total number of data points included in the analysis, 20. The between-study SD was estimated to be 0.12 [95% credible interval (CrI) 0.01 to 0.50], which implies mild to moderate heterogeneity between studies in treatment effects.

All treatments were associated with beneficial treatment effects relative to PBO with the greatest effect being associated with IFX. All treatment effects were statistically significant at a conventional 5% level. IFX was associated with the greatest effect –0.92 (95% CrI –1.27 to –0.56) and was most likely to be the most effective treatment (probability of being the best = 0.93).

Table 13 presents the probabilities of achieving each of the following categories: no response, response and remission for the base-case induction phase. IFX was associated with the highest probability of moving from no response to response and no response to remission respectively. The effects of ADA and GOL on each transition probability were comparable.

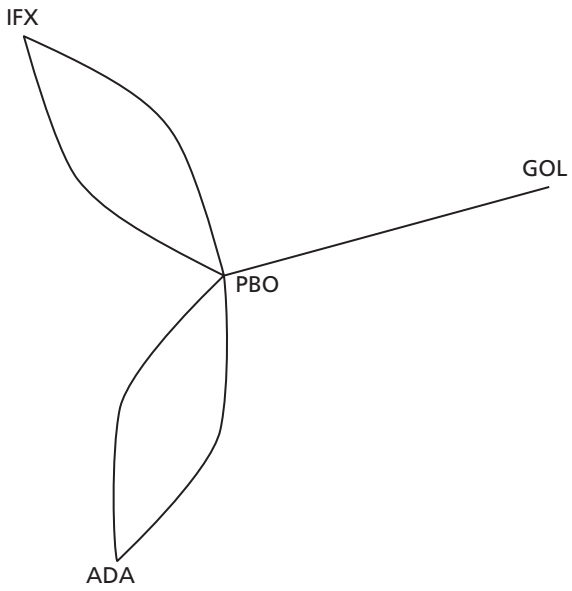

FIGURE 13 Base case: network of evidence for the induction phase. Note: solid line indicates a two-arm trial.

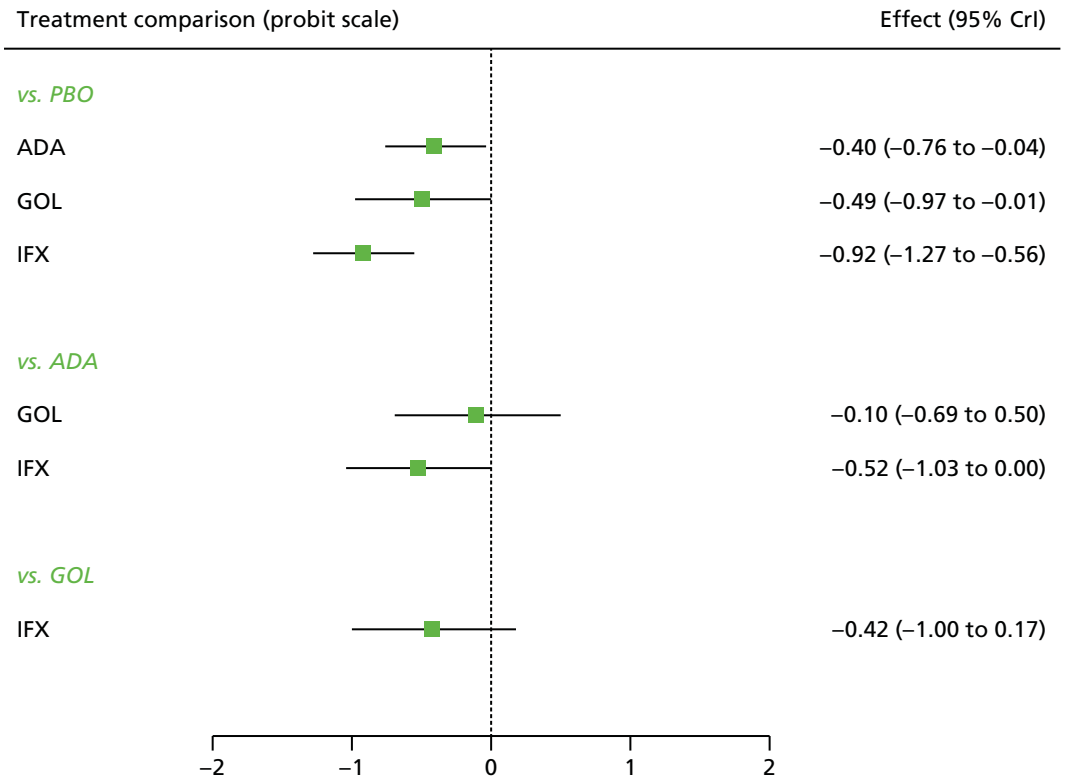

FIGURE 14 Base case: comparative effect of anti-TNF-α treatment on clinical response/remission in the induction phase [SD ~ HN(0,0.32²)].

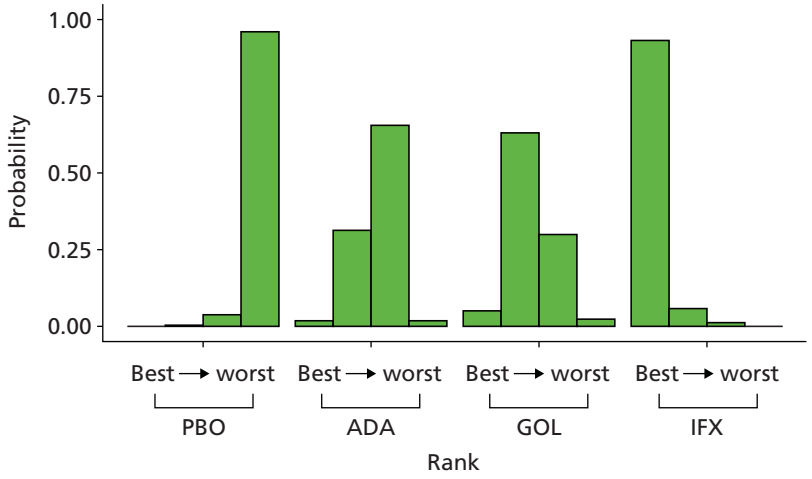

FIGURE 15 Base case: ranking probability histograms for the induction phase.

TABLE 13 Base case: probabilities of being in each category for the induction phase

	No response			Response			Remission		
Treatment	Mean	Median	95% CrI	Mean	Median	95% CrI	Mean	Median	95% CrI
PBO	0.640	0.641	0.568 to 0.706	0.260	0.260	0.214 to 0.308	0.099	0.097	0.062 to 0.147
ADA	0.485	0.485	0.330 to 0.642	0.324	0.327	0.247 to 0.385	0.190	0.185	0.092 to 0.322
GOL	0.448	0.447	0.262 to 0.645	0.333	0.337	0.244 to 0.393	0.219	0.212	0.094 to 0.390
IFX	0.292	0.289	0.170 to 0.438	0.351	0.353	0.280 to 0.412	0.356	0.352	0.209 to 0.523

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Base case: maintenance phase 8–32 weeks

Patients starting in response A NMA was used to compare the effects of ADA, GOL and IFX relative to PBO on clinical response in the maintenance phase at 8–32 weeks for patients starting in response. Data were available from four studies comparing two or three treatments.[45,48,49] *Figure 16* presents the network of evidence for the base-case maintenance phase at 8–32 weeks for patients starting in response.

Figure 17 presents the effects of each treatment relative to PBO on the probit scale for the base-case maintenance phase at 8–32 weeks for patients starting in response. *Figure 18* presents the probabilities of treatment rankings for this analysis. There was some suggestion that the model did not represent the data well with the total residual deviance, 11.73, being smaller than would be expected given the total number of data points included in the analysis, 18. The probability of observing a value < 11.73 was 0.139, which means that it could be a chance event. All four studies had smaller residual deviances than expected (ULTRA2: deviance 3.0 compared with four data points;[45] ACT1: deviance 2.1 compared with four data points;[49] ACT2: deviance 2.66 compared with four data points;[49] and PURSUIT: deviance 4.0 compared with six data points).[48] The between-study SD was estimated to be 0.17 (95% CrI 0.01 to 0.61), which implies mild to moderate heterogeneity between studies in treatment effects.

All treatments were associated with beneficial treatment effects relative to PBO with the greatest effect being associated with 100 mg of GOL. However, none of the treatment effects were statistically significant at a conventional 5% level. 100 mg of GOL was associated with the greatest effect –0.42 (95% CrI –0.78 to 0.29) and was most likely to be the most effective treatment (probability of being the best = 0.47).

Table 14 presents the probabilities of achieving each of the following categories: no response, response and remission for the base-case maintenance phase at 8–32 weeks for patients starting in response. 100 mg of GOL was associated with the highest probability of moving from response to remission and staying in the response state at 8–32 weeks. It was also associated with the smallest probability of moving from response to no response. The probabilities of staying in response were comparable among all treatments at 8–32 weeks.

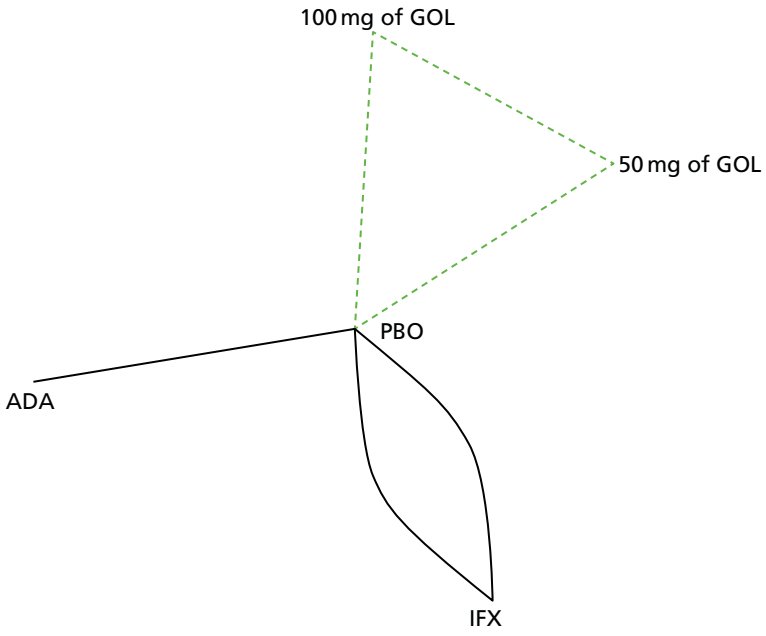

FIGURE 16 Base case: network of evidence for the maintenance phase at 8–32 weeks for patients starting in response. Note: solid line indicates a two-arm trial and dashed line indicates a three-arm study.

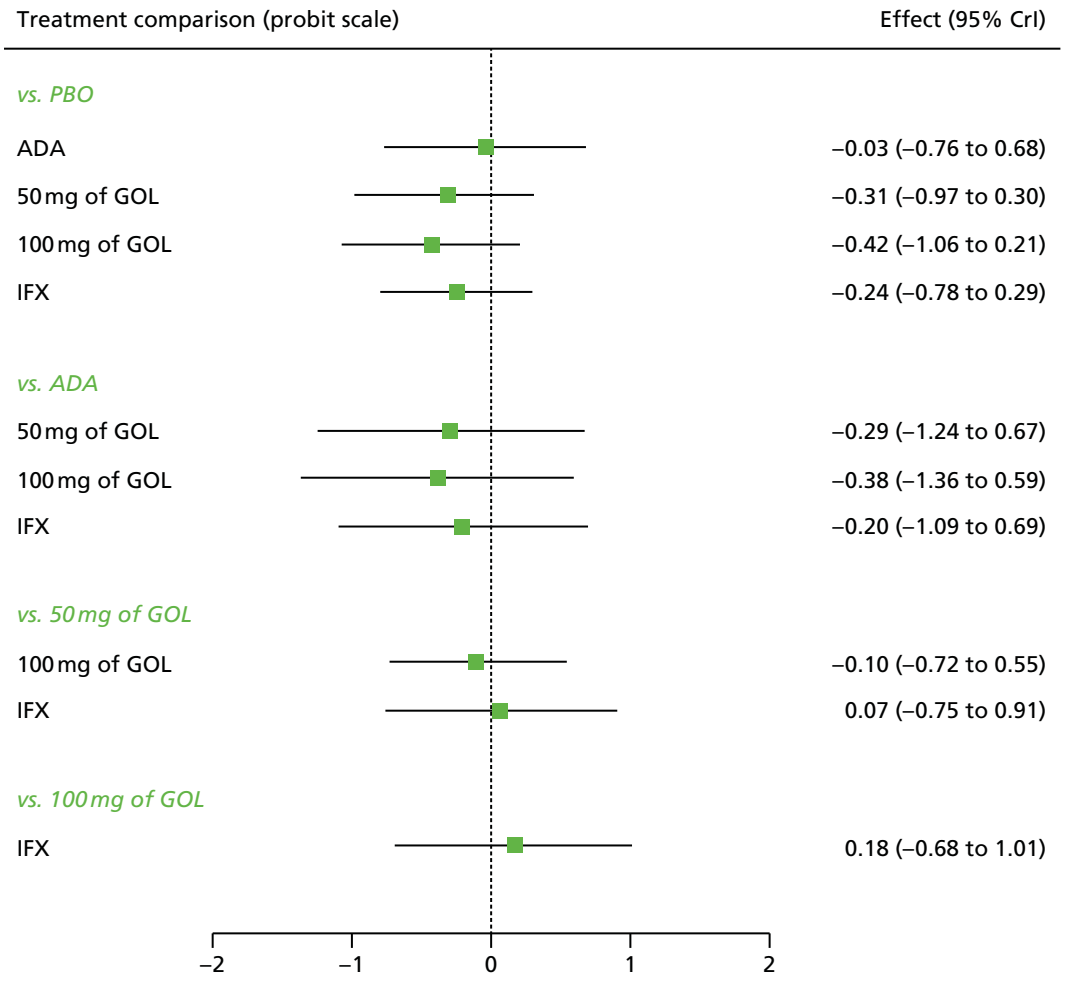

FIGURE 17 Base case: comparative effect of anti-TNF-α treatment on clinical response/remission in the maintenance phase at 8–32 weeks for patients starting in response [SD ~ HN(0,0.32²)].

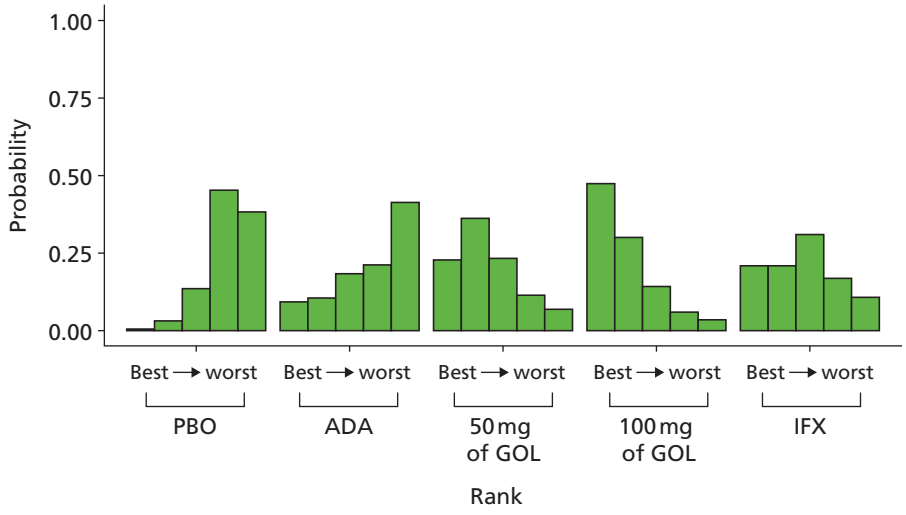

FIGURE 18 Base case: ranking probability histograms for the maintenance phase at 8–32 weeks for patients starting in response. Note: the horizontal axis represents the rank of each treatment, i.e., from the best rank (left hand side) to the worst rank (right hand side) within each treatment.

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TABLE 14 Base case: probabilities of being in each category for the maintenance phase at 8–32 weeks for patients starting in response

	No response			Response			Remission		
Treatment	Mean	Median	95% CrI	Mean	Median	95% CrI	Mean	Median	95% CrI
PBO	0.524	0.525	0.426 to 0.622	0.270	0.270	0.198 to 0.341	0.206	0.202	0.117 to 0.311
ADA	0.512	0.512	0.230 to 0.782	0.261	0.267	0.140 to 0.354	0.227	0.211	0.055 to 0.493
50 mg of GOL	0.403	0.399	0.173 to 0.660	0.283	0.285	0.176 to 0.374	0.313	0.303	0.108 to 0.588
100 mg of GOL	0.368	0.360	0.149 to 0.619	0.285	0.288	0.176 to 0.377	0.347	0.338	0.129 to 0.623
IFX	0.432	0.430	0.220 to 0.659	0.282	0.283	0.189 to 0.371	0.286	0.276	0.109 to 0.518

Patients starting in remission A NMA was used to compare the effects of ADA, GOL and IFX relative to PBO on clinical response in the maintenance phase at 8–32 weeks for patients starting in remission. Data were available from four studies comparing two or three treatments.[45,48,49] *Figure 19* presents the network of evidence for the base-case maintenance phase at 8–32 weeks for patients starting in remission.

Figure 20 presents the effects of each treatment relative to PBO on the probit scale for the base-case maintenance phase at 8–32 weeks for patients starting in remission. *Figure 21* presents the probabilities of treatment rankings for this analysis. The model fitted the data well, with the total residual deviance, 18.20, being close to the total number of data points included in the analysis, 18. The between-study SD was estimated to be 0.18 (95% CrI 0.01 to 0.64), which implies mild to moderate heterogeneity between studies in treatment effects.

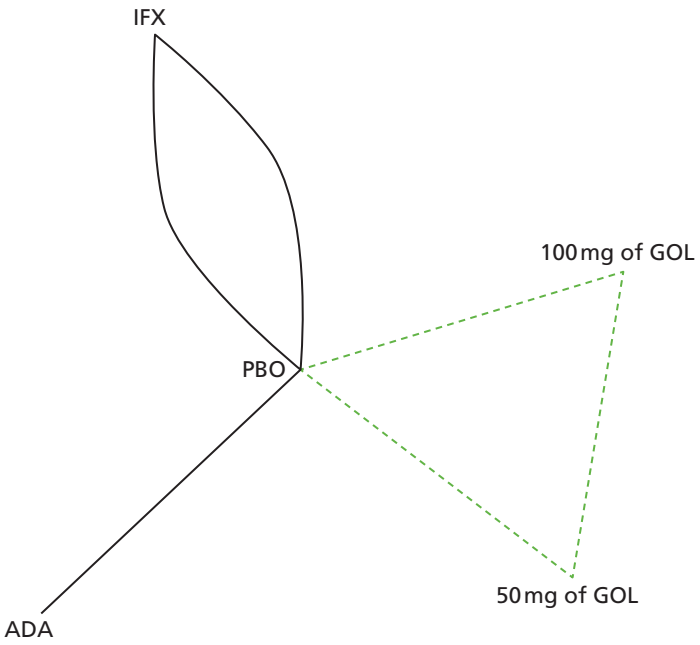

FIGURE 19 Base case: network of evidence for the maintenance phase at 8–32 weeks for patients starting in remission. Note: solid line indicates a two-arm trial; dashed line indicates a three-arm study.

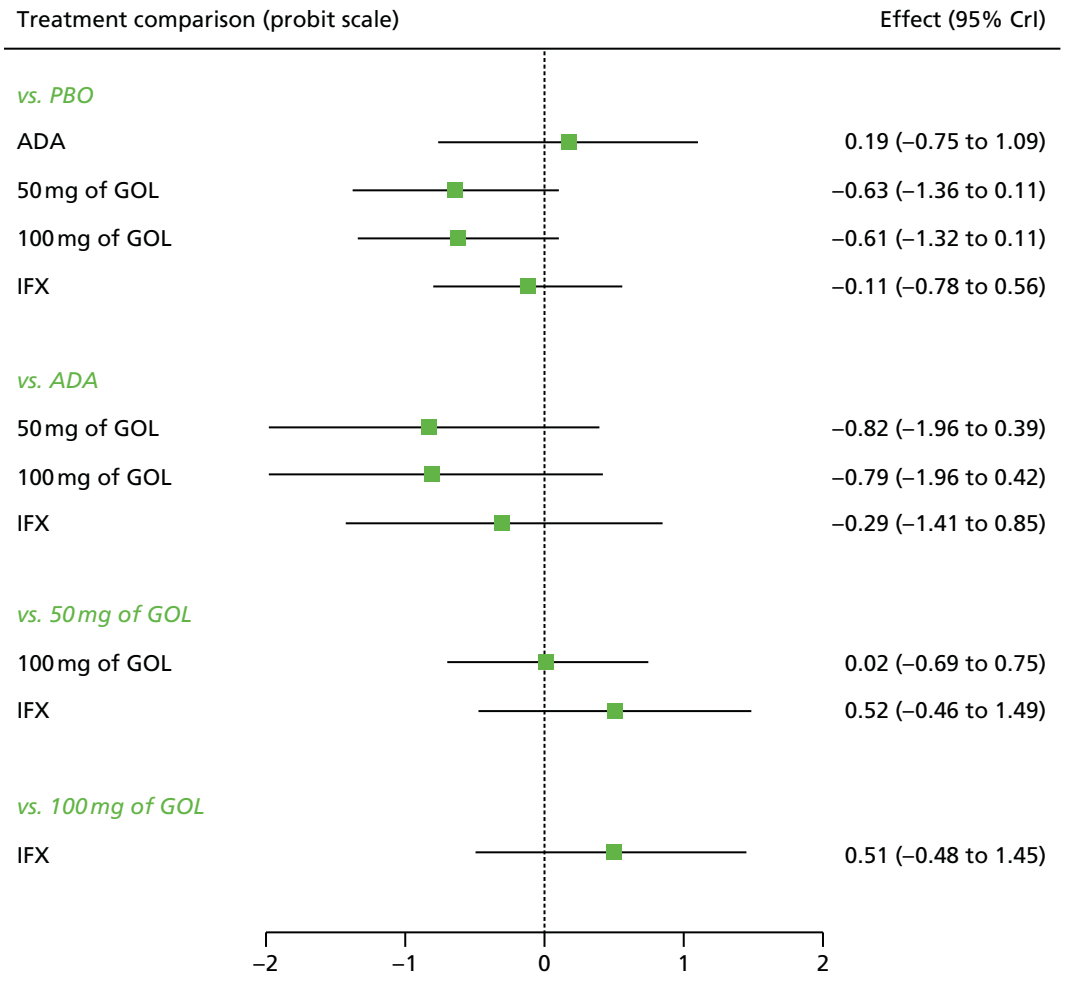

FIGURE 20 Base case: comparative effect of anti-TNF-α treatment on clinical response/remission in the maintenance phase at 8–32 weeks for patients starting in remission [SD ~ HN(0,0.32²)].

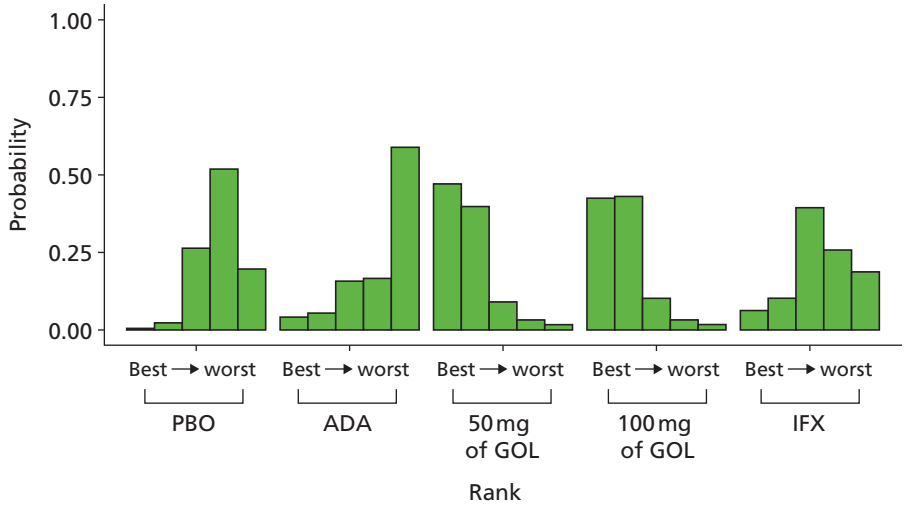

FIGURE 21 Base case: ranking probability histograms for the maintenance phase at 8–32 weeks for patients starting in remission.

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All treatments except ADA were associated with beneficial treatment effects relative to PBO with the greatest effects being associated with 50 mg of GOL (–0.63, 95% CrI –1.36 to 0.11) and 100 mg of GOL (–0.61, 95% CrI –1.32 to 0.11). However, none of the treatment effects was statistically significant at a conventional 5% level. 50 mg and 100 mg of GOL was most likely to be the most effective treatments (probability of being the best = 0.47 and 0.42 respectively).

Table 15 presents the probabilities of achieving each of the following categories: no response, response and remission for the base-case maintenance phase at 8–32 weeks for patients starting in remission. 50 mg and 100 mg of GOL were associated with the highest probability of staying in remission and the smallest probability of moving from remission to response or remission no response at 8–32 weeks.

Base case: maintenance phase 32–52 weeks

Patients starting in response A NMA was used to compare the effects of ADA, GOL and IFX relative to PBO on clinical response in the maintenance phase for patients starting in response at 32–52 weeks. Data were available from three studies comparing two or three treatments.[45,48,49] *Figure 22* presents the network of evidence for the base-case maintenance phase at 32–52 weeks for patients starting in response.

Figure 23 presents the effects of each treatment relative to PBO on the probit scale for the base-case maintenance phase 32–52 weeks for patients starting in response. *Figure 24* presents the probabilities of treatment rankings for this analysis. The model fitted the data reasonably well, with the total residual deviance, 12.88, being close to the total number of data points included in the analysis, 14. The between-study SD was estimated to be 0.21 (95% CrI 0.01 to 0.71), which implies mild to moderate heterogeneity between studies in treatment effects.

All treatments except 100 mg of ADA and GOL were associated with beneficial treatment effects relative to PBO with the greatest effect being associated with 50 mg of GOL; however, none of the treatment effects was statistically significant at a conventional 5% level. IFX was associated with the greatest effect –0.36 (95% CrI –1.33 to 0.62) and was most likely to be the most effective treatment (probability of being the best = 0.56).

Table 16 presents the probabilities of achieving each of the following categories: no response, response and remission for the base-case maintenance phase at 32–52 weeks for patients starting in response. IFX was associated with the highest probability of moving from response to remission and the smallest probability of moving from response to no response at 32–52 weeks. The probabilities of staying in the response state were comparable among treatments at 32–52 weeks.

TABLE 15 Base case: probabilities of being in each category for the maintenance phase at 8–32 weeks for patients starting in remission

	No response			Response			Remission		
Treatment	Mean	Median	95% CrI	Mean	Median	95% CrI	Mean	Median	95% CrI
PBO	0.353	0.347	0.168 to 0.572	0.180	0.174	0.070 to 0.316	0.467	0.466	0.225 to 0.708
ADA	0.428	0.420	0.099 to 0.803	0.166	0.164	0.053 to 0.297	0.406	0.392	0.083 to 0.804
50 mg of GOL	0.177	0.152	0.027 to 0.457	0.136	0.131	0.028 to 0.283	0.687	0.708	0.321 to 0.933
100 mg of GOL	0.182	0.158	0.029 to 0.469	0.138	0.134	0.030 to 0.285	0.680	0.700	0.322 to 0.929
IFX	0.325	0.309	0.084 to 0.648	0.169	0.165	0.057 to 0.304	0.506	0.509	0.178 to 0.829

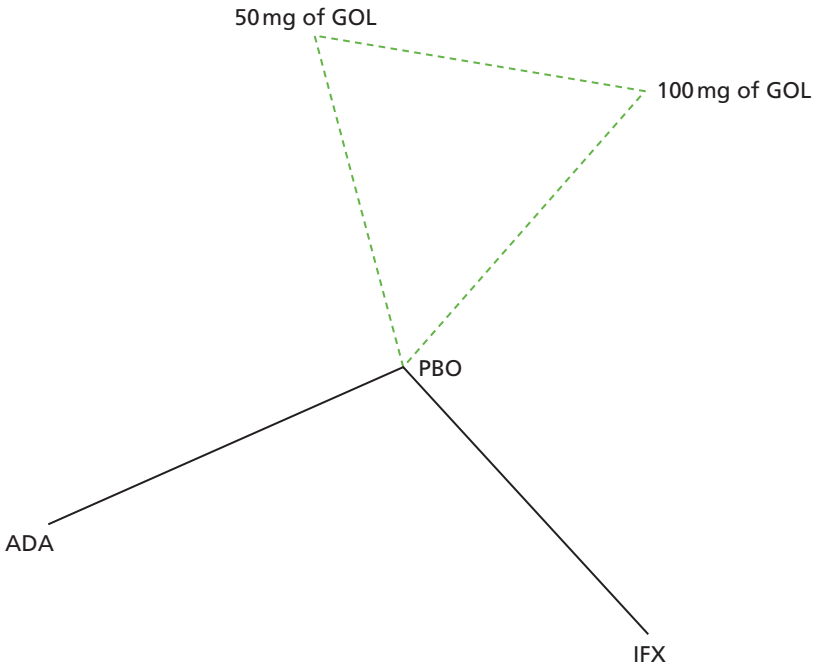

FIGURE 22 Base case: network of evidence for the maintenance phase at 32–52 weeks for patients starting in response. Note: solid line indicates a two-arm trial; dashed line indicates a three-arm study.

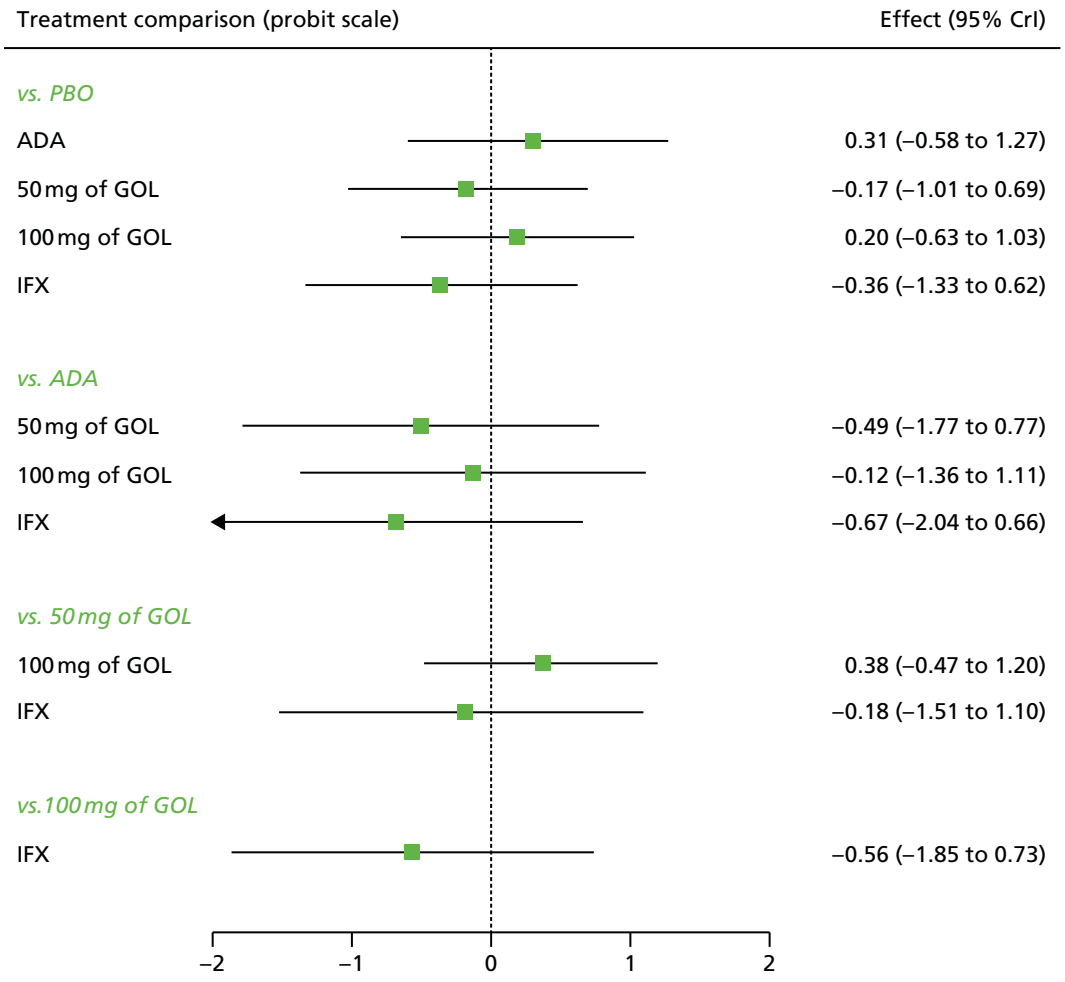

FIGURE 23 Base case: comparative effect of anti-TNF-α treatment on clinical response/remission in the maintenance phase at 32–52 weeks for patients starting in response [SD ~ HN(0,0.32^2)].

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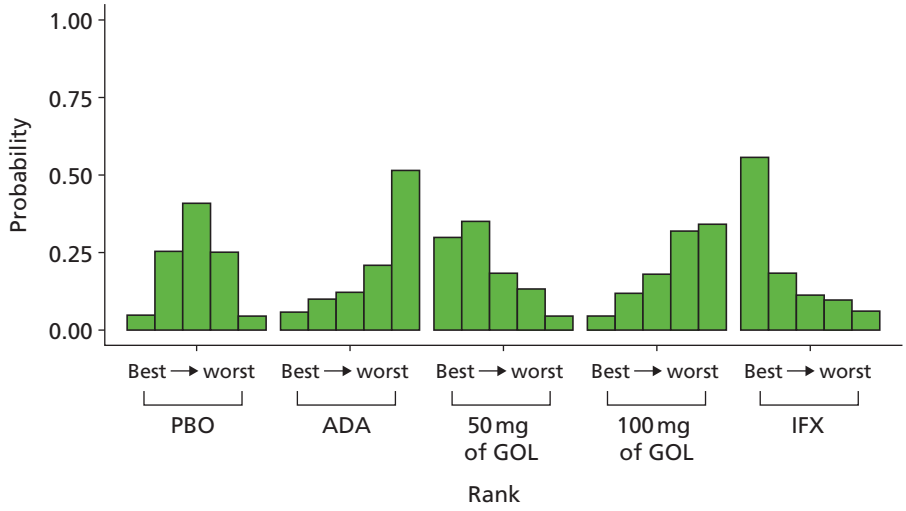

FIGURE 24 Base case: ranking probability histograms for the maintenance phase at 32–52 weeks for patients starting in response.

TABLE 16 Base case: probabilities of being in each category for the maintenance phase at 32–52 weeks for patients starting in response

	No response			Response			Remission		
Treatment	Mean	Median	95% CrI	Mean	Median	95% CrI	Mean	Median	95% CrI
PBO	0.338	0.319	0.066 to 0.711	0.370	0.378	0.122 to 0.604	0.292	0.259	0.027 to 0.717
ADA	0.450	0.440	0.063 to 0.889	0.327	0.340	0.067 to 0.562	0.223	0.167	0.005 to 0.716
50 mg of GOL	0.295	0.258	0.025 to 0.750	0.353	0.363	0.081 to 0.616	0.352	0.319	0.021 to 0.842
100 mg of GOL	0.410	0.393	0.055 to 0.852	0.342	0.353	0.083 to 0.581	0.248	0.199	0.009 to 0.741
IFX	0.250	0.205	0.013 to 0.716	0.341	0.353	0.065 to 0.621	0.409	0.385	0.029 to 0.892

Patients starting in remission A NMA was used to compare the effects of ADA, GOL and IFX relative to PBO on clinical response in the maintenance phase at 32–52 weeks for patients starting in remission. Data were available from three studies comparing two or three treatments.[45,48,49] *Figure 25* presents the network of evidence for the base-case maintenance phase at 32–52 weeks for patients starting in remission.

Figure 26 presents the effects of each treatment relative to PBO on the probit scale for the base-case maintenance phase at 32–52 weeks for patients starting in remission. *Figure 27* presents the probabilities of treatment rankings for this analysis. The model fitted the data well, with the total residual deviance, 18.46, being close to the total number of data points included in the analysis, 18. The between-study SD was estimated to be 0.21 (95% CrI 0.01 to 0.72), which implies mild to moderate heterogeneity between studies in treatment effects.

All treatments except 50 mg of GOL were associated with beneficial treatment effects relative to PBO with the greatest effect being associated with ADA. However, only the treatment effects of ADA were statistically significant at a conventional 5% level. ADA was associated with the greatest effect –1.04 (95% CrI –1.93 to –0.12) and was most likely to be the most effective treatment (probability of being the best = 0.84).

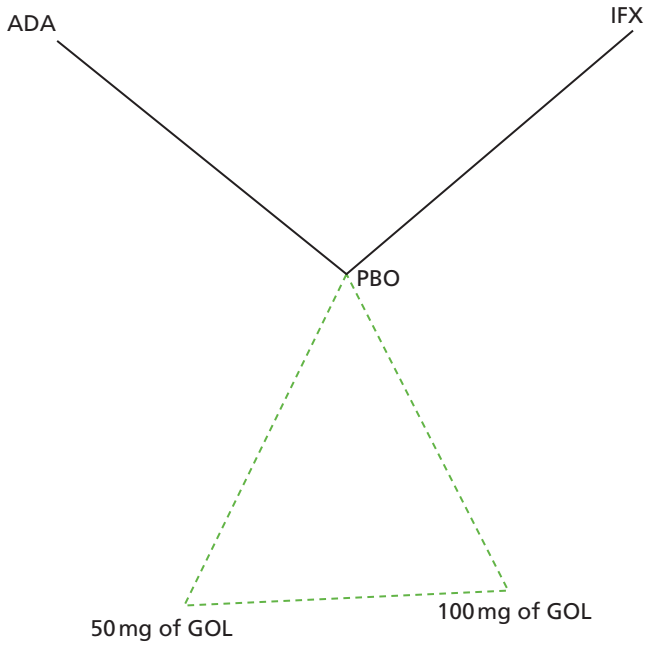

FIGURE 25 Base case: network of evidence for the maintenance phase at 32–52 weeks for patients starting in remission. Note: solid line indicates a two-arm trial; dashed line indicates a three-arm study.

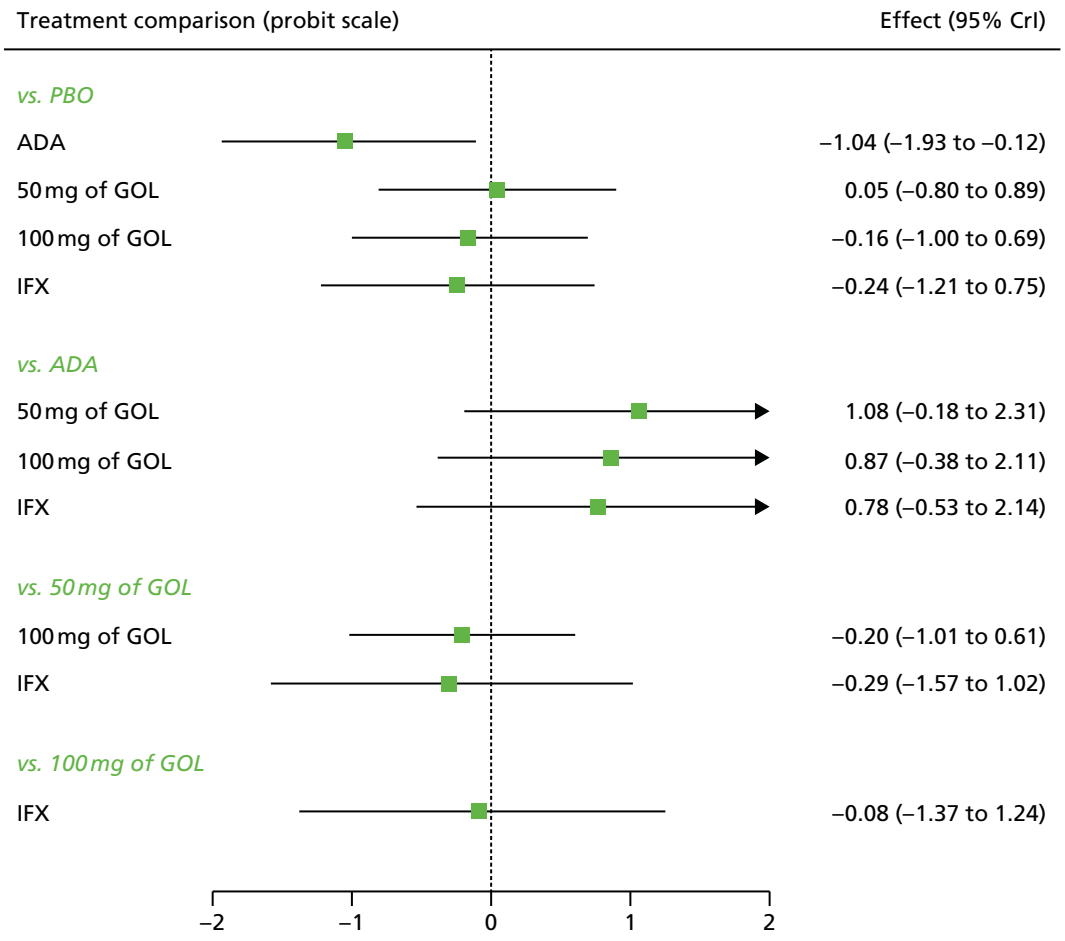

FIGURE 26 Base case: comparative effect of anti-TNF-α treatment on clinical response/remission in the maintenance phase at 32–52 weeks for patients starting in remission [SD ~ HN(0,0.32^2)].

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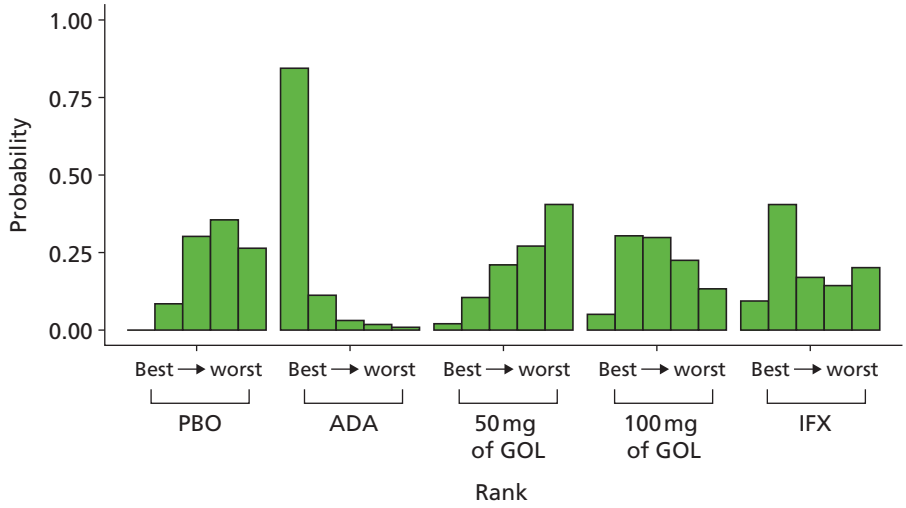

FIGURE 27 Base case: ranking probability histograms for the maintenance phase at 32–52 weeks for patients starting in remission.

Table 17 presents the probabilities of achieving each of the following categories: no response, response and remission for the base-case maintenance phase at 32–52 weeks for patients starting in remission. ADA was associated with the highest probability of staying in remission and the smallest probability of moving from remission to response or from remission to no response at 32–52 weeks.

Sensitivity analysis 1: induction phase

Sensitivity analysis 1 involved replacing ULTRA2 anti-TNF-α-naive data with ULTRA2 ITT data. A NMA was used to compare the effects of ADA, GOL and IFX relative to PBO on clinical response in the induction phase. Data were available from five studies comparing two treatments.[44,45,47,49] *Figure 28* presents the network of evidence for the sensitivity analysis 1 induction phase.

Figure 29 presents the effects of each treatment relative to PBO on the probit scale for the sensitivity analysis 1 induction phase. *Figure 30* presents the probabilities of treatment rankings for this analysis. The model fitted the data reasonably well, with the total residual deviance, 17.08, being close to the total number of data points included in the analysis, 20. The between-study SD was estimated to be 0.11 (95% CrI 0.01 to 0.47), which implies mild heterogeneity between studies in treatment effects.

TABLE 17 Base case: probabilities of being in each category for the maintenance phase at 32–52 weeks for patients starting in remission

	No response			Response			Remission		
Treatment	Mean	Median	95% CrI	Mean	Median	95% CrI	Mean	Median	95% CrI
PBO	0.301	0.296	0.174 to 0.449	0.164	0.147	0.029 to 0.449	0.536	0.548	0.237 to 0.734
ADA	0.081	0.059	0.005 to 0.288	0.084	0.061	0.005 to 0.337	0.834	0.874	0.447 to 0.985
50 mg of GOL	0.329	0.314	0.080 to 0.664	0.155	0.141	0.024 to 0.415	0.515	0.523	0.135 to 0.851
100 mg of GOL	0.266	0.245	0.052 to 0.604	0.147	0.132	0.020 to 0.417	0.587	0.604	0.169 to 0.894
IFX	0.247	0.220	0.033 to 0.613	0.140	0.126	0.017 to 0.413	0.613	0.634	0.174 to 0.928

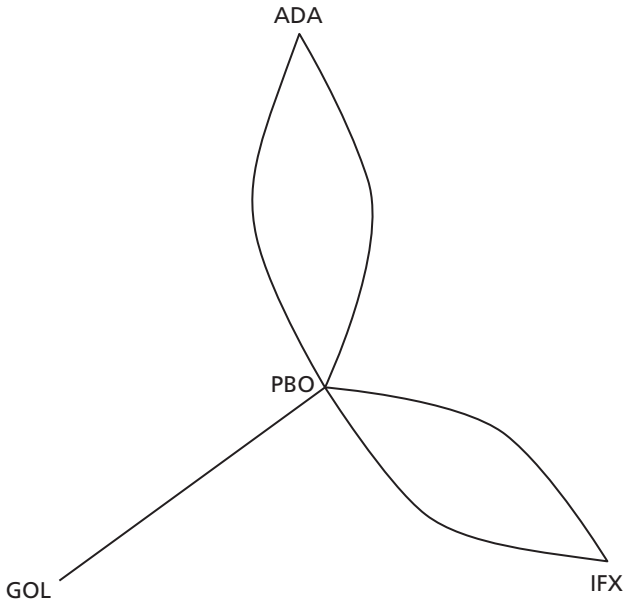

FIGURE 28 Sensitivity analysis 1: network of evidence for the induction phase. Note: solid line indicates a two-arm trial.

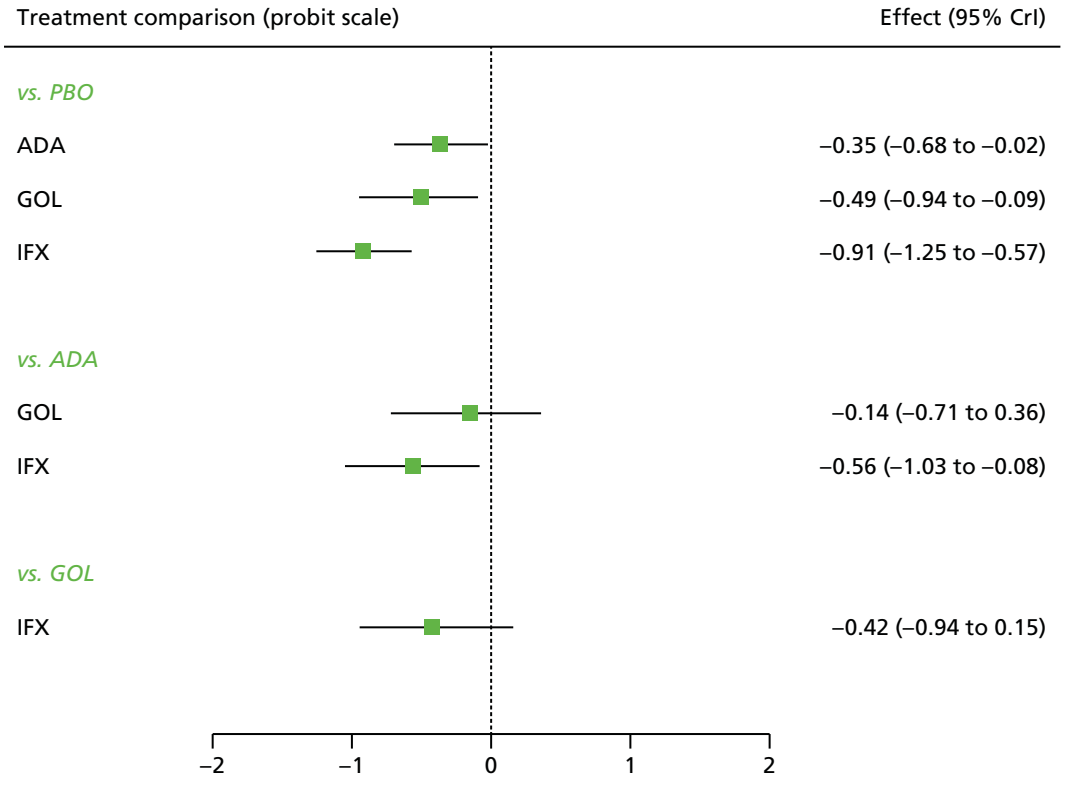

FIGURE 29 Sensitivity analysis 1: comparative effect of anti-TNF-α treatment on clinical response/remission in the induction phase [SD ~ HN(0,0.32^2)].

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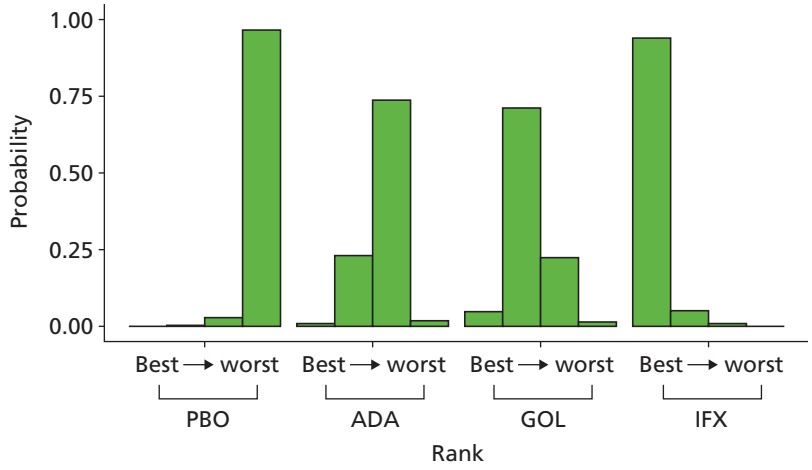

FIGURE 30 Sensitivity analysis 1: ranking probability histograms for the induction phase.

All treatments were associated with beneficial treatment effects relative to PBO with the greatest effect being associated with IFX (–0.91, 95% CrI –1.25 to –0.57). All treatment effects were statistically significant at a conventional 5% level. IFX was most likely to be the most effective treatment (probability of being the best = 0.94).

Table 18 presents the probabilities of achieving each of the following categories: no response, response and remission for the sensitivity analysis 1 induction phase. IFX was associated with the highest probability of moving from no response to response and from no response to remission.

Sensitivity analysis 1: maintenance phase 8–32 weeks

Patients starting in response A NMA was used to compare the effects of ADA, GOL and IFX relative to PBO on clinical response in the maintenance phase for patients starting in response at 8–32 weeks. Data were available from four studies comparing two or three treatments.[45,48,49] *Figure 31* presents the network of evidence for the sensitivity analysis 1 maintenance phase at 8–32 weeks for patients starting in response.

Figure 32 presents the effects of each treatment relative to PBO on the probit scale for the sensitivity analysis 1 maintenance phase at 8–32 weeks for patients starting in response. *Figure 33* presents the probabilities of treatment rankings for this analysis. There was some suggestion that model did not represent the data well with the total residual deviance, 11.54, being smaller than would be expected given the total number of data points included in the analysis, 18. The probability of observing a value < 11.54 was 0.130, which means that this could be a chance event. Similar to the base-case analysis, all four studies had smaller residual deviances than expected. The between-study SD was estimated to be 0.17 (95% CrI 0.01 to 0.63), which implies mild to moderate heterogeneity between studies in treatment effects.

TABLE 18 Sensitivity analysis 1: probabilities of being in each category for the induction phase

	No response			Response			Remission		
Treatment	Mean	Median	95% CrI	Mean	Median	95% CrI	Mean	Median	95% CrI
PBO	0.649	0.649	0.586 to 0.710	0.255	0.255	0.212 to 0.298	0.096	0.095	0.062 to 0.140
ADA	0.513	0.512	0.372 to 0.652	0.315	0.317	0.240 to 0.375	0.173	0.169	0.088 to 0.286
GOL	0.456	0.456	0.283 to 0.631	0.330	0.334	0.250 to 0.389	0.214	0.207	0.101 to 0.368
IFX	0.302	0.298	0.180 to 0.441	0.351	0.353	0.281 to 0.409	0.347	0.345	0.208 to 0.506

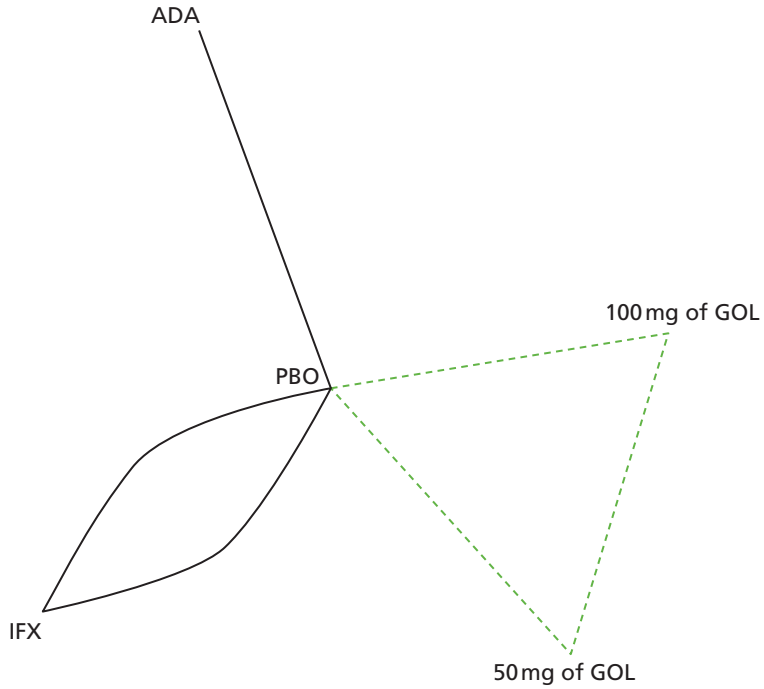

FIGURE 31 Sensitivity analysis 1: network of evidence for the maintenance phase at 8–32 weeks for patients starting in response. Note: solid line indicates a two-arm trial; dashed line indicates a three-arm study.

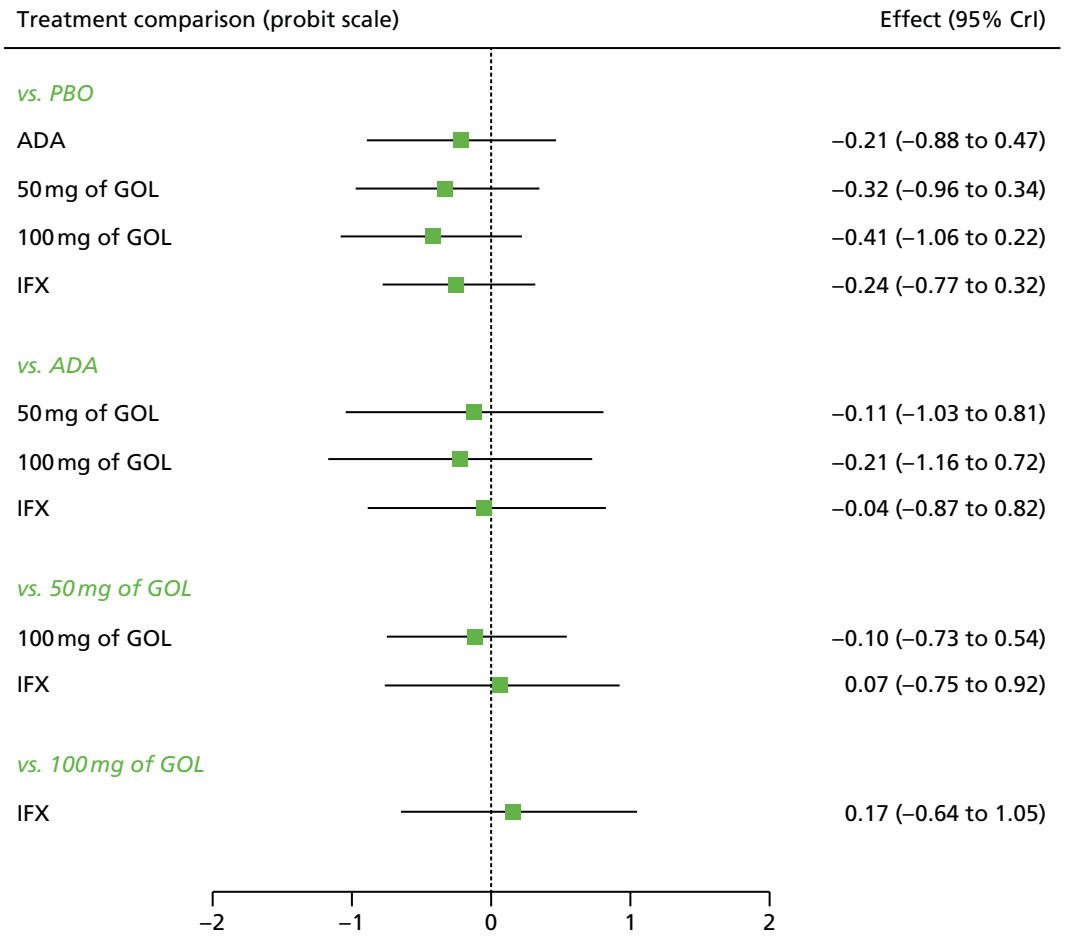

FIGURE 32 Sensitivity analysis 1: comparative effect of anti-TNF-α treatment on clinical response/remission in the maintenance phase at 8–32 weeks for patients starting in response [SD ~ HN(0,0.32²)].

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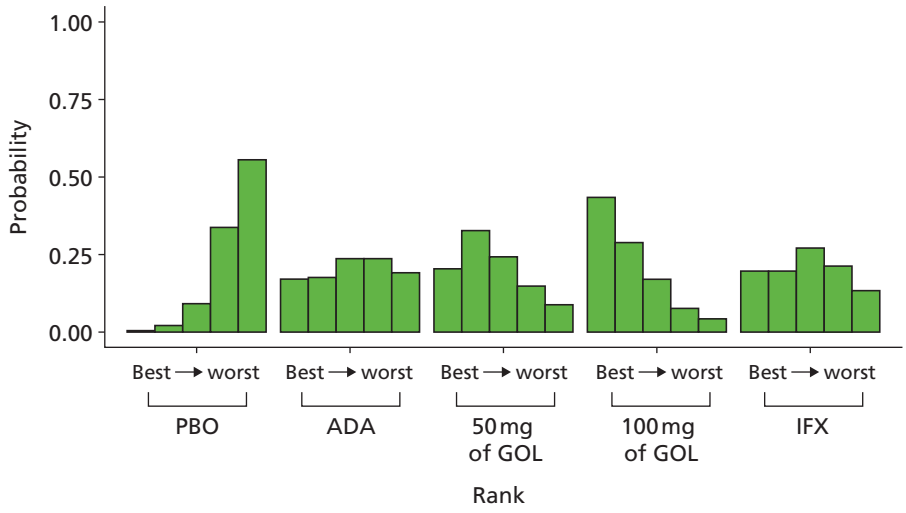

FIGURE 33 Sensitivity analysis 1: ranking probability histograms for the maintenance phase at 8–32 weeks for patients starting in response.

All treatments were associated with beneficial treatment effects relative to PBO with the greatest effect being associated with 100 mg of GOL (–0.41, 95% CrI –1.06 to 0.22); however, none of the treatment effects was statistically significant at a conventional 5% level. A treatment of 100 mg of GOL was most likely to be the most effective (probability of being the best = 0.43).

Table 19 presents the probabilities of achieving each of the following categories: no response, response and remission for the sensitivity analysis 1 maintenance phase at 8–32 weeks starting in response. A treatment of 100 mg of GOL was associated with the highest probability of moving from response to remission and the smallest probability of moving from response to no response at 8–32 weeks. The probabilities of staying in the response state were comparable among treatments.

Patients starting in remission A NMA was used to compare the effects of ADA, GOL and IFX relative to PBO on clinical response in the maintenance phase at 8–32 weeks for patients starting in remission. Data were available from four studies comparing two or three treatments.[45,48,49] *Figure 34* presents the network of evidence for the sensitivity analysis 1 maintenance phase at 8–32 weeks for patients starting in remission.

TABLE 19 Sensitivity analysis 1: probabilities of being in each category for the maintenance phase at 8–32 weeks for patients starting in response

	No response			Response			Remission		
Treatment	Mean	Median	95% CrI	Mean	Median	95% CrI	Mean	Median	95% CrI
PBO	0.548	0.548	0.447 to 0.649	0.269	0.267	0.199 to 0.361	0.183	0.181	0.085 to 0.282
ADA	0.468	0.467	0.210 to 0.744	0.279	0.283	0.158 to 0.391	0.252	0.240	0.059 to 0.525
50 mg of GOL	0.427	0.423	0.190 to 0.688	0.289	0.289	0.176 to 0.412	0.284	0.273	0.081 to 0.552
100 mg of GOL	0.390	0.384	0.162 to 0.649	0.293	0.292	0.182 to 0.421	0.318	0.310	0.098 to 0.591
IFX	0.453	0.451	0.237 to 0.685	0.286	0.287	0.186 to 0.403	0.260	0.252	0.082 to 0.490

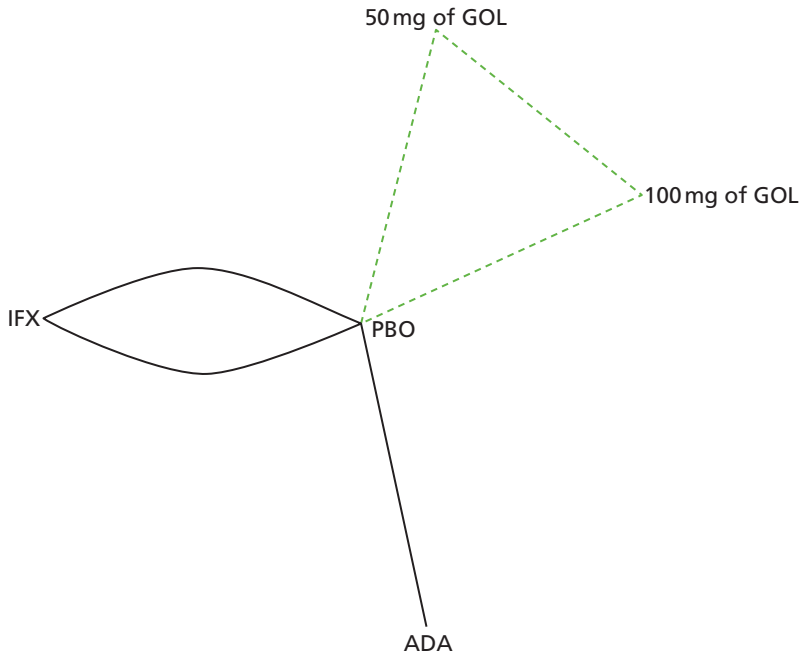

FIGURE 34 Sensitivity analysis 1: network of evidence for the maintenance phase at 8–32 weeks for patients starting in remission. Note: solid line indicates a two-arm trial; dashed line indicates a three-arm study.

Figure 35 presents the effects of each treatment relative to PBO on the probit scale for the sensitivity analysis 1 maintenance phase at 8–32 weeks for patients starting in remission. *Figure 36* presents the probabilities of treatment rankings for this analysis. The model fitted the data reasonably well, with the total residual deviance, 15.29, being close to the total number of data points included in the analysis, 18. The between-study SD was estimated to be 0.19 (95% CrI 0.01 to 0.65), which implies mild to moderate heterogeneity between studies in treatment effects.

All treatments were associated with beneficial treatment effects relative to PBO with the greatest effects being associated with 50 mg of GOL (–0.62, 95% CrI –1.36 to 0.11) and 100 mg of GOL (–0.61, 95% CrI –1.34 to 0.13). However, none of the treatment effects was statistically significant at a conventional 5% level. A treatment of 50 mg and 100 mg of GOL were most likely to be the most effective (probability of being the best = 0.44 and 0.41 respectively).

Table 20 presents the probabilities of achieving each of the following categories: no response, response and remission for the sensitivity analysis 1 maintenance phase at 8–32 weeks starting in remission. A treatment of 50 mg and 100 mg of GOL were associated with the highest probability of staying in remission and the smallest probability of moving from remission to no response and from remission to response at 8–32 weeks.

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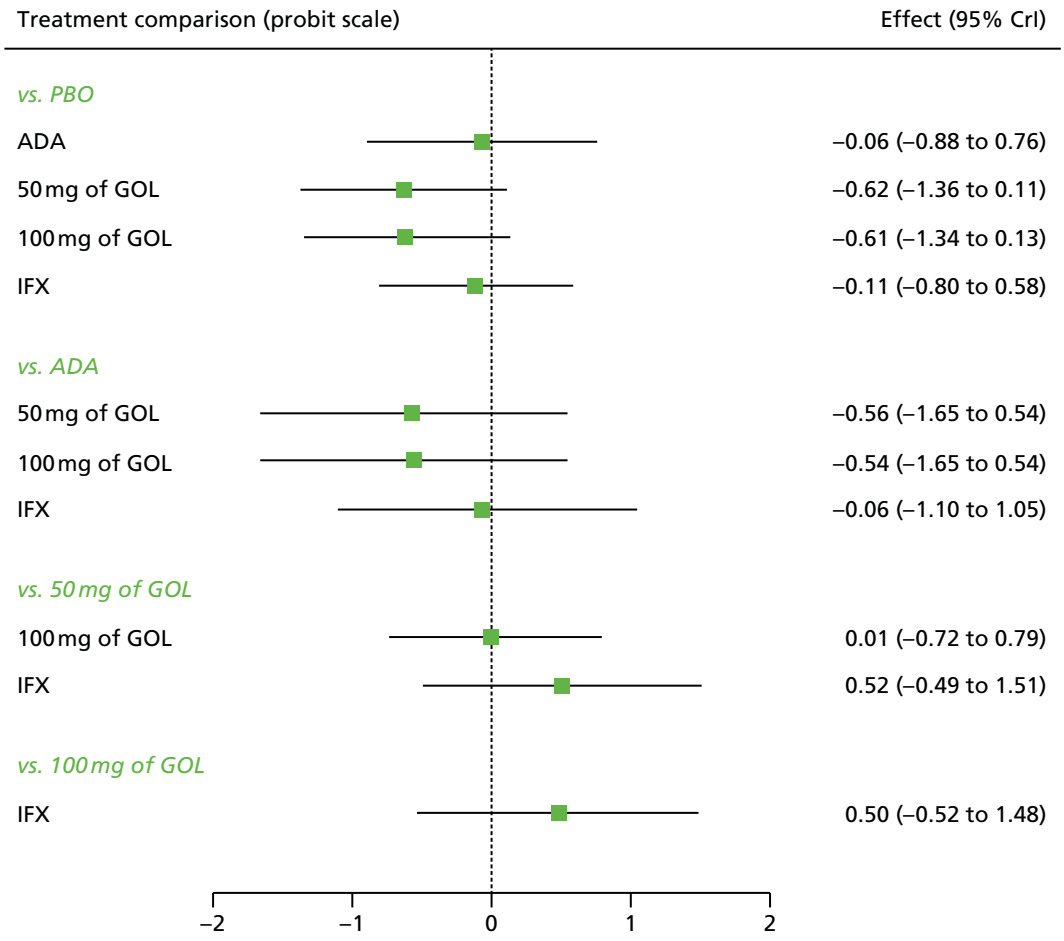

FIGURE 35 Sensitivity analysis 1: comparative effect of anti-TNF-α treatment on clinical response/remission in the maintenance phase at 8–32 weeks for patients starting in remission [SD ~ HN(0,0.32²)].

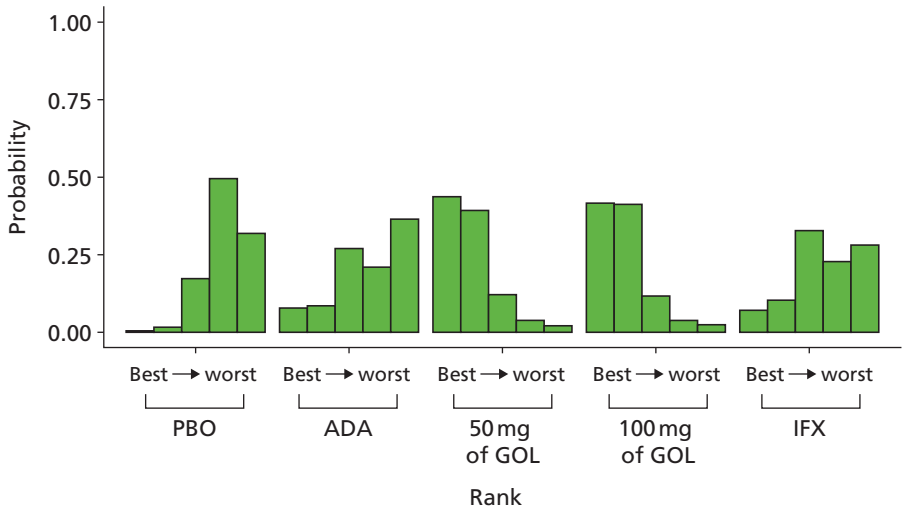

FIGURE 36 Sensitivity analysis 1: ranking probability histograms for the maintenance phase at 8–32 weeks for patients starting in remission.

TABLE 20 Sensitivity analysis 1: probabilities of being in each category for the maintenance phase at 8–32 weeks for patients starting in remission

	No response			Response			Remission		
Treatment	Mean	Median	95% CrI	Mean	Median	95% CrI	Mean	Median	95% CrI
PBO	0.392	0.389	0.217 to 0.584	0.180	0.175	0.078 to 0.309	0.428	0.426	0.218 to 0.650
ADA	0.379	0.365	0.096 to 0.736	0.167	0.164	0.06 to 0.3	0.454	0.450	0.128 to 0.807
50 mg of GOL	0.204	0.182	0.036 to 0.493	0.143	0.139	0.036 to 0.285	0.653	0.669	0.300 to 0.914
100 mg of GOL	0.207	0.188	0.038 to 0.494	0.144	0.140	0.037 to 0.287	0.648	0.662	0.303 to 0.911
IFX	0.359	0.347	0.107 to 0.679	0.170	0.166	0.065 to 0.301	0.471	0.470	0.165 to 0.793

Sensitivity analysis 1: maintenance phase 32–52 weeks

Patients starting in response A NMA was used to compare the effects of ADA, GOL and IFX relative to PBO on clinical response in the maintenance phase for patients starting in response at 32–52 weeks. Data were available from three studies comparing two or three treatments.[45,48,49] *Figure 37* presents the network of evidence for the sensitivity analysis 1 maintenance phase at 32–52 weeks for patients starting in response.

Figure 38 presents the effects of each treatment relative to PBO on the probit scale for the sensitivity analysis 1 maintenance phase 32–52 weeks for patients starting in response. *Figure 39* presents the probabilities of treatment rankings for this analysis. The model fitted the data reasonably well, with the total residual deviance, 12.32, being close to the total number of data points included in the analysis, 14. The between-study SD was estimated to be 0.21 (95% CrI 0.01 to 0.72), which implies mild to moderate heterogeneity between studies in treatment effects.

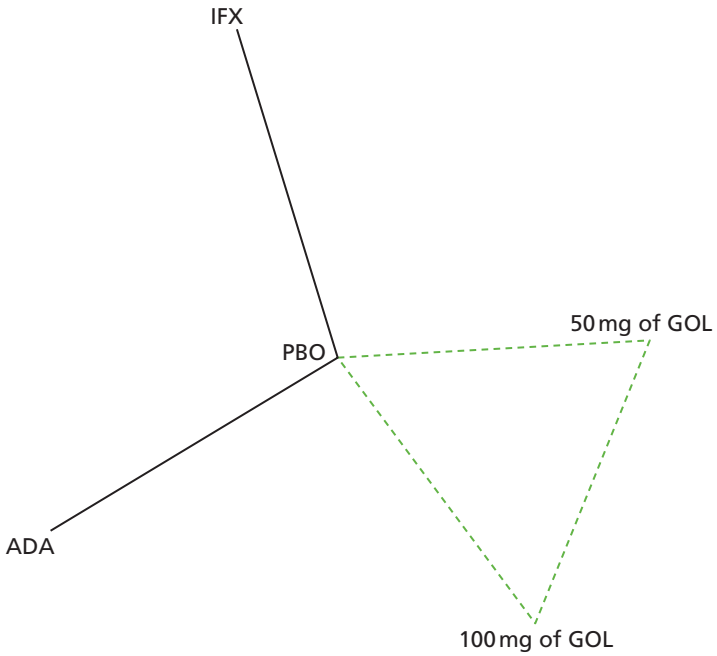

FIGURE 37 Sensitivity analysis 1: network of evidence for the maintenance phase at 32–52 weeks for patients starting in response. Note: solid line indicates a two-arm trial; dashed line indicates a three-arm study.

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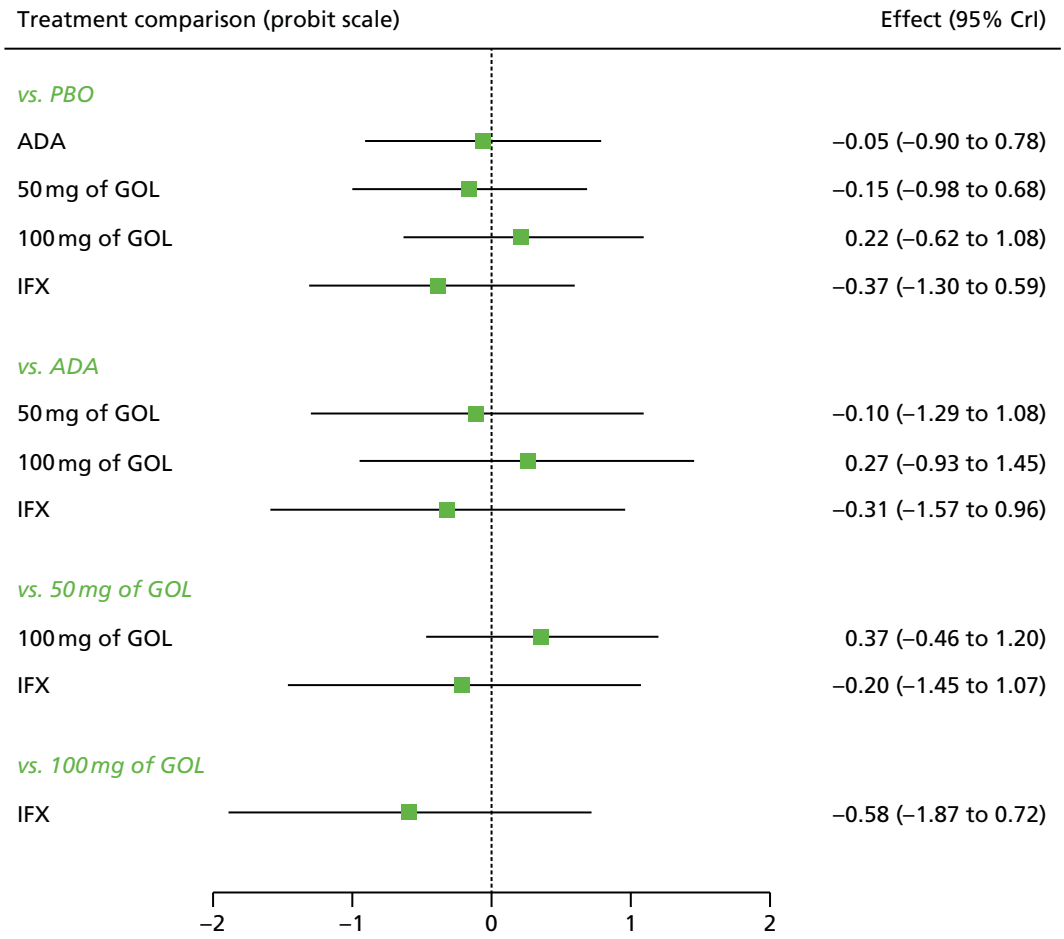

FIGURE 38 Sensitivity analysis 1: comparative effect of anti-TNF-α treatment on clinical response/remission in the maintenance phase at 32–52 weeks for patients starting in response [SD ~ HN(0,0.32^2)].

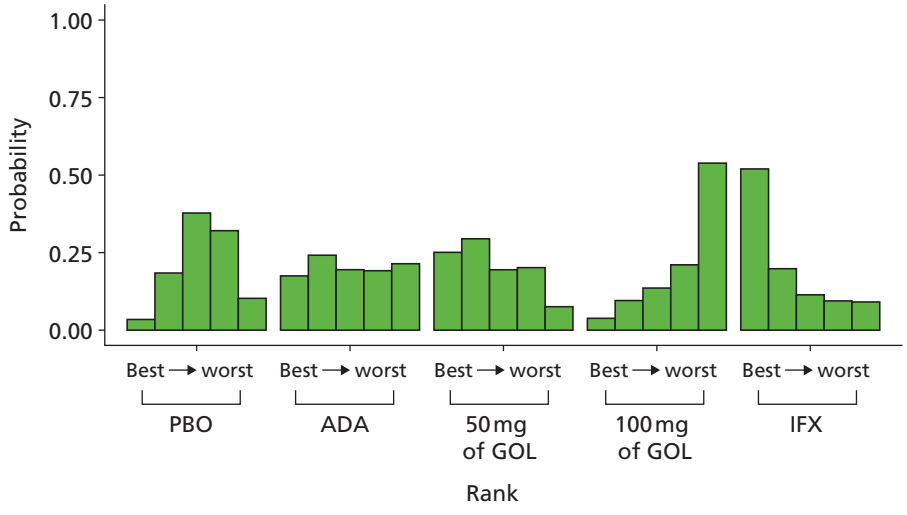

FIGURE 39 Sensitivity analysis 1: ranking probability histograms for the maintenance phase at 32–52 weeks for patients starting in response.

All treatments except 100 mg of GOL were associated with beneficial treatment effects relative to PBO with the greatest effect being associated with IFX (–0.37; 95% CrI –1.30 to 0.59); however, none of the treatment effects was statistically significant at a conventional 5% level. IFX was most likely to be the most effective treatment (probability of being the best = 0.52).

Table 21 presents the probabilities of achieving each of the following categories: no response, response and remission for the sensitivity analysis 1 maintenance phase at 32–52 weeks starting in response. IFX was associated with the highest probability of moving from response to remission and the smallest probability of moving from response to no response at 32–52 weeks. The probabilities of staying in the response state were comparable among treatments at 32–52 weeks.

Patients starting in remission

A NMA was used to compare the effects of ADA, GOL and IFX relative to PBO on clinical response in the maintenance phase at 32–52 weeks for patients starting in remission. Data were available from three studies comparing two or three treatments.[45,48,49] *Figure 40* presents the network of evidence for the sensitivity analysis 1 maintenance phase at 32–52 weeks for patients starting in remission.

Figure 41 presents the effects of each treatment relative to PBO on the probit scale for the sensitivity analysis 1 maintenance phase at 32–52 weeks for patients starting in remission. *Figure 42* presents the probabilities of treatment rankings for this analysis. The model fitted the data reasonably well, with the total residual deviance, 17.73, being close to the total number of data points included in the analysis, 14. The between-study SD was estimated to be 0.22 (95% CrI 0.01 to 0.72), which implies mild to moderate heterogeneity between studies in treatment effects.

All treatments except 50 mg of GOL were associated with beneficial treatment effects relative to PBO with the greatest effect being associated with ADA (–0.86; 95% CrI –1.71 to 0.00); however, only the treatment effects of ADA were statistically significant at a conventional 5% level. ADA was most likely to be the most effective treatment (probability of being the best = 0.78).

Table 22 presents the probabilities of achieving each of the following categories: no response, response and remission for the sensitivity analysis 1 maintenance phase at 32–52 weeks starting in remission. ADA was associated with the highest probability of staying in remission and the smallest probability of moving from remission to response or from remission to no response at 32–52 weeks.

TABLE 21 Sensitivity analysis 1: probabilities of being in each category for the maintenance phase at 32–52 weeks for patients starting in response

	No response			Response			Remission		
Treatment	Mean	Median	95% CrI	Mean	Median	95% CrI	Mean	Median	95% CrI
PBO	0.338	0.317	0.064 to 0.718	0.373	0.378	0.118 to 0.628	0.29	0.259	0.019 to 0.714
ADA	0.332	0.300	0.031 to 0.790	0.354	0.363	0.084 to 0.625	0.314	0.276	0.013 to 0.812
50 mg of GOL	0.302	0.269	0.024 to 0.769	0.355	0.364	0.077 to 0.632	0.344	0.308	0.015 to 0.844
100 mg of GOL	0.417	0.401	0.053 to 0.854	0.341	0.352	0.077 to 0.595	0.242	0.192	0.006 to 0.742
IFX	0.249	0.201	0.012 to 0.730	0.343	0.353	0.063 to 0.643	0.408	0.387	0.022 to 0.898

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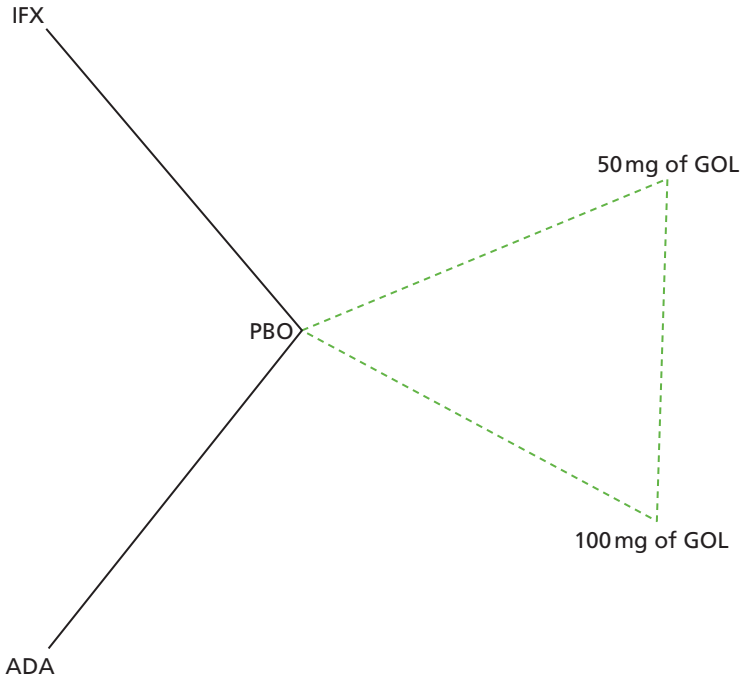

FIGURE 40 Sensitivity analysis 1: network of evidence for the maintenance phase at 32–52 weeks for patients starting in remission. Note: solid line indicates a two-arm trial; dashed line indicates a three-arm study.

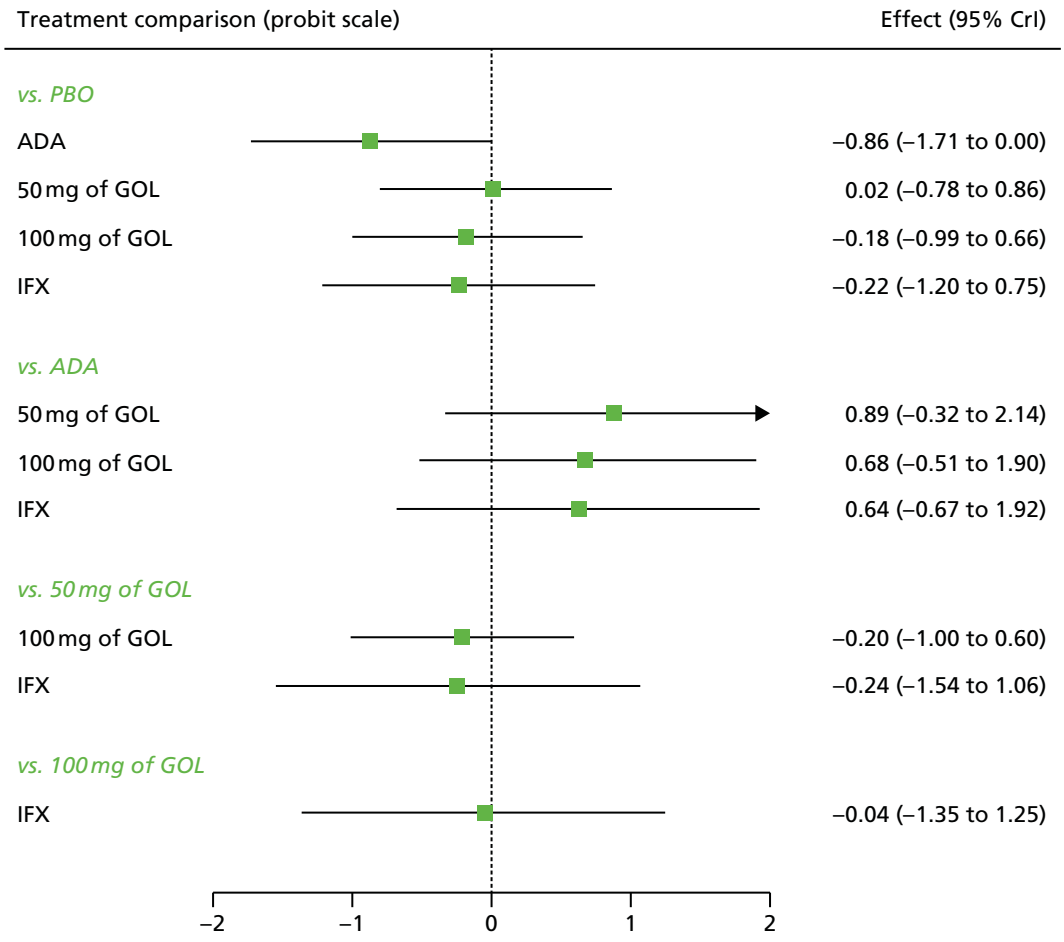

FIGURE 41 Sensitivity analysis 1: comparative effect of anti-TNF-α treatment on clinical response/remission in the maintenance phase at 32–52 weeks for patients starting in remission [SD ~ HN(0,0.32^2)].

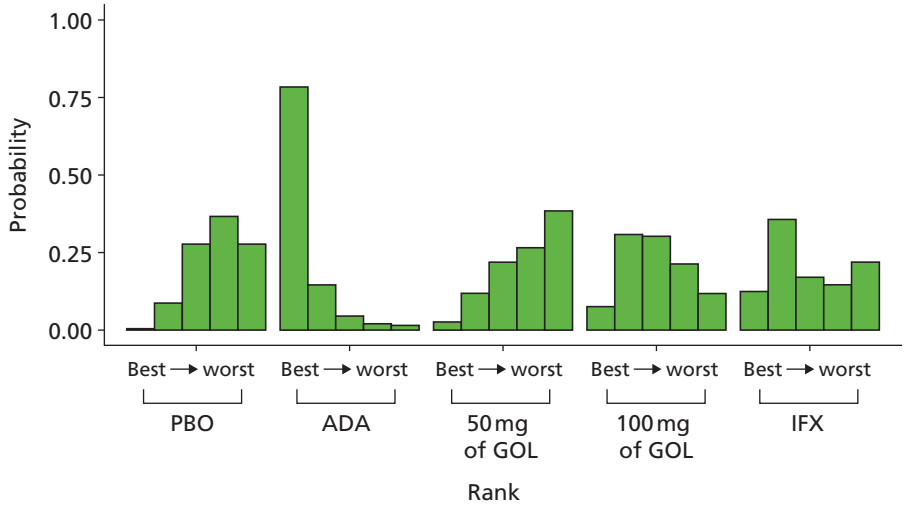

FIGURE 42 Sensitivity analysis 1: ranking probability histograms for the maintenance phase at 32–52 weeks for patients starting in remission.

TABLE 22 Sensitivity analysis 1: probabilities of being in each category for the maintenance phase at 32–52 weeks for patients starting in remission

	No response			Response			Remission		
Treatment	Mean	Median	95% CrI	Mean	Median	95% CrI	Mean	Median	95% CrI
PBO	0.302	0.299	0.177 to 0.448	0.167	0.155	0.030 to 0.396	0.530	0.539	0.270 to 0.727
ADA	0.104	0.082	0.010 to 0.324	0.098	0.081	0.008 to 0.308	0.797	0.828	0.426 to 0.974
50 mg of GOL	0.324	0.307	0.082 to 0.664	0.158	0.147	0.026 to 0.374	0.519	0.526	0.145 to 0.842
100 mg of GOL	0.260	0.239	0.053 to 0.591	0.149	0.136	0.022 to 0.374	0.591	0.605	0.200 to 0.890
IFX	0.254	0.225	0.035 to 0.620	0.144	0.132	0.019 to 0.367	0.603	0.620	0.186 to 0.918

Sensitivity analysis 2: induction phase

Sensitivity analysis 2 involved including Suzuki *et al.*[46] A NMA was used to compare the effects of ADA, GOL and IFX relative to PBO on clinical response in the induction phase. Data were available from six studies comparing two treatments.[44–47,49] *Figure 43* presents the network of evidence for the sensitivity analysis 2 induction phase.

Figure 44 presents the effects of each treatment relative to PBO on the probit scale for the sensitivity analysis 2 induction phase. *Figure 45* presents the probabilities of treatment rankings for this analysis. The model fitted the data well, with the total residual deviance, 24.36, being close to the total number of data points included in the analysis, 24. The between-study SD was estimated to be 0.10 (95% CrI 0.01 to 0.41), which implies mild heterogeneity between studies in treatment effects.

All treatments were associated with beneficial treatment effects relative to PBO with the greatest effect being associated with IFX (–0.92, 95% CrI –1.24 to –0.60). All treatment effects were statistically significant at a conventional 5% level. IFX was most likely to be the most effective treatment (probability of being the best = 0.96).

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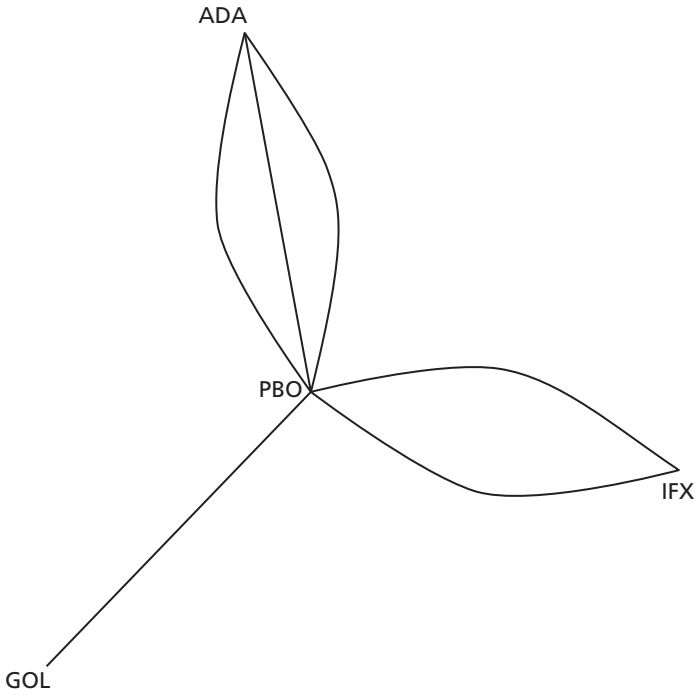

FIGURE 43 Sensitivity analysis 2: network of evidence for the induction phase. Note: solid line indicates a two-arm trial.

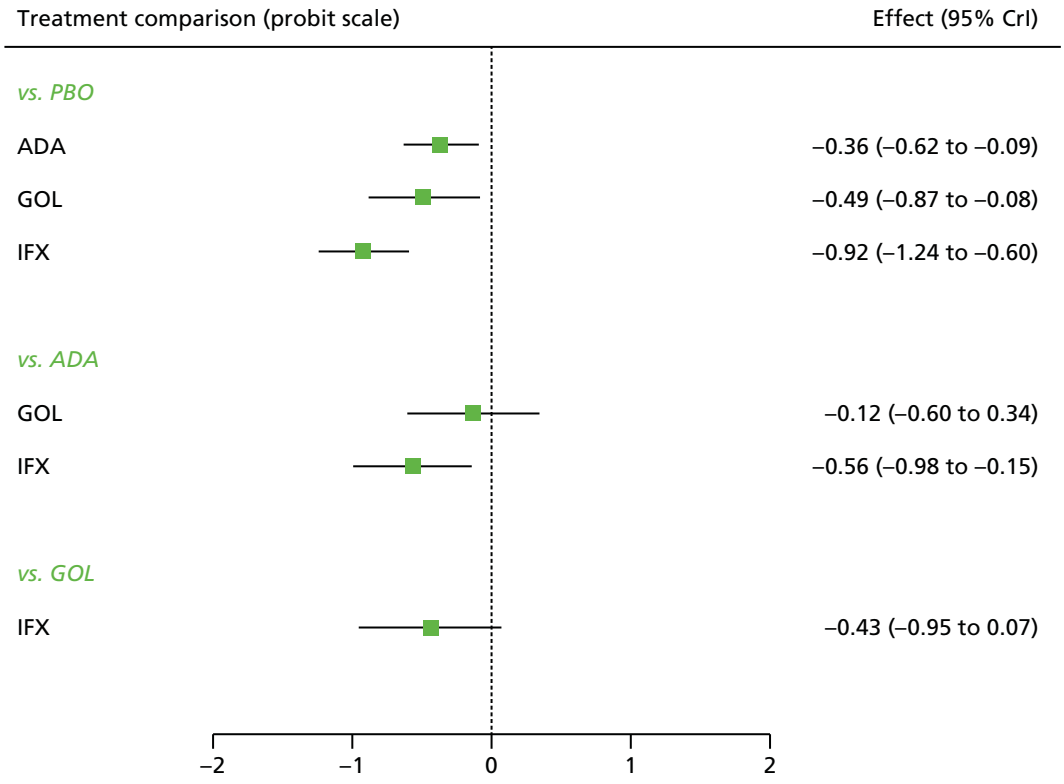

FIGURE 44 Sensitivity analysis 2: comparative effect of anti-TNF-α treatment on clinical response/remission in the induction phase [SD ~ HN(0,0.32^2)].

FIGURE 45 Sensitivity analysis 2: ranking probability histograms for the induction phase.

Table 23 presents the probabilities of achieving each of the following categories: no response, response and remission for the sensitivity analysis 2 induction phase. IFX was associated with the highest probability of moving from no response to response and from no response to remission.

Sensitivity analysis 2: maintenance phase 8–32 weeks

Patients starting in response A NMA was used to compare the effects of ADA, GOL and IFX relative to PBO on clinical response in the maintenance phase response at 8–32 weeks for patients starting in response. Data were available from five studies comparing two or three treatments.[45,46,48,49] *Figure 46* presents the network of evidence for the sensitivity analysis 2 maintenance phase at 8–32 weeks for patients starting in response.

Figure 47 presents the effects of each treatment relative to PBO on the probit scale for the sensitivity analysis 2 maintenance phase at 8–32 weeks for patients starting in response. *Figure 48* presents the probabilities of treatment rankings for this analysis. There was some suggestion that model did not represent the data well with the total residual deviance, 14.80, being smaller than would be expected given the total number of data points included in the analysis, 22. The probability of observing a value < 14.8 is 0.129, which means that this could be a chance event. Similar to the base-case analysis, all five studies had smaller residual deviance than expected. The between-study SD was estimated to be 0.16 (95% CrI 0.01 to 0.58), which implies mild to moderate heterogeneity between studies in treatment effects.

All treatments were associated with beneficial treatment effects relative to PBO with the greatest effect being associated with 100 mg of GOL (–0.43; 95% CrI–1.03 to 0.19); however, none of the treatment effects was statistically significant at a conventional 5% level. A treatment of 100 mg of GOL was most likely to be the most effective (probability of being the best = 0.44).

TABLE 23 Sensitivity analysis 2: probabilities of being in each category for the induction phase

	No response			Response			Remission		
Treatment	Mean	Median	95% CrI	Mean	Median	95% CrI	Mean	Median	95% CrI
PBO	0.642	0.642	0.585 to 0.696	0.260	0.263	0.225 to 0.301	0.095	0.094	0.065 to 0.132
ADA	0.502	0.500	0.384 to 0.623	0.326	0.327	0.264 to 0.377	0.173	0.170	0.099 to 0.264
GOL	0.452	0.450	0.298 to 0.624	0.339	0.343	0.266 to 0.392	0.209	0.204	0.060 to 0.344
IFX	0.292	0.252	0.183 to 0.421	0.360	0.360	0.305 to 0.411	0.348	0.347	0.068 to 0.488

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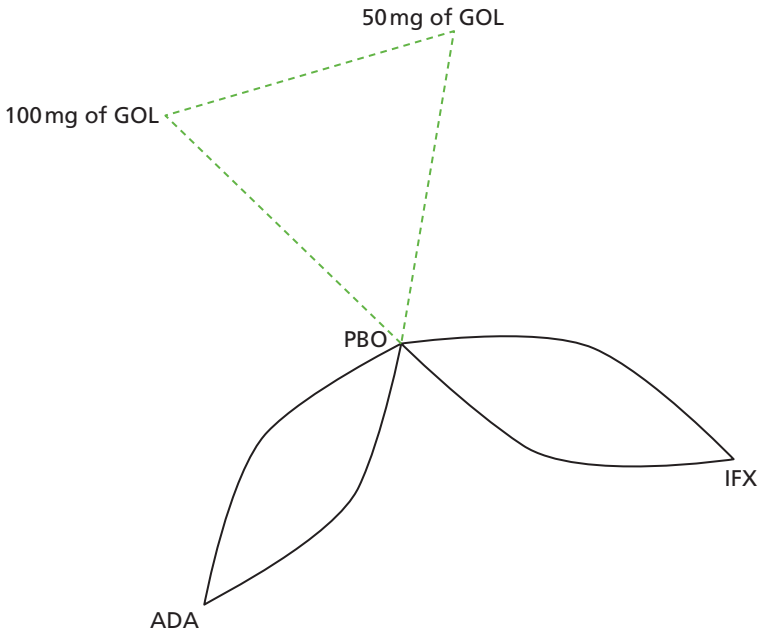

FIGURE 46 Sensitivity analysis 2: network of evidence for the maintenance phase at 8–32 weeks for patients starting in response. Note: solid line indicates a two-arm trial; dashed line indicates a three-arm study.

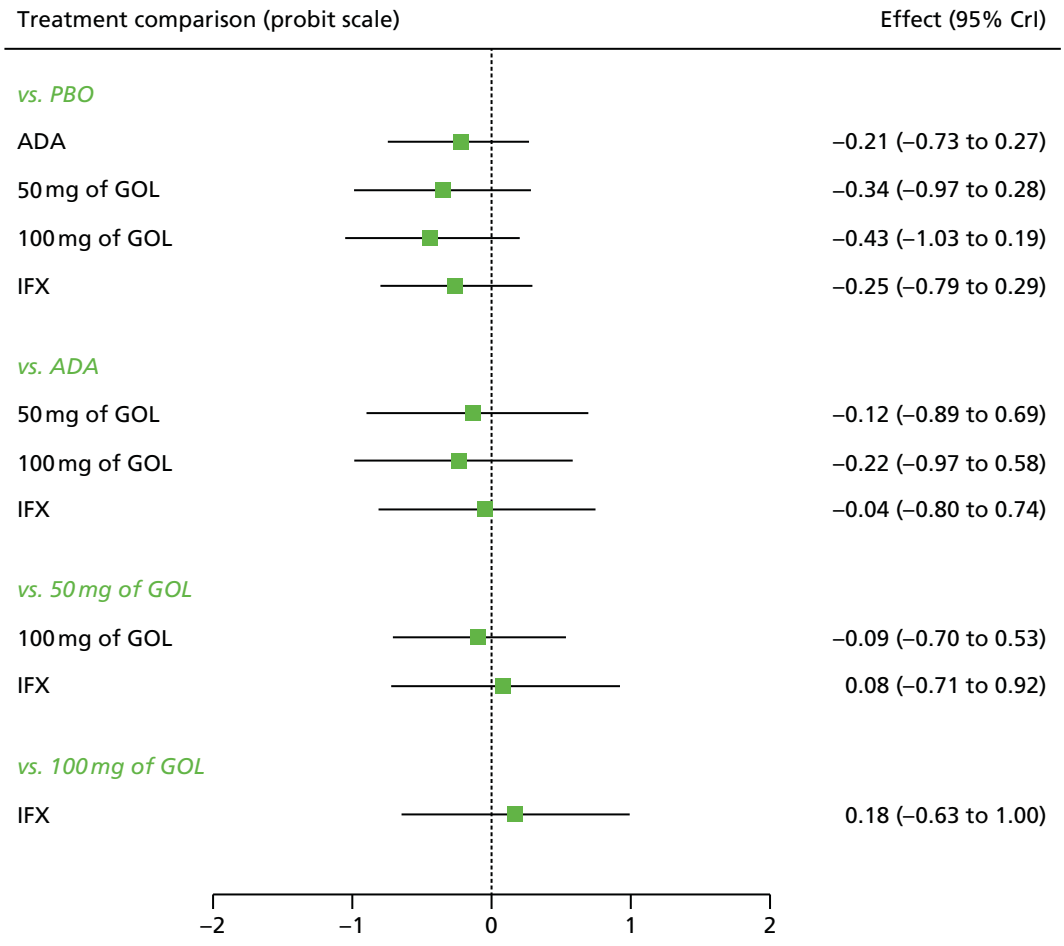

FIGURE 47 Sensitivity analysis 2: comparative effect of anti-TNF-α treatment on clinical response/remission in the maintenance phase at 8–32 weeks for patients starting in response [SD ~ HN(0,0.32^2)].

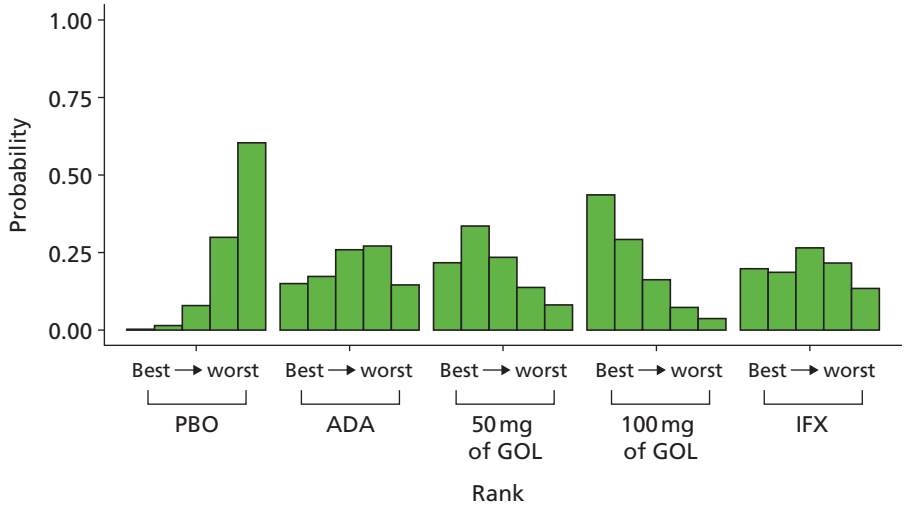

FIGURE 48 Sensitivity analysis 2: ranking probability histograms for the maintenance phase at 8–32 weeks for patients starting in response.

Table 24 presents the probabilities of achieving each of the following categories: no response, response and remission for the sensitivity analysis 2 maintenance phase at 8–32 weeks for patients starting in response. A treatment of 100 mg of GOL was associated with the highest probability of moving from response to remission and the smallest probability of moving from response to no response at 8–32 weeks. The probabilities of staying in the response state were comparable among treatments.

Patients starting in remission

A NMA was used to compare the effects of ADA, GOL and IFX relative to PBO on clinical response in the maintenance phase at 8–32 weeks for patients starting in remission. Data were available from five studies comparing two or three treatments.[45,46,48,49] *Figure 49* presents the network of evidence for the sensitivity analysis 2 maintenance phase at 8–32 weeks for patients starting in remission.

Figure 50 presents the effects of each treatment relative to PBO on the probit scale for the sensitivity analysis 2 maintenance phase at 8–32 weeks for patients starting in remission. *Figure 51* presents the probabilities of treatment rankings for this analysis. The model fitted the data well, with the total residual deviance, 21.05, being close to the total number of data points included in the analysis, 22. The between-study SD was estimated to be 0.17 (95% CrI 0.01 to 0.60), which implies mild to moderate heterogeneity between studies in treatment effects.

TABLE 24 Sensitivity analysis 2: probabilities of being in each category for the maintenance phase at 8–32 weeks for patients starting in response

	No response			Response			Remission		
Treatment	Mean	Median	95% CrI	Mean	Median	95% CrI	Mean	Median	95% CrI
PBO	0.525	0.525	0.437 to 0.609	0.274	0.274	0.220 to 0.329	0.201	0.199	0.130 to 0.286
ADA	0.441	0.441	0.238 to 0.647	0.286	0.288	0.209 to 0.354	0.273	0.263	0.116 to 0.485
50 mg of GOL	0.398	0.393	0.174 to 0.649	0.289	0.292	0.199 to 0.357	0.313	0.305	0.116 to 0.569
100 mg of GOL	0.363	0.356	0.158 to 0.617	0.291	0.293	0.200 to 0.360	0.346	0.338	0.132 to 0.598
IFX	0.429	0.425	0.222 to 0.657	0.287	0.289	0.204 to 0.352	0.284	0.276	0.110 to 0.504

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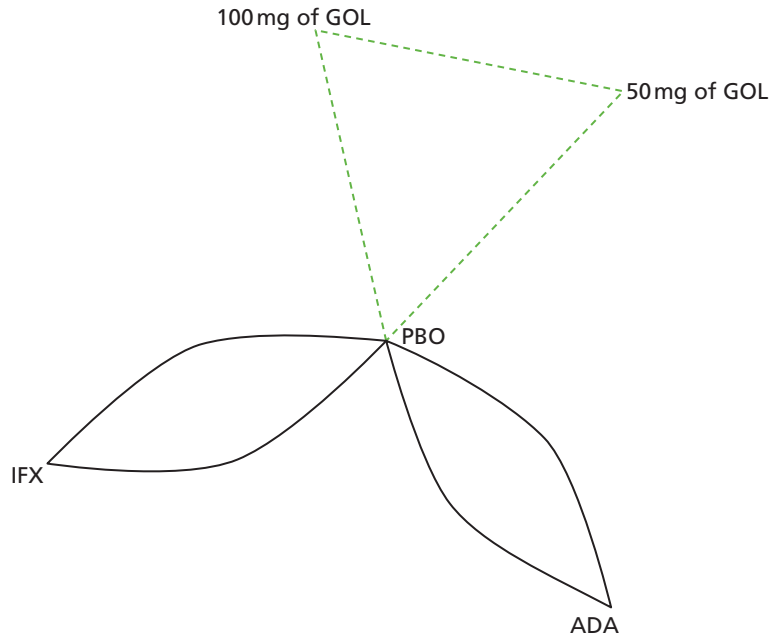

FIGURE 49 Sensitivity analysis 2: network of evidence for the maintenance phase at 8–32 weeks for patients starting in remission. Note: solid line indicates a two-arm trial; dashed line indicates a three-arm study.

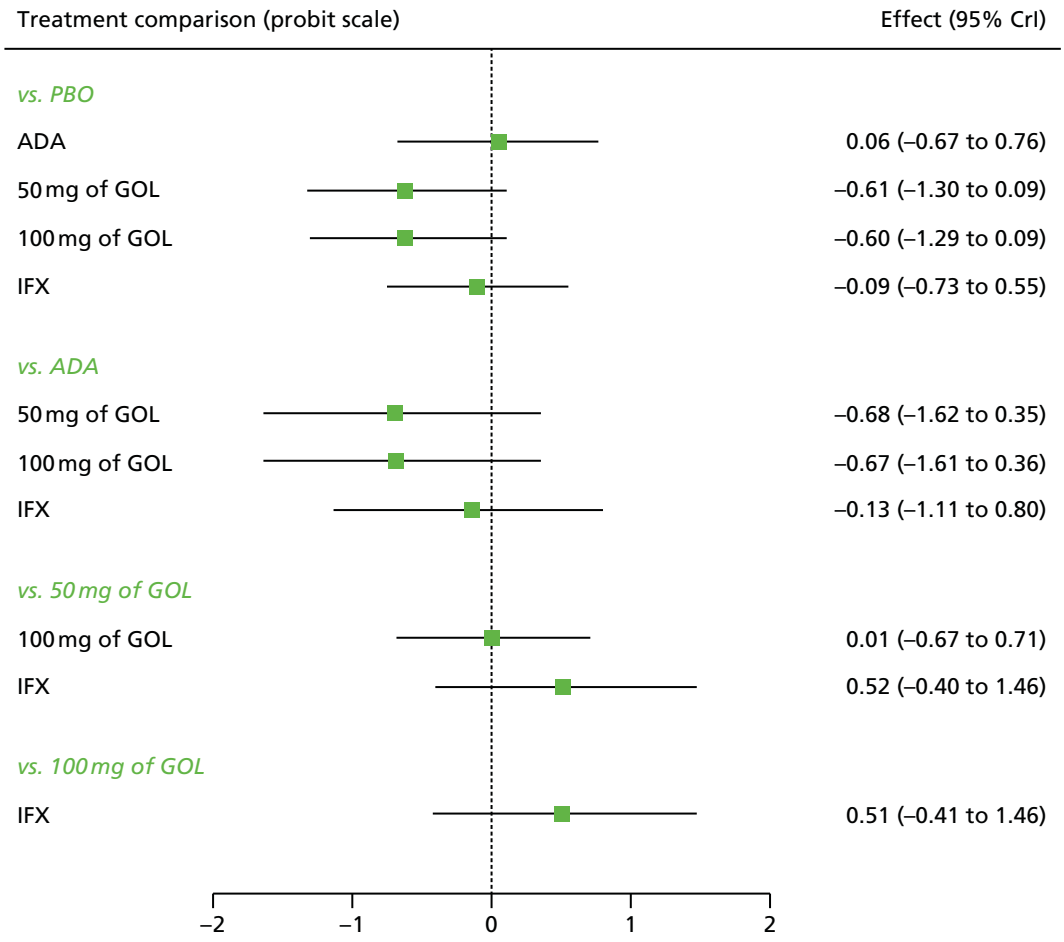

FIGURE 50 Sensitivity analysis 2: comparative effect of anti-TNF-α treatment on clinical response/remission in the maintenance phase at 8–32 weeks for patients starting in remission [SD ~ HN(0,0.32^2)].

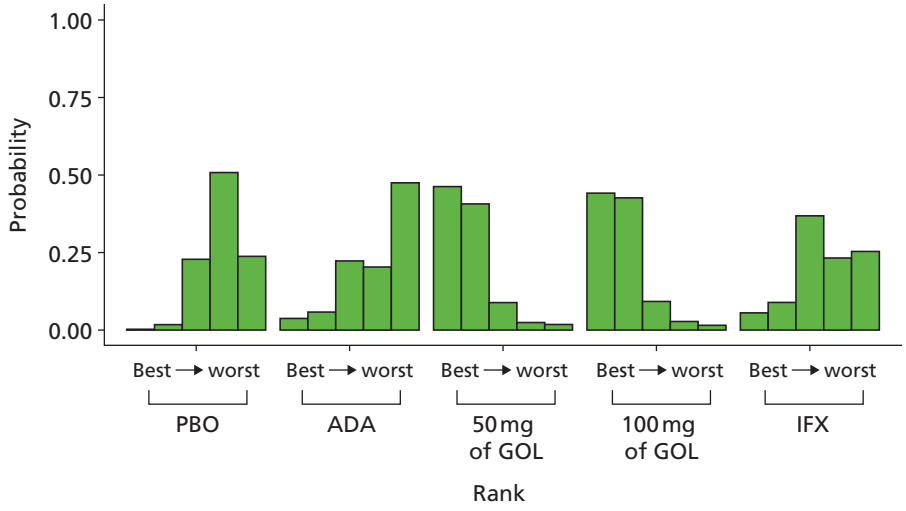

FIGURE 51 Sensitivity analysis 2: ranking probability histograms for the maintenance phase at 8–32 weeks for patients starting in remission.

All treatments except ADA were associated with beneficial treatment effects relative to PBO with the greatest effects being associated with 50 mg of GOL (–0.61; 95% CrI –1.30 to 0.09) and 100 mg of GOL (–0.60; 95% CrI –1.29 to 0.09); however, none of the treatment effects was statistically significant at a conventional 5% level. Treatments of 50 mg and 100 mg of GOL was most likely to be the most effective (probability of being the best = 0.46 and 0.44 respectively).

Table 25 presents the probabilities of achieving each of the following categories: no response, response and remission for the sensitivity analysis 2 maintenance phase at 8–32 weeks starting in remission. Treatments of 50 mg and 100 mg of GOL were associated with the highest probability of staying in remission and the smallest probability of moving from remission to no response and from remission to response at 8–32 weeks.

TABLE 25 Sensitivity analysis 2: probabilities of being in each category for the maintenance phase at 8–32 weeks for patients starting in remission

	No response			Response			Remission		
Treatment	Mean	Median	95% CrI	Mean	Median	95% CrI	Mean	Median	95% CrI
PBO	0.354	0.350	0.191 to 0.540	0.187	0.183	0.103 to 0.294	0.459	0.459	0.250 to 0.666
ADA	0.381	0.371	0.114 to 0.701	0.178	0.175	0.085 to 0.286	0.441	0.434	0.144 to 0.769
50 mg of GOL	0.179	0.159	0.034 to 0.442	0.143	0.139	0.043 to 0.264	0.678	0.695	0.353 to 0.915
100 mg of GOL	0.181	0.162	0.035 to 0.443	0.144	0.141	0.044 to 0.264	0.675	0.691	0.349 to 0.913
IFX	0.331	0.318	0.103 to 0.626	0.177	0.174	0.082 to 0.286	0.492	0.493	0.195 to 0.790

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Sensitivity analysis 2: maintenance phase 32–52 weeks

Patients starting in response A NMA was used to compare the effects of ADA, GOL and IFX relative to PBO on clinical response in the maintenance phase for patients starting in response at 32–52 weeks. Data were available from four studies comparing two or three treatments.[45,46,48,49] *Figure 52* presents the network of evidence for the sensitivity analysis 2 maintenance phase at 32–52 weeks for patients starting in response.

Figure 53 presents the effects of each treatment relative to PBO on the probit scale for the sensitivity analysis 2 maintenance phase 32–52 weeks for patients starting in response. *Figure 54* presents the probabilities of treatment rankings for this analysis. The model fitted the data reasonably well, with the total residual deviance, 15.92, being close to the total number of data points included in the analysis, 18. The between-study SD was estimated to be 0.20 (95% CrI 0.01 to 0.67), which implies mild to moderate heterogeneity between studies in treatment effects.

All treatments except ADA and 100 mg of GOL were associated with beneficial treatment effects relative to PBO with the greatest effect being associated with IFX (–0.36; 95% CrI –1.29 to 0.58); however, none of the treatment effects was statistically significant at a conventional 5% level. IFX was most likely to be the most effective treatment (probability of being the best = 0.57).

Table 26 presents the probabilities of achieving each of the following categories: no response, response and remission for the sensitivity analysis 2 maintenance phase at 32–52 weeks for patients starting in response. IFX was associated with the highest probability of moving from response to remission and the smallest probability of moving from response to no response at 32–52 weeks. The probabilities of staying in response were comparable among treatments at 32–52 weeks.

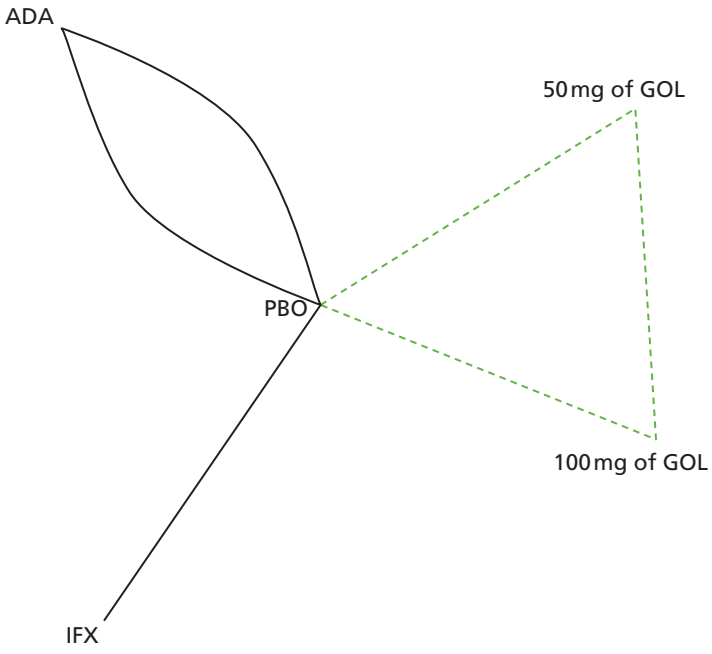

FIGURE 52 Sensitivity analysis 2: network of evidence for the maintenance phase for patients starting in response at 32–52 weeks. Note: solid line indicates a two-arm trial; dashed line indicates a three-arm study.

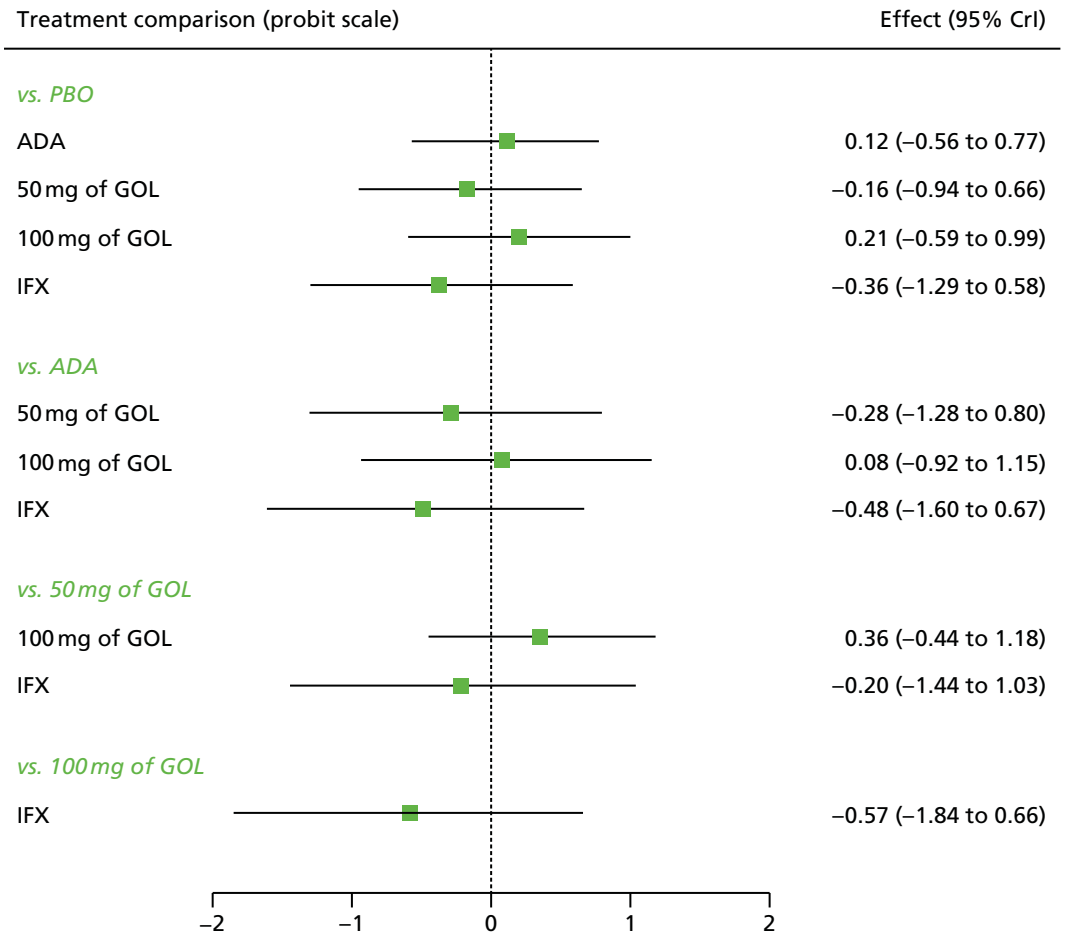

FIGURE 53 Sensitivity analysis 2: comparative effect of anti-TNF-α treatment on clinical response/remission in the maintenance phase at 32–52 weeks for patients starting in response [SD ~ HN(0,0.32²)].

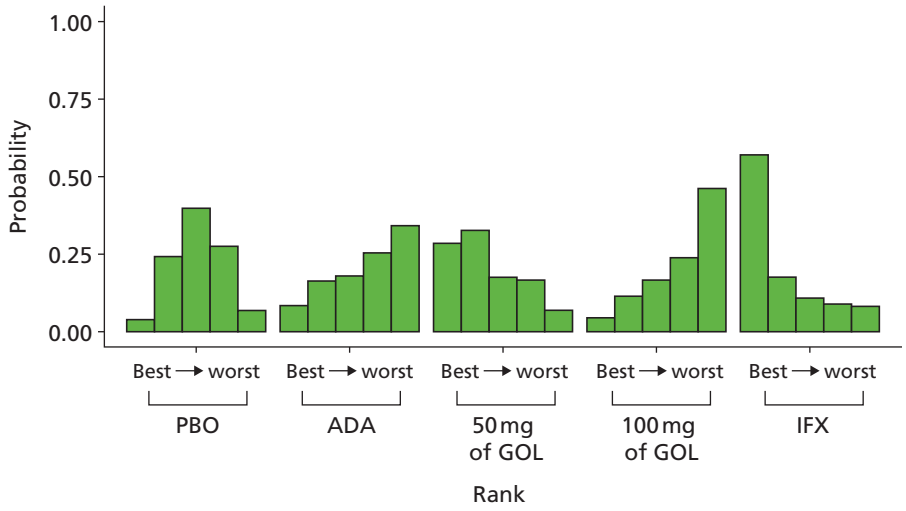

FIGURE 54 Sensitivity analysis 2: ranking probability histograms for the maintenance phase at 32–52 weeks for patients starting in response.

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TABLE 26 Sensitivity analysis 2: probabilities of being in each category for the maintenance phase at 32–52 weeks for patients starting in response

	No response			Response			Remission		
Treatment	Mean	Median	95% CrI	Mean	Median	95% CrI	Mean	Median	95% CrI
PBO	0.322	0.318	0.189 to 0.472	0.393	0.398	0.200 to 0.544	0.286	0.278	0.107 to 0.520
ADA	0.371	0.363	0.130 to 0.661	0.371	0.378	0.176 to 0.524	0.259	0.238	0.05 to 0.576
50 mg of GOL	0.283	0.265	0.066 to 0.606	0.370	0.378	0.153 to 0.545	0.347	0.332	0.069 to 0.713
100 mg of GOL	0.404	0.395	0.128 to 0.730	0.359	0.368	0.153 to 0.521	0.237	0.211	0.035 to 0.579
IFX	0.230	0.202	0.030 to 0.575	0.352	0.363	0.115 to 0.542	0.418	0.410	0.081 to 0.820

Patients starting in remission

A NMA was used to compare the effects of ADA, GOL and IFX relative to PBO on clinical response in the maintenance phase at 32–52 weeks for patients starting in remission. Data were available from four studies comparing two or three treatments.[45,48,49] *Figure 55* presents the network of evidence for the sensitivity analysis 2 maintenance phase at 32–52 weeks for patients starting in remission.

Figure 56 presents the effects of each treatment relative to PBO on the probit scale for the sensitivity analysis 2 maintenance phase at 32–52 weeks for patients starting in remission. *Figure 57* presents the probabilities of treatment rankings for this analysis. The model fitted the data reasonably well, with the total residual deviance, 21.07, being close to the total number of data points included in the analysis, 18. The between-study SD was estimated to be 0.18 (95% CrI 0.01 to 0.65), which implies mild to moderate heterogeneity between studies in treatment effects.

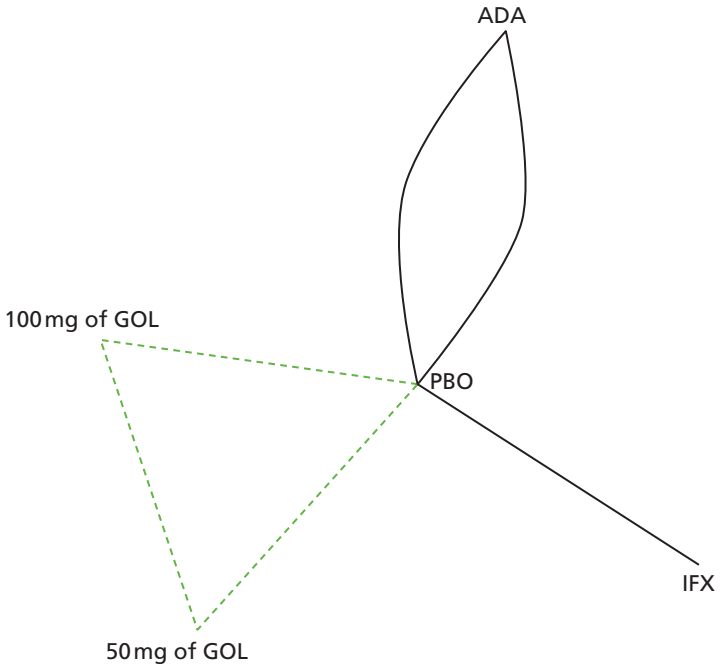

FIGURE 55 Sensitivity analysis 2: network of evidence for the maintenance phase at 32–52 weeks for patients starting in remission. Note: solid line indicates a two-arm trial; dashed line indicates a three-arm study.

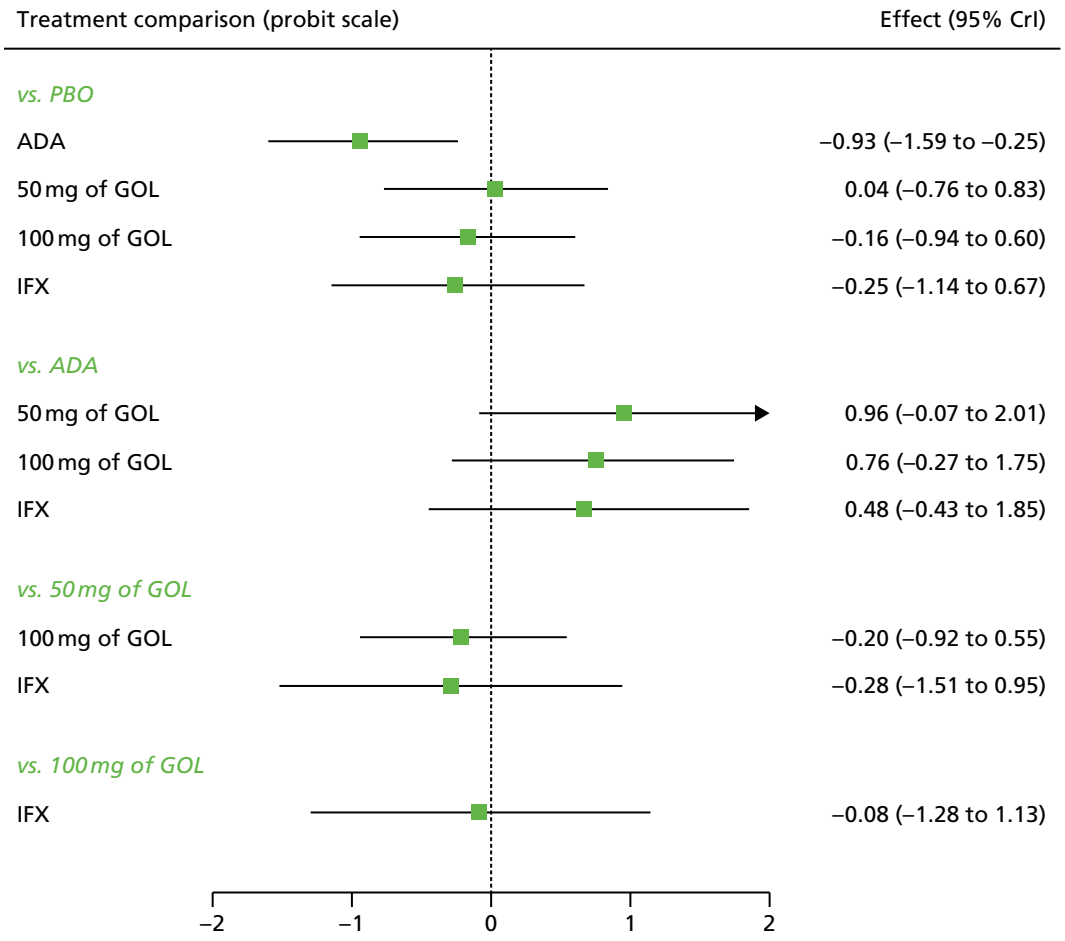

FIGURE 56 Sensitivity analysis 2: comparative effect of anti-TNF-α treatment on clinical response/remission in the maintenance phase at 32–52 weeks for patients starting in remission [SD ~ HN(0,0.32²)].

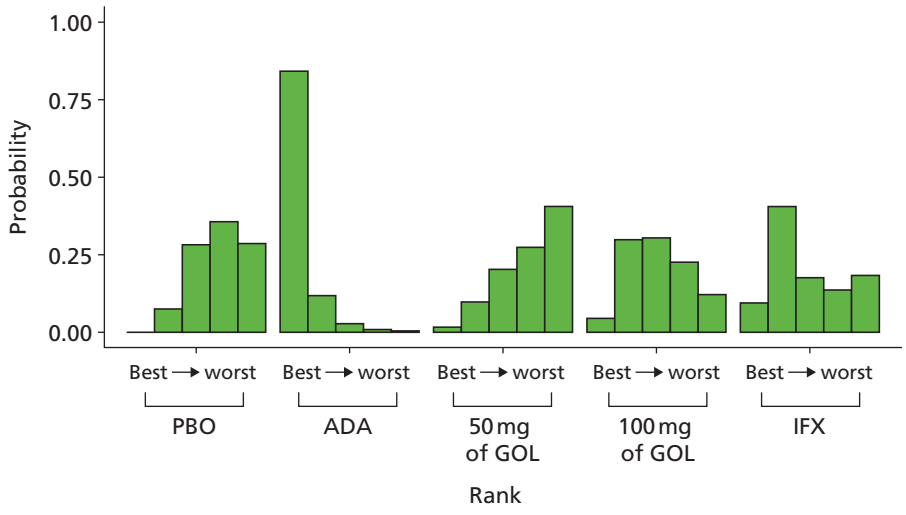

FIGURE 57 Sensitivity analysis 2: ranking probability histograms for the maintenance phase at 32–52 weeks for patients starting in remission.

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All treatments except 50 mg of GOL were associated with beneficial treatment effects relative to PBO with the greatest effect being associated with ADA (–0.93, 95% CrI –1.59 to –0.25); however, only the effect of ADA was statistically significant at a conventional 5% level. ADA was most likely to be the most effective treatment (probability of being the best = 0.84).

Table 27 presents the probabilities of achieving each of the following categories: no response, response and remission for the sensitivity analysis 2 maintenance phase at 32–52 weeks starting in remission. ADA was associated with the highest probability of staying in remission and the smallest probability of moving from remission to response or no response at 32–52 weeks.

Sensitivity analysis 3: induction phase

Sensitivity analysis 3 involved replacing ULTRA2 anti-TNF-α-naive data with ULTRA2 ITT data and including data from Suzuki *et al.*[46] A NMA was used to compare the effects of ADA, GOL and IFX relative to PBO on clinical response in the induction phase. Data were available from six studies comparing two treatments.[44–47,49] *Figure 58* presents the network of evidence for the sensitivity analysis 3 induction phase.

TABLE 27 Sensitivity analysis 2: probabilities of being in each category for the maintenance phase at 32–52 weeks for patients starting in remission

	No response			Response			Remission		
Treatment	Mean	Median	95% CrI	Mean	Median	95% CrI	Mean	Median	95% CrI
PBO	0.296	0.294	0.183 to 0.422	0.198	0.184	0.043 to 0.445	0.505	0.514	0.233 to 0.71
ADA	0.085	0.070	0.013 to 0.239	0.111	0.092	0.012 to 0.339	0.804	0.830	0.493 to 0.963
50 mg of GOL	0.320	0.307	0.083 to 0.633	0.188	0.176	0.035 to 0.425	0.492	0.494	0.137 to 0.83
100 mg of GOL	0.258	0.24	0.059 to 0.558	0.180	0.165	0.030 to 0.425	0.563	0.573	0.186 to 0.872
IFX	0.239	0.214	0.040 to 0.581	0.171	0.157	0.026 to 0.416	0.590	0.609	0.176 to 0.906

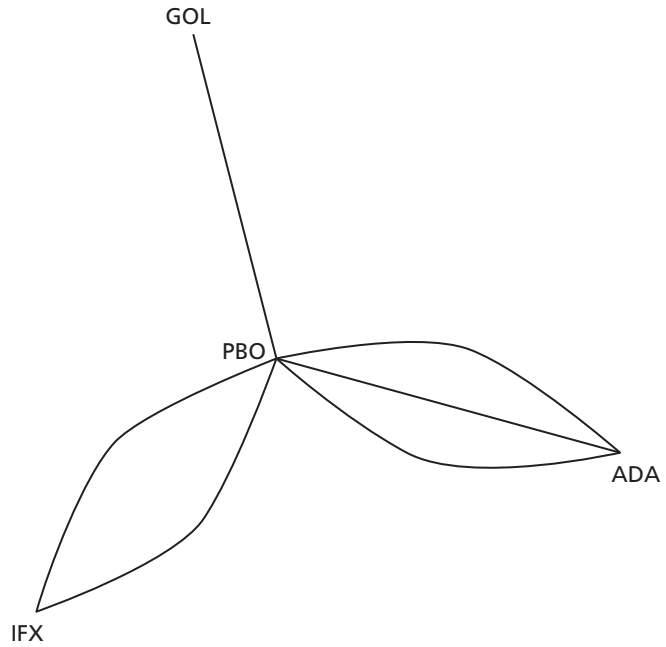

FIGURE 58 Sensitivity analysis 3: network of evidence for the induction phase. Note: solid line indicates a two-arm trial.

Figure 59 presents the effects of each treatment relative to PBO on the probit scale for the sensitivity analysis 3 induction phase. *Figure 60* presents the probabilities of treatment rankings for this analysis. The model fitted the data well, with the total residual deviance, 23.63, being close to the total number of data points included in the analysis, 24. The between-study SD was estimated to be 0.09 (95% CrI 0.00 to 0.38), which implies mild heterogeneity between studies in treatment effects.

All treatments were associated with beneficial treatment effects relative to PBO with the greatest effect being associated with IFX (–0.91; 95% CrI –1.21 to –0.62). All the treatment effects were statistically significant at a conventional 5% level. IFX was most likely to be the most effective treatment (probability of being the best = 0.97).

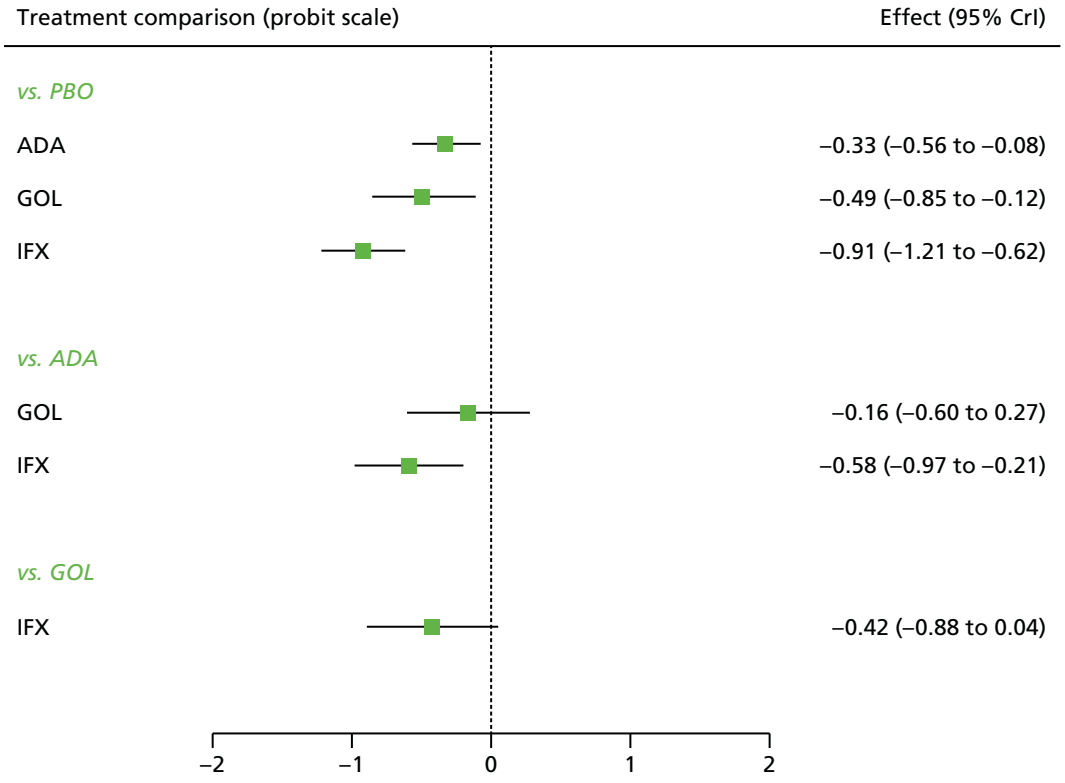

FIGURE 59 Sensitivity analysis 3: comparative effect of anti-TNF-α treatment on clinical response/remission in the induction phase [SD ~ HN(0,0.32^2)].

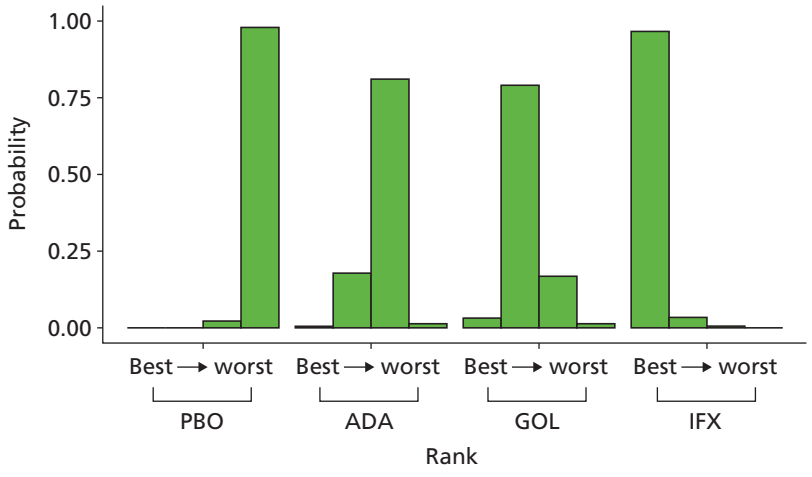

FIGURE 60 Sensitivity analysis 3: ranking probability histograms for the induction phase.

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Table 28 presents the probabilities of achieving each of the following categories: no response, response and remission for the sensitivity analysis 3 induction phase. IFX was associated with the highest probability of moving from no response to response and no response to remission.

Sensitivity analysis 3: maintenance phase 8–32 weeks

Patients starting in response A NMA was used to compare the effects of ADA, GOL and IFX relative to PBO on clinical response in the maintenance phase for patients starting in response at 8–32 weeks. Data were available from five studies comparing two or three treatments.[45,46,48,49] *Figure 61* presents the network of evidence for the sensitivity analysis 3 maintenance phase at 8–32 weeks for patients starting in response.

Figure 62 presents the effects of each treatment relative to PBO on the probit scale for the sensitivity analysis 3 maintenance phase at 8–32 weeks for patients starting in response. *Figure 63* presents the probabilities of treatment rankings for this analysis. There was some suggestion that model did not represent the data well with the total residual deviance, 14.05, being smaller than would be expected given the total number of data points included in the analysis, 22. The probability of observing a value < 14.05 is 0.100, which means that this could have occurred by chance. Similar to the base-case analysis, all 5 studies had smaller residual deviance than expected. The between-study SD was estimated to be 0.15 (95% CrI 0.01 to 0.55), which implies mild to moderate heterogeneity between studies in treatment effects.

TABLE 28 Sensitivity analysis 3: probabilities of being in each category for the induction phase

	No response			Response			Remission		
Treatment	Mean	Median	95% CrI	Mean	Median	95% CrI	Mean	Median	95% CrI
PBO	0.649	0.650	0.596 to 0.699	0.258	0.258	0.222 to 0.294	0.093	0.092	0.064 to 0.128
ADA	0.521	0.519	0.414 to 0.632	0.317	0.319	0.257 to 0.367	0.162	0.160	0.095 to 0.241
GOL	0.458	0.456	0.315 to 0.610	0.336	0.339	0.267 to 0.387	0.205	0.201	0.106 to 0.331
IFX	0.301	0.264	0.196 to 0.419	0.358	0.360	0.304 to 0.408	0.340	0.338	0.222 to 0.477

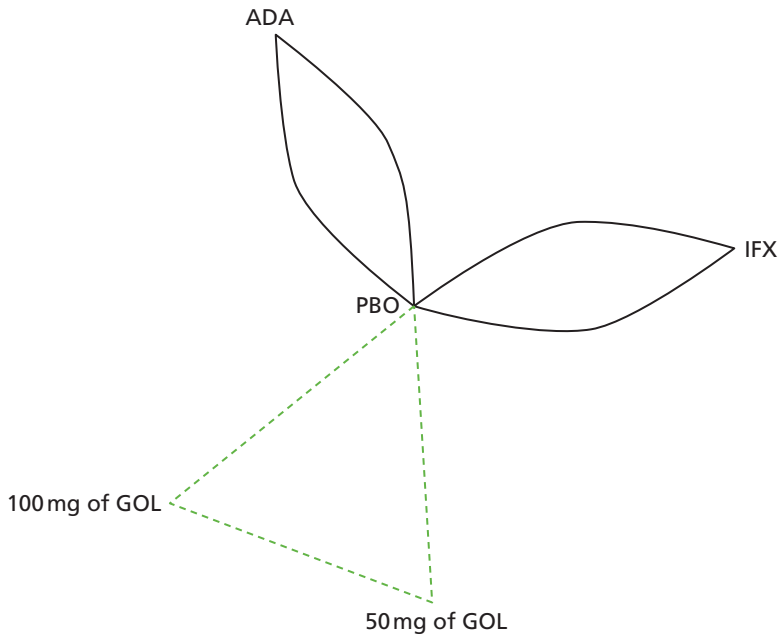

FIGURE 61 Sensitivity analysis 3: network of evidence for the maintenance phase at 8–32 weeks for patients starting in response. Note: solid line indicates a two-arm trial; dashed line indicates a three-arm study.

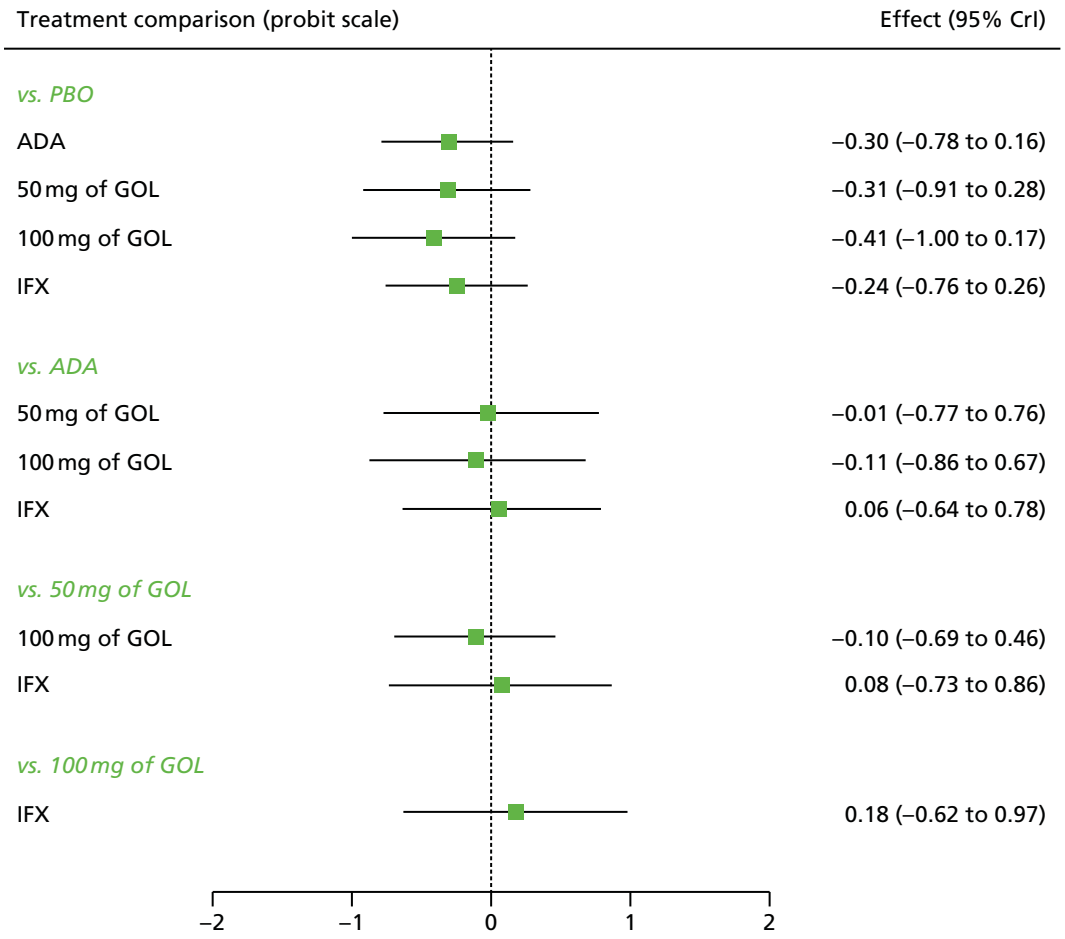

FIGURE 62 Sensitivity analysis 3: comparative effect of anti-TNF-α treatment on clinical response/remission in the maintenance phase at 8–32 weeks for patients starting in response [SD ~ HN(0,0.32²)].

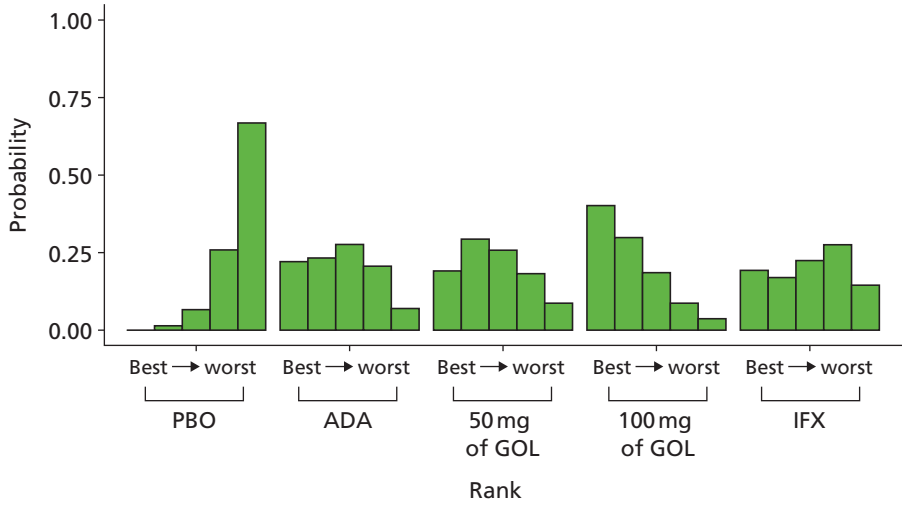

FIGURE 63 Sensitivity analysis 3: ranking probability histograms for the maintenance phase at 8–32 weeks for patients starting in response.

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All treatments were associated with beneficial treatment effects relative to PBO with the greatest effect being associated with 100 mg of GOL; however, none of the treatment effects was statistically significant at a conventional 5% level. A treatment of 100 mg of GOL was most likely to be the most effective (probability of being the best = 0.40).

Table 29 presents the probabilities of achieving each of the following categories: no response, response and remission for the sensitivity analysis 3 maintenance phase at 8–32 weeks starting in response. A treatment of 100 mg of GOL was associated with the highest probability of moving from response to remission and the smallest probability of moving from response to no response at 8–32 weeks. The probabilities of staying in response were comparable among treatments.

Patients starting in remission

A NMA was used to compare the effects of ADA, GOL and IFX relative to PBO on clinical response in the maintenance phase at 8–32 weeks for patients starting in remission. Data were available from five studies comparing two or three treatments.[45,46,48,49] *Figure 64* presents the network of evidence for the sensitivity analysis 3 maintenance phase at 8–32 weeks for patients starting in remission.

Figure 65 presents the effects of each treatment relative to PBO on the probit scale for the sensitivity analysis 3 maintenance phase at 8–32 weeks for patients starting in remission. *Figure 66* presents the probabilities of treatment rankings for this analysis. The model fitted the data reasonably well, with the total residual deviance, 17.77, being close to the total number of data points included in the analysis, 22. The between-study SD was estimated to be 0.16 (95% CrI 0.01 to 0.59), which implies mild to moderate heterogeneity between studies in treatment effects.

All treatments were associated with beneficial treatment effects relative to PBO with the greatest effects being associated with 50 mg of GOL (–0.62, 95% CrI –1.33 to 0.06) and 100 mg of GOL (–0.61, 95% CrI –1.29 to 0.07); however, none of the treatment effects was statistically significant at a conventional 5% level. A treatment of 50 mg and 100 mg of GOL were most likely to be the most effective treatments (probability of being the best = 0.46 and 0.44 respectively).

Table 30 presents the probabilities of achieving each of the following categories: no response, response and remission for the sensitivity analysis 3 maintenance phase at 8–32 weeks starting in remission. A treatment of 50 mg and 100 mg of GOL were associated with the highest probability of staying in remission and the smallest probability of moving from remission to no response and from remission to response at 8–32 weeks.

TABLE 29 Sensitivity analysis 3: probabilities of being in each category for the maintenance phase at 8–32 weeks for patients starting in response

	No response			Response			Remission		
Treatment	Mean	Median	95% CrI	Mean	Median	95% CrI	Mean	Median	95% CrI
PBO	0.545	0.545	0.459 to 0.630	0.270	0.270	0.223 to 0.32	0.185	0.183	0.120 to 0.260
ADA	0.427	0.425	0.243 to 0.626	0.292	0.293	0.223 to 0.353	0.280	0.274	0.129 to 0.470
50 mg of GOL	0.425	0.422	0.202 to 0.669	0.289	0.290	0.204 to 0.354	0.287	0.276	0.107 to 0.523
100 mg of GOL	0.386	0.382	0.176 to 0.628	0.293	0.294	0.213 to 0.356	0.321	0.313	0.129 to 0.560
IFX	0.451	0.449	0.246 to 0.664	0.287	0.289	0.211 to 0.349	0.262	0.255	0.109 to 0.465

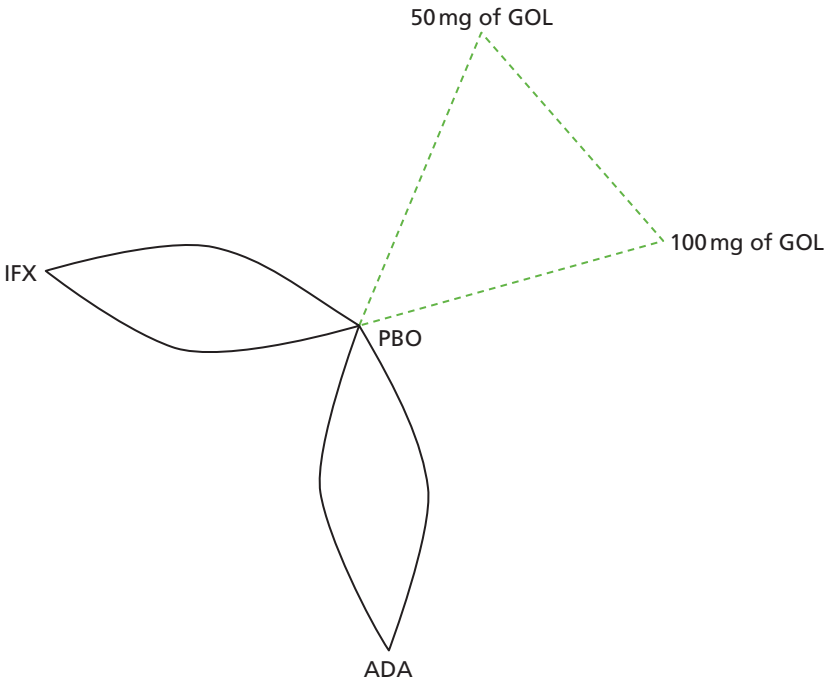

FIGURE 64 Sensitivity analysis 3: network of evidence for maintenance phase at 8–32 weeks for patients starting in remission. Note: solid line indicates a two-arm trial; dashed line indicates a three-arm study.

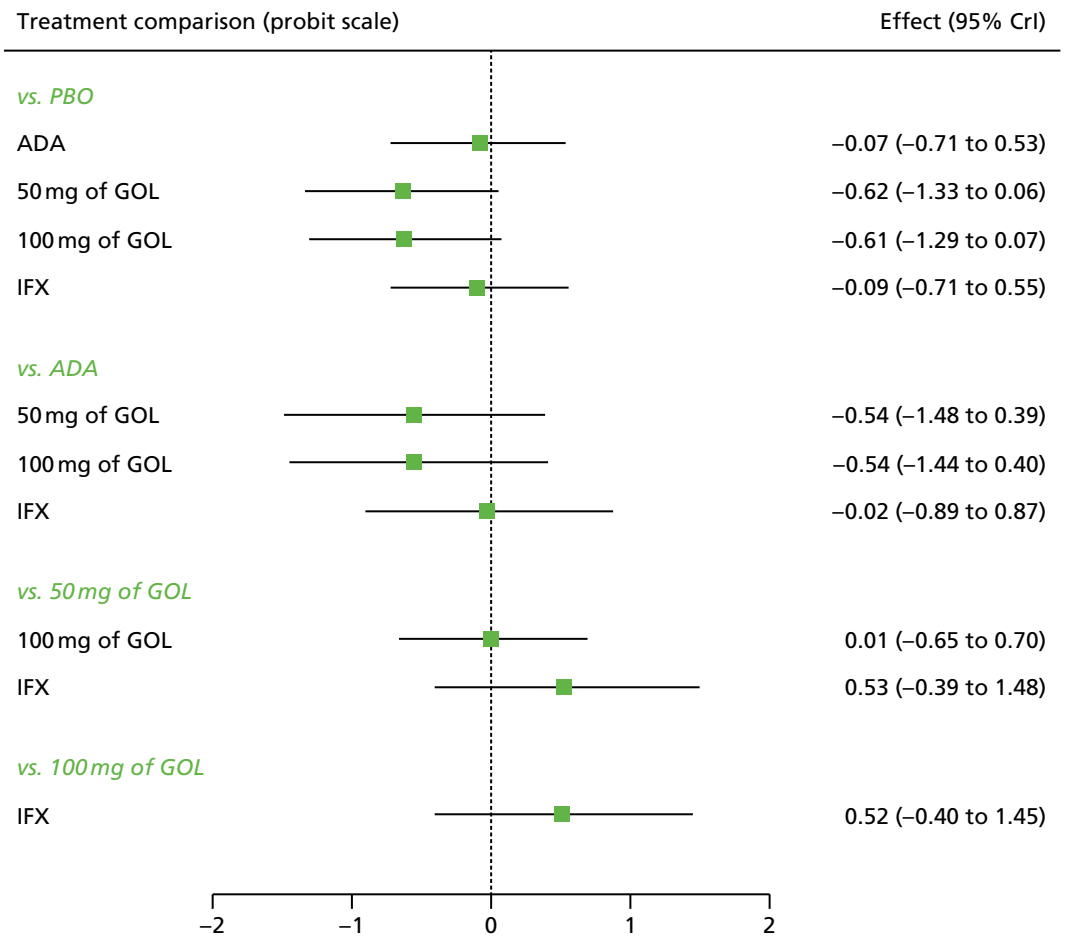

FIGURE 65 Sensitivity analysis 3: comparative effect of anti-TNF-α treatment on clinical response/remission in the maintenance phase at 8–32 weeks for patients starting in remission [SD ~ HN(0,0.32^2)].

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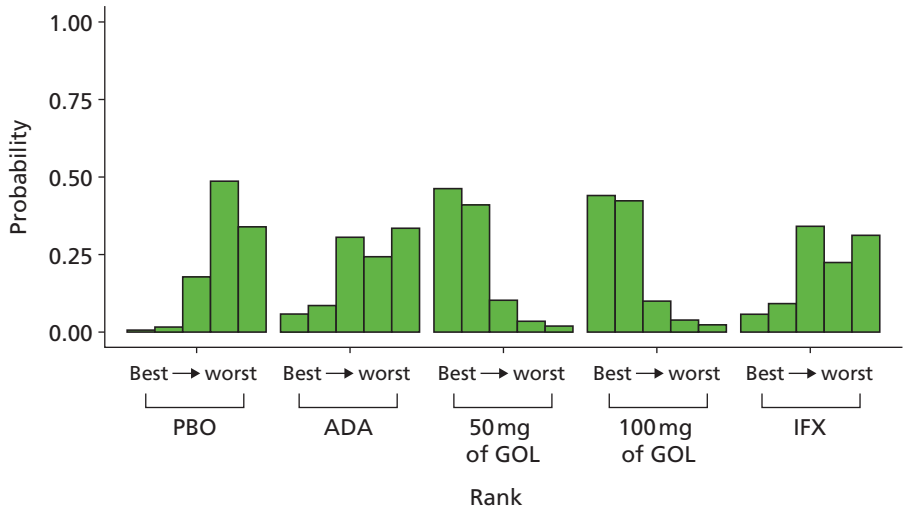

FIGURE 66 Sensitivity analysis 3: ranking probability histograms for the maintenance phase at 8–32 weeks for patients starting in remission.

TABLE 30 Sensitivity analysis 3: probabilities of being in each category for the maintenance phase at 8–32 weeks for patients starting in remission

	No response			Response			Remission		
Treatment	Mean	Median	95% CrI	Mean	Median	95% CrI	Mean	Median	95% CrI
PBO	0.389	0.386	0.240 to 0.556	0.185	0.180	0.102 to 0.291	0.426	0.425	0.242 to 0.613
ADA	0.367	0.358	0.132 to 0.649	0.177	0.172	0.086 to 0.286	0.456	0.452	0.183 to 0.751
50 mg of GOL	0.199	0.182	0.043 to 0.451	0.147	0.144	0.047 to 0.264	0.654	0.664	0.342 to 0.900
100 mg of GOL	0.202	0.184	0.046 to 0.465	0.148	0.144	0.049 to 0.270	0.650	0.663	0.332 to 0.890
IFX	0.363	0.352	0.130 to 0.655	0.176	0.172	0.084 to 0.284	0.461	0.461	0.178 to 0.753

Sensitivity analysis 3: maintenance phase 32–52 weeks

Patients starting in response A NMA was used to compare the effects of ADA, GOL and IFX relative to PBO on clinical response in the maintenance phase for patients starting in response at 32–52 weeks. Data were available from four studies comparing two or three treatments.[45,46,48,49] *Figure 67* presents the network of evidence for the sensitivity analysis 3 maintenance phase at 32–52 weeks for patients starting in response.

Figure 68 presents the effects of each treatment relative to PBO on the probit scale for the sensitivity analysis 3 maintenance phase 32–52 weeks for patients starting in response. *Figure 69* presents the probabilities of treatment rankings for this analysis. The model fitted the data reasonably well, with the total residual deviance, 15.21, being close to the total number of data points included in the analysis, 18. The between-study SD was estimated to be 0.18 (95% CrI 0.01 to 0.64), which implies mild to moderate heterogeneity between studies in treatment effects.

All treatments except 100 mg of GOL were associated with beneficial treatment effects relative to PBO with the greatest effect being associated with IFX (–0.38, 95% CrI –1.27 to 0.55). However, none of the treatment effects was statistically significant at a conventional 5% level. IFX was most likely to be the most effective treatment (probability of being the best = 0.55).

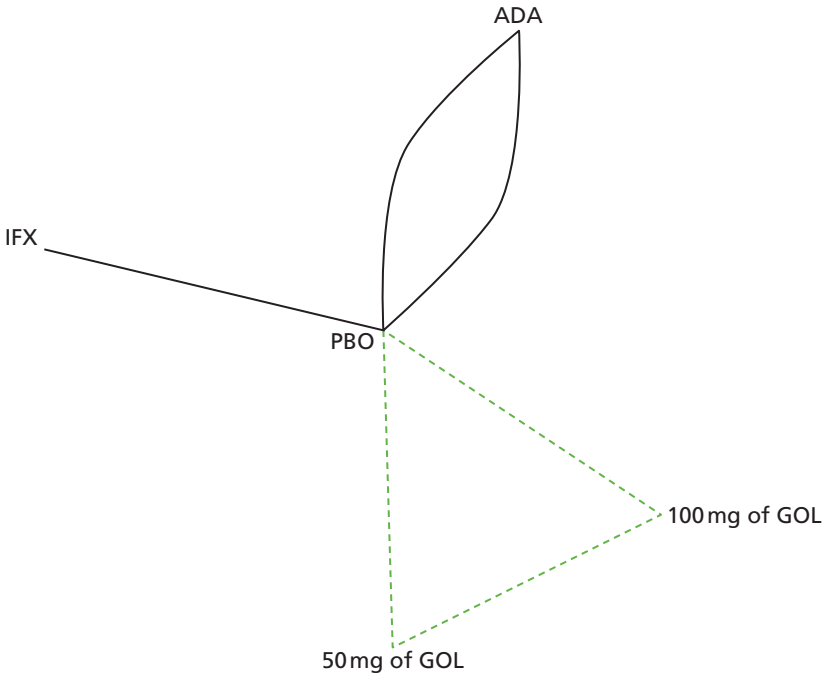

FIGURE 67 Sensitivity analysis 3: network of evidence for the maintenance phase at 32–52 weeks for patients starting in response. Note: solid line indicates a two-arm trial; dashed line indicates a three-arm study.

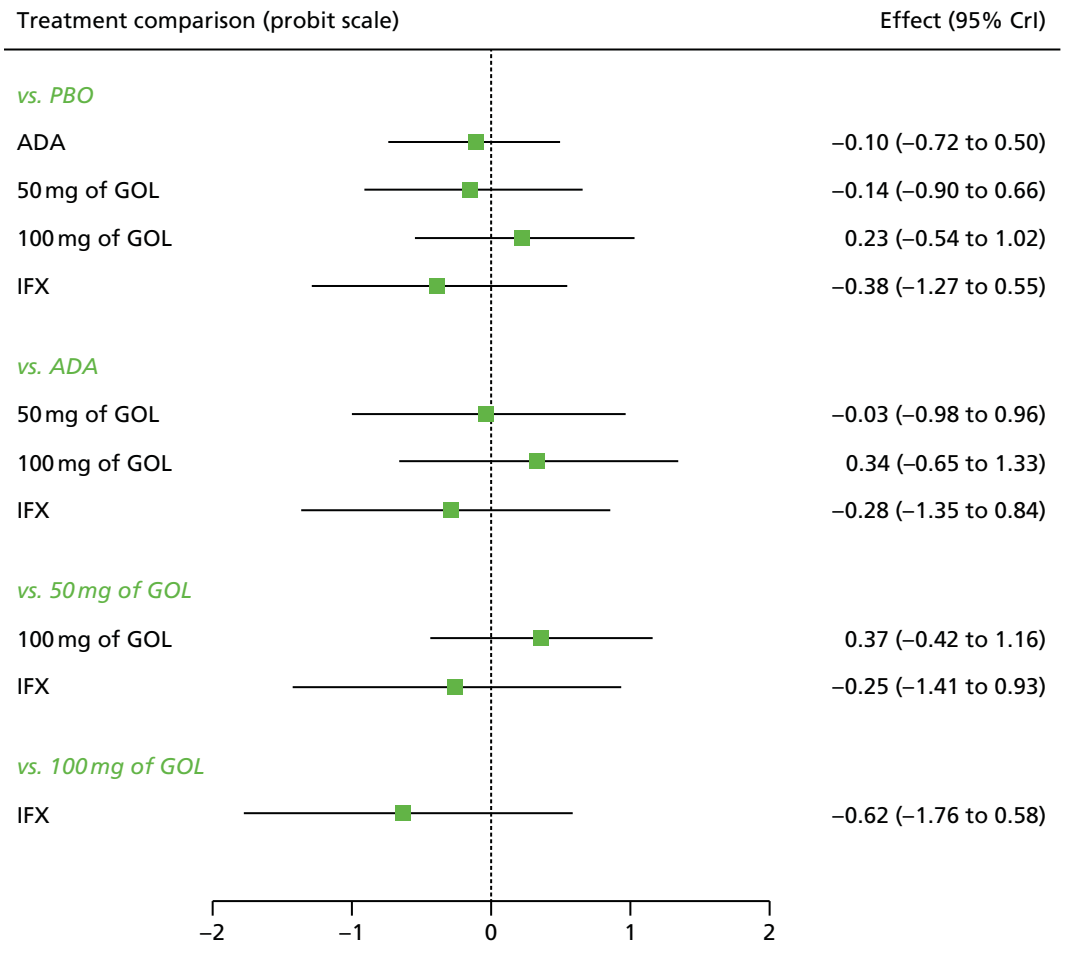

FIGURE 68 Sensitivity analysis 3: comparative effect of anti-TNF-α treatment on clinical response/remission in the maintenance phase at 32–52 weeks for patients starting in response [SD ~ HN(0,0.32²)].

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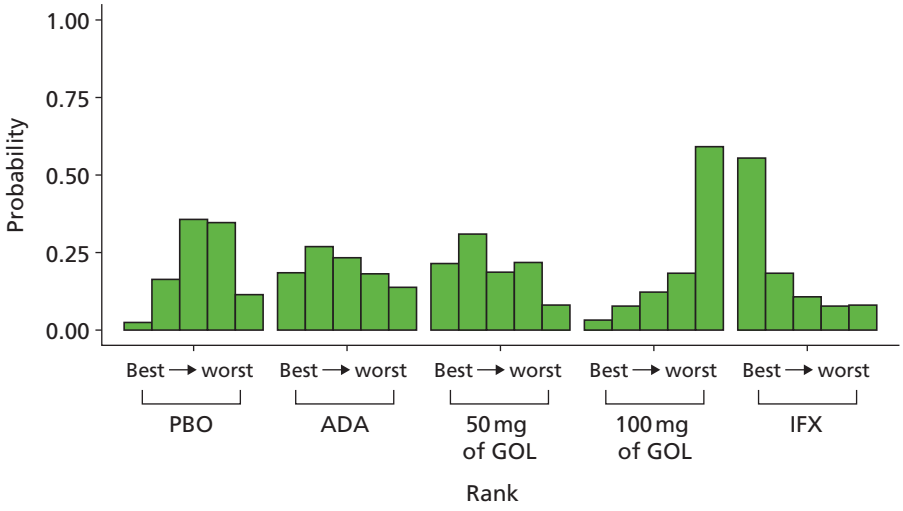

FIGURE 69 Sensitivity analysis 3: ranking probability histograms for the maintenance phase at 32–52 weeks for patients starting in response.

Table 31 presents the probabilities of achieving each of the following categories: no response, response and remission for the sensitivity analysis 3 maintenance phase at 32–52 weeks for patients starting in response. IFX was associated with the highest probability of moving from response to remission, and the smallest probability of moving from response to no response at 32–52 weeks. The probabilities of staying in response were comparable among treatments at 32–52 weeks.

Patients starting in remission

A NMA was used to compare the effects of ADA, GOL and IFX relative to PBO on clinical response in the maintenance phase at 32–52 weeks for patients starting in remission. Data were available from four studies comparing two or three treatments.[45,46,48,49] *Figure 70* presents the network of evidence for the sensitivity analysis 3 maintenance phase at 32–52 weeks for patients starting in remission.

Figure 71 presents the effects of each treatment relative to PBO on the probit scale for the sensitivity analysis 3 maintenance phase at 32–52 weeks for patients starting in remission. *Figure 72* presents the probabilities of treatment rankings for this analysis. The model fitted the data reasonably well, with the total residual deviance, 20.55, being close to the total number of data points included in the analysis, 18. The between-study SD was estimated to be 0.18 (95% CrI 0.01 to 0.65), which implies mild to moderate heterogeneity between studies in treatment effects.

TABLE 31 Sensitivity analysis 3: probabilities of being in each category for the maintenance phase at 32–52 weeks for patients starting in response

	No response			Response			Remission		
Treatment	Mean	Median	95% CrI	Mean	Median	95% CrI	Mean	Median	95% CrI
PBO	0.344	0.340	0.218 to 0.484	0.393	0.395	0.252 to 0.514	0.263	0.257	0.114 to 0.449
ADA	0.314	0.304	0.109 to 0.580	0.382	0.385	0.219 to 0.520	0.305	0.290	0.086 to 0.605
50 mg of GOL	0.309	0.293	0.081 to 0.625	0.374	0.380	0.191 to 0.514	0.317	0.302	0.067 to 0.661
100 mg of GOL	0.436	0.431	0.149 to 0.759	0.354	0.363	0.172 to 0.490	0.210	0.187	0.031 to 0.520
IFX	0.240	0.213	0.041 to 0.575	0.358	0.369	0.151 to 0.513	0.402	0.392	0.088 to 0.771

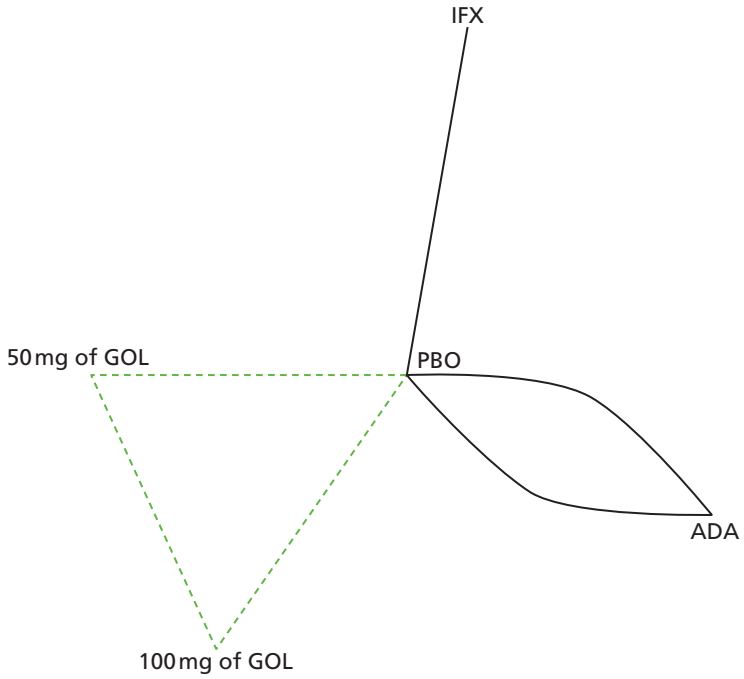

FIGURE 70 Sensitivity analysis 3: network of evidence for the maintenance phase at 32–52 weeks for patients starting in remission. Note: solid line indicates a two-arm trial; dashed line indicates a three-arm study.

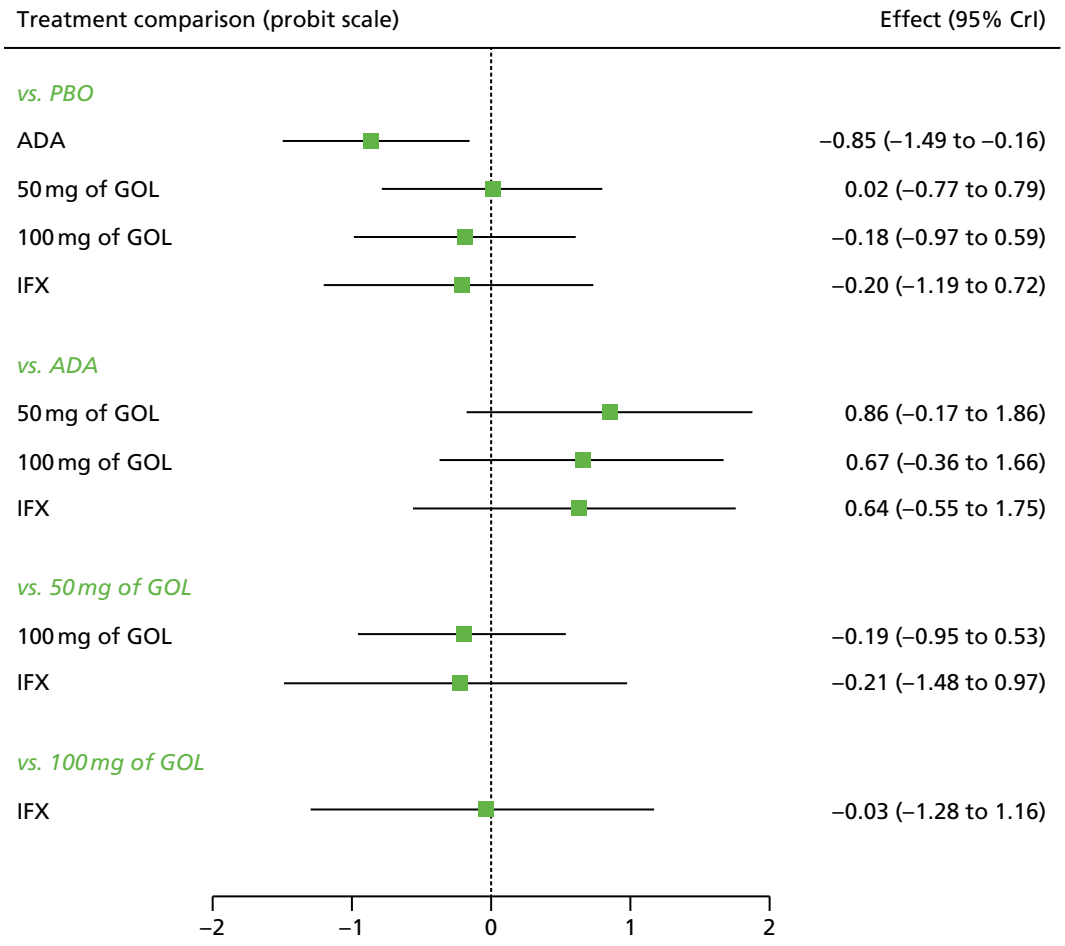

FIGURE 71 Sensitivity analysis 3: comparative effect of anti-TNF-α treatment on clinical response/remission in the maintenance phase at 32–52 weeks for patients starting in remission [SD ~ HN(0,0.32^2)].

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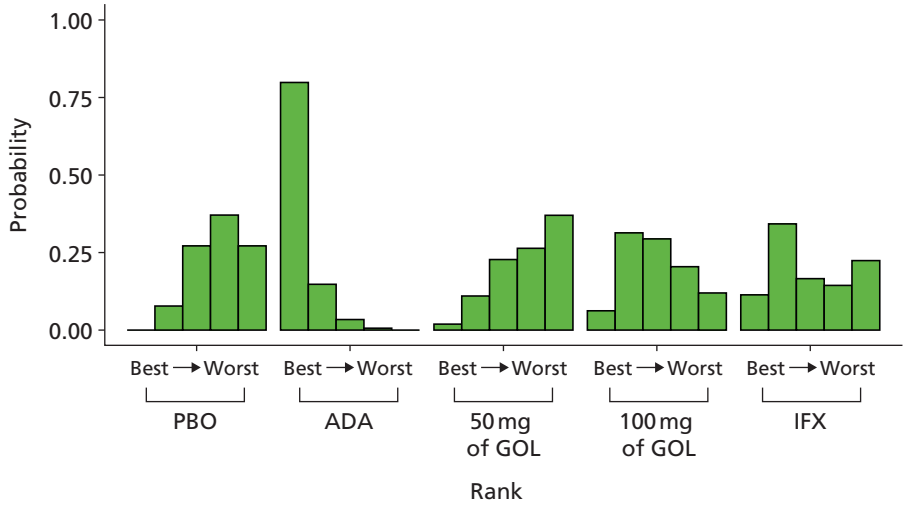

FIGURE 72 Sensitivity analysis 3: ranking probability histograms for the maintenance phase at 32–52 weeks for patients starting in remission.

All treatments except 50 mg of GOL were associated with beneficial treatment effects relative to PBO with the greatest effect being associated with ADA (–0.85, 95% CrI –1.49 to –0.16); however, only the effect of ADA was statistically significant at a conventional 5% level. ADA was most likely to be the most effective treatment (probability of being the best = 0.80).

Table 32 presents the probabilities of achieving each of the following categories: no response, response and remission for the sensitivity analysis 3 maintenance phase at 32–52 weeks for patients starting in remission. ADA was associated with the highest probability of staying in remission and the smallest probability of moving from remission to response or no response at 32–52 weeks.

TABLE 32 Sensitivity analysis 3: probabilities of being in each category for the maintenance phase at 32–52 weeks for patients starting in remission

	No response			Response			Remission		
Treatment	Mean	Median	95% CrI	Mean	Median	95% CrI	Mean	Median	95% CrI
PBO	0.296	0.293	0.187 to 0.422	0.202	0.188	0.042 to 0.44	0.502	0.511	0.246 to 0.706
ADA	0.097	0.082	0.016 to 0.267	0.123	0.104	0.014 to 0.343	0.781	0.805	0.464 to 0.955
50 mg of GOL	0.313	0.299	0.083 to 0.625	0.191	0.178	0.036 to 0.423	0.496	0.501	0.144 to 0.821
100 mg of GOL	0.252	0.235	0.057 to 0.544	0.182	0.168	0.03 to 0.418	0.566	0.577	0.197 to 0.868
IFX	0.250	0.229	0.037 to 0.588	0.176	0.163	0.025 to 0.413	0.574	0.582	0.178 to 0.911

Biosimilars to infliximab

As defined by the EMA, a biosimilar is a biological medicine developed with the aim of being similar to an already existing biological medicine (or reference medicine).[71] In this assessment, the reference medicine is IFX. Two biosimilars to IFX were also considered within the scope of this assessment: Remsima and Inflectra. The EMA has stated that a biosimilar and reference medicine may display differences owing to their complex nature and methods of production and that, in the approval process, any differences need to be demonstrated not to affect safety or effectiveness.[71]

A submission[72] was made to NICE for consideration as part of the current assessment by the manufacturers of Remsima. However, no sponsor submission was presented by Hospira, the manufacturers of Inflectra. EPAR reports were available for both Remsima[73] and Inflectra.[74]

In June 2013, the EMA CHMP recommended authorisation of Remsima and Inflectra as biosimilars to IFX, reported to be the first authorisation in the European Union for a biosimilar monoclonal antibody. Both Remsima and Inflectra were developed as the product CT-P13.

It was stated in the EPARs for Remsima and Inflectra that an extensive comparability exercise between CT-P13 and Remicade was undertaken, which found the major characteristics and biological activities of Remsima/Inflectra to be comparable with Remicade.

The clinical programme to evaluate CT-P13 was based on two main clinical trials:

- a pharmacokinetic equivalence study performed in adult patients with AS [Study CT-P13 1.1, Programme evaLuating the Autoimmune disease iNvEstigational drug CT-P13 in ankylosing spondylitis patients (PLANET-AS)]
- a therapeutic equivalence study of CT-P13 compared with Remicade in adult patients with active rheumatoid arthritis [Study CT-P13 3.1, Programme evaLuating the Autoimmune disease iNvEstigational drug CT-P13 in rheumatoid arthritis patients (PLANET-RA)].

Both studies were planned with a 1-year treatment duration and primary endpoints were evaluated at 30 weeks. Further efficacy and safety data up to 54 weeks were submitted during the EMA assessment.

A third study (CT-P13 1.2) was a small pilot study in RA patients with purpose of facilitating pivotal trial (CT-P13 3.1) conduct.

Study CT-P13 1.1, PLANET-AS

PLANET-AS was a prospective Phase I, randomised double-blind multicentre study, in which 250 patients were randomised (CT-P13 $n = 125$, Remicade $n = 125$). Patients received CT-P13 (5 mg/kg) or Remicade (5 mg/kg) at weeks 0, 2 and 6 and then every 8 weeks to week 54. The primary objective of the study was to demonstrate comparable pharmacokinetics of CT-P13 and Remicade at steady state (between weeks 22 and 30). The primary parameters evaluated were the area under the plasma concentration time curve from time zero to time t (AUC_T) and maximum serum concentrations (C_{max}) after dose 5 (weeks 22–30), with secondary parameters being average concentration at steady state ($C_{av,\ ss}$), minimum concentration immediately before next dose at steady state ($C_{min\ ss}$), terminal elimination half-life ($T_{1/2}$), total-body clearance at steady state (CL_{ss}) and volume of distribution at steady state (V_{ss}). Additional observed parameters were maximum serum concentrations (C_{max}), minimum concentration immediately before next dose (C_{min}) and time to reach maximum serum concentrations C_{max} (T_{max}) after each dose. Efficacy parameters included the proportion of patients achieving clinical response according to the assessment in AS response criteria (ASAS20 and ASAS40). The EPARs reported that PLANET-AS demonstrated that (at 5 mg/kg) pharmacokinetic behaviour between CT-P13 and Remicade was similar, a view that was also supported by pharmacokinetic data from RA patients in study CT-P13 3.1 (PLANET-RA). Furthermore, the EPARs also stated that the proportions of patients experiencing clinical response according to the ASAS20 and ASAS40 criteria at weeks 14 and 30 were similar across the CT-P13 and Remicade groups.

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Study CT-P13 3.1, PLANET-RA

PLANET-RA was a prospective Phase III, randomised, double-blind, multicentre study, in which 302 patients were randomised to CT-P13 and 304 to Remicade (randomisation was stratified by geographical region and baseline CRP level). Patients received CT-P13 or Remicade at 3 mg/kg at weeks 0, 2, 6 and then every 8 weeks up to 54 weeks (administered in combination with a stable dose of methotrexate and folic acid). The primary objective of the trial was to demonstrate that CT-P13 was equivalent to Remicade up to week 30 in efficacy as measured by ACR20. Secondary objectives were ACR20, ACR50 and ACR70 responses at weeks 14 and 30, Disease Activity Score 28 at weeks 14 and 30, European League Against Rheumatism response at weeks 14 and 30, Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index at weeks 14 and 30 and SF-36 at weeks 14 and 30.

Fewer patients randomised to the CT-P13 arm ($n = 69$, 22.8%) discontinued PLANET-RA by week 54 than patients in Remicade arm ($n = 82$, 27.0%). Patients received CT-P13 and Remicade at the RA dose of 3 mg/kg. It was stated in the EPARs that a similar proportion of patients at week 30 in the CT-P13 (184/302, 60.9%) and Remicade (178/304, 58.6%) arms achieved ACR20 response (*Table 33*).

Furthermore, at week 30, the findings for the secondary end points (including ACR50, ACR70 and decrease in Disease Activity Score 28) were also described as being consistent with the results of the primary end point. Efficacy results were reported to be comparable between treatment arms up to week 54. It was concluded in the EPAR that PLANET-RA provided that robust evidence of therapeutic equivalence between CT-P13 and Remicade. ACR responses between CT-P13 and Remicade remained comparable through the 12-month PLANET-RA extension study.[73]

The safety profile of CT-P13 was evaluated in the clinical studies described above. A total of 871 patients were included in the safety population. It was reported in the EPARs that the type and incidence of adverse drug reactions with CT-P13 and Remicade were broadly similar and that no new safety concern was identified. Additionally, it was stated that no marked differences in immunogenicity between CT-P13 and Remicade were observed up to 54 weeks, with comparable effects of antibodies on efficacy and safety. Although there was a numerical imbalance described in SAEs observed in study CT-P13 3.1 (PLANET-RA) (with a higher number of serious infections), reported numbers were stated to be low and, therefore, the CHMP concluded that this observed difference was likely to be due to chance.

In summary, the EMA considered CT-P13 to be biosimilar to the reference product Remicade and judged that the submitted data in the submissions for Remsima and Inflectra allowed for extrapolation to all other indications of Remicade.

TABLE 33 The ACR20/50/70 responders at week 30 in PLANET-RA (all randomised population)

Treatment arm	*n*/*N* (%)	Estimate of treatment difference	95% CI of treatment difference
ACR20: CT-P13	184/302 (60.9)	0.02	–0.06 to 0.10
ACR20: Remicade	178/304 (58.6)		
ACR50: CT-P13	105/248 (42.3)	0.02	–0.07 to 0.10
ACR50: Remicade	102/251 (40.6)		
ACR70: CT-P13	50/248 (20.2)	0.02	–0.05 to 0.09
ACR70: Remicade	45/251 (17.9)		

An ECCO position statement was presented by Danese and Gomollon[75] stating that the use of biosimilars in patients with IBD requires clinical trials in the IBD patient population to allow comparison between the biosimilar and reference products, on the basis of potential differences in manufacturing and structure that could lead to important differences in immunogenicity and efficacy. However, a subsequent statement issued on behalf of the Working Party on Similar Biological (Biosimilar) Medicinal Products of the CHMP argued that no pharmacokinetic and safety issues are known to be particular to IBD, the most responsive known population (RA) was assessed for immunogenicity and that the data submitted allow extrapolation to patients with IBD.[76]

Discussion

A total of 10 RCTs were identified in the clinical effectiveness systematic review, of which nine[44–51] related to adults and one[52] was conducted in a paediatric population. All of the adult RCTs were performed against PBO (with the exception of UC-SUCCESS[51]) and were a maximum of 1 year in study duration. No head-to-head RCTs were identified in which interventions of interest were assessed against each other.

The risks of bias associated with included RCTs were assessed using the Cochrane risk-of-bias instrument. Only three RCTs could be considered as being at overall low risk of bias as allocation concealment, blinded outcome assessment and completeness of outcome data were all judged as low risk. It should be noted that one of the maintenance trials (PURSUIT-Maintenance[48]) rerandomised patients who had previously responded to GOL induction therapy in two previous trials; the extent of this potential bias on patient outcomes is unclear.

The outcome measures pre-specified in the final NICE scope were all addressed by the included trial evidence, with the exception of rates of relapse. Clinical response and remission data based on complete Mayo scores were well reported across trials. Evidence was identified to demonstrate that patients receiving IFX, ADA or GOL were more likely than patients receiving PBO to achieve clinical response and remission at induction and maintenance time points. Patients in the UC-SUCCESS[51] trial who received combination treatment with IFX and AZA experienced the most favourable rates of steroid-free remission compared with IFX and AZA treatment groups. Seven RCTs performed in adult populations contributed data on clinical response and remission at induction or maintenance time points to NMAs.

Based on the NMA, in the induction phase, all treatments were associated with statistically significant beneficial effects relative to PBO with the greatest effect being associated with IFX. IFX was also associated with the highest probability of moving from no response to response and from no response to remission. The effects of ADA and GOL on these two probabilities were broadly comparable.

For patients classified as responders at the end of the induction phase, treatment effects were not statistically significant, although the greatest effect was associated with 100 mg of GOL at 8–32 weeks. A treatment of 100 mg of GOL was associated with the highest probability of moving from response to remission and staying in response and the smallest probability of moving from response to no response. However, at 32–52 weeks, only IFX and 50 mg of GOL were associated with beneficial effects on clinical response, although the effects were not statistically significant. IFX was associated with the highest probability of moving from response to remission and staying in response and the smallest probability of moving from response to no response at 32–52 weeks. The probabilities of staying in response were comparable among treatments at both 8–32 weeks and 32–52 weeks.

For patients classified as being in remission at the end of the induction phase, all treatments except for ADA were associated with beneficial treatment effects relative to PBO with the greatest effect being associated with 50 mg and 100 mg of GOL, although the effects were not statistically significant at 8–32 weeks. A treatment of 50 mg and 100 mg of GOL were associated with the highest probability of staying in remission and the smallest probability of moving from remission to response and from remission

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to no response. At 32–52 weeks, all treatments except 50 mg of GOL were associated with beneficial treatment effects relative to PBO, with the greatest effect being associated with ADA (the only treatment with statistically significant effect). ADA was associated with the highest probability of staying in remission and the smallest probability of moving from remission to response and from remission to no response.

Sensitivity analyses were conducted by replacing ULTRA2 anti-TNF-α-naive data with ULTRA2 ITT data (sensitivity analysis 1), including Suzuki *et al.*[46] (sensitivity analysis 2), and replacing ULTRA2 anti-TNF-α-naive data with ULTRA2 ITT data plus including Suzuki *et al.*[46] (sensitivity analysis 3). The results suggested that when ULTRA2 ITT data were replaced by ULTRA2 anti-TNF-α-naive data for patients starting in remission at 8–32 weeks and in response at 32–52 weeks, the estimate of the effect of ADA on clinical response changed from being slightly worse than PBO to being slightly better than PBO. However, the estimates were associated with considerable uncertainty.

Available data on hospitalisation outcomes were very limited, but suggested that outcomes may be more favourable for ADA-treated and IFX-treated patients than PBO-treated patients (with no data available from GOL trials). Data on surgical intervention were also very sparse, with a potential inconclusive benefit for intervention-treated patients compared with PBO. No trials reported whether surgical outcomes were elective or emergency in nature; however, more data are required to demonstrate the impact of interventions on hospitalisation and surgical intervention more conclusively. Data were available from a single trial to support the use of IFX in induction and maintenance treatment in a paediatric population.

The main safety issues highlighted in the RCT evidence appeared to be generally consistent with those previously discussed in the respective SmPCs (including serious infections, malignancies and administration site reactions). Deaths occurring during and after the study period were described in some trials evaluating GOL (PURSUIT-Maintenance[48]) and IFX (ACTs[49]), of which infection or malignancy were most commonly implicated. This underlines the importance of monitoring and treating serious infections and malignancies in patients receiving immunosuppressive treatment.

The trials included in the clinical effectiveness systematic review typically excluded patients with ulcerative proctitis, patients with fulminant/acute severe disease, those with a history of or at imminent risk of bowel surgery, pregnant or lactating women, and patients with diseases of the central nervous system (e.g. demyelinating disease). Furthermore, patients with history of serious infection and immunodeficiency were also typically excluded, as were individuals with a history of malignancy or signs of dysplasia. Therefore, the effects of ADA, GOL or IFX in these UC populations are unknown.

Two biosimilars (Remsima and Inflectra) to Remicade were considered as part of the evidence base for IFX as part of this assessment. The sponsor submission received from the manufacturers of Remsima and the EPAR reports for Remsima and Inflectra indicated that both biosimilars were approved by the EMA on the basis of reported similar pharmacokinetic and efficacy (demonstrated in AS and RA patients) profiles to Remicade. No further trials of Remsima or Inflectra were identified in the course of this assessment.

Chapter 4 Assessment of cost-effectiveness

Systematic review of existing cost-effectiveness evidence

Methods

Identification of studies

A comprehensive search was undertaken to systematically identify literature relating to the cost-effectiveness of IFX, ADA and GOL for treating moderate to severe UC after the failure of conventional therapy. The search strategy comprised the following main elements:

- searching of electronic databases
- contact with experts in the field
- hand-searching of bibliographies of retrieved papers.

The following electronic databases were searched from inception for economic evaluations:

- MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations: via Ovid – 1946 to January 2014.
- EMBASE: via Ovid – 1974 to January 2014.
- Cochrane Library: via Wiley Interscience
    - CDSR – 1996 to January 2014
    - DARE – 1995 to January 2014
    - CCRT – 1995 to January 2014
    - Cochrane Methodology Register – 1904 to January 2014
    - HTA database – 1995 to January 2014
    - NHS EED – 1995 to January 2014.
- CINAHL: via EBSCO*host* – 1982 to January 2014.
- Web of Science Citation Index: via Web of Knowledge – 1900 to January 2014.
- Conference Proceedings Citation Index: via Web of Knowledge – 1990 to January 2014.
- BIOSIS Previews: via Web of Knowledge – 1969 to January 2014.
- EconLit: via Ovid – 1886 to January 2014.

The MEDLINE search strategy is presented in *Appendix 9*. The search strategy combined free text and MeSH or thesaurus terms relating to *ulcerative colitis*, with free text and MeSH or thesaurus terms relating to *infliximab, adalimumab and golimumab* combined with highly sensitive economic filters to retrieve economic evaluations. The search strategy was translated across all databases. No date or language restrictions were applied. Literature searches were conducted during January 2014. References were collected in a bibliographic management database and duplicates were removed.

Inclusion/exclusion criteria

Studies were included in the systematic review if they reported full economic evaluations comparing IFX, ADA and/or GOL, against each other or against any other intervention, within their licensed indications for the treatment of patients with moderate to severe UC. The inclusion and exclusion criteria applied within the systematic review are presented in *Box 1*. Studies were included only if they were reported as full papers; conference abstracts were excluded from the review as they present insufficient detail to allow for a rigorous assessment of study quality.

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BOX 1 Inclusion and exclusion criteria for review of cost-effectiveness studies

Inclusion criteria

- Full economic evaluations comparing IFX, ADA and/or GOL against each other or any other intervention for the treatment of patients with moderate to severe UC.

Exclusion criteria

- Studies assessing biologicals in the acute setting (e.g. management of UC exacerbations).
- Studies in which the same biological is used in all treatment groups within the analysis.
- Non-comparative studies and partial economic evaluations (e.g. costing studies).
- Abstracts, letters and commentaries.
- Studies not reported in English.
- Studies relating to patients with diseases other than UC.

Review methods

The results of the economic searches were sifted by title and abstract. The full papers of studies that potentially met the inclusion criteria were retrieved for further inspection. Studies included in the systematic review were critically appraised using the Drummond checklist for economic evaluations.[77] In addition, the manufacturers of the products considered within this appraisal submitted economic evidence to NICE; these models were assessed in terms of the extent to which they meet the NICE reference case.[78] The structure and formulae included in the manufacturers' submission models were scrutinised by two members of the Assessment Group (PT and HB). It should be noted that this appraisal includes an update of Technology Appraisal Guidance 140;[79] the economic evaluation reported within the 2007 Schering Plough submission to NICE[80] is not included in this review as it has previously been critiqued for NICE;[81] however, one of the studies included in the review[82] reports an analysis of this model.

Results

The systematic searches identified a total of 907 potentially relevant citations (*Table 34* and *Figure 73*). In addition, 4 manufacturers' submissions were received by NICE.[62,64,66,72] Two of the four submissions were submitted by the same manufacturer – one relating to GOL and one relating to IFX; as these relate to

TABLE 34 Summary of search results for existing economic evaluations

Database	Date range	Date searched	Number of results
MEDLINE (via Ovid)	1946 to January 2014	15 January 2014	96
EMBASE (via Ovid)	1974 to January 2014	15 January 2014	372
CINAHL (via EBSCO*host*)	1982 to January 2014	22 January 2014	23
Science Citation Index and Social Science Citation Index (via Web of Knowledge)	1900 to January 2014	22 January 2014	243
BIOSIS (via Web of Knowledge)	1969 to January 2014	22 January 2014	186
Cochrane HTA (via Wiley)	1991 to January 2014	21 January 2014	30
Cochrane DARE (via Wiley)	1991 to January 2014	21 January 2014	28
Cochrane EED (via Wiley)	1991 to January 2014	21 January 2014	24
EconLit (via Ovid)	1886 to January 2014	15 January 2014	1

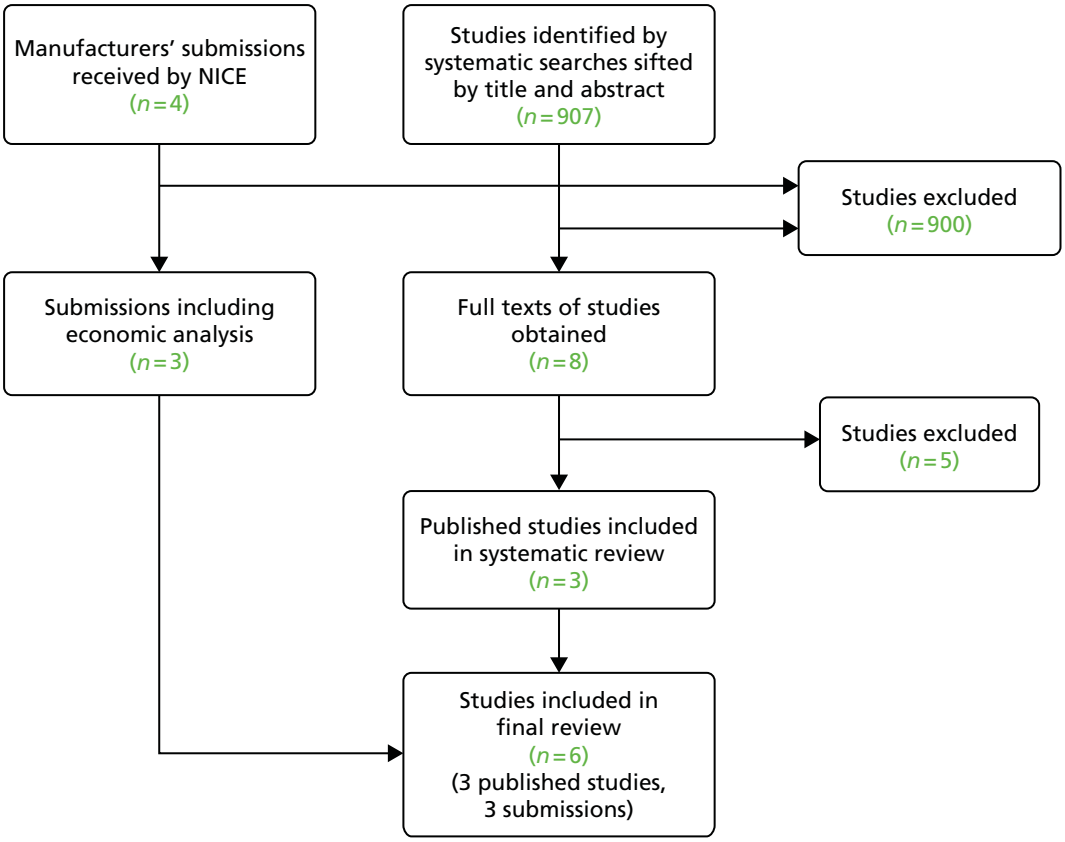

FIGURE 73 Study selection results for review of economic evaluations.

virtually identical models, they are considered as a single analysis within this assessment.[64,66] Three of the manufacturer's submissions to NICE[62,64,66] included economic analyses; the submission from Celltrion[72] did not include any economic analysis. Fourteen studies were excluded as they were available only in abstract form. A total of three published studies and three manufacturers' submissions reported economic analyses relating to the use of biologicals for the treatment of moderate to severe UC (*Table 35*).

Review of published economic evaluations presents a summary and critical appraisal of the three published economic studies included in this review.[82–84] *Cost-effectiveness evaluation of golimumab (with Patient Access Scheme), infliximab and adalimumab relative to colectomy for moderate to severe ulcerative colitis in the UK (MSD submissions[64,66])* and *Adalimumab, golimumab and infliximab, for the treatment of ulcerative colitis (subacute) – AbbVie submission*[62] present critical reviews of the individual manufacturers' submissions from AbbVie and MSD, respectively.[62,64,66]

Review of published economic evaluations

Park et al.[83]

Park *et al.*[83] report the methods and results of an economic analysis of early colectomy plus ileal pouch anal anastomosis (IPAA) versus standard medical therapy in patients with severe UC in the USA. The model population is intended to reflect 21-year old patients with newly diagnosed pancolitis UC confirmed by colonoscopic biopsies. The economic analysis compares two sequences of treatments: (1) immediate colectomy with IPAA; and (2) standard medical therapy, which is assumed to comprise a sequence of (i) 2 g of mesalamine per day; (ii) 125 mg of AZA per day; (iii) 5 mg/kg/dose of IFX every 8 weeks; (iv) 1.5 mg of tacrolimus b.i.d.; and (v) colectomy + IPAA. The analysis does not consider the comparative cost-effectiveness of alternative sequences of medical treatments. The authors purport to have adopted a societal perspective; however, it does not appear that any indirect costs borne outside the health sector (e.g. lost productivity or out-of-pocket expenses) have been included in the economic analysis. It would be

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TABLE 35 Summary table of included published studies

Study	Year of publication	Perspective	Economic comparisons	Outcome measure	Time horizon	Conflicts of interest
Included published economic evaluations						
Park *et al.*[83]	2012	USA (payer)	Colectomy + IPAA vs. standard medical care (including IFX)	QALYs	Lifetime	Non-commercial
Tsai *et al.*[82]	2008	UK NHS	IFX vs. standard care	QALYs	10 years	Study funded by Schering-Plough
Xie *et al.*[84]	2009	Canadian (public payer)	IFX vs. usual care	QALYs	5 years	Three out of six authors disclosed a conflict of interest
Included manufacturers' submissions						
AbbVie submission[62]	N/A	UK NHS	ADA vs. conventional non-biological treatment	QALYs	10 years	Manufacturer of ADA (AbbVie)
MSD submission[64,66]	N/A	UK NHS	Pairwise comparisons of IFX, GOL, ADA and immediate colectomy	QALYs	10 years	Manufacturer of IFX and GOL (MSD)

IPAA, Ileal pouch anal anastomosis; N/A, not applicable; QALY, quality-adjusted life-year.

more accurate to describe the adopted perspective as that of the health-care payer. Health economic results are presented in terms of the incremental cost per quality-adjusted life-year (QALY) gained over a lifetime horizon. In line with the reference case set out in Gold *et al.*,[85] costs and health outcomes were discounted at a rate of 3% per year. Costs were valued at 2009 prices.

The economic analysis uses a Markov approach to evaluate relevant events, costs and health outcomes. The duration of each Markov cycle is not entirely clear from the paper;[83] the text indicates that the first cycle is 3 months in duration and the cycle length appears to be 8 weekly thereafter. However, the table of parameter values presented within the paper suggests that probability parameters are defined according to various time intervals. In addition, the text does not mention whether or not a half-cycle correction has been applied. The precise health states adopted in the model are also not entirely clear from the text; while a model diagram is presented in the paper, this details the sequences of treatments in each group but does not specify the relevant clinical events that patients may experience. It appears that separate states are assigned for patients who are on treatment, in remission, experiencing UC flare, postcolectomy and experiencing death. With respect to medical treatment, the model appears to separate response and remission based on the Simple Colitis Activity Index (SCAI) score.[86] The model also includes the possibility of patients developing colorectal cancer, which is assumed to result in colectomy. It appears that the model does not include an excess risk of death due to colorectal cancer. Patients enter the model at the point of being hospitalised during their initial flare definitively diagnosing them of pancolitis UC through endoscopic biopsies. Although this may indicate a more severe population than that stated within the scope of this appraisal, the model uses RCT evidence from studies that relate to a moderate to severe UC population[49] and assumes that the flare is resolvable without surgery. Following diagnosis, patients are then assumed to receive i.v. methylprednisolone and subsequently mesalamine as maintenance therapy once they are able to tolerate oral medicines. Patients progress along the treatment pathway to IFX, tacrolimus and potentially colectomy + IPAA if remission is not achieved. Patients in the intervention group within the model bypass all medical treatments and immediately undergo surgery. Different cost and HRQoL estimates are applied to each health state.

Treatment benefits are defined differently for surgery and medical treatment. For the standard medical therapy group, treatment benefits are characterised as response, remission and UC flare rates. For the surgery group, treatment benefits are determined according to colectomy success rates, the avoidance of AEs (pouchitis and infertility), the requirement for antibiotics, and remission rates for antibiotics. Effectiveness data were drawn from a number of sources including RCTs and non-randomised studies.[49,87–99] The effectiveness of IFX in inducing and maintaining response and remission was based on the results of the ACT1 and ACT2 studies.[49] The rate of developing colorectal cancer was derived from an observational study.[100] The approach for determining the effectiveness of medical and surgical treatment options is essentially a naive indirect comparison and, as such, the results of the analysis should be interpreted with a degree of caution.

Health utilities were assigned for the following events and states: UC flare (0.48), remission (0.91), post-colectomy (0.87), and infertility following IPAA (0.74). Health utilities were drawn from a variety of sources.[101–104] The elicitation methods from which these estimates were derived were not consistently clear. Although several studies used the time trade-off (TTO) method, the study reportedly used to derive a disutility for female infertility is not a quality-of-life valuation study and actually relates to the medical costs of epididymitis and orchitis in men;[104] it is unclear how the information contained within this paper has been used to inform the economic analysis.

The model includes resource costs associated with diagnosis of pancolitis UC, drug therapy, colectomy + IPAA, managing pouchitis and the diagnosis of colorectal cancer. The costs associated with hospitalisations, outpatient visits, procedures and laboratory costs were estimated using national reimbursements from the Centers for Medicare and Medicaid Services and average reimbursement rates from all patient billing records in 2009 at Stanford University Medical Center. The Office of Statewide Health Planning and Development tables were used to validate institutional rates with the intention of reflecting national average cost estimates. Wholesale costs of medical therapies were estimated by prices from online pharmacies and were validated against the drug costs at Lucile Packard Children's Hospital pharmacy.

The analysis includes deterministic sensitivity analysis and probabilistic sensitivity analysis (PSA). Results are presented as mean costs and QALYs, incremental cost-effectiveness ratios (ICERs), one-way deterministic sensitivity analyses and summary results of the probability of achieving the greatest net benefit at a given willingness-to-pay threshold.

Table 36 presents the headline results of the economic analysis. The analysis indicates that standard medical treatment produces more health (0.06 QALYs) at a considerably greater cost than colectomy + IPAA (US$88,607). The incremental cost-effectiveness of standard medical treatment versus colectomy + IPAA is estimated to be US$1,476,783 per QALY gained.

TABLE 36 Headline cost-effectiveness results presented by Park *et al.*[83]

Strategy	QALYs (95% CI)	Costs (95% CI)	Incremental QALYs (95% CI)	Incremental costs (95% CI)	ICER (95% CI)
Colectomy + IPAA	20.72 (17.53 to 22.76)	US$147,763 (US$137,013 to US$158,904)	–	–	US$1,476,783 (dominated to US$3,281,923)
Standard medical treatment	20.78 (18.45 to 22.37)	US$236,370 (US$219,057 to US$255,328)	0.06 (–0.72 to 1.03)	US$88,607 (US$73,726 to US$105,865)	

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Assuming a willingness-to-pay threshold of US$50,000 per QALY gained, the probability that colectomy + IPAA produces the greatest net benefit is approximately 1.0. Assuming a willingness-to-pay threshold of US$100,000 per QALY gained, the probability that colectomy + IPAA produces the greatest net benefit is approximately 0.96. The sensitivity analysis indicates that the utility of the cure state after receiving colectomy + IPAA was the only variable which reduced the ICER to below US$100,000 per QALY gained. The authors state that the level of HRQoL for patients with UC would need to be very low in order for exhaustive medical therapy in severe UC to be cost-effective.

The Park *et al.*[83] study clearly addresses the question of whether or not colectomy + IPAA is cost-effective in comparison with medical management over a lifetime horizon. However, the description of the mathematical model is unclear, hence the assumptions underpinning the analysis are not transparent and their credibility is difficult to judge. The population reflected in the economic analysis is only partially relevant to the scope of this appraisal as the patients considered within the model are by definition hospitalised for UC flare. However, the model also appears to assume that the flare can be resolved; hence, patients may go on to receive biological therapy in a non-acute setting. Given the absence of head-to-head trials comparing medical and surgical management options, the need for an indirect comparison is inevitable and may lead to bias in the model results. It is also noteworthy that the study relates to a US setting and, therefore, its relevance to UK clinical practice may be questionable.

Tsai et al.[82]

Tsai *et al.*[82] report the methods and results of an economic analysis that compares two IFX-based strategies with standard care in patients with moderate to severe UC from the perspective of the UK NHS. The model structure and parameter values appear to be very similar to the economic analysis submitted to NICE to inform technology appraisal TA140,[28] although it should be noted that the total cost estimates for each group reported by Tsai *et al.*[82] differ to those reported within the manufacturers' submission.[80] Patients within the model were assumed to have a mean body weight of 73.1 kg. The base-case scenario evaluated a treatment strategy of 5 mg/kg of IFX every 8 weeks only for patients achieving response while a secondary analysis evaluated 5 mg/kg of IFX every 8 weeks for patients achieving and maintaining remission following induction. Standard care was assumed to include colectomy + IPAA and other medications (5-ASAs, corticosteroids and immunosuppressants). Cost-effectiveness was assessed in terms of the incremental cost per QALY gained over a 10-year time horizon for each comparison of IFX versus standard care. A fully incremental analysis was not undertaken between the two responder/remission stopping rule treatment approaches. The perspective adopted was that of the NHS. Costs borne by Personal Social Services (PSS) were not included in the model. The authors note that although productivity costs are substantial for patients with UC, these were not included in the economic analysis. Costs and health outcomes were discounted at a rate of 3.5% per year. Costs were valued at 2006–7 prices.

The economic evaluation takes the form of a Markov model, as shown in *Figure 74*. The model appears to include eleven health states: (1) mild (responders); (2) moderate-severe (responders); (3) remission (responders); (4) mild (non-responders); (5) moderate-severe (non-responders); (6) remission (non-responders); (7) temporary discontinuers; (8) surgery (tunnel state); (9) post-surgery remission; (10) post-surgery complications; and (11) death. The cycle length used within the model was specified according to the time intervals of the assessment visits in the ACT1 and ACT2 studies.[49] The first cycle was 8 weeks in duration, followed by 6 weeks in cycle 2, followed by 8 weeks for all subsequent cycles. It should be noted that within the ACT trials, the assessments at these time points were based on partial Mayo scores and may not correspond to full Mayo scores (the latter of which includes endoscopic visualisation).[105] The paper does not mention whether a half-cycle correction was applied to account for the timing of events within the model.

All patients enter the model in the moderate to severe health state. At the end of each cycle, patients achieving a Mayo score of 0–2 and 3–5 transit to the remission state and mild health state, respectively, and continue to receive the same treatment. Patients who do not achieve remission or response are classified as non-responders. A 'temporary discontinuers' state is included for patients experiencing

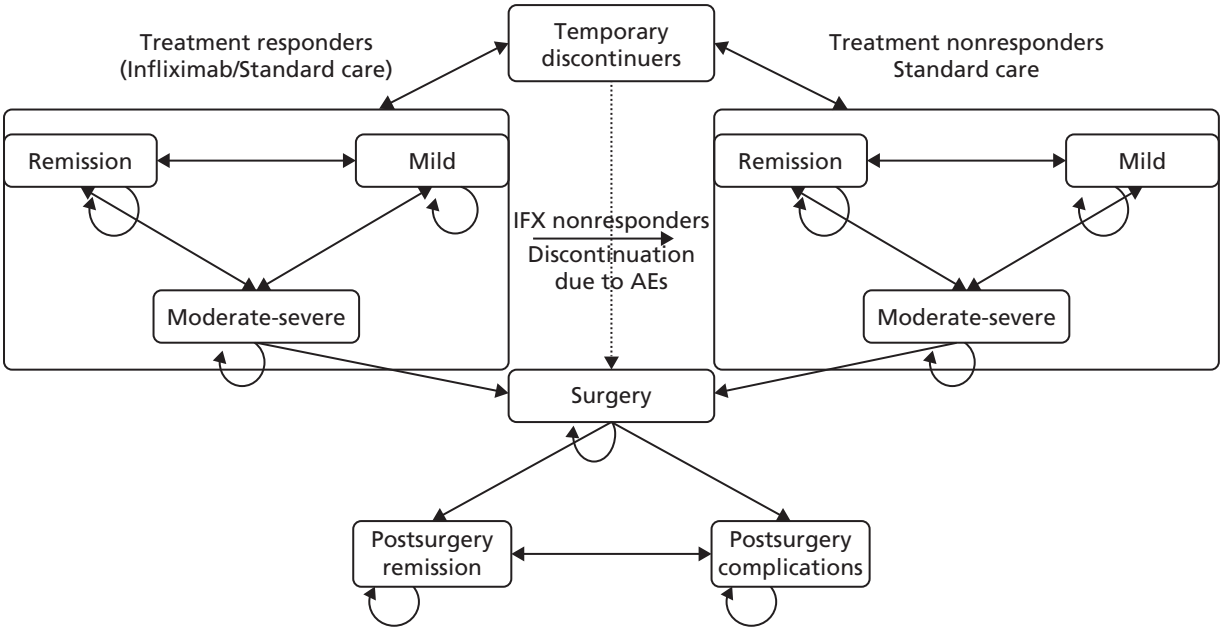

FIGURE 74 Model diagram presented by Tsai *et al.*[82] Reproduced with permission from Tsai HH, Punekar YS, Morris J, Fortun P, A model of the long-term cost effectiveness of scheduled maintenance treatment with infliximab for moderate-to-severe ulcerative colitis, *Aliment Pharmacol Ther* 2008;**28**:1230–9, © 2008 The Authors. Journal compilation © 2008 Blackwell Publishing Ltd.

temporary AEs, which is a tunnel state which is applied for one 8-week cycle. After resolution of AEs, these patients return to their prior health state. Non-responders and patients permanently discontinuing active treatment (e.g. owing to AEs) transit to the corresponding non-responder states and cannot restart IFX treatment. Patients in the moderate to severe states can undergo surgery, which may result in complications. Different costs and utilities are applied to each health state. The model does not include any survival difference between the competing treatments hence the differences in QALYs are driven entirely by differences in sojourn time in each health state.

Transition probabilities in each group were estimated using data from the ACT1 and ACT2 studies.[49] No details are provided within the paper with respect to how these studies were pooled. Transition probabilities for patients in the responder states for IFX and standard care were drawn from the treatment and PBO arms of these trials, respectively. Transition probabilities for non-responders for both groups were drawn from PBO arms of the ACT studies.[49] As ACT1 employed a longer study duration than ACT2, the former trial alone was used to estimate transition probabilities beyond 30 weeks. The ACT1 and ACT2 studies were also used to estimate the probabilities of temporary discontinuation based on the observed AE rates. Transition probabilities for patients undergoing surgery were derived from the literature.[106–108] None of the transition probabilities applied within the model are reported in the paper.

Health-related quality-of-life values are assigned for remission (0.88), mild (0.76), moderate-severe (0.42), temporary discontinuers (0.42), surgery (0.61), post-surgery remission (0.61), post-surgery complications (0.55). Utility values for UC states are stated to have been drawn from an EQ-5D survey of UC patients; however, this appears to be misreferenced as the publication title relates to resource use in patients with CD.[109] Health utility values for patients who were temporary discontinuers and for those with post-surgical complications were drawn from Arseneau *et al.*[110] The text states that these utilities were indexed to the Woehl utility set to avoid any implausible results using regression analysis. No further details are provided regarding this regression analysis.

The model includes treatment- and state-specific costs associated with drug acquisition and administration, consultant visits, hospitalisations, blood tests and endoscopy. The sources used to value the costs of drug acquisition and administration are unclear. The model includes the costs of concomitant medications based

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on the baseline characteristics of patients in the ACT1 and ACT2 studies,[49] and assumes that the use of immunosuppressants and 5-ASAs remain constant while corticosteroid use declines linearly over time for patients responding and achieving remission. The costs associated with non-SAEs were calculated separately but are not detailed. The costs associated with severe AEs were assumed to be subsumed within the costs of hospitalisation. The costs of colectomy + IPAA were based on NHS Reference Costs.[111] Hospitalisation rates for the IFX and standard care groups were based on the ACT1 and ACT2 trials[49] and were valued using NHS Reference Costs. In addition, health-care resource use associated with pre-surgical UC states was estimated from a panel of six UK gastroenterologists; these resource-use estimates were valued using national published cost estimates.

The model results are presented as mean costs and QALYs for each treatment group. The economic analysis includes one-way deterministic sensitivity analysis and PSA. Decision uncertainty is represented using cost-effectiveness planes.

Table 37 presents the results of the economic analysis. Within the base-case analysis, in which medical treatment is assumed to be continued only for those patients in whom response is achieved, IFX is estimated to produce an additional 0.75 QALYs at an additional cost of £20,662, which corresponds to an ICER of £27,424 per QALY gained. Within the secondary analysis, in which patients are assumed to continue treatment only if they achieve and maintain remission, IFX is estimated to produce an additional 0.39 QALYs at an additional cost of £7615, which corresponds to an ICER of £19,696 per QALY gained. It should be noted that the estimates of absolute costs and absolute QALYs for the standard care group differ between the two analyses. Although the alternative treatment stopping rules clearly influence which patients continue to receive IFX and the duration over which patients would receive biological therapy, it is unclear why this would affect outcomes for the standard care group.

In the responders sensitivity analysis, the ICER ranged from £21,066 per QALY gained (lower patient weight) to £86,320 per QALY gained (1-year time horizon). The results of all other deterministic sensitivity analyses in the responder comparison produced an ICER below £32,000 per QALY gained. In the more stringent remission only analysis, the deterministic sensitivity analyses produced ICERs in the range £14,728 per QALY gained (lower patient weight) to £46,765 per QALY gained (1-year time horizon). The results of all other deterministic sensitivity analyses in the remission only comparison produced ICERs below £23,000 per QALY gained. The results of the probabilistic analysis are presented in the form of cost-effectiveness planes. The authors state that 'The PSA showed that the results were robust with [the] majority of simulations clustered together. In both responder and remission treatment strategies, IFX SMT resulted in additional QALYs at an additional cost compared to standard care.'[82] The probabilistic results for the remission only scenario appear somewhat dubious as the samples appear to be truncated at the *y*-axis of the cost-effectiveness plane (the estimates of incremental QALYs for IFX vs. standard care cannot drop below zero). The underlying reason for this within the model is unclear.

TABLE 37 Headline cost-effectiveness results presented by Tsai *et al.*[82]

Strategy	QALYs	Costs	Incremental QALYs	Incremental costs	ICER
Base-case scenario (responders only)					
IFX	4.591	£66,460	0.75	£20,662	£27,424
Standard care	3.838	£45,798	–	–	
Secondary analysis (remission only)					
IFX	4.154	£53,874	0.39	£7615	£19,696
Standard care	3.767	£46,259	–	–	

As noted earlier, the Tsai *et al.*[82] analysis appears to be based on the same model submitted to NICE as part of TA140 (not reviewed here).[28] While the QALY estimates reported within Tsai *et al.*[82] are virtually the same as those reported within the manufacturers' submission to NICE,[80] the incremental costs reported by Tsai *et al.*[82] are lower than those contained within the manufacturers' submission. Consequently, the ICERs presented by Tsai *et al.*[82] are lower than those reported within the NICE submission (responders only analysis ICER = £27,424 per QALY gained[82] vs. £33,866 per QALY gained;[80] remission only analysis £19,696 per QALY gained[82] vs. £25,044 per QALY gained[80]).

Overall, the Tsai *et al.*[82] model appears to follow a plausible model structure and includes the majority of costs and outcomes relevant to the decision problem. It is also noteworthy that this is the only published UK analysis included in this review. In general, the paper performs well against the Drummond checklist. The two notable issues relate to the absence of other biological therapies (this is reasonable as GOL and ADA did not have a UK marketing authorisation at the time of publication) and immediate colectomy as comparators and the use of a short time horizon.

Xie et al.[84]

Xie *et al.*[84] report a cost-effectiveness analysis comparing IFX plus ADA versus usual care in patients with moderate to severe refractory UC in Canada. Patients were assumed to be 40 years of age with a mean body weight of 80 kg. The model adopts a Markov approach and costs and outcomes are evaluated over a 5-year time horizon. Three options were compared within the economic analysis: (1) 'strategy A' – 'usual care', which includes conventional medical treatment (5-ASAs plus immunosuppressants) without anti-TNF-α drugs; (2) 'strategy B' – '5 mg/kg of IFX plus ADA initial and maintenance therapy', which includes 5 mg/kg of IFX followed by a switch to ADA if there is no response to initial therapy or if response is lost during maintenance therapy; and (3) 'strategy C' – '5 mg/kg and 10 mg/kg of IFX + ADA', which involves initial therapy using 5 mg/kg of IFX and, if there is no response, the dose is escalated to 10 mg/kg of IFX, then if response is lost during maintenance therapy, switch to ADA (*Figure 75*). Surgery is included in the pathway for all three treatment groups within the model but is not included as a comparator. Costs and health outcomes were discounted at a rate of 5% per year. All costs were valued at 2008 prices.

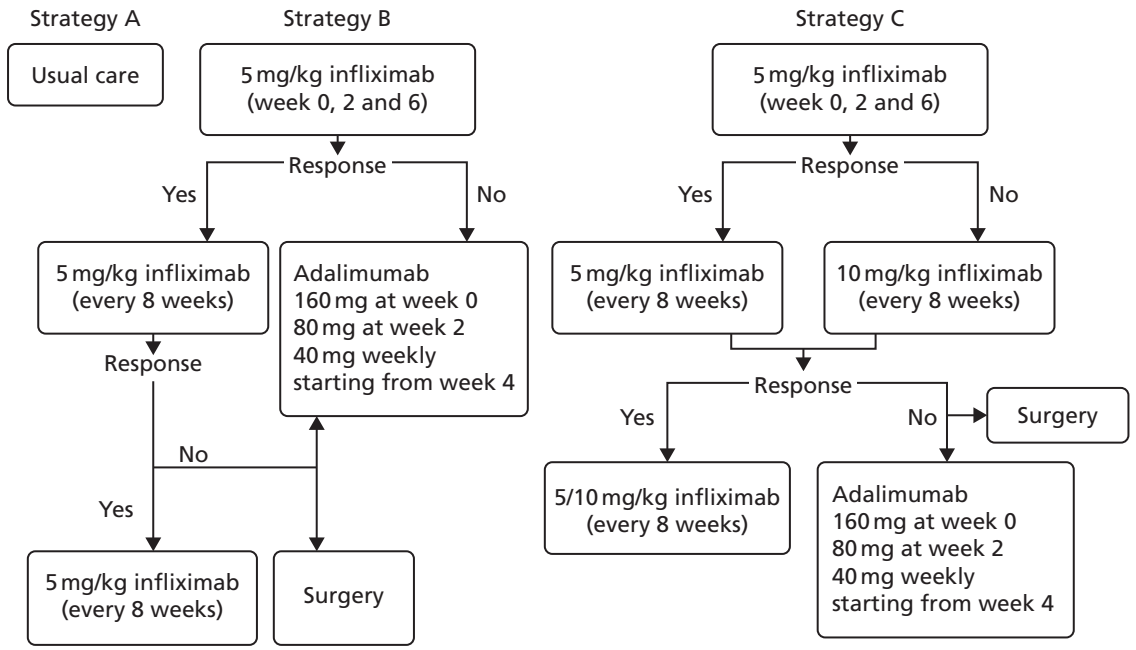

FIGURE 75 Treatment sequences evaluated by Xie *et al.*[84] This article is published under license to BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

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The model includes five mutually exclusive health states: (1) remission, which is defined as a total Mayo score of ≤ 2 points without individual subscores exceeding 1 point; (2) active UC, which includes those patients who do not respond and those who do respond but do not achieve remission; (3) surgery, which is a tunnel state; (4) surgical remission; and (5) surgical complication (*Figure 76*). The model adopts a variable cycle length according to the timing of full Mayo score assessments adopted in the ACT1 and ACT2 studies (0–8 weeks, 9–30 weeks, 31–54 weeks, then 27 weekly thereafter).[49] Patients enter the model in the active moderate to severe state and following initial therapy either achieve remission or not. Those patients who achieve remission may subsequently lose response and transit to active UC or they may maintain remission. For responders in the active UC state, patients may achieve remission or remain in the active UC state with maintenance. Patients who are non-responders can undergo colectomy + IPAA, switch to ADA (strategy B) or receive an increased dose of IFX (strategy C). Following surgery, patients may experience complications, which may or may not be resolved. These complications may arise immediately after surgery or at a later timepoint. Death is not included as an event in the model owing to the short time horizon. Different costs and utilities are applied to each model health state.

The majority of clinical parameters within the model were drawn from the ACT1 and ACT2 studies,[49] derived using a fixed-effects meta-analysis. Remission rates in responders and non-responders were estimated as time-independent parameters based on the ACT1 and ACT2 studies.[49] The authors note that remission rates drawn from the PBO arms of the ACT trials reflect the use of active concomitant medications. Rates of early and late surgery were drawn from a RCT reported by Jarnerot *et al.*[112] and a non-randomised cohort study reported by Hoie *et al.*[107] Rates of complications and the probability of their resolution were derived from non-randomised studies.[113,114] Remission rates, the probabilities of maintaining remission over time and the proportion of non-responding patients in those with active UC for each treatment group were modelled as time-dependent parameters based on the ACT1 and ACT2 studies.[49] Owing to the absence of randomised evidence at the time of the analysis, remission rates for ADA were assumed to be equivalent those for 5 mg/kg of IFX. The model did not incorporate the effects of AEs on health outcomes or costs as the ACT1 and ACT2 studies[49] reported that the proportions of patients with any AE were similar among the IFX and standard care groups.

The model includes four utility values: remission (0.79), active UC (0.32), surgical remission (0.68) and surgical complications (0.49). The model makes no distinction between the HRQoL outcomes for patients who achieve response but not remission and patients who do not achieve response; this may be considered as a very pessimistic assumption that could bias against IFX and ADA therapy, particularly given the low valuation of HRQoL for patients with active UC. All health utilities were drawn from a previous economic modelling study reported by Arseneau *et al.*[110] The method of utility elicitation within this study appears to be TTO.

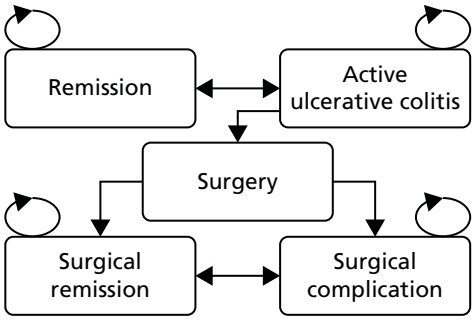

FIGURE 76 Model diagram presented by Xie *et al.*[84] This article is published under license to BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The model includes the costs associated with drug acquisition, drug administration, colectomy and IPAA, medical examination and the management of surgical complications. Drug acquisition costs were drawn from provincial drug benefit lists (including an 8% mark-up). The costs of medical examinations were derived from the Ontario Schedule of Benefits. The costs of surgery were derived from the literature.[115]

The results of the economic analysis are presented as mean costs and QALYs and ICERs for each treatment group based on point estimates of parameters. Pairwise comparisons are presented for the IFX and ADA options versus usual care. A fully incremental analysis between all options in the model is reported in the text. PSA was also conducted with decision uncertainty represented using cost-effectiveness acceptability curves (CEACs).

Table 38 presents the headline cost-effectiveness results reported by Xie *et al.*[84] The model analysis suggests that the strategy B is expected to produce more health gain than strategies A and C. Strategy C is dominated by strategy B. The incremental cost-effectiveness of strategy B versus usual care was estimated to be approximately CA$358,823 per QALY gained.

The PSA suggests that assuming a willingness-to-pay threshold of CA$150,000 per QALY gained, the probability that usual care is optimal is approximately 1.0. The deterministic sensitivity analysis suggests that the lowest ICER is achieved by increasing the utility for remission (ICER = CA$273,081 per QALY gained for strategy B vs. strategy A and CA$428,676 per QALY gained for strategy C vs. strategy A), while the highest ICER is achieved by lowering the utility for remission (ICER = CA$527,236 per QALY for strategy B vs. strategy A, CA$889,227 per QALY gained for strategy C vs. strategy A).

Overall, the analysis reported by Xie *et al.*[84] appears to adequately address the decision problem using a generally appropriate model. However, the analysis is limited by the use of a short time horizon, the absence of surgery as a comparator and questionable assumptions regarding the health gains associated with achieving response without remission.

Discussion of published economic evaluations

Three published economic analyses met the inclusion criteria for the systematic review. One analysis compared early colectomy + IPAA versus standard medical treatment,[83] one compared IFX versus usual care,[82] and the third compared IFX plus ADA versus usual care.[84] Only one study (Tsai *et al.*[82]) was undertaken from the perspective of the UK NHS. The included studies were broadly consistent in terms of the disease-specific factors included in the analyses; all analyses included remission and response, and surgery as a consequence of ineffective medical treatment. Only one study (Park *et al.*[83]) included the increased risk of colorectal cancer associated with UC within the analysis. One study (Xie *et al.*[84]) did not include mortality for any patient group in the model. Only Park *et al.*[83] included surgery as a treatment option; the other options focused solely on medical treatment strategies. The study reported by Xie *et al.*[84] included ADA as part of the pathway; however, owing to a lack of RCT evidence at the time of the analysis, the authors assumed that ADA was equivalent to 5 mg/kg of IFX and this assumption may not be appropriate given more recent evidence.[44,49] None of the included studies evaluated the cost-effectiveness of GOL versus any other treatment. The time horizons considered in the economic analyses differ considerably, ranging from 5 years to the patient's remaining lifetime. It is also noteworthy that although

TABLE 38 Headline cost-effectiveness results reported by Xie *et al.*[84]

Strategy	QALYs	Cost	Incremental QALYs	Incremental cost	ICER
Strategy B (IFX + ADA)	2.18	CA$82,756	0.16	CA$58,488	CA$358,823
Strategy C [IFX (plus dose escalation) + ADA]	2.15	CA$101,272	–	–	Dominated
Strategy A (usual care)	2.02	CA$24,268	–	–	–

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the study reported by Tsai *et al.*[82] reported favourable results for IFX (<£30,000 per QALY gained), Xie *et al.*[84] reported considerably less favourable estimates (> CA$350,000 per QALY gained). This contrasting finding may in part be explained by differences in assumptions regarding the level of HRQoL attributable to patients achieving response but not remission. Overall, none of the included studies present sufficient evidence relating to the cost-effectiveness of IFX, ADA and GOL versus standard medical or surgical treatment options for moderate to severe UC from the perspective of the UK NHS and PSS.

The next sections present a critique of the economic evidence submitted by the manufacturers of IFX, ADA and GOL.

Cost-effectiveness evaluation of golimumab (with Patient Access Scheme), infliximab and adalimumab relative to colectomy for moderate to severe ulcerative colitis in the UK (MSD submissions[64,66])

The MSD submissions include details of a systematic review of previous models together with the methods and results of a de novo model developed to assess the cost-effectiveness of ADA, GOL and IFX and standard non-biological treatment for moderate to severe UC. Although MSD submitted two de novo models and two submission reports,[64,66] these relate to virtually the same overall model and analysis, hence they are detailed and critiqued together within this section.

Summary of manufacturers' review of existing economic analyses

The MSD submissions include a systematic review of economic evaluations of treatments for UC. The manufacturer undertook searches in EMBASE, PubMed and the NHS EED to identify published economic evaluations in UC to help inform the model structure and relevant parameters. A total of 12 published health economic analyses were included in the MSD review.[82,84,116–125] Several of these studies do not include biological treatment options and some of the analyses relate to the management of severe UC exacerbations which is beyond the scope of this appraisal. The MSD review highlights the following points with respect to previous health economic analyses:

- Markov models are commonly used to evaluate treatments for UC
- all of the published models report outcomes in terms of QALYs/life-years gained
- none of the studies included all relevant therapies
- there is variability in parameter sources and values between economic studies
- resource-use estimates used in published models are typically derived from experts in the field rather than empirical research studies.

The MSD submissions also highlight a distinction between two distinct types of models: (1) Markov models in which the model structure is based on sequences of therapies; and (2) Markov models in which the model structure is based on severity. The MSD submissions do not report the results of these previous economic analyses; hence they are not discussed further here.

MSD model scope

The MSD model compares 160 mg/80 mg/40 mg of ADA, 5 mg/kg of IFX, 200 mg/100 mg/50 mg (100 mg for some patients with higher body weight after the initial induction dosing) of GOL and standard non-biological treatment for patients with moderate to severe UC who have failed previous drug treatment. Standard non-biological treatment is assumed to be immediate colectomy. The perspective of the analysis is that of the UK NHS. GOL is assumed to be given at an initial dose of 200 mg, followed by 100 mg at week 2, then 50 mg every 4 weeks thereafter for patients with body weight < 80 kg. For those patients with body mass ≥ 80 kg, GOL is assumed to be given as an initial dose of 200 mg, followed by 100 mg at week 2, then 100 mg every 4 weeks thereafter. IFX is assumed to be given at a dose of 5 mg/kg followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. ADA is assumed to be given as 160 mg at week 0 (the dose can be administered as four injections in one day or as two injections per day for two consecutive days) and 80 mg at week 2. After induction treatment, 50% of patients are assumed to receive the recommended dose of 40 mg every other

week while the remainder are assumed to receive 40 mg every week. The MSD submission states that 22.9% patients in the ULTRA2 trial require dose escalation but also states that experts advising on the submission suggested that the actual proportion of patients in clinical practice may be as high as 80%. The manufacturer argues that the assumption that 50% patients dose escalate is conservative.

Patients receiving biological treatments who achieve a response or remission at induction are assumed to continue maintenance therapy with the same biological treatment. The model does not include sequences in which alternative biologicals are used. GOL and ADA are assumed to be given as subcutaneous injections while IFX is given as an i.v. infusion. For all treatment options, a proportion of patients are also assumed to receive ongoing 'background' non-biological therapies including 5-ASAs, corticosteroids and immunosuppressants. Standard clinical management, defined in the NICE scope as 'a combination of aminosalicylates (sulfasalazine, mesalazine, balsalazide or olsalazine), corticosteroids (beclomethasone, budesonide, hydrocortisone or prednisolone), and thiopurines (mercaptopurine or AZA), calcineurin inhibitors and surgical intervention',[36] is not included as a treatment option in the MSD economic analysis. Upon model entry, patients are assumed to be 40 years of age and 56% are assumed to be male. The model uses a 2-monthly cycle length. Costs and health outcomes are discounted at a rate of 3.5% each year and are evaluated over a 10-year time horizon.

MSD model structure

The MSD model structure is shown in *Figures 77* and *78*. The model adopts a hybrid approach whereby an initial decision tree is used to determine the probabilities of induction response or remission for biological drug treatments, together with the probabilities of survival and the incidence of complications for patients undergoing immediate colectomy, while a Markov component is used to estimate long-term outcomes for maintenance drug therapy and surgery. The decision tree structure is identical for all biological drug treatments and includes initial outcomes defined in terms of no response, response and remission.

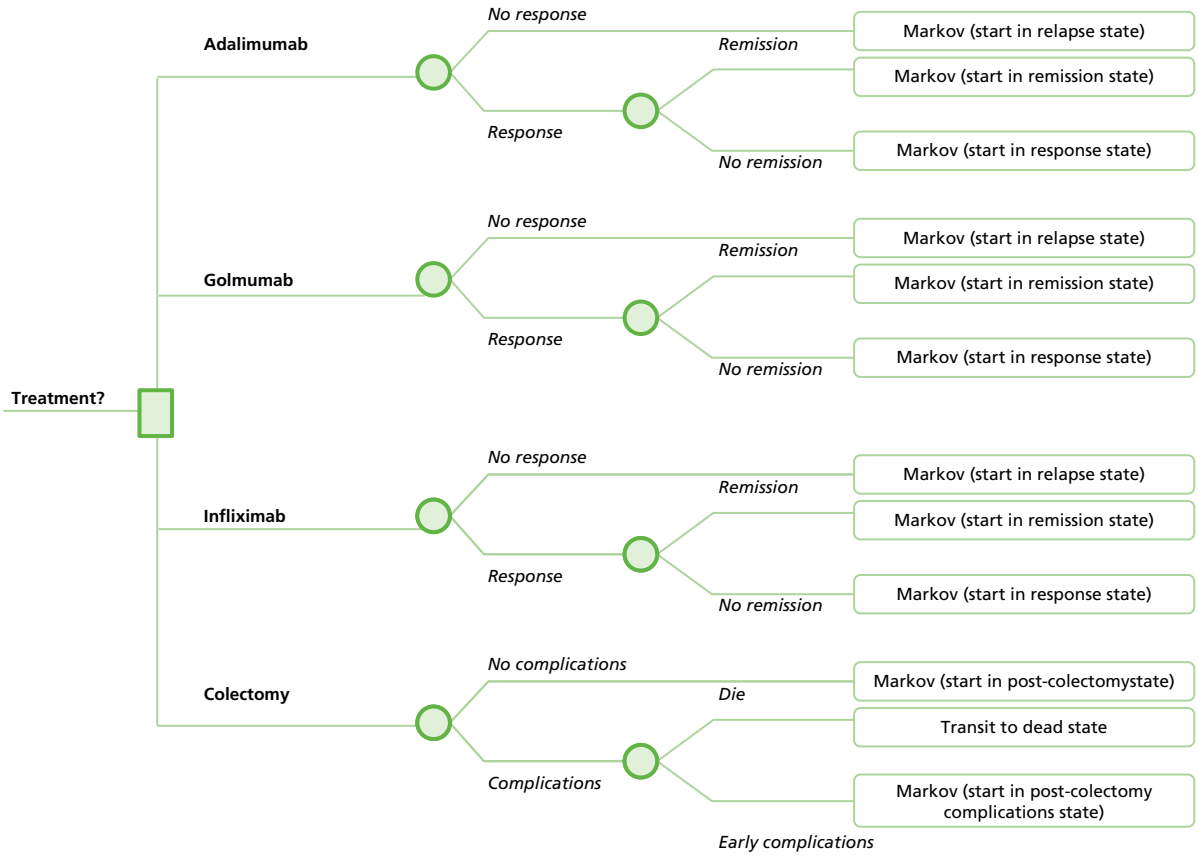

FIGURE 77 Merck Sharp & Dohme Ltd model structure (redrawn by the Assessment Group).

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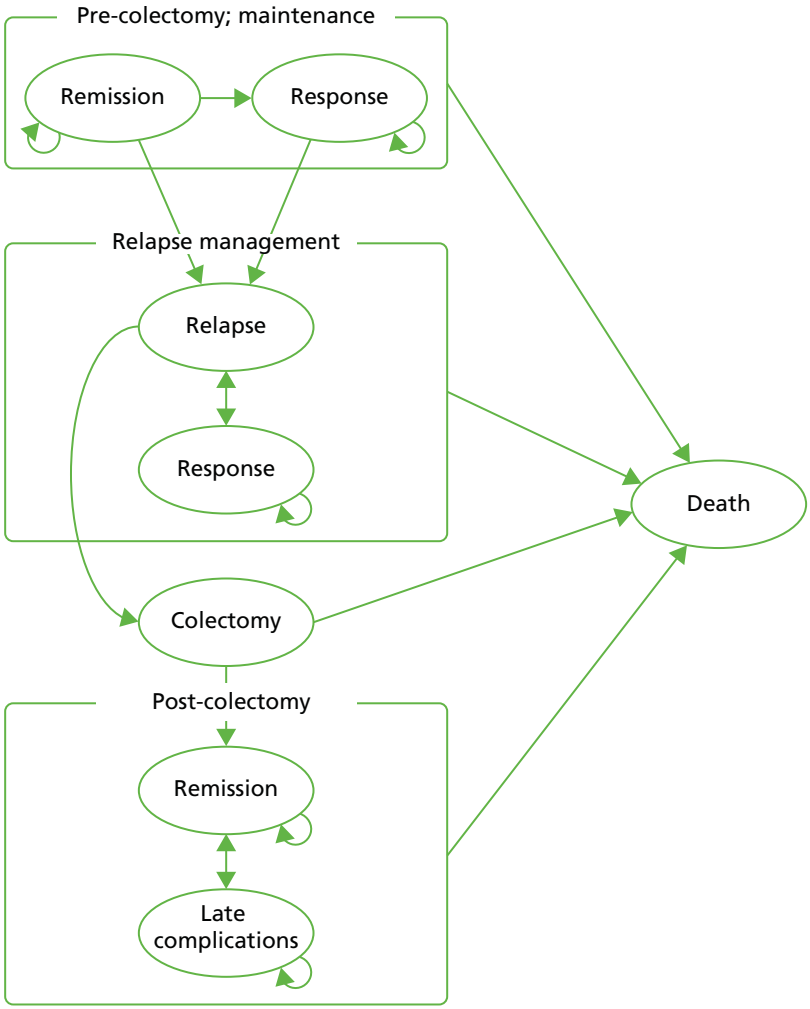

FIGURE 78 Merck Sharp & Dohme Ltd model Markov component.[64,66] Reproduced with permission.

For the standard care (colectomy) option, the decision tree outcomes are different and instead relate to the probabilities of surviving surgery and experiencing early complications resulting from that surgery. The Markov model comprises eight mutually exclusive health states: (1) response (pre-colectomy; maintenance); (2) remission (pre-colectomy; maintenance); (3) response (relapse management); (4) relapse (relapse management); (5) colectomy; (6) remission (post-colectomy); (7) late complications (post-colectomy); and (8) death.

For the biological treatment groups, patients are initially allocated to no response, response or remission based on the results of a de novo NMA of induction therapy trials[44,47–49,126] undertaken by the manufacturer. Patients in whom response or remission is achieved at induction are assumed to remain on maintenance treatment using the same biological treatment. Subsequent model transitions are informed by a separate NMA based on the results of the trials of biological maintenance therapies.[44,47,49] Patients who do not respond to induction therapy, and those who lose response during maintenance treatment, are assumed to enter the relapse management state and receive i.v. steroids. Patients who respond to i.v. steroids then transit to the 'Response (relapse management)' state at which time they either continue responding or relapse. Patients who do not respond are assumed to undergo immediate colectomy. Colectomy is dealt with as a tunnel state; following surgery a small proportion of patients are assumed to die while the remainder are assumed to be in post-colectomy remission. Patients who survive their surgery are assumed to be at ongoing risk of post-colectomy complications (anal fistula, bowel obstruction and pouchitis). A small proportion of patients receiving drug treatment are assumed to be at risk of serious infection and hospitalisation.

The model uses simple matrix multiplication to determine health state populations during each model cycle based on the state population in the previous Markov cycle and a single time-independent transition matrix over the entire time horizon. Costs and utilities are attached to each health state. Total QALYs are modelled as a function of sojourn time in each health state, mortality associated with colectomy and other-cause (general population risk) mortality.

Evidence sources used to inform the MSD model parameters

A summary of evidence sources used to inform the model's parameters is presented in *Table 39*.

Methods for modelling effectiveness

Estimates of relative effectiveness of biological treatments versus conventional non-biological non-surgical treatment were derived from NMA models of induction and maintenance therapy undertaken by the manufacturer.[64,66]

The baseline model employed within the MSD NMA model is not discussed within the submissions.[64,66] The MSD economic model includes a worksheet named 'Input Efficacy and Trans Prob' in which the probabilities of response and remission for non-biological therapy are inputted as 0.36 and 0.09 for induction treatment, and 0.83 and 0.86 per 2-month cycle of maintenance therapy respectively. The source is stated in the model as 'Average study effect of PBO controlled trials in random effects NMA of induction response'. No additional detail on the baseline model is provided within the MSD submissions; thus, it is not possible to determine whether or not these estimates are appropriate.

Relative treatment effects were drawn from de novo NMAs undertaken by the manufacturer, based on the results of a systematic literature review. Separate analyses were undertaken for induction and maintenance therapy. For induction, a NMA was undertaken using data from six RCTs.[44,45,47–49] For maintenance treatment, relative treatment effects were based on a NMA of three RCTs.[45,47,49] The evidence networks employed in the manufacturer's NMAs are presented in *Figures 79* and *80* respectively. It should be noted that the manufacturer's NMA includes non-licensed indications of IFX, although these are not included in the health economic analysis.

TABLE 39 Summary table of evidence sources used to inform the MSD model parameters

Parameter group	Source
Pre-colectomy transition probabilities excluding death: standard non-biological treatment	Manufacturer's NMA: average study effect of PBO controlled trials in random effects NMA of induction response[64,66]
ORs for biological treatment effects	ORs derived from manufacturer's NMA[64,66]
Effectiveness of i.v. steroids following failure of biological treatment	Model fitted to ensure 27% relapsers require colectomy based on Turner *et al.*[126]
Probability of serious infection	Grijalva *et al.*[127]
Health utilities for pre-colectomy response/ remission	EQ-5D estimates from the PURSUIT trial[47,48] in the GOL model, EQ-5D estimates from the ACT1 and ACT2[49] trials in the IFX model
Health utilities for post-colectomy states[a]	Woehl *et al.*[109] Tsai *et al.*[82] Health Outcomes Data Analysis Repository, Punekar and Hawkins,[120] Chaudhary and Fan,[116] Arseneau *et al.*[110]
Resource use	PURSUIT trial,[47] ACT1 and ACT2 trials[49] and interviews with nine gastroenterologists[64,66]
Unit costs[a]	Curtis *et al.*[128] NHS Reference Costs[129]

a Sources for some HRQoL parameters are not clear from the MSD submissions.

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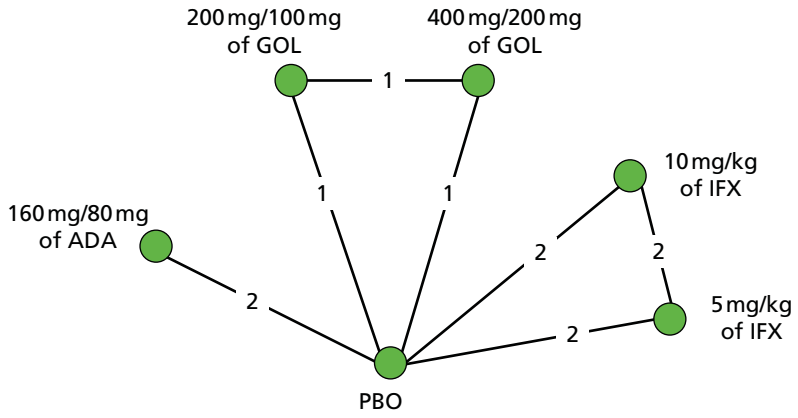

FIGURE 79 Evidence network for induction therapy.[64,66] Reproduced with permission.

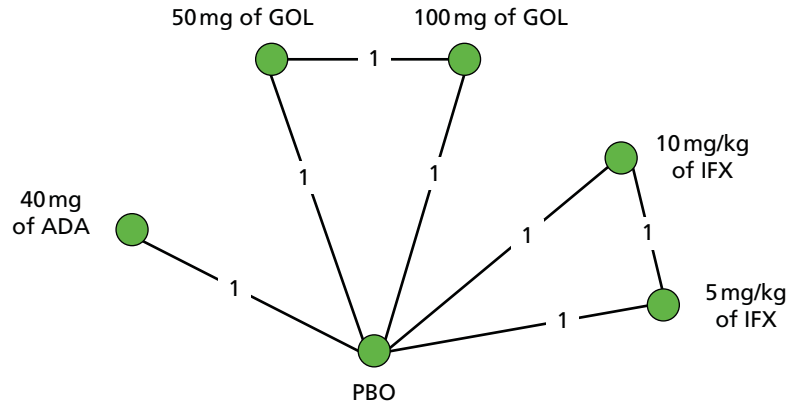

FIGURE 80 Evidence network for maintenance therapy.[64,66] Reproduced with permission.

The NMAs use logistic regression models to estimate treatment effects, given an assumption that the data are binomial (separate models are used to estimate the odds of sustained response and the odds of sustained remission respectively). Relative treatment effects were parameterised in terms of ORs and are converted to relative risks in the health economic model. In instances whereby only one RCT informed each treatment (which was predominantly the case for the maintenance outcomes), heterogeneity could not be estimated and, therefore, a fixed-effects model was employed. When multiple studies were available, a random-effects approach was used.[64,66] The NMA model for maintenance therapy includes a complex 'novel' imputation of estimates of sustained response and sustained remission for GOL from the PURSUIT trial using data from the non-randomised PBO group (see MSD GOL submission p. 55[66]). The results of the manufacturer's NMA are presented in *Tables 40* and *41* respectively.

Table 42 illustrates how the ORs are applied within the transition matrix for maintenance therapy within the health economic model, using the ADA treatment group as an example.

It should be noted that the matrix employed within the MSD models does not match the transitions implied by the diagram within the MSD submissions[64,66] (see *Figure 78*). In the executable model, patients who have previously achieved a response can either maintain or lose that response, but they cannot improve (i.e. they cannot subsequently transit to the remission state). Patients who have previously achieved remission can either maintain or lose that remission. However, upon losing remission, the patient cannot transit directly to relapse – they transit to the response state first. This means that no additional patients can achieve remission after induction and no patients with remission can completely lose response during any given model cycle. It is also noteworthy that patients who discontinue treatment with a

TABLE 40 Manufacturer's NMA results: induction treatment

Intervention	OR	Lower 95% CrI	Upper 95% CrI
Induction response (reference PBO)			
200 mg/100 mg of GOL	2.12	1.01	3.95
400 mg/200 mg of GOL	2.47	1.19	4.65
5 mg/kg of IFX	4.12	2.08	8.14
10 mg/kg of IFX	3.81	1.95	7.59
160 mg/kg of ADA	1.87	0.96	3.65
Induction remission (reference PBO)			
200 mg/100 mg of GOL	2.99	1.32	6.28
400 mg/200 mg of GOL	3.32	1.56	7.23
5 mg/kg of IFX	5.27	2.60	11.64
10 mg/kg of IFX	3.90	1.88	8.56
160 mg/kg of ADA	2.25	1.08	4.72

TABLE 41 Manufacturer's NMA results: maintenance treatment

Intervention	OR	Lower 95% CrI	Upper 95% CrI
Sustained response (reference PBO)			
40 mg/kg of ADA	1.31	0.67	2.59
5 mg/kg of IFX	2.12	1.02	4.54
10 mg/kg of IFX	2.51	1.17	5.51
50 mg of GOL	1.51	0.94	2.47
100 mg of GOL	1.75	1.08	2.84
50–100 mg of GOL	1.62	1.07	2.50
PBO following GOL	0.78	0.47	1.28
Sustained remission (reference PBO)			
40 mg/kg of ADA	0.76	0.22	2.56
5 mg/kg of IFX	1.30	0.44	4.05
10 mg/kg of IFX	2.26	0.73	7.49
50 mg of GOL	0.83	0.29	2.40
100 mg of GOL	0.98	0.36	2.78
50–100 mg of GOL	0.92	0.36	2.45
PBO following GOL	0.45	0.15	1.34

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TABLE 42 Transition matrix for ADA

Health state	Response (pre-colectomy; maintenance)	Remission (pre-colectomy; maintenance)	Response (relapse management)	Relapse (relapse management)	Colectomy	Remission (postcolectomy)	Late complications (postcolectomy)	Death related to UC
Response (pre-colectomy; maintenance)	0.86[a]	0.00	0.00	0.14[b]	0.00	0.00	0.00	0.00
Remission (pre-colectomy; maintenance)	0.17[c]	0.83[d]	0.00	0.00[e]	0.00	0.00	0.00	0.00
Response (relapse management)	0.00	0.00	0.83	0.17	0.00	0.00	0.00	0.00
Relapse (relapse management)	0.00	0.00	0.73	0.00	0.27	0.00	0.00	0.00
Colectomy	0.00	0.00	0.00	0.00	0.00	0.97	0.00	0.03
Remission (postcolectomy)	0.00	0.00	0.00	0.00	0.00	0.99	0.01	0.00
Late complications (postcolectomy)	0.00	0.00	0.00	0.00	0.00	1.00	0.00	0.00

a Probability of maintaining response on non-biological × relative risk of maintaining response on biological treatment.
b Probability of relapse calculated as one minus the sum of the row of probabilities.
c One minus probability of sustained remission on non-biological × relative risk of sustained remission on biological treatment.
d Probability of maintaining remission calculated as one minus the sum of the row of probabilities.
e Transition probability set to zero for all biological treatments.

biological treatment transit very quickly to colectomy (27% of all non-responding relapsers during each 2-month cycle). This estimate was based on a meta-regression of studies describing the short-term outcomes for adult and paediatric patients treated with i.v. corticosteroids, with or without ciclosporin, for exacerbations of UC.[126]

The model also includes a small risk of experiencing serious infection owing to the use of immunosuppressants and biological therapies based on Grijalva *et al.*[127] The model assumes a hazard ratio of 1.10 for all biological therapies and a baseline risk of 0.16 for non-biological therapy.

Health-related quality of life

The health utility values used in the MSD model are presented in *Table 41*. Health utilities associated with failure, response, and remission as a result of induction and maintenance treatment, and utility values assigned to the health states 'Response (pre-colectomy; maintenance)' and 'Remission (pre-colectomy; maintenance)' are assumed to be the same for all biologicals, based on EQ-5D valuations derived from the PURSUIT trial[47] within the GOL model and the ACT1 trial[49] within the IFX models. The MSD submission suggests that disutilities for AEs associated with biologicals are likely to be captured within these estimates. Different utilities are assumed for the achievement of the same outcome at induction and maintenance (i.e. the utility for response at induction is not the same as the utility for response at maintenance). Utility values for colectomy, postcolectomy and early and late complications of colectomy were based on estimates reported within the literature, although the precise sources are not clear from the MSD submissions[64,66] (*Table 43*).

Resource use and costs

The model includes direct costs of drug acquisition, consultant visits, endoscopy, inpatient hospital admissions, colectomy, management of surgery-related complications, AEs and other UC costs. A Patient Access Scheme (PAS), in which the price of 100 mg of GOL is assumed to be equal to that of 50 mg of GOL, is applied within the model. It should be noted that at the time of writing, this had not been approved by the Department of Health.

TABLE 43 Health utility values used in the MSD models

Health state	Utility value (GOL model; IFX model)	Valuation method and source (GOL model; IFX model)
Response (pre-colectomy; induction)	0.80; 0.79	EQ-5D PURSUIT trial;[47] ACT1 trial[49]
Remission (pre-colectomy; induction)	0.86; 0.84	EQ-5D PURSUIT trial;[47] ACT1 trial[49]
No response (pre-colectomy; induction)	0.70; 0.70	EQ-5D PURSUIT trial;[47] ACT1 trial[49]
Response (pre-colectomy; maintenance)	0.80; 0.82	EQ-5D PURSUIT trial;[47] ACT1 trial[49]
Remission (pre-colectomy; maintenance)	0.89; 0.88	EQ-5D PURSUIT trial;[47] ACT1 trial[49]
Response (relapse management)	0.76; 0.76	EQ-5D PURSUIT trial;[47] ACT1 trial[49]
Relapse (relapse management)	0.42; 0.42	EQ-5D estimates from Tsai *et al.*;[82] however, the primary source of these estimates (Woehl *et al.*[109]) appears to be misreferenced as the cited reference is not a health valuation study and does not report utilities
Colectomy	0.56; 056[a]	Unclear. Appears to be based on data from Health Outcomes Data Analysis Repository reported within Punekar and Hawkins.[120] Disutility for early complications based on TTO study reported by Arseneau *et al.*[110]
Remission (postcolectomy)	0.60; 0.60	
Late complications (postcolectomy)	0.60; 0.60	

a Includes disutility for proportion of patients experiencing early complications of surgery.

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Drug acquisition costs

Cost of non-biological 'background' therapies

The usage and per-cycle costs of non-biological background therapies assumed within the model are presented in *Tables 44* and *45*. Patients in the standard non-biological treatment group are assumed to receive 4 g of mesalazine daily (if acute) or 2 g of mesalazine daily (if chronic), 2–2.5 mg/kg of AZA daily, 1–1.5 mg/kg of 6-MP daily, 500 mg of ciprofloxacin twice daily and 25–50 mg of prednisolone per day. The same use of background therapies is assumed for all biological treatment arms. However, it should be noted that in the colectomy group, patients are assumed to undergo immediate colectomy, so the actual drug acquisition cost for the colectomy group is zero within the model. Patients in the biological treatment groups are assumed to receive the same 'background therapies' with the exception of ciprofloxacin (although as described above, this is applied as a zero cost in the colectomy group). Resource-use estimates for these therapies appear to be based on the PBO arm of the PURSUIT trial[47] within the GOL model and from the PBO arm of the ACT1 and ACT2 trials[49] within the IFX model. These are similar, but not the same (see *Tables 44* and *45*); as with the utility values, the justification for using different assumptions concerning resource use in each model is not clear. The source of the unit costs is not reported within the submission, but estimates appear to be drawn from the *British National Formulary* (BNF[37]).

Biological therapies

Table 46 shows the biological acquisition costs per cycle for each treatment group. The table indicates that the estimated costs of induction using IFX is markedly higher than that for ADA and GOL; however, the costs of maintenance therapy per cycle are broadly similar for all biologicals.

TABLE 44 Background therapies resource use and costs used in MSD GOL model

Treatment group	Background therapies included (proportion of patients)	Cost per cycle (£)
Induction treatment		
Standard non-biological treatment	Mesalazine (0.83), AZA (0.15), 6-MP (0.15), ciprofloxacin (0.00), prednisolone (1.00)	251.43[a]
ADA	Mesalazine (0.81), AZA (0.16), 6-MP (0.16), prednisolone (0.44)	200.03
GOL	Mesalazine (0.81), AZA (0.16), 6-MP (0.16), prednisolone (0.44)	200.03
IFX	Mesalazine (0.81), AZA (0.16), 6-MP (0.16), prednisolone (0.44)	200.03
Maintenance treatment		
Standard non-biological treatment	Mesalazine (0.80), AZA (0.16), 6-MP (0.16), ciprofloxacin (0.00), prednisolone (0.49)	121.15[a]
ADA	Mesalazine (0.80), AZA (0.15), 6-MP (0.15), prednisolone (0.51)	120.98
GOL	Mesalazine (0.80), AZA (0.15), 6-MP (0.15), prednisolone (0.51)	120.98
IFX	Mesalazine (0.80), AZA (0.15), 6-MP (0.15), prednisolone (0.51)	120.98
Relapse management (following prior treatment failure)		
Relapse management	Mesalazine (0.80), AZA (0.16), 6-MP (0.16), ciprofloxacin (0.00), prednisolone (0.49)	121.15
Relapse management (i.v. steroids)	Mesalazine (0.83), AZA (0.15), 6-MP (0.15), ciprofloxacin (0.00), prednisolone (1.00), i.v. prednisolone (1.00)	405.43

a Acquisition costs not included in model results for standard non-biological treatment.

TABLE 45 Background therapies resource use and costs used in MSD IFX model

Treatment group	Background therapies included (proportion of patients)	Cost per cycle (£)
Induction treatment		
Standard non-biological treatment	Mesalazine (0.71), AZA (0.15), 6-MP (0.15), ciprofloxacin (0.00), prednisolone (1.00)	233.57[a]
ADA	Mesalazine (0.72), AZA (0.36), 6-MP (0.13), prednisolone (0.54)	191.11
GOL	Mesalazine (0.72), AZA (0.36), 6-MP (0.13), prednisolone (0.54)	191.11
IFX	Mesalazine (0.72), AZA (0.36), 6-MP (0.13), prednisolone (0.54)	191.11
Maintenance treatment		
Standard non-biological treatment	Mesalazine (0.71), AZA (0.15), 6-MP (0.15), ciprofloxacin (0.00), prednisolone (0.57)	118.10[a]
ADA	Mesalazine (0.72), AZA (0.36), 6-MP (0.13), prednisolone (0.54)	113.99
GOL	Mesalazine (0.72), AZA (0.36), 6-MP (0.13), prednisolone (0.54)	113.99
IFX	Mesalazine (0.72), AZA (0.36), 6-MP (0.13), prednisolone (0.54)	113.99
Relapse management (following prior treatment failure)		
Relapse management	Mesalazine (0.71), AZA (0.29), 6-MP (0.15), ciprofloxacin (0.00), prednisolone (0.57)	118.10
Relapse management (i.v. steroids)	Mesalazine (0.71), AZA (0.29), 6-MP (0.15), ciprofloxacin (0.00), prednisolone (1.00), i.v. prednisolone (1.00)	387.57

a Acquisition costs not included in model results for colectomy group.

TABLE 46 Biologic treatment resource use and costs used in MSD models

Treatment group	Assumed regimen	Cost per cycle (£)
Induction treatment (8-week cycle)		
ADA	All patients receive 1 × 160 mg of ADA + 1 × 80 mg of ADA + 3 × 40 mg of ADA	3169.26
GOL	All patients receive 2 × 100 mg of GOL + 1 × 100 mg of GOL	3051.88
IFX	All patients receive 12 × 100 mg of IFX over three administrations	5497.44
Maintenance treatment (2-month cycles)		
ADA	50% patients receive 40 mg of ADA EW (4.33 doses/cycle); 50% patients receive 40 mg of ADA EW (8.67 doses/cycle)	2288.91
GOL	31.6% patients receive 100 mg of GOL every 4 weeks; 68.4% patients receive 50 mg of GOL every 4 weeks	1653.10
IFX	All patients receive 5 mg/kg of IFX every 8 weeks	1985.19

EW, every week.

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Health state resource costs

Tables 47 and *48* present the health state costs (excluding drug acquisition) for the biological and colectomy groups respectively. The resource-use estimates underpinning these cost estimates were reported to be based on interviews with nine expert gastroenterologists. Resource use was costed using standard costing sources.[128,130]

Model evaluation and uncertainty analysis

The results of the economic analysis are presented as pairwise ICERs and are interpreted as net monetary benefits (NMBs) assuming a willingness-to-pay threshold of £30,000 per QALY gained. Incremental CEACs are also presented within the submission (see MSD GOL submission,[66] p. 122). Uncertainty surrounding estimates of incremental costs and health outcomes was examined using deterministic sensitivity analyses and PSA. The results of the deterministic analyses are presented as tornado diagrams and the results of the PSA are presented as cost-effectiveness planes and CEACs.

MSD model results

Tables 49 and *50* present the results within the GOL and IFX submissions respectively[64,66] (note: the fully incremental analysis presented here has been undertaken by the Assessment Group rather than by the manufacturer).

TABLE 47 Other health state costs (£) per 2-month cycle: biological treatments

State and treatment phase	Consultant visit cost	Endoscopy cost	Inpatient cost	Colectomy cost	Late complications cost	Other UC cost	AE cost	Total cost per cycle
Response; induction phase	91.58	18.32	0.00	0.00	0.00	1.80	29.37	141.07
Remission; induction phase	43.70	4.97	0.00	0.00	0.00	1.80	29.37	79.84
Failure; induction phase	162.76	40.30	0.00	0.00	0.00	1.80	29.37	234.22
Response (pre-colectomy; maintenance)	91.58	18.32	0.00	0.00	0.00	1.80	29.37	141.07
Remission (pre-colectomy; maintenance)	43.70	4.97	0.00	0.00	0.00	1.80	29.37	79.84
Response (relapse management)	91.58	18.32	0.00	0.00	0.00	1.80	26.74	138.44
Relapse (relapse management)	162.76	40.30	350.86	0.00	0.00	3.44	26.74	584.09
Colectomy	162.76	40.30	0.00	8967.94	0.00	3.44	0.00	9174.42
Remission (postcolectomy)	53.12	45.27	0.00	0.00	0.00	0.92	0.00	99.30
Late complications (postcolectomy)	67.77	26.17	0.00	0.00	2446.85	1.85	0.00	2542.64

TABLE 48 Other health state costs (£) 2-month cycle: colectomy group[a]

State and treatment phase	Consultant visit cost	Endoscopy cost	Colectomy cost without early complications	Cost early complications of colectomy	Colectomy cost	Late complications cost	Other UC cost	Total cost per cycle
Death due to colectomy. Remission (postcolectomy) due to colectomy	162.76	40.30	7619.25	4029.61	8967.94	0.00	3.44	20,823.28
Remission (postcolectomy) due to colectomy	162.76	40.30	7619.25	4029.61	8967.94	0.00	3.44	20,823.28
Colectomy	162.76	40.30	7619.25	4029.61	8967.94	0.00	3.44	20,823.28
Remission (postcolectomy)	53.12	45.27	0.00	0.00	0.00	0.00	0.92	99.30
Late complications (postcolectomy)	67.77	26.17	0.00	0.00	0.00	2446.85	1.85	2542.64

a The model includes 10 further rows of costs by state for the colectomy group, however none of these influences the model results.

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TABLE 49 Model results from GOL submission[66] (including PAS)

Treatment	QALYs	Costs (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
Probabilistic model results					
IFX	5.70	44,382.28	0.16	13,003.60	80,318
GOL	5.54	31,378.68	0.56	15,610.91	27,994
ADA	5.49	32,096.50	–	–	Dominated
Colectomy	4.98	15,767.78	–	–	–
Results based on point estimates of parameters					
IFX	5.65	43,091.60	0.15	12,196.82	80,866
GOL	5.50	30,894.78	0.55	15,100.53	27,322
ADA	5.45	31,370.28	–	–	Dominated
Colectomy	4.95	15,794.26	–	–	–

TABLE 50 Model results from IFX submission[64] (including PAS)

Treatment	QALYs	Costs (£)	Incremental QALYs	Incremental cost(£)	ICER (£)
Probabilistic model results					
IFX	5.71	44,189.50	0.17	12,841.74	75,998
GOL	5.54	31,347.76	0.57	15,522.79	27,163
ADA	5.48	32,123.34	–	–	Dominated
Colectomy	4.97	15,824.96	–	–	–
Results based on point estimates of parameters					
IFX	5.66	42,919.73	0.16	12,166.45	77,599
GOL	5.51	30,753.28	0.56	14,963.69	26,569
ADA	5.45	31,237.38	–	–	Dominated
Colectomy	4.94	15,789.59	–	–	–

The model results suggest that IFX is expected to produce the greatest QALY gain, followed by GOL and ADA. ADA is expected to be less effective and more expensive than GOL, hence it is ruled out because of simple dominance. The ICER for GOL versus colectomy is expected to be approximately £27,000–28,000 per QALY gained. The ICER for IFX versus GOL is expected to be approximately £76,000–80,000 per QALY gained. The probabilistic results are slightly different from those derived from point estimates of parameters, but the ICERs appear stable.

Figure 81 presents the results of the PSA in the form of a cost-effectiveness plane for each biological treatment relative to immediate colectomy. It can be seen that the results overlap considerably for ADA and GOL; however, the plane indicates a generally higher overall cost for IFX. The dispersion of sampled incremental QALY gains for IFX versus colectomy is greater than that for ADA and GOL versus colectomy.

Figure 82 presents incremental CEACs for all options in the model. The CEACs suggest that at willingness-to-pay thresholds of £25,000 per QALY gained or lower, immediate colectomy has the highest probability of producing the greatest net benefit. At a willingness-to-pay threshold of £30,000 per QALY gained, GOL has the highest probability of producing the greatest net benefit, although this is only very slightly higher than 0.50.

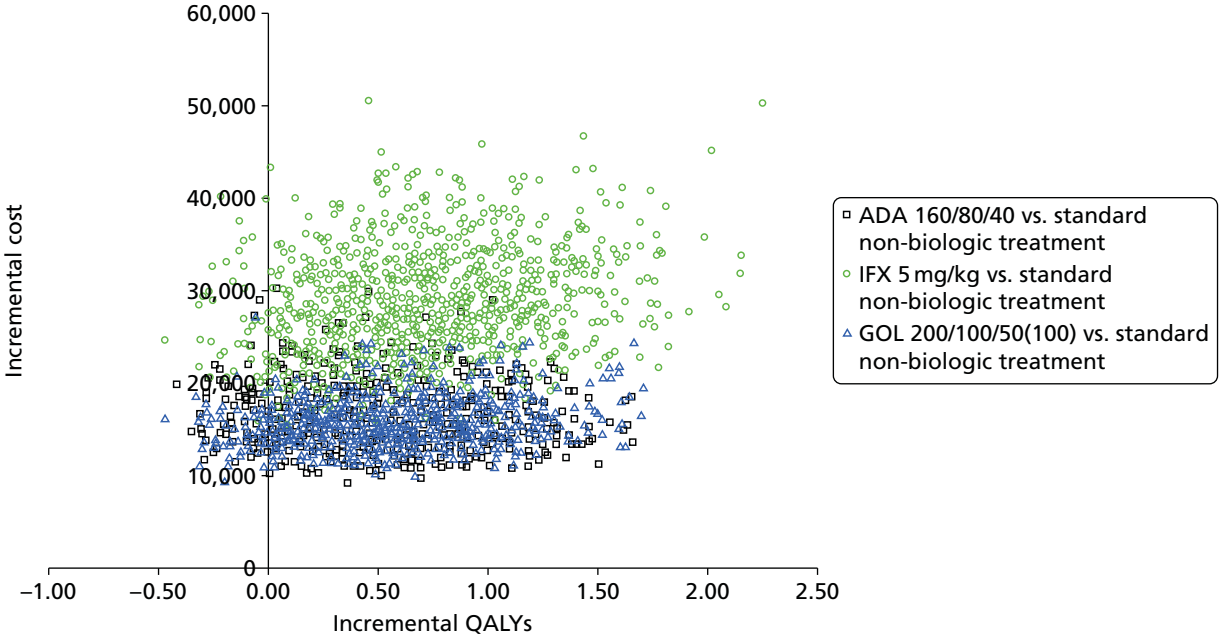

FIGURE 81 Cost-effectiveness plane from MSD model.[64,66] Reproduced with permission.

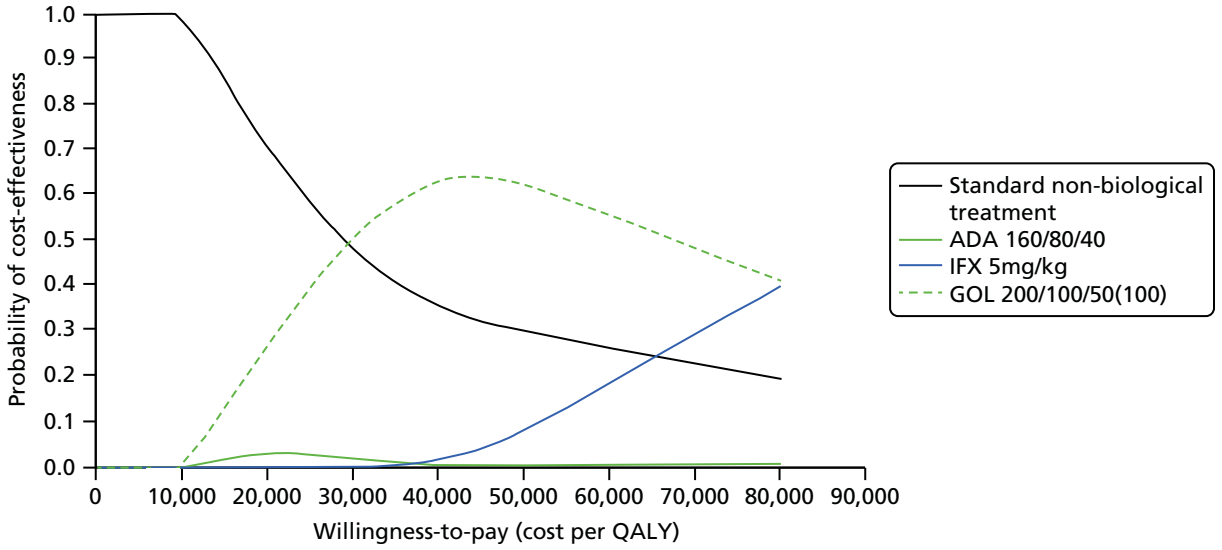

FIGURE 82 Incremental CEACs from MSD model.[64,66] Reproduced with permission.

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A number of deterministic sensitivity analyses are also presented; however, these are difficult to interpret as both IFX and GOL are compared in a pairwise manner against colectomy using incremental QALYs, incremental costs and incremental NMB. Deterministic sensitivity analyses are not presented between competing biological therapies. The deterministic sensitivity analyses indicate that the cost-effectiveness results for GOL versus colectomy are sensitive to the utility values for post-colectomy remission,[66] while the cost-effectiveness results for IFX versus colectomy are sensitive to the utility value for post-colectomy remission.[64]

Critical appraisal of the MSD model

The main issues identified by the Assessment Group are presented in *Box 2*.

Deviations from NICE reference case and final NICE scope

The extent to which the economic analyses reported in the MSD submissions adhere to the NICE reference case is presented in *Table 51*.

Overall, the MSD economic analyses are generally in line with the NICE reference case. However, the analysis does make one important deviation from the final NICE scope with respect to the options included in the economic analysis; non-biological treatment is assumed to be immediate colectomy. Standard clinical management, which is defined in the NICE scope as 'a combination of aminosalicylates (sulfasalazine, mesalazine, balsalazide or olsalazine), corticosteroids (beclomethasone, budesonide, hydrocortisone or prednisolone), and thiopurines (mercaptopurine or AZA), calcineurin inhibitors and surgical intervention',[36] is not included in the MSD model. The omission of non-biological non-surgical treatment options from the MSD model is neither discussed nor justified in the MSD submissions.[64,66]

It is also noteworthy that the MSD model adopts a 10-year time horizon; at this point around 96% of patients in the model are still alive in each treatment group. The MSD submissions state that 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'. The modelled profiles of incremental costs and benefits are slightly different when a longer time horizon is adopted. It is reasonable to suggest that the manufacturer should have examined the impact of using different time horizons within their economic analysis.

BOX 2 Main problems and concerns relating to the MSD model

1. Deviations from the NICE reference case and final NICE scope, particularly with respect to omission of conventional non-surgical management as a comparator.
2. Assumption that treatment failure is equivalent to severe exacerbation.
3. Questionable use of evidence concerning improving and worsening of inflammation.
4. Questionable validity of use of novel methods for including non-randomised data from PURSUIT.
5. Lack of clarity regarding the NMA model.
6. Inconsistencies between results of the MSD GOL and IFX models.
7. Lack of clarity regarding the identification, selection and use of certain model parameters.
8. Complex implementation of the model.
9. Failure to undertake an incremental analysis.
10. Inclusion of a PAS for GOL which has not yet been agreed by the Department of Health.

TABLE 51 Adherence of the MSD model to the NICE reference case[78]

Element of HTA	Reference case	Assessment Group comments
Defining the decision problem	The scope developed by the Institute	The scope of the analysis deviates from the final scope from NICE. Non-biological treatment is assumed to be immediate colectomy. Standard clinical management, defined in the NICE scope as 'a combination of aminosalicylates (sulfasalazine, mesalazine, balsalazide or olsalazine), corticosteroids (beclomethasone, budesonide, hydrocortisone or prednisolone), and thiopurines (mercaptopurine or AZA), calcineurin inhibitors and surgical intervention',[36] is not included as a treatment option within the model
Comparator(s)	As listed in the scope developed by NICE	
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Health outcomes reflect those of patients with UC
Perspective on costs	NHS and PSS	The economic analysis was undertaken from the perspective of the UK NHS. PSS costs are not mentioned in the submission
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	The economic evaluation takes the form of a cost-effectiveness analysis. Analyses are presented as pairwise comparisons rather than a fully incremental economic analysis of all options
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Costs and outcomes are evaluated over a 10-year time horizon. Analyses over a lifetime horizon are not presented in the manufacturers' submission
Synthesis of evidence on health effects	Based on systematic review	Outcomes are synthesised using NMA models using studies identified through a systematic review
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	Health outcomes are reported in terms of life-years gained and QALYs gained
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	All utilities except the disutility for surgery-related complications are based on EQ-5D measurements from UC patients and are valued by the general public
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No equity weighting is applied
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	The economic analysis was undertaken from the perspective of the UK NHS. The sources for prices are not entirely clear
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	The model uses a discount rate of 3.5% for costs and health outcomes

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Assumption that treatment failure is equivalent to severe exacerbation

Related to the issue regarding the lack of conventional drug therapies as the comparator for the economic analysis (see *Deviations from NICE reference case and final NICE scope*), the MSD economic models appear to also confuse the severity of the patient populations and the associated treatment pathway included in the model. Although the scope of the appraisal relates to patients with moderate to severe UC who have failed conventional treatment, the modelled pathway after failure of biological therapy, and the choice of non-biological comparators included in the analysis, appear to relate to a population with more severe disease and no further medical treatment options are considered. The pathway represented by the model after failure of biological therapy (or in its absence) appears to assume that failure to achieve an induction response, or that the loss of response during maintenance therapy, is synonymous with an acute UC exacerbation. As noted by the MSD submissions, surgery for UC is typically indicated for (1) patients with life-threatening complications (e.g. toxic megacolon or colonic perforation); (2) dysplasia or proven cancer; or (3) severe disease characterised by treatment refractoriness, frequent flare-ups, extracolonic manifestations, chronic corticosteroid dependence, side effects/intolerance/complications from medications (in particular corticosteroids), or according to clinical judgement.[64,66] After failing biological treatment, the MSD model assumes that all patients who have failed biological therapy will receive i.v. steroids and rapidly progress to colectomy (27% of all relapsing patients during each 2-month cycle). This fails to reflect the possibility that patients may continue to receive, and may still obtain clinical benefit from, non-biological medical treatment options as defined in the NICE scope (5-ASAs, immunotherapies and/or steroids).

After removing mortality, the MSD model suggests that within 1 year (the approximate duration of the maintenance trials[45,47,49]), 15–20% patients are in the colectomy/post-colectomy health states (*Figure 83*).

This contrasts with the colectomy rates observed within the RCTs included in the systematic review [see *Chapter 3*, *Assessment of effectiveness, Rates of surgical intervention (both elective and emergency)* 0.7% to 5.8% in in individual trial arms at approximately 1 year]. The manufacturer's model also suggests that for patients receiving biological treatments, 59–70% will have undergone surgery within 5 years and 89–93% will have undergone surgery within 10 years (note: the precise values differ by biological treatment group). These rates are very high and fail to reflect both the possibility of benefit from further medical therapies and the element of patient choice in deciding whether or not to undergo colectomy. If surgery really was the only remaining treatment option for these patients, it would not have been possible (or ethical) to undertake any of the trials included in this assessment.

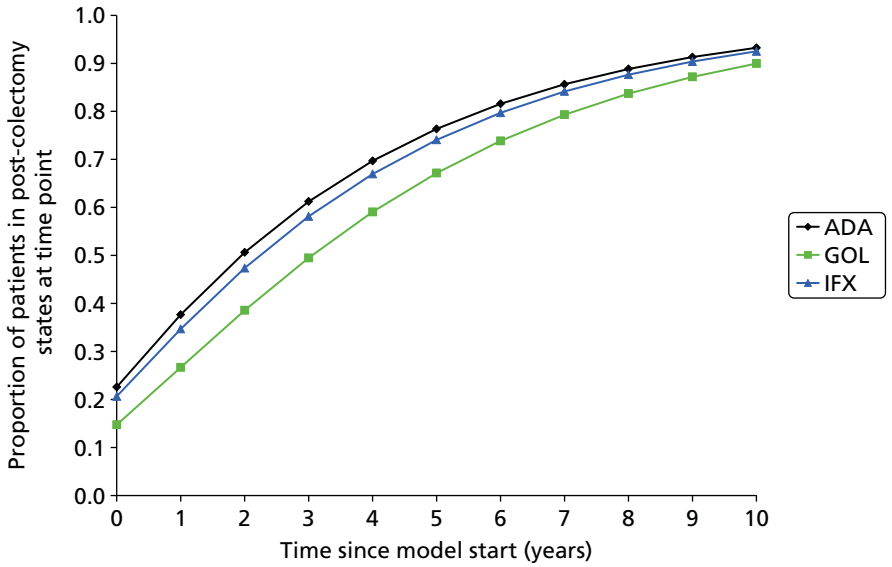

FIGURE 83 Proportion of patients in post-colectomy states over time (excluding mortality).

Further to this point, the study reported by Turner *et al.*,[126] which is used to inform the probability of requiring surgery for active UC, is a systematic review of studies describing the short-term outcome of adult and paediatric patients treated with i.v. corticosteroids, with or without ciclosporin, for exacerbations of UC. Within this published analysis, retrospective and prospective studies evaluating adult or paediatric UC patients admitted for first or subsequent exacerbation, who were severe enough to require i.v. corticosteroid therapy, were included if the short-term outcome and/or analysis of predictors of response were reported. This appears to confuse treatment failure with acute exacerbation of UC. The Assessment Group do not believe that either the narrow choice of remaining viable comparators or the treatment pathways assumed within the MSD models are representative of the clinical management of patients with moderate to severe UC in England and Wales.

Questionable use of evidence concerning improving and worsening of inflammation

The NMA model uses separate models to produce information on the probability of sustained remission and the probability of sustained response. Within the health economic models, the ORs estimated using the NMA models are applied to the probability of remaining in the states of remission and response, respectively. The NMA logistic regression models treat these data as binomial – a patient either stays in their existing state or they do not. However, the data are multinomial – the observed data from the trials indicates that some patients who lost remission transited to response while others transited to no response, and some patients in response subsequently achieved remission, some achieved sustained response and some lost response. The structural assumptions employed within the transition matrix (see *Table 42*) do not reflect this, with some plausible transitions being assigned probabilities of zero. Although this problem is a likely consequence of the limitations of the published data from the ULTRA2 trial,[45] it poorly reflects the characteristics of the actual observed data.

Questionable validity of use of methods for including non-randomised data from PURSUIT

The MSD submissions state that 'PURSUIT used a non-conventional trial design, and thus, conventional NMA techniques would not have sufficed for producing comparative effect estimates between GOL, IFX, and ADA. This NMA employed novel techniques of optimising the use of all available data.'[64,66] This approach was used to 'downgrade' the available evidence for PBO within the PURSUIT maintenance trial as patients randomised to PBO were prior GOL induction responders. Based on the information provided in the manufacturers' submission (see MSD GOL submission,[66] table 13 footnotes and text on pp. 55–7), the Assessment Group was unable to logically follow or replicate the calculations used to generate hypothetical values for the PBO group. However, the Assessment Group does believe that the manufacturer's 'novel' method involves omitting the randomised data and instead uses a manipulation of the non-randomised PBO arm data as an input into the NMA. Such manipulation of observed trial data should be viewed with considerable caution. The Assessment Group believe that it would have been more appropriate to use more established methods of bias adjustment (e.g. the methods adopted by Turner and Spiegelhalter[131]) and/or to use the published ITT data and examine the likely impact of the bias using sensitivity analyses.

Lack of clarity regarding the network meta-analysis model

The NMA model is not reported in detail within either of the MSD submissions and the WinBUGS code was not reported (although this was provided to the Assessment Group during the clarification process). In addition, the baseline model is not described, although the health economic model indicates that baseline probabilities of achieving induction response/remission and maintaining response/remission were derived from 'Average study effect of PBO controlled trials in random effects NMA of induction response'. The appropriateness of these values is unclear.

Inconsistencies between results of the Merck Sharp & Dohme Ltd golimumab and infliximab models

The IFX model and GOL model are based on the same structure and the same decision problem. However the results are different between the models. In response to a request for clarification on the cause of this discrepancy, the manufacturer stated that the two models use different inputs for health utilities; the IFX

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model uses utility data from the ACT1 and ACT2 trials while the GOL model uses utility data from the PURSUIT trial. The IFX model also uses different assumptions about the use of conventional non-biological therapies compared with the GOL model. The justification for using different utility and resource-use assumptions in two models that are attempting to reflect exactly the same decision problem is inappropriate. It should also be noted that when the PURSUIT utility vector and resource-use assumptions were inserted into the IFX model, the results still did not coincide.

Lack of clarity regarding the identification, selection and use of certain model parameters

In several instances, the justification for selecting particular parameter sources is unclear. In particular, the justification of the dosing and frequency of background therapies, and the justification for unit costs is not described within the MSD submissions.[64,66]

Complex implementation of the model

Conceptually, the submitted MSD models are simple Markov models employing eleven health states and four treatment groups. However, the implementation of these models is complex. The model employs 30 worksheets, many of which were locked as read-only. This limited the ability of the Assessment Group to verify the inputs and formulae used in the model.

Failure to undertake an incremental analysis

The MSD submissions do not include an incremental analysis in which each treatment option is compared against its next best non-dominated alternative. Instead, pairwise comparisons are made using NMB given a willingness-to-pay threshold of £30,000 per QALY gained. The IFX submission states that:

> *The ICER for infliximab versus standard non-biologic treatment (colectomy) is £37,682. The positive impact of infliximab in terms of reducing the Burden of Illness and mitigating the Wider Societal Impact of the condition represents additional value for consideration by the committee. Taking into account the shortfall in quality of life, and in the ability of people to contribute to society as a result of their experience with moderately to severely active UC, it is likely that infliximab represents a cost-effective treatment in first-line biologic treatment of UC.*
>
> *MSD. Manufacturer submission of evidence: IFX (Remicade)*[64]

The GOL submission states that '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'.[66]

Importantly, both of these economic conclusions are based on a comparison of biological therapy versus immediate colectomy. A fully incremental analysis is presented in *Tables 49* and *50*. Given the ordering of QALY gains across all treatment options, IFX should be compared against GOL, thus resulting in a considerably higher ICER of approximately £75,000–80,000 per QALY gained (note: the discussion around the discrepancy between model results, see *Inconsistencies between results of the Merck Sharp & Dohme Ltd golimumab and infliximab models*).

Inclusion of a Patient Access Scheme for golimumab which has not yet been agreed by the Department of Health

Both MSD submissions include a PAS in which 100 mg of GOL will be made available at the same price as 50 mg of GOL (see MSD GOL submission,[66] p. 8). However, at the time of this assessment, the proposed PAS had not been agreed with the Department of Health. Although the MSD submissions include a secondary analysis in which the PAS is not included, the absence of fully incremental comparisons by the manufacturer (see *Failure to undertake an incremental analysis*) clouds the correct interpretation of the economic analysis. The amended results of this fully incremental analysis, which excludes the PAS, are shown in *Tables 52* and *53*.

TABLE 52 Model results from GOL submission[66] (excluding PAS)

Treatment	QALYs	Costs (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
Probabilistic model results					
IFX	5.67	44,122.45	0.21	11,911.17	56,268
GOL	5.50	37,306.74	–	–	Extendedly dominated
ADA	5.45	32,211.28	0.53	16,409.68	30,724
Colectomy	4.92	15,801.60	–	–	–
Results based on point estimates of parameters					
IFX	5.65	43,091.60	0.20	11,721.32	57,980
GOL	5.50	36,805.33	–	–	Extendedly dominated
ADA	5.45	31,370.28	0.50	15,576.02	31,069
Colectomy	4.95	15,794.26	–	–	–

TABLE 53 Model results from IFX submission[64] (excluding PAS)

Treatment	QALYs	Costs (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
Probabilistic model results					
IFX	5.68	44,126.44	0.22	11,920.92	53,258
GOL	5.51	37,198.73	–	–	Extendedly dominated
ADA	5.46	32,205.53	0.54	16,445.78	30,428
Colectomy	4.92	15,759.75	–	–	–
Results based on point estimates of parameters					
IFX	5.66	42,919.73	0.21	11,682.36	55,5077
GOL	5.51	36,663.51	–	–	Extendedly dominated
ADA	5.45	31,237.38	0.51	15,447.78	30,319
Colectomy	4.94	15,789.59	–	–	–

The exclusion of the PAS discount for 100 mg of GOL results in a situation whereby ADA is no longer dominated and GOL is ruled out because of extended dominance. Based on this version of the model, the ICER for ADA versus colectomy is approximately £30,000 per QALY gained. The ICER for IFX versus ADA is at best £53,258 per QALY gained.

Adalimumab, golimumab and infliximab, for the treatment of ulcerative colitis (subacute): AbbVie submission[62]

The AbbVie submission details the methods and results of a de novo health economic model developed to assess the cost-effectiveness of ADA versus 'standard of care' (conventional non-biological therapies) for the treatment of moderate to severe UC.

AbbVie model scope

The AbbVie model includes a comparison of two options: (1) ADA and (2) 'standard of care' (standard non-biological therapies) for the treatment of moderate to severe UC from the perspective of the UK NHS. The intervention arm (ADA plus standard non-biological therapies) begins with an induction dose of 160 mg of ADA at week 0, followed by 80 mg of ADA at week 2, and a maintenance dose of 40 mg of

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ADA every other week starting from week 4. At week 8, those patients who achieve remission or response continue to receive ADA, and those patients who have lost response to the initial treatment can dose-escalate to 40 mg of ADA every week. At week 104, patients in the moderate to severe health state are assumed to discontinue ADA and subsequently receive conventional non-biological treatment only. The comparator group within the model comprises conventional non-biological drug treatments (anti-inflammatory drugs or immunosuppressants). Patients without response or remission in either treatment group can progress to colectomy at any time. Surgery is assumed to be reserved for patients who have failed both biological and non-biological drug treatments but is not evaluated as a treatment comparator in the model. Other biological agents used for the treatment of UC (GOL and IFX) are not included in the AbbVie economic analysis.

The economic evaluation takes the form of a cost–utility analysis whereby the primary health economic outcome is the incremental cost per QALY gained over a 10-year time horizon. The base-case population considered relates to patients with moderate to severe UC who are have not previously been exposed to anti-TNF-α therapy and those who have previously been exposed to anti-TNF-α therapy (excluding ADA). Patients who are naive to anti-TNF-α agents were evaluated as a secondary sensitivity analysis. Patients are assumed to have a mean body mass of 75 kg and the starting age of patients entering the model is unclear in both the submission and the model. Costs and health outcomes are discounted at 3.5%. Costs were valued at 2013 prices.

AbbVie model structure

The model adopts a Markov approach using a 2-week cycle length (*Figure 84*). The model includes a total of 11 health states: three pre-surgery states for ADA, three pre-surgery states for conventional treatments, one surgery state and four post-surgery states. These states are: (1) mild (ADA); (2) remission (ADA); (3) moderate to severe (ADA); (4) mild (conventional treatment); (5) remission (conventional treatment); (6) moderate to severe (conventional treatment); (7) surgery; (8) post surgery without complications; (9) transient complications; (10) chronic complications; and (11) surgery-related death.

The three pre-surgery health states (remission, mild, and moderate to severe disease states) were defined using the Mayo scoring system (or partial Mayo scores if full Mayo scores were not available).

The model comprises two treatment phases: (1) an induction phase; and (2) a maintenance phase. The induction phase relates to the first 8 weeks of treatment, in line with recommendations from the EMA.[132] For the ADA group, patients who are in the remission or mild disease states at this time point are assumed to continue to receive ADA into the maintenance period (8–52 weeks). At the end of week 8, patients in the moderate to severe disease state are assumed to be non-responders to ADA; these patients

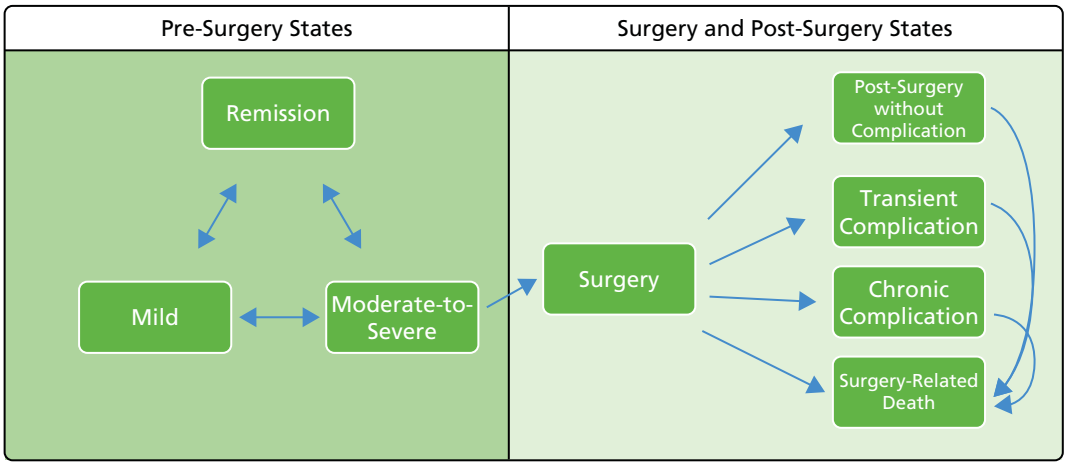

FIGURE 84 AbbVie model structure.[62] Reproduced with permission.

discontinue treatment with ADA and subsequently receive conventional non-biological therapy. Between week 8 and week 104, patients who have previously achieved remission or response but subsequently lost that response or remission are assumed to either discontinue ADA treatment or to dose escalate to 40 mg of ADA every week. Within the conventional management group, patients transit between the conventional management health states without entering the biological states.

For both the ADA and the conventional management groups, only patients in the moderate to severe health state are allowed to transit to surgery. Surgery is treated as a tunnel state, whereby patients can remain in that state for one cycle only. Patients can transit between the 'transient complication' state and 'post-surgery without complication' state during any cycle. Patients experiencing chronic complications are assumed to remain in that state until the time horizon has been exhausted. Patients undergoing surgery are assumed to be at an increased risk of death. Other-cause mortality is not included in the model. All patients enter the model in the pre-surgery moderate to severe state, in line with the inclusion criteria for the ULTRA2 trial.[45] A half-cycle correction was applied to costs and QALYs. The main driver of health benefits within the model relates to HRQoL benefits associated with increased sojourn time in the pre-surgical health states.

Serious and severe AEs were not considered in the AbbVie model; the manufacturers' submission notes that most AEs experienced by patients in the ULTRA2 trial[45] were non-serious and considered to be unrelated to the study drugs.[62] In addition, the manufacturer highlights that the ULTRA2 trial reported slightly higher incidences of serious and severe AEs in the PBO arm than in the ADA arm of the trial; therefore, considering serious and severe AEs in the model would have increased medical costs and reduced health gains within the conventional management group.[62] Therefore, the exclusion of these events represents a conservative assumption.

The model includes the costs associated with drug acquisition, medical costs related to disease states, hospitalisation, surgery, surgery-related complications and costs associated with surgery-related death.

The model uses simple matrix multiplication to determine health state populations during each model cycle based on the state population in the previous Markov cycle and a series of time-dependent transition matrices. Costs and utilities are attached to each health state. Total QALYs are modelled as a function of sojourn time in each health state, together with an indirect survival benefit for ADA as a consequence of reduced rates of surgery (and hence surgical-related mortality) for this group.

Evidence used to inform the model parameters

A summary of evidence sources used to inform the main groups of parameters within the model is presented in *Table 54*.

Methods for modelling effectiveness

For the most part, estimates of baseline and relative effectiveness were taken from the ULTRA2 study and the ULTRA1/2 extension study,[45,62,126] although other literature was used to inform transitions that were not observed within these studies.[121,133] Efficacy data on response/remission from the ULTRA1 trial were not used in the AbbVie model. Transition probabilities between pre-surgery health states were calculated using trial data from ULTRA2[45,126] for weeks 8–104 while transitions between states for cycles from week 104 to 520 were based on data from the ULTRA1/2 extension study[62] for ADA and ULTRA2[45,126] for conventional management. Discontinuations owing to other reasons, such as AEs, were also considered based on trial data.

Four matrices of time-dependent transition probabilities are used within the AbbVie model, according to four time intervals; these are described below.

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TABLE 54 Summary table of evidence sources used to inform the AbbVie model parameters

Parameter group	Source
Transition probabilities: pre-surgical states	ULTRA2 trial[45,126] and ULTRA1/2 extension study[62] and other literature[121,133] with the cycle length of matrix probabilities adjusted using Eigenvalue decomposition
Transition probabilities: rate of surgery	Hillson *et al.*[134]
Transition probabilities: post-surgery complications and surgery related-mortality	Transition complications rates estimated from Swenson *et al.*[115] Chronic complication rates estimated using studies by Johnson *et al.*[135] (fertility), Kruasz andDuek[136] (male impotence) and Abdelrazeq *et al.*[137] (chronic pouchitis). Perioperative and post-operative mortality risks were estimated using a study reported by Roberts *et al.*[138]
Health utilities for pre-colectomy response/remission	EQ-5D study published as a poster by Swinburn *et al.*[139]
Health utilities for post-colectomy states	Utility values for postsurgery without complication and transient complication based on estimates reported by Tsai *et al.*[82] Utility values for chronic complications based on Arseneau *et al.*,[110] Hu *et al.*[140] and Smith and Roberts[141]
Resource use	ADA dosing and dose escalation based on SmPC and experience within the ULTRA2 trial.[45,126] Use of conventional non-biological treatments was based on UC-related medication usage rates for all subjects at baseline, as observed in the ULTRA 2trial.[45,126] Disease state resource use was based on the estimates reported by Tsai *et al.*[82] Rates of hospitalisation were based on a mixed effects regression analysis of ULTRA1 and ULTRA2 trial data[62]
Unit costs	Drug acquisition costs (biologicals and conventional treatments) were taken from the MIMS.[142] Hospitalisation costs were based on NHS Reference Costs[130] Other unit costs derived from literature[82,115,143]

MIMS, Monthly Index of Medical Specialities.

Transition probabilities: adalimumab group

Period 1 (weeks 0–8)

In the induction period, transitions from the moderate to severe state were based on the ADA arm of the ULTRA2 trial.[45,126] As ULTRA2 did not recruit patients with prior response or remission (because it was an induction trial), this study cannot provide information relating to transitions from these states to other states within the first 8-week period. Instead, the probabilities of maintaining remission and response were based on studies reported by Kane *et al.*[133] (assuming the probability of maintaining remission reflects that of 'adherent patients') and Odes *et al.*[121] A constant hazard was assumed to obtain the 8-week probability in both cases.

Period 2 (weeks 8–52)

Transition probabilities were based on a cross-tabulation of data on the number of patients in each health state from the ADA arm of the ULTRA2 trial.[45,126]

Period 3 (weeks 52–104)

Data from the ULTRA1 and ULTRA2 extension study[62] were used to derive transition probabilities for the three pre-surgery health states. As patients in the moderate to severe state within the ADA group of the model are assumed to discontinue biological treatment, only those patients who were randomised to the ADA arm and who had remission or mild disease at week 8 in the ULTRA1/2 extension study[62] were included in the analysis.

Period 4 (weeks 104–260)

Data from week 48 to week 144 of the ULTRA1/2 extension study[62] were used to generate the transition matrix. A multinomial logit regression model was constructed to estimate the transition matrix during each 48-week interval. The dependent variables were the three pre-surgery health states and the independent variables were the health states in the previous visit. The logit model estimates mean predicted probabilities of being in one of the health states given a specific health state at the previous visit.

These four transition matrices were then converted to 2-week probabilities using Eigenvalue matrix decomposition methods reported by Craig and Sendi.[144] The resulting matrices are shown in *Table 55*.

Transition probabilities: conventional management group

Period 1 (weeks 0–8)

In the induction period, transitions from the moderate to severe state were based on the PBO group outcomes within the ULTRA2 trial.[45] As with the ADA matrix for the induction period, estimates of maintaining remission and response were based on studies reported by Kane *et al.*[133] (assuming the probability of maintaining remission reflects that of 'non-adherent patients') and Odes *et al.*[121] A constant hazard was assumed to obtain the 8-week probability in both cases.

TABLE 55 Adalimumab group: 2-week transition probabilities for pre-surgery states by time interval

	To state			
From state	Remission	Mild	Moderate to severe	Surgery
From week 0–8				
Remission	0.9974	0.0007	0.0019	–
Mild	0.0003	0.9981	0.0016	–
Moderate to severe	0.0551	0.0986	0.8432	0.0031
From week 8–52				
Remission	0.9700	0.0164	0.0136	–
Mild	0.0349	0.9400	0.0251	–
Moderate to severe	0.0001	0.0215	0.9753	0.0031
From week 52–104				
Remission	0.9889	0.0000	0.0111	–
Mild	0.0178	0.9436	0.0385	–
Moderate to severe	0.0275	0.0217	0.9477	0.0031
Week 104 onward				
Remission	0.9949	0.0047	0.0004[a]	–
Mild	0.0113	0.9869	0.0018[a]	–
Moderate to severe	0.0037	0.0019	0.9463[a]	0.0031

a A total of 4.54% of patients reaching the moderate to severe disease state after week 104 discontinue ADA treatment and subsequently receive conventional treatment.

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Period 2 (weeks 8–52)

Transition probabilities were based on a cross-tabulation of data on the number of patients in each health state from the PBO arm of the ULTRA2 trial.[45,126]

Periods 3 and 4 (weeks 52–260)

Transition probabilities for each cycle were assumed to reflect those estimated for period 2 (weeks 8–52).

As with the ADA group, these four transition matrices were then converted to 2-week probabilities using Eigen matrix decomposition methods reported by Craig and Sendi.[144] The resulting matrices are shown in *Table 56*.

Transitions between surgery and post-surgical states

Transitions between surgery and post-surgical health states were based on the literature rather than the clinical studies of ADA. Complication rates were estimated from a study reported by Swenson *et al.*[115] Chronic complication rates were estimated using studies by Johnson *et al.*[135] (fertility), Kruasz and Duek[136] (male impotence) and Abdelrazeq *et al.*[137] (chronic pouchitis). Perioperative and post-operative mortality risks were estimated using a study reported by Roberts *et al.*[138] taking account of background mortality rates. The underlying transition rates are assumed to be time independent. The resulting matrix is shown in *Table 57*.

TABLE 56 Conventional management group: 2-week transition probabilities for pre-surgery states by time interval

	To state			
From state	Remission	Mild	Moderate to severe	Surgery
From week 0–8				
Remission	0.9799	0.0044	0.0157	–
Mild	0.0013	0.9844	0.0143	–
Moderate to severe	0.0291	0.0882	0.8796	0.0031
From week 8–52 (and subsequent cycles)				
Remission	0.9696	0.0028	0.0276	–
Mild	0.0170	0.9217	0.0613	–
Moderate to severe	0.0017	0.0074	0.9878	0.0031

TABLE 57 Transition matrix for surgery and post-surgical states (all time periods, both treatment groups)

	To state				
From state	Surgery	Post-surgery without complication	Transient complication	Chronic complication	Death
Surgery	0.0000	0.7708	0.0101	0.1919	0.0272
Post-surgery without complication	0.0000	0.9893	0.0101	0.0000	0.0006
Transient complication	0.0000	0.9994	0.0000	0.0000	0.0006
Chronic complication	0.0000	0.0000	0.0000	0.9994	0.0006
Death	0.0000	0.0000	0.0000	0.0000	1.0000

Health-related quality of life

Table 58 reports the HRQoL values used in the AbbVie model and their sources.

The AbbVie submission argues that although it would have been possible to map SF-6D utility estimates from the ULTRA2 trial onto the EQ-5D, this is likely to overestimate the level of HRQoL of patients with more severe disease. Health utilities for the pre-surgery states were instead sourced from an EQ-5D study of 230 patients with UC reported by Swinburn *et al.*[139] This study has been published in abstract form only; however, further details are provided in appendix 3 of the AbbVie submission.[62] Utility values for the states of post surgery without complications and post surgery with transient complications were taken from Tsai *et al.*[82] The utility for the chronic complication state was estimated by using a weighted value of rates and HRQoL impacts of chronic pouchitis (Arseneau *et al.*[110]), infertility (Hu *et al.*[140] and male sexual dysfunction (Smith and Roberts[141]).

Resource use and costs

Table 59 summarises the values of the resource use and cost parameters used in the AbbVie model.

Drug acquisition costs (adalimumab and conventional management)

Usage of ADA was based on its licensed indication[132] together with estimates of relative dose intensity for dose escalating patients based on the primary analysis of data from the ULTRA2 trial[45] and the ULTRA1/2 extension study.[62] The use of conventional non-biological therapies was assumed to reflect the baseline usage of these therapies within the ULTRA2 trial.[45,126] The drug acquisition costs for ADA and conventional non-biological therapies were obtained from the Monthly Index of Medical Specialities (MIMS) database.[142]

TABLE 58 Health utilities assumed in the AbbVie model[62]

Disease State	Utility	Source
Remission	0.91	Swinburn *et al.*[139]
Mild	0.80	Swinburn *et al.*[139]
Moderate to severe	0.55	Swinburn *et al.*[139]
Surgery	0.55	Assumed to same as moderate to severe state
Post-surgery without complication	0.61	Tsai *et al.*[82]
Transient complication	0.55	Tsai *et al.*[82]
Chronic complication	0.43	Weighted mean of Arseneau *et al.*,[110] Hu *et al.*[140] and Smith and Roberts[141]

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TABLE 59 Drug resource cost parameters used in the AbbVie model

Parameters[a]	Parameter values	Sources
ADA dose escalation: increased dose intensity compared with 40 mg EOW		
Week 8–52 maintenance phase	7.40%	Primary analysis of ULTRA2[45] and ULTRA1 and ULTRA2 extension study[62]
Week 52–104 maintenance phase	24.06%	
Beyond week 104 maintenance phase	21.49%	
Use of conventional therapies		
Mesalazine	47.0%	Based on baseline usage in ULTRA2[45,126]
Sulfasalazine	7.3%	
Balsalazide	5.9%	
Olsalazine	0.2%	
AZA	28.3%	
Mercaptopurine	6.7%	
Drug acquisition costs		
ADA unit price (40 mg)	£352.14	MIMS (March 2014)
Mesalazine	£20.59	MIMS (March 2014)
Sulfasalazine	£2.93	
Balsalazide	£13.10	
Olsalazine	£9.88	
AZA	£2.89	
Mercaptopurine	£105.99	
Total weighted conventional therapy cost per 2-week cycle	£18.60	

EOW, every other week; MIMS, Monthly Index of Medical Specialities.
a Assumptions regarding specific products, doses, frequency and price are not clear from the AbbVie submission.

Health state resource costs

Other UC health state costs assumed in the AbbVie model are summarised in *Table 60*.

The frequency of hospitalisations per 2-week cycle was estimated according to treatment arm and disease severity using mixed effects regression on pooled data from the ULTRA1 and ULTRA2 trials.[44,126] Other disease state resource use (consultant visits, blood tests and emergency/elective endoscopies) were taken from Tsai *et al.*[82] and uplifted to current prices.[128] Hospitalisation and post-surgery terminal care costs were obtained from NHS Reference Costs 2012/13.[130] The costs of surgery and managing complications were taken from Buchanan *et al.*[143] and Swenson *et al.*[115]

Model evaluation and uncertainty analysis

The results of the AbbVie economic analysis are presented as an ICER; this is based on the point estimates of parameters rather than the expectation of the mean. Uncertainty surrounding incremental costs and outcomes was examined using deterministic sensitivity analyses and PSA. The PSA was undertaken over 1000 Monte Carlo samples. The results of the deterministic analyses are presented as tornado diagrams while the results of the PSA are presented as cost-effectiveness planes and CEACs.

TABLE 60 Other health state costs used in the AbbVie model

Parameters	Values	Sources
Hospitalisations per 2-week cycle		
Remission: ADA	0.0008	Mixed effects regression analysis of ULTRA1 and ULTRA2 trial data[44,126]
Mild: ADA	0.0013	
Moderate to severe: ADA	0.0042	
Remission: conventional management	0.0017	
Mild: conventional management	0.0029	
Moderate to severe: conventional management	0.0094	
Hospitalisation costs		
Cost per hospitalisation	£3533	NHS Reference Costs 2012/13[130] (Major Gastrointestinal Disorders with CC score 0, elective inpatient, PA25B)
Pre-surgery disease state costs (excluding hospitalisation) per 2-week cycle		
Remission	£20.31	Derived using Tsai *et al.*[82] Includes blood tests, consultation visits, and endoscopies
Mild	£67.87	
Moderate to severe	£203.27	
Post-surgery disease state costs per 2-week cycle		
Surgery	£13,071	Based on Buchanan *et al.*[143] and inflated to 2013 prices
Postsurgery without complication	£118.63	Derived using Tsai *et al.*[82] including blood tests, consultation visits, and endoscopies No hospitalisations were considered for post-surgery without complication
Transient complication	£8826.05	Based on Swenson *et al.*,[115] inflated and exchange-rate adjusted to 2013 prices
Chronic complication	£118.63	Assumed to be the same as postsurgery without complication
Terminal care	£3533	NHS Reference Costs 2012/13[130] (Major Gastrointestinal Disorders with CC score 0, elective inpatient, PA25B)

AbbVie model results

Tables 61 and *62* present the results of the AbbVie model for the base-case analysis and the secondary analysis of the subgroup of patients who are anti-TNF-α naive. Note that the probabilistic ICERs presented in these tables have been generated by the Assessment Group.

The base-case analysis of the model indicates that over a 10-year time horizon, ADA is expected to generate an additional 0.73 QALYs at an incremental cost of £25,335 per patient. This leads to an ICER of £34,590 per QALY gained. The results of the model based on the point estimates of parameters are very similar to those produced using the probabilistic model.

The deterministic subgroup analysis of anti-TNF-α-naive patients indicates that over a 10-year time horizon, ADA is expected to generate an additional 0.87 QALYs at an incremental cost of £31,140 per patient. This leads to an ICER of £35,970 per QALY gained. It was not possible to generate probabilistic estimates for the subgroup analysis as the subgroup model does not include a PSA subroutine.

Figures 85 and *86* present the cost-effectiveness plane and CEACs for the base-case analysis.

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TABLE 61 Model results obtained from the AbbVie model: base-case analysis

Treatment	QALYs	Costs	Incremental QALYs	Incremental costs	ICER
Probabilistic model results[a]					
ADA	Treatment-specific costs and QALYs not stored in PSA subroutine		0.73	£25,335	£34,590
Conventional management			–	–	
Results based on point estimates of parameters					
ADA	5.73	£76,392	0.74	£25,446	£34,417
Conventional management	4.99	£50,946	–	–	

a Generated by the Assessment Group.

TABLE 62 Model results obtained from the AbbVie model: anti-TNF-α-naive subgroup

Treatment	QALYs	Costs	Incremental QALYs	Incremental costs	ICER
Probabilistic model results[a]					
ADA	Subgroup model does not allow for PSA				
Conventional management					
Results based on point estimates of parameters					
ADA	6.00	£79,799	0.87	£31,140	£35,970
Conventional management	5.140	£48,659	–	–	

a Generated by the Assessment Group.

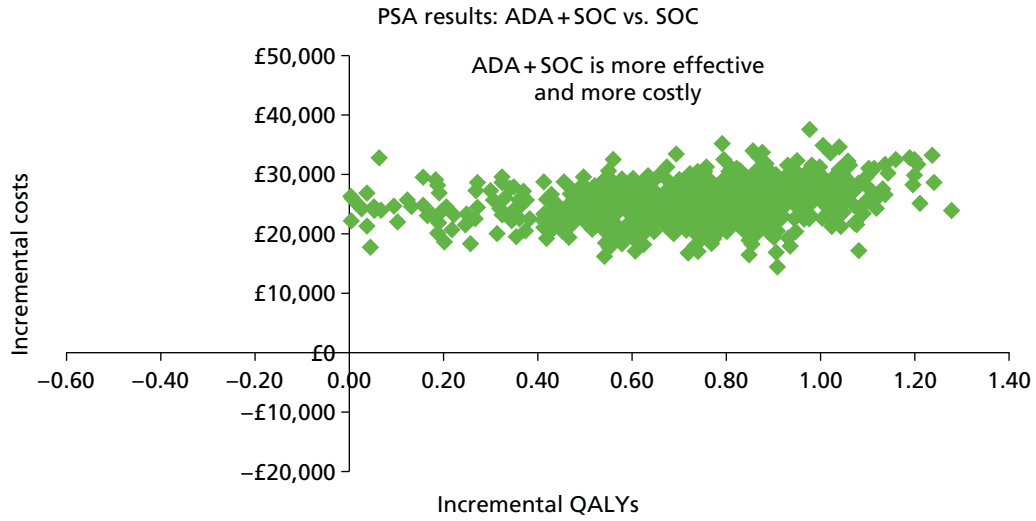

FIGURE 85 Cost-effectiveness plane reported by AbbVie: base-case analysis.[62] Reproduced with permission.

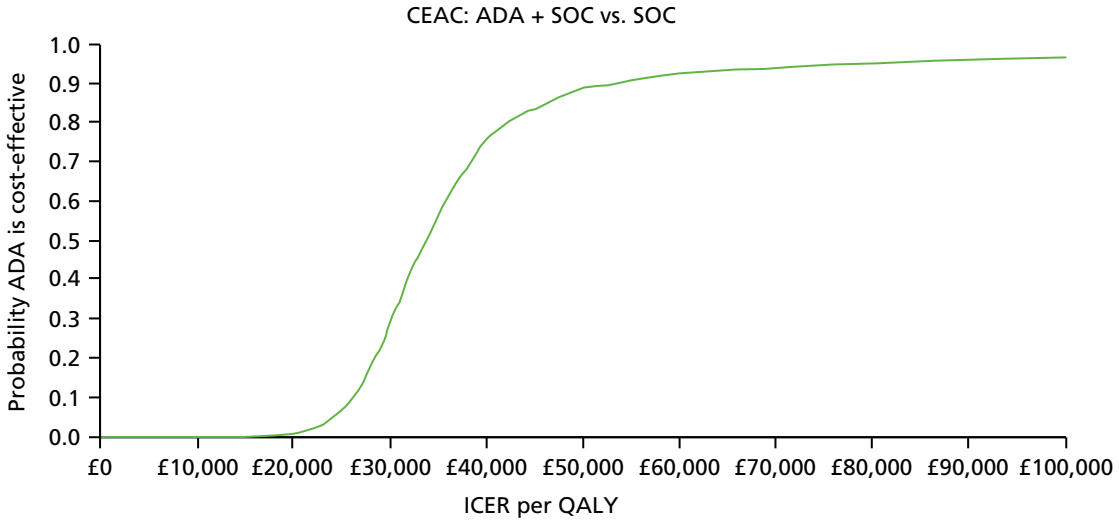

FIGURE 86 Cost-effectiveness acceptability curve reported by AbbVie: base-case analysis. Adapted from AbbVie submission.[62]

The cost-effectiveness plane indicates that ADA is consistently expected to be more effective and more expensive than conventional management. Assuming a willingness-to-pay threshold of £20,000 per QALY gained, the probability that ADA produces more net benefit than conventional management is approximately 0.01. Assuming a willingness-to-pay threshold of £30,000 per QALY gained, the probability that ADA produces more net benefit than conventional management is approximately 0.30.

The deterministic sensitivity analysis undertaken by the manufacturer indicate that the model is most sensitive to assumptions concerning disease state costs and the health state utilities. Given the narrow scope of the AbbVie economic analysis, the cost-effectiveness of ADA compared with other biological therapies or surgery is unknown.

Critical appraisal of the AbbVie model

The main issues identified by the Assessment Group are presented in *Box 3* and discussed below.

Deviations from NICE reference case and final NICE scope

The extent to which the economic analyses reported in the AbbVie submissions adhere to the NICE reference case is presented in *Table 63*.

Overall, the economic analysis undertaken by AbbVie is generally in line with the NICE reference case. However, similar to the MSD submissions,[64,66] the two most notable concerns relate to the choice of comparators and the adoption of a short model time horizon (10 years).

BOX 3 Main problems and concerns relating to the AbbVie model

1. Deviations from the NICE reference case and final NICE scope, particularly with respect to omission of other biologicals and surgery as comparators.
2. Questionable choice of cycle length necessitating the use of other external evidence on transition probabilities, which should not be required.
3. Concerns regarding the selection and use of evidence to inform HRQoL parameters.
4. Questionable source of surgery rate.

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TABLE 63 Adherence of the AbbVie model to the NICE reference case[78]

Element of HTA	Reference case	Assessment Group comments
Defining the decision problem	The scope developed by the institute (NICE)	The scope of the analysis deviates from the final scope from NICE
Comparator(s)	As listed in the scope developed by NICE	The comparator is limited to 'standard of care' (conventional non-biological therapies) only. The model does not include other biological agents (IFX and GOL) included in the final NICE scope. The model does not include surgery as a comparator
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Health outcomes reflect those of patients with UC
Perspective on costs	NHS and PSS	The economic analysis was undertaken from the perspective of the UK NHS. PSS costs are not mentioned in the submission
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	The economic analysis takes the form of a cost–utility analysis of the two included options
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Costs and outcomes are evaluated over a 10-year time horizon. Analyses over a lifetime horizon are not presented in the manufacturers' submission nor are they possible within the implemented model structure
Synthesis of evidence on health effects	Based on systematic review	Although the submission mentions other relevant trials of IFX and GOL, the manufacturer opted to undertake a 'within-trial' analysis of ADA vs. conventional management using efficacy data from the ULTRA2 trial[45,126] only
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults	Health effects are assessed in terms of QALYs. The EQ-5D has been used to assign specific utility values for health states, but weighted averages from other instruments (i.e. TTO) have also been used to value the post-surgery chronic complications health state
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	It would have been possible to map from the SF-6D in the ULTRA2 trial[45,126] to the EQ-5D. Instead, the manufacturer used data from Swinburn *et al.*[139] to value pre-surgery states
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No equity weighting is applied
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	The economic analysis was undertaken from the perspective of the UK NHS
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	The model uses a discount rate of 3.5% for costs and health outcomes

The AbbVie economic analysis includes only two treatment options: (1) ADA; and (2) conventional non-biological treatments. The analysis excludes other relevant biological therapies for the treatment of UC (IFX and GOL) and elective surgery. The appendix to the main submission states that:

> *Other anti-TNF therapies which are being appraised as part of this NICE MTA, namely infliximab and golimumab, were not considered as comparators in the present evaluation as they are not NICE recommended for this patient population and therefore would not form routine standard of care at present.*
>
> *AbbVie submission to NICE*[62]

However, IFX and GOL were listed in the final NICE scope and hence they should have been included in the economic analysis. As a consequence of their omission, the AbbVie model adopts a very narrow scope and provides no information regarding the comparative cost-effectiveness of the full range of biological treatment options within this appraisal.

The main submission from AbbVie states a number of arguments regarding why it would not be appropriate to undertake a formal NMA (see AbbVie submission,[62] pp. 67–8). The main arguments stated are:

- Differences in Mayo score estimation between the relevant trials.
- PBO responses have been shown to differ markedly depending on the severity of the trial population, study design and country or region in which the trial was conducted.
- Other differences in trial design, that is, the use of adaptive design in the PURSUIT trial,[47] differences in time points for the assessment of induction response, eligibility criteria relating to prior treatment failures, prior use of biologicals, steroid tapering, open-label escape allowance, timing of efficacy assessments and study durations.

However the Assessment Group do not agree that a NMA is inappropriate and AbbVie's justifications for not undertaking such an analysis appear to be flawed. Notably, UC is a chronic disease characterised by ongoing inflammation over time; fluctuations in Mayo score evaluations over the course of 3 days are likely to be minor and hence the use of alternative scoring systems between trials is unlikely to produce any substantial bias. Furthermore, no two trials are identical. Although it is useful to highlight potential sources of heterogeneity between studies (and this is done well by AbbVie), the Assessment Group does not believe that the presence of this heterogeneity provides a sufficient basis for ignoring treatment options relevant to the decision problem.

In addition, the AbbVie model explicitly excludes elective colectomy as a comparator from the analysis. The appendix to the main AbbVie submission states that:

> *Surgery is an important treatment option in UC clinical management and is reserved for patients who have an inadequate response with, are contraindicated to or intolerant of conventional standard of care. Surgery is unlikely to be a first line option for moderately to severely active UC patients. Consistent with this approach, surgery is included in the model as the treatment option for a proportion of patients who failed SOC or ADA+SOC treatment, but not as a comparator to ADA+SOC.*
>
> *AbbVie submission to NICE*[62]

As this option was specified in the final agreed NICE scope, and because the appraisal does not relate to first-line treatment, it should have been included in the economic analysis.

It should also be noted that the AbbVie model time horizon is constrained to 10 years (260 2-week cycles). This shorter time horizon is used as a justification for excluding other-cause mortality from the model. The model does not include the functionality to consider longer time horizons; it is unclear whether or not the profiles of incremental costs and health outcomes for ADA versus conventional management would be similar over longer time horizons.

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Questionable choice of cycle length necessitating the use of other evidence on transition probabilities

The cycle length adopted within the AbbVie model is 2 weeks. This short cycle length was selected 'to accommodate the ADA dosing schedule.'[62] Given that all patients enter the model in the 'moderate to severe' health state in line with the ULTRA2 trial, this choice of cycle length leads to a necessity to incorporate data from other literature[121,133] to populate the transition probabilities from the 'mild' and 'remission' health states to other health states. As a consequence, there is some discrepancy between the observed pre-surgery health state distribution following induction in the ULTRA2 trial[45,126] and the pre-surgery health state distribution following induction estimated by the model (*Table 64*). Given a longer cycle length for induction, that is the 6 weeks used in the trial, it would have been unnecessary to include other data on transition probabilities and the predictions of the model would have likely been more accurate.

Concerns regarding the selection and use of evidence to inform health-related quality-of-life parameters

The ULTRA2 trial[45,126] did not collect HRQoL data from patients using the EQ-5D; however, the SF-36 instrument was included and could be used to derive SF-6D utility values. The manufacturer explored mapping the SF-6D values to the EQ-5D but noted that this would likely overestimate the level of HRQoL of patients with more severe disease. Instead, the manufacturer used data from Swinburn *et al.*[139] to value the pre-surgery health states in the model. Although the Swinburn *et al.*[139] study has been published only in abstract and poster form, more detail is provided in appendix 3 of the main AbbVie submission.[62] It is noteworthy that the difference in utility for the post-surgery state and the active UC state in the selected utility values within the AbbVie model (0.61–0.55 = 0.06) is smaller than that observed within other EQ-5D UC valuation studies (e.g. Woehl *et al.*[145] estimated this difference to be approximately 0.71 – 0.41 = 0.30). Therefore, the AbbVie model does not assume that surgery results in a substantial increase in HRQoL in patients with active disease.

It is also noteworthy that the choices made with respect to the HRQoL values for other post-surgery health states are not clear from the submission. In particular, the methods for identifying and selecting studies to value the chronic complications,[110,140,141] and the weightings given to each, are unclear from the AbbVie submission.[62] What is clear is that the three valuation studies used to inform the chronic complications utility values used different health instruments; Hu *et al.*[140] is based on committee valuations using the Health Utility Index, Arseneau *et al.*[110] reported TTO valuations by UC patients and Smith and Roberts[141] report TTO and VAS valuations. Producing a weighted mean utility from studies that use different elicitation methods may produce conceptually inconsistent rankings of identical health states. However, this parameter does not have a material impact on the ICER.

TABLE 64 Comparison of observed and predicted induction outcomes

Treatment group	No response	Response	Remission
ADA group (observed)	0.52	0.33	0.16
ADA group (predicted)	0.51	0.31	0.17
Discrepancy in ADA group (observed – predicted)	0.01	0.02	–0.01
PBO group (observed)	0.67	0.24	0.09
PBO group (predicted)	0.61	0.29	0.09
Discrepancy in PBO group (observed – predicted)	0.07	–0.05	–0.01

Questionable source of surgery rate

The AbbVie model estimates the 2-week probability of undergoing surgery from a 1-year study reported by Hillson *et al.*[134] This study was a retrospective analysis of medical claims with and without UC identified from a population of approximately 500,000 employees, retirees and dependants in the USA. This does not specifically relate to a moderate to severe UC population and the use of a 1-year study to estimate long-term risk is concerning, particularly given the availability of other longer studies undertaken in more relevant UC populations (see *Evidence used to inform the model's parameters*).

De novo Assessment Group model

Introduction

In light of the limitations of the models submitted by the manufacturers (see *Systematic review of existing cost-effectiveness evidence*), the Assessment Group developed a de novo health economic model to assess the cost-effectiveness of second-line IFX, ADA and GOL, conventional non-biological therapies and immediate colectomy for the treatment of patients with moderate to severe UC.

Methods

Model scope

The scope of the economic analysis follows the NICE reference case (summarised in *Box 4*).

The analysis compares IFX, ADA and GOL against each other and against conventional non-biological therapy (comprising a mix of 5-ASAs, immunosuppressants and corticosteroids) and immediate colectomy. IFX is assumed to be given at a dose of 5 mg/kg on three visits during induction and subsequently at a dose of 5 mg/kg every 8 weeks for patients who go on to receive maintenance therapy. ADA is assumed to be given at one dose of 160 mg, one dose of 80 mg and two doses of 40 mg during the induction phase; a dose of 40 mg every other week is assumed for patients who go on to receive maintenance therapy. A fixed proportion of ADA patients (27%) are assumed to escalate to a 40 mg every week dosing regimen, based on data reported in the AbbVie submission.[62] GOL is assumed to be given as one dose of 200 mg and one dose of 100 mg during induction treatment, with subsequent maintenance therapy given

BOX 4 Scope of the Assessment Group economic analysis

Population: patients with moderate to severe UC who have failed at least one prior therapy.[a]

Interventions and comparators: 160 mg/80 mg/40 mg of ADA; 5 mg/kg of IFX; 200 mg/100 mg/100 mg (50 mg) of GOL; conventional non-biological therapy (comprising a mix of 5-ASAs, immunosuppressants and corticosteroids); and elective surgery.

Economic outcome: incremental cost per QALY gained.

Perspective: NHS and PSS.

Time horizon: lifetime.

Discount rate: 3.5%.

a The base-case analysis relates to an adult UC population; a secondary analysis is considered for the paediatric population.

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at a dose of 100 mg every 4 weeks for patients with body mass ≥ 80 kg or 50 mg every 4 weeks for patients with body mass < 80 kg. IFX is assumed to be administered in a day-case setting while the administration of GOL and ADA is not assumed to require any additional NHS resources (no costs are included for training patients to self-inject). Patients in the non-surgical treatment groups are assumed to receive conventional background therapies (5-ASAs, immunosuppressants and corticosteroids). Surgery is included in the economic analysis both as a comparator within the analysis and also as a downstream component of the pathway for patients in the biological and non-biological treatment groups.

The population within the economic analysis relates specifically to patients with moderate to severe UC who have failed at least one prior therapy, as reflected in the RCTs included in the systematic review of clinical effectiveness (see *Chapter 3*). Patient characteristics are based on the trials included in the systematic review.[44,47–49,126] Patients are assumed to enter the model aged 40 years with a mean body mass of 77 kg. Thirty two per cent of patients are assumed to have a body mass > 80 kg. Although the main economic analysis relates to adult patients with UC, a scenario analysis is also presented which compares IFX with conventional drug treatment and immediate colectomy in paediatric patients with UC (note: GOL and ADA do not currently have marketing authorisations in paediatric patients[66,132]). This secondary analysis should be considered exploratory as the efficacy data are drawn from trials undertaken within an adult UC population. The economic evaluation takes the form of a cost–utility analysis; the primary health economic outcome is the incremental cost per QALY gained. All treatment options are evaluated within a fully incremental analysis within the base case. The perspective of the economic analysis relates to that of the NHS and PSS. All costs and outcomes are discounted at 3.5%. Costs and health outcomes are evaluated over a lifetime horizon in the base case; shorter time horizons are considered as secondary scenario analyses.

Model structure

The Assessment Group model adopts a Markov structure with eight mutually exclusive health states (*Figure 87*). The model health states are defined according to whether the patient is alive or dead, the non-surgical treatment the patient is currently receiving (biological therapy or non-biological therapy), their prior history of colectomy and their current level of disease control (remission, response and active UC). Remission and response to treatment are classified according to the Mayo score, as defined within the trials included in the systematic review (see *Chapter 3*). Remission is defined as a Mayo score of ≤ 2 points with no individual subscore of > 1 point. Response is defined as a decrease from baseline in the total Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point or an absolute subscore for rectal bleeding of 0 or 1. As remission is a subset of the broader category of response, these are dealt with as mutually exclusive ordered categorical data (see *Chapter 3, Methods for network meta-analysis*). Patients without either response or remission are defined as having active (moderate to severe) UC. The model includes the following health states: (1) on biological treatment – active UC; (2) on biological treatment – response; (3) on biological treatment – remission; (4) on conventional treatment – active UC; (5) on conventional treatment – response; (6) on conventional treatment – remission; (7) post-surgery (with or without complications); and (8) dead. Surgery is not included as a state but rather it is incorporated as an event; patients undergoing colectomy are assumed to transit to the post-surgery state if they survive their surgery and the dead state if they do not.

The model time horizon is divided into two main phases: (1) induction and (2) maintenance. The model adopts an 8-week cycle length for the induction phase and a 26-week cycle length during the subsequent maintenance phase. During the induction phase, patients receiving biological treatment who achieve response or remission are assumed to continue receiving the same biological treatment as maintenance therapy. Patients who do not achieve response or remission during biological induction therapy are assumed to discontinue that biological treatments and subsequently receive conventional non-biological treatments. Patients in the conventional treatment group are assumed to continue receiving conventional therapy irrespective of their response to induction therapy. Patients in the immediate colectomy group are assumed to undergo surgery during the induction phase of the model and subsequently remain in the post-surgery state. All patients have a probability of dying from other causes during the induction cycle.

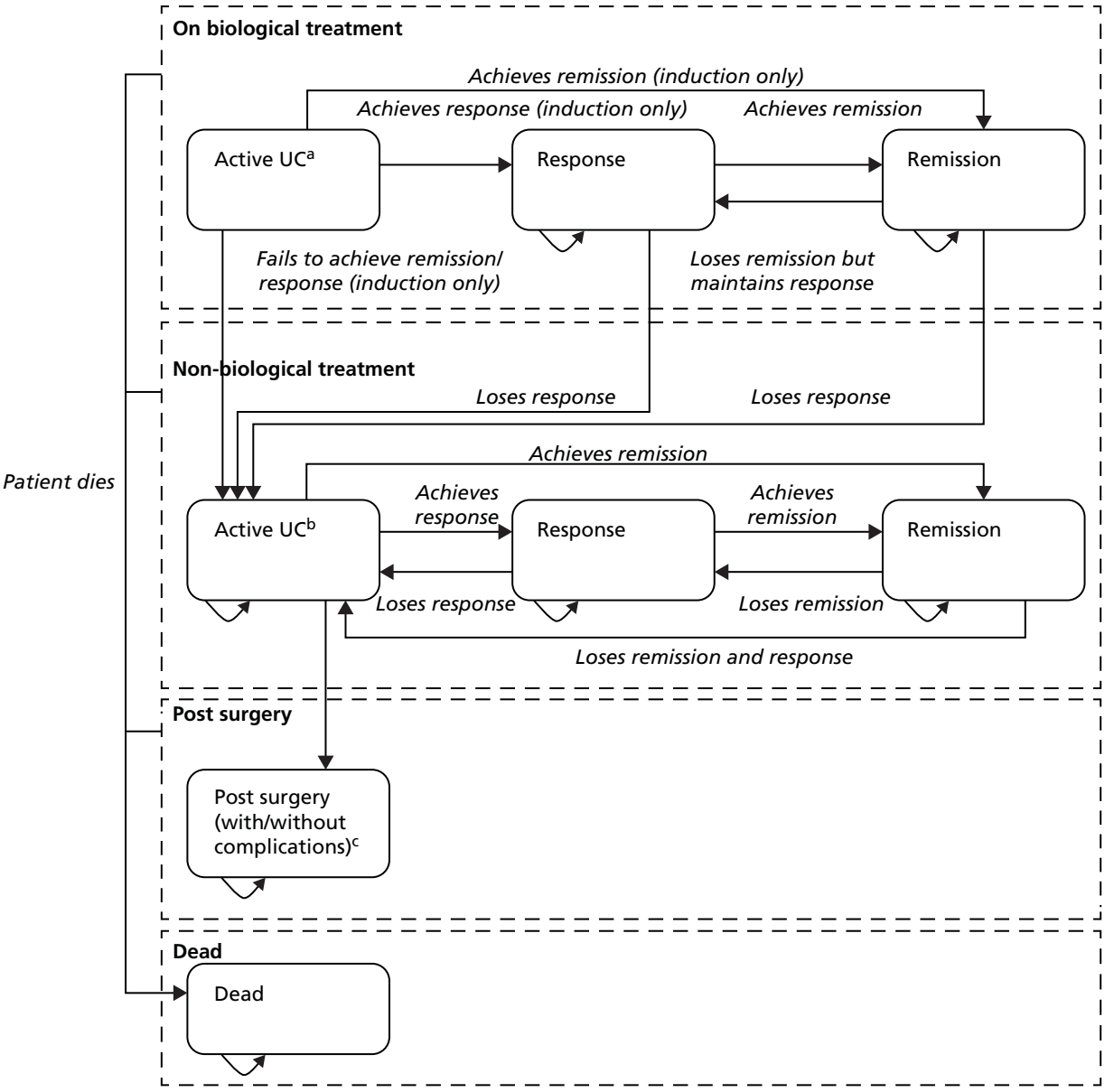

FIGURE 87 Assessment Group model structure (induction and maintenance phases). a, Patients in the IFX, ADA and GOL groups begin in this portion of the model; b, patients in the conventional non-biological management group begin in this portion of the model; and c, patients in the immediate colectomy group begin in this portion of the model.

During the maintenance phase, patients receiving biological therapy are assumed to continue receiving the same biological treatment for as long as they continue to maintain response/remission. If patients receiving biological therapy lose their response at any point they are assumed to transit to the active UC state and subsequently receive conventional therapy. Patients in the conventional treatment group, and those who have previously achieved but lost response to biological therapy, are assumed to continue receiving conventional therapy irrespective of whether they achieve response or remission to that conventional therapy. A time-independent probability of undergoing surgery is applied to those patients receiving conventional treatment with active UC; the model assumes that this only possible within the active UC state. Patients in the immediate colectomy group, and those who have undergone surgery after receiving biological/conventional treatment, remain in the post-surgery state for the remainder of the model time horizon. All patients have a probability of dying from other causes during each model cycle.

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Different levels of HRQoL are assigned to each model health state. Disutilities are assigned to those patients who develop chronic pouchitis – other complications of surgery are assumed to be transient and are assumed not to have a long-term impact on patients' HRQoL. QALY gains in each arm of the model are driven by sojourn time in each of the model's health states and differential rates of surgery across the biological groups, the conventional management group and the immediate colectomy group. Resource costs are assigned in terms of drug acquisition, drug administration (IFX only), surgery and related complications and UC health state costs (elective/emergency endoscopy, blood tests, consultant visits and hospitalisations.

The probability of residing in each health state during a given model cycle is estimated using simple matrix multiplication. Transitions between states are handled within a three-stage competing risks framework whereby (1) patients undergo transitions between each of the pre-surgical UC treatment states based on individual transition probabilities estimated using the NMAs (see *Chapter 3, Assessment of effectiveness*) and the estimated colectomy rate; (2) the populations of the post-surgery and dead states are adjusted to reflect surgical mortality rates; and (3) the remaining surviving population is adjusted to account for other-cause mortality conditional on the patient cohort's current age. Given the different durations of the induction and maintenance phases, a half-cycle correction is not applied within the model.

Key model assumptions

The Assessment Group model makes the following key assumptions:

- At the beginning of the maintenance phase, the decision to continue therapy with IFX, ADA and GOL is determined by the achievement of response or remission at the end of induction.
- During each maintenance cycle, the decision to continue therapy with IFX, ADA and GOL is determined by the achievement/maintenance of response or remission at the end of the previous maintenance cycle.
- Patients who discontinue biological therapy are assumed to receive conventional treatment.
- Patients with active UC receiving conventional treatment may undergo colectomy during any cycle; patients receiving biological therapy will receive at least one cycle of conventional treatment before transiting to surgery.
- Patients' HRQoL is assumed to be determined by their level of disease control, whether or not they have previously undergone colectomy, and the incidence of post-surgical complications.
- With the exception of chronic pouchitis, all surgery-related complications are assumed to occur during the first cycle following surgery.
- With the exception of chronic pouchitis, surgical complications are assumed to be transient and can be resolved either through further surgery or through medical management.
- The medical management of surgery-related complications is assumed to require a 7-day admission on a gastroenterology ward.
- The incidence of chronic pouchitis is assumed to be associated with ongoing additional treatment costs and a decrement in patients' level of HRQoL.

Evidence used to inform the model's parameters

Table 65 summarises the evidence sources used to inform the groups of parameters within the model. These are described in further detail in the following sections.

Patient characteristics

Patient characteristics were based on data reported within the trials included in the systematic review[44,47–49,126] (see *Chapter 3*). Patients are assumed to enter the model aged 40 years, 43% of patients are assumed to be female and patients are assumed to have a mean body mass of 77 kg. Thirty two per cent of patients are assumed to have a body mass > 80 kg; this estimate was drawn from the MSD GOL model.[66]

TABLE 65 Summary of evidence sources used to inform the model's parameter values

Parameter group	Source(s) used to inform parameter values
Patient characteristics (starting age, mean body mass, proportion of patients with body mass > 80 kg, proportion of patients who are female)	Patient age, mean body mass and the probability that a patient is female were derived from the RCTs included in the systematic review of clinical effectiveness (see *Chapter 3*). The proportion of patients with body mass > 80 kg was taken from the MSD GOL model[66]
Pre-surgical health state transition rates induction phase	De novo NMA of induction trials
Pre-surgical health state transition rates maintenance phase	De novo NMA of maintenance trials
Surgery rate during each maintenance cycle	Solberg *et al.*[10]
Probability of perioperative mortality	UK IBD Audit 2012[146]
Probability of other-cause mortality conditional on age and sex	ONS life tables for England and Wales 2009–2011[147]
Health state utilities for all pre-surgical and post-surgical states	Woehl *et al.*[145]
Disutility associated with chronic pouchitis	Arseneau *et al.*[110]
Biological drug regimen schedules	Based on the SmPCs and trials for IFX, ADA and GOL[132,148,149]
Biological drug regimen usage, duration and dosing	Expert opinion (personal communication: Professor Alan Lobo, Consultant Gastroenterologist, Sheffield Teaching Hospitals)
Probability of surgery-related complications and proportion of cases requiring surgery/medical treatment	Arai *et al.*[108]
Use of other related resources for the management of UC	Tsai *et al.*[82]
Relative risk of hospitalisation for biologicals vs. conventional treatment	MSD submissions[64,66]
Unit costs	BNF[37] and NHS Reference Costs 2012/13[130]

ONS, Office for National Statistics.

Transition probabilities for biological and non-biological therapies

The methods for the NMA models are described in *Chapter 3, Methods for network meta-analysis*. *Table 66* presents the means and 95% CrIs for transitions within the model (note: all patients in the colectomy group who survive their surgery are assumed to transit immediately to the post-surgery group).

It should be noted that beyond 1 year, the model repeatedly uses the transition probabilities derived within the maintenance phase 2 NMA.

Surgery rate

The rate at which patients with moderate to severe UC progress to colectomy was based on estimates from the literature. A focused MEDLINE search was undertaken to identify studies reporting long-term rates of colectomy in patients with moderate to severe UC. MEDLINE was searched from inception to April 2014 using a simple search comprising two search terms: 'ulcerative colitis/exp' and 'colectomy rate.tw.' Studies were considered for inclusion in the economic model if they reported on long-term colectomy rates and if they either related to the moderate to severe population as a collective group of patients, or if they reported on colectomy rates in moderate and severe UC populations separately.

The MEDLINE search identified 70 citations. Of these, only six studies were identified that reported on long-term colectomy rates for patients in a selected moderate to severe UC population (*Table 67*).

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TABLE 66 Transition probabilities applied in the Assessment Group model

Transition	Conventional non-biological treatment (95% CrI)	5 mg/kg of IFX (95% CrI)	160 mg/80 mg/ 40 mg of ADA (95% CrI)	200 mg/100 mg/ 50 mg of GOL (95% CrI)	200 mg/100 mg/ 100 mg of GOL (95% CrI)
Induction phase					
TP no response to no response	0.64 (0.57 to 0.71)	0.29 (0.17 to 0.44)	0.49 (0.33 to 0.64)	0.45 (0.26 to 0.64)	0.45 (0.26 to 0.64)
TP no response to response	0.26 (0.21 to 0.31)	0.35 (0.28 to 0.41)	0.32 (0.25 to 0.39)	0.33 (0.24 to 0.39)	0.33 (0.24 to 0.39)
TP no response to remission	0.10 (0.06 to 0.15)	0.36 (0.21 to 0.52)	0.19 (0.09 to 0.32)	0.22 (0.09 to 0.39)	0.22 (0.09 to 0.39)
Maintenance phase 1					
TP no response to no response	0.85 (0.75 to 0.92)	1.00[a]	1.00[a]	1.00[a]	1.00[a]
TP no response to response	0.10 (0.04 to 0.17)	0.00	0.00	0.00	0.00
TP no response to remission	0.06 (0.02 to 0.11)	0.00	0.00	0.00	0.00
TP response to no response	0.52 (0.43 to 0.62)	0.43 (0.22 to 0.66)	0.51 (0.23 to 0.78)	0.40 (0.17 to 0.66)	0.37 (0.15 to 0.62)
TP response to response	0.27 (0.20 to 0.34)	0.28 (0.19 to 0.37)	0.26 (0.14 to 0.35)	0.28 (0.18 to 0.37)	0.29 (0.18 to 0.38)
TP response to remission	0.21 (0.12 to 0.31)	0.29 (0.11 to 0.52)	0.23 (0.05 to 0.49)	0.31 (0.11 to 0.59)	0.35 (0.13 to 0.62)
TP remission to no response	0.35 (0.17 to 0.57)	0.32 (0.08 to 0.65)	0.43 (0.10 to 0.80)	0.18 (0.03 to 0.46)	0.18 (0.03 to 0.47)
TP remission to response	0.18 (0.07 to 0.32)	0.17 (0.06 to 0.30)	0.17 (0.05 to 0.30)	0.14 (0.03 to 0.28)	0.14 (0.03 to 0.28)
TP remission to remission	0.47 (0.23 to 0.71)	0.51 (0.18 to 0.83)	0.41 (0.08 to 0.80)	0.69 (0.32 to 0.93)	0.68 (0.32 to 0.93)
Maintenance phase 2					
TP no response to no response	0.97 (0.93 to 1.00)	1.00[a]	1.00[a]	1.00[a]	1.00[a]
TP no response to response	0.02 (0.00 to 0.05)	0.00	0.00	0.00	0.00
TP no response to remission	0.01 (0.00 to 0.04)	0.00	0.00	0.00	0.00
TP response to no response	0.34 (0.07 to 0.71)	0.25 (0.01 to 0.72)	0.45 (0.06 to 0.89)	0.30 (0.02 to 0.75)	0.41 (0.05 to 0.85)
TP response to response	0.37 (0.12 to 0.60)	0.34 (0.06 to 0.62)	0.33 (0.07 to 0.56)	0.35 (0.08 to 0.62)	0.34 (0.08 to 0.58)
TP response to remission	0.29 (0.03 to 0.72)	0.41 (0.03 to 0.89)	0.22 (0.01 to 0.72)	0.35 (0.02 to 0.84)	0.25 (0.01 to 0.74)
TP remission to no response	0.30 (0.17 to 0.45)	0.25 (0.03 to 0.61)	0.08 (0.01 to 0.29)	0.33 (0.08 to 0.66)	0.27 (0.05 to 0.60)

TABLE 66 Transition probabilities applied in the Assessment Group model (*continued*)

Transition	Conventional non-biological treatment (95% CrI)	5 mg/kg of IFX (95% CrI)	160 mg/80 mg/ 40 mg of ADA (95% CrI)	200 mg/100 mg/ 50 mg of GOL (95% CrI)	200 mg/100 mg/ 100 mg of GOL (95% CrI)
TP remission to response	0.16 (0.03 to 0.45)	0.14 (0.02 to 0.41)	0.08 (0.00 to 0.34)	0.16 (0.02 to 0.41)	0.15 (0.02 to 0.42)
TP remission to remission	0.54 (0.24 to 0.73)	0.61 (0.17 to 0.93)	0.83 (0.45 to 0.99)	0.52 (0.14 to 0.85)	0.59 (0.17 to 0.89)

TP, transition probability.
a Patients on biological treatment in active UC (no response) are assumed to discontinue and subsequently receive conventional non-biological treatments.

TABLE 67 Summary of studies reporting on long-term colectomy rates in UC population

Study	Population	Follow-up duration	Reported colectomy rate
Actis *et al.*[150]	Patients admitted consecutively to study unit with an attack of UC and treated with ciclosporin between January 1991 and December 1999 (responders available for analysis, $n = 34$)	7 years	24/34 (65%)
Gower-Rousseau *et al.*[151]	All patients from the EPIMAD registry diagnosed with UC between January 1988 and December 2002 and who were < 17 years old at the time of diagnosis ($n = 113$)	Median 6.42 years (range 3.83–10.42 years)	Approximately 25% (Kaplan–Meier estimate)
Molnár *et al.*[152]	UC patients admitted between 1998 and 2005 to tertiary clinic because of severe exacerbation of UC requiring parenteral CS therapy ($n = 183$)	Average 4.4 years (range 1.1–10 years)	16/110 (14.5%) steroid-responders, 29/73 (39.7%) steroid- refractory, overall = 24.6%
Mocciaro *et al.*[153]	Two historical cohorts of UC patients with severe relapse refractory to i.v. steroid treatment administered according to the 'Oxford regimen' ($n = 65$)	Mean 6.23 years (± 5.07 years)	IFX group = 60%, ciclosporin group = 30%
Gustavsson *et al.*[13]	158 patients with UC treated in 1975–82 with i.v. CS treatment	Median 14.42 years (range 0.33–22.58 years)	All UC ($n = 147$): colectomy rate = approximately 50%, mild UC ($n = 20$): colectomy rate = approximately 40%, moderate UC ($n = 45$): colectomy rate = approximately 50%, severe UC ($n = 61$): colectomy rate = approximately 62%
Solberg *et al.*[10]	Population-based cohort of 843 patients with IBD was enrolled in south-eastern Norway	Cohort followed up at 1, 5 and 10 years	Cumulative colectomy rate after 10 years = 9.8% (95% CI 7.4% to12.4%)

CS, corticosteroid.

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Several studies report estimates for patients who have been hospitalised for UC flare; these are likely to overestimate the true colectomy rate in the moderate to severe population. On consideration of the remaining studies, the study reported by Solberg *et al.*[10] was selected for inclusion in the model as this study was large (423 patients completed 10-year follow-up) and did not specifically relate to patients who had experienced UC flare. A constant 6-month colectomy rate of 0.0051 was applied within the model. Uncertainty surrounding this probability was modelled using a beta distribution.

Mortality

The model includes two types of mortality: perioperative mortality associated with colectomy and other-cause mortality. Additional risks of death, for example owing to the increased risk of colorectal cancer, are excluded from the model as this risk is likely to be small. Perioperative mortality rates were taken from the third round of the UK IBD audit.[146] Within the 2012 publication of the UK IBD audit, there were 28 deaths reported among 807 elective and emergency surgical episodes in adult patients with UC; a probability of death of 0.03 is assumed within the cycle in which the patient undergoes surgery. Other-cause mortality was modelled according to age- and sex-specific life tables from the Office for National Statistics.[147] The annual probability of death during each model cycle was adjusted to reflect the duration of induction and maintenance cycles (8 weeks and 26 weeks respectively) using standard methods.[154] Uncertainty surrounding the perioperative mortality rate was modelled using a beta distribution. No uncertainty was modelled for other-cause mortality.

Probability of experiencing surgery-related complications

The trials used to inform the efficacy parameters do not include details of surgery-related complications. Instead, the model uses data reported in Arai *et al.*[108] to inform parameters relating to the probability of experiencing transient and chronic surgery-related complications and the probabilities that these complications are treated using medical or surgical approaches. Given the types of complications reported in Arai *et al.*[108] (*Table 68*), the model assumes that all are transient with the exception only of pouchitis. Therefore, the model assumes that 47.3% (140/296) patients will develop transient complications, with a further 5% of patients developing chronic pouchitis. Based on the reported timing of complications within the Arai *et al.* study,[108] the model assumes that all transient complications will arise and will be resolved during the first cycle following surgery (in those patients who survive their surgery). Chronic pouchitis is assumed to continue for the remainder of the patient's lifetime. The model assumes that 19% of complications require further surgery, while the remaining 81% require medical treatment only.

TABLE 68 Surgery-related complication frequency and treatment approach[108]

	Complication frequency		Treatment approach	
Complication type	Number of participants with early complication	Number of participants with late complication	Medical	Surgical
Anastomotic stricture	7	56	63	0
Staple line ulcer	9	31	38	2
Pouchitis	0	16	16	0
Bowel obstruction	6	15	16	5
Proctitis	1	17	18	0
Pelvic sepsis	12	2	1	13
Peritoneal abscess	3	0	0	3
Anal fistula	0	12	2	8
Incisional hernia	1	11	0	4
Total	39	160	154	35

Health-related quality of life

Within the model, HRQoL is assigned according to the level of disease control achieved with drug therapy (active UC, response, remission), whether or not the patient has previously undergone colectomy and whether or not the patient is experiencing post-surgical complications. The same utility values are used for all biological and non-biological drug treatments. The Assessment Group undertook a systematic review of studies reporting valuations of states relating to different levels of UC control and postsurgery.

Searches were undertaken to identify utilities literature relating to UC, specifically using the EQ-5D instrument. The following electronic databases were searched from inception for utility published studies:

- MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations: via Ovid – 1946 to January 2014.
- EMBASE: via Ovid – 1974 to January 2014.
- Cochrane Library: via Wiley Interscience
    - CDSR – 1996 to January 2014
    - DARE – 1995 to January 2014
    - CCRT – 1995 to January 2014
    - Cochrane Methodology Register – 1904 to January 2014
    - HTA database – 1995 to January 2014
    - NHS EED – 1995 to January 2014.
- CINAHL: via EBSCO*host* – 1982 to January 2014.
- Web of Science Citation Index: via Web of Knowledge – 1900 to January 2014.
- Conference Proceedings Citation Index: via Web of Knowledge – 1990 to January 2014.
- BIOSIS Previews: via Web of Knowledge – 1969 to January 2014.
- EconLit: via Ovid – 1886 to January 2014.

The MEDLINE search strategies are presented in *Appendix 10*. The search strategy combined free text and MeSH or thesaurus terms relating to UC combined with terms for specific utility measures or more general utility terms. The search strategy was translated across all databases. No date or language restrictions were applied. Literature searches were conducted during January and February 2014. References were collected in a bibliographic management database, and duplicates were removed. The results of the search are summarised in *Table 69*.

TABLE 69 European Quality of Life-5 Dimensions utilities search results

Database	Date range	Date searched	Number of results
MEDLINE (via Ovid)	1946 to January 2014	29 January 2014	52
EMBASE (via Ovid)	1974 to January 2014	29 January 2014	113
CINAHL (via EBSCO*host*)	1982 to January 2014	4 February 2014	0
Science Citation Index and Social Science Citation Index (via Web of Knowledge)	1900 to January 2014	4 February 2014	5
BIOSIS (via Web of Knowledge)	1969 to January 2014	4 February 2014	4
CDSR (via Wiley)	1991 to January 2014	29 January 2014	0
CENTRAL (via Wiley)	1991 to January 2014	29 January 2014	2
Cochrane HTA (via Wiley)	1991 to January 2014	29 January 2014	0
Cochrane DARE (via Wiley)	1991 to January 2014	29 January 2014	0
Cochrane EED (via Wiley)	1991 to January 2014	29 January 2014	0
EconLit (via Ovid)	1886 to January 2014	29 January 2014	1

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Studies were considered potentially includable if they reported EQ-5D utility estimates for multiple UC health states or if they reported valuations of post-surgery states. The study selection process is shown in *Figure 88*.

Of the 177 deduplicated, potentially relevant studies, the full papers of 53 citations were retrieved for more detailed examination by the Assessment Group based on their titles and abstracts. Of these 53 citations, 10 studies reported EQ-5D estimates for one or more health states relevant to the model.[47,49,139,145,155] Seven of these studies reported estimates for multiple pre-surgery UC health states[64,66,139,145,155–157] and the remaining three studies reported estimates only for post-surgery state only (*Table 70*).[158–160] Of the 10 potentially relevant EQ-5D studies, those reported by Woehl *et al.*[145] and Swinburn *et al.*[139] appear to be the most useful as they are UK based, included a fairly large number of patients ($n = 180$ and $n = 230$, respectively) and have the greatest coverage of the health states in the model (see *Table 70*).

The study reported by Swinburn *et al.*[139] examines the impact of colectomy on the HRQoL of patients with UC. A total of 330 participants were recruited into the study, comprising 230 UC patients (30 of whom had previously undergone surgery) together with 100 age- and sex-matched controls. EQ-5D utilities were collected via online survey. For both post-surgery patients versus non-surgery patients and post-surgery patients versus controls, EQ-5D utility scores were compared across IBDQ disease severity. Seventy-eight patients had remission, 47 patients had mild disease, 31 patients had moderate disease and 44 patients had severe disease. The utility for patients post surgery was reported to be 0.59 (95% CI 0.55 to 0.63). For patients who had not undergone surgery, the scores for each disease severity are: remission utility = 0.91 (95% CI 0.87 to 0.95), mild disease utility = 0.80 (95% CI 0.70 to 0.85), moderate disease utility = 0.68 (95% CI 0.58 to 0.78) and severe disease utility = 0.45 (95% CI 0.35 to 0.55). Across the total UC pre-surgery population, the mean EQ-5D utility was reported to be 0.75 (95% CI 0.71 to 0.79). Similarly, for the matched controls, the mean EQ-5D utility was estimated to be 0.79 (95% CI 0.75 to 0.83). Swinburn *et al.*[139] report that, on average, post-surgery patients reported lower HRQoL scores than non-surgery patients ($p = 0.016$) and matched controls ($p = 0.03$).

Woehl *et al.*[145] collected EQ-5D utility scores from 180 patients with active UC. Within this study population, the mean age was 55.0 years (SD 14.2) and the mean age at diagnosis was 34.1 years (SD 14.6). UC disease severity groups were categorised by SCAI-2 and were compared with patients with IPAA and ileostomy. The mean EQ-5D score was 0.73 (SD 0.29). Mean EQ-5D utilities were reported to be 0.87 (SD 0.15) for remission, 0.76 (SD 0.18) for mild disease, and 0.41 (SD 0.34) for moderate to severe disease. Patients who had undergone IPAA reported an EQ-5D utility of 0.71 (SD 0.29) while patients with an ileostomy reported an EQ-5D score of 0.72 (SD 0.35). Therefore, the health utility scores for these surgery states were slightly below a mild disease severity. The difference between these five groups was statistically significant ($p = 0.001$).

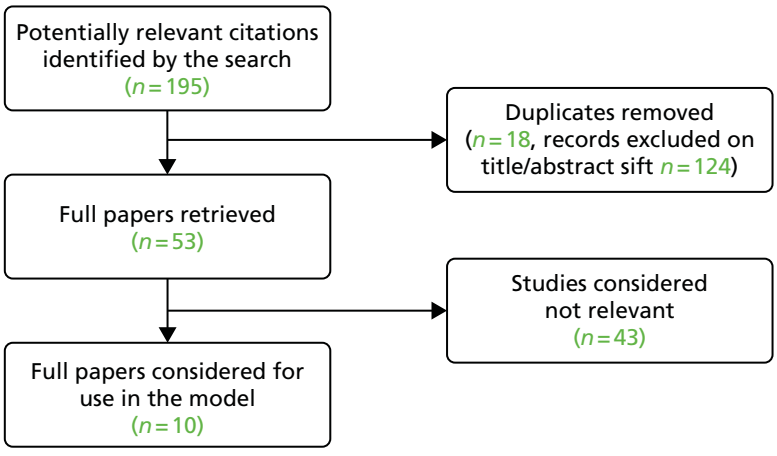

FIGURE 88 Study selection results.

TABLE 70 Characteristics and findings of studies included in the systematic review of utility values

State/study	ACT1 and ACT2[64,66]	PURSUIT[64,66]	[a]Swinburn *et al.*[139]	Woehl *et al.*[145]	[a]Casellas[155]	[a]Leidl[156]	Vaizey[157]	Van der Valk[158]	Richards[159]	Kuruvilla[160]
Study characteristics										
Sample size	486[b]	464	230	180	528	232	173	982	56	59
Country	Various	Various	UK	UK	Spain	Germany (UK tariff)	UK	The Netherlands	UK	USA
Health state valuations										
Remission (ranges of utilities reported by the company)	0.84–0.88	0.86–0.89	0.91	0.87	1.00	0.91	0.86	NR	NR	NR
Response (ranges of utilities reported by the company)	0.79–0.82	0.80	0.80	0.76	0.70	0.74	0.77	NR	NR	NR
Active UC (utilities)	NR	NR	0.55	0.41	0.55	0.63	0.66	NR	NR	NR
Post surgery (utilities)	NR	NR	0.59	0.71–0.72	NR	NR	NR	0.85[c]	0.85	0.90[c]
Post-surgery complications	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

NR, not reported.
a Approximate estimates based on graph reported in Swinburn *et al.*[139]
b Licensed arms only.
c Same value reported for pouch and for ileostomy.

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In the base-case analysis of the Assessment Group model, the Woehl *et al.*[145] study was selected as the valuation for the surgery state (0.71 to 0.72) is more consistent with the other post-surgery valuations identified[158–160] as compared with the Swinburn *et al.*[139] study.

In order to maintain the ordinal ranking of remission, response and active UC states, remission was modelled as a baseline utility score parameter, with disutilities used to value the reductions in health associated with the loss of remission and the loss of response relative to a baseline of remission. The utility parameter for response is therefore modelled as *Utility (remission) minus disutility (loss of remission)* while the utility parameter for active UC is modelled as *Utility (remission) minus disutility (loss of remission) minus disutility (loss of response).* The utility score for post-surgery was based on the mean value reported by Woehl *et al.*[145] (this parameter was not characterised as a health decrement). Uncertainty surrounding the parameters describing remission utility and post-surgery utility was modelled using beta distributions, assuming that an equal number of patients were in each UC state. The disutility parameters were based on the mean and variance of the differences between the health states; this method ensures that the notionally better health state always has a monotonically better valuation than that for the notionally worse health state.

As the studies identified for inclusion in the review did not identify any studies that employed the EQ-5D to value the health loss associated with surgery-related complications, other sources were required. The Assessment Group model adopts a similar approach to the AbbVie model to value this health decrement based on the difference between the surgery and chronic pouchitis valuations reported by Arseneau *et al.*[110] (TTO valuation: 0.57 – 0.40 = 0.17). It should be noted that this study used scenario-based TTO elicitation methods and, therefore, deviates from the NICE reference case.[78] Health losses associated with transient complications of surgery are assumed not to last long enough to decrease HRQoL. The utility values in the model were not adjusted by age. The final utility vector for each treatment option is shown in *Table 71*.

Resource costs

The model includes resource costs related to drug acquisition, drug administration (IFX only), consultant visits, emergency and elective endoscopy, hospitalisations, blood tests, surgery and the management of surgery-related complications.

Biological drug resource use, acquisition and cost

Table 72 shows the dosing regimens and associated costs for each of the biological options within the model. With the exception of GOL induction therapy, the biological regimen assumed reflects the wording of the SmPC for that product.[132,148,149] It should be noted that the SmPC for GOL recommends that continued therapy should be reconsidered in patients who show no evidence of therapeutic benefit within 12–14 weeks (after four doses). However, the PURSUIT-SC trial[47] evaluated clinical benefits at 6 weeks

TABLE 71 Utility vectors for all states and treatment options

	Receiving biological treatment			Receiving standard care			
Treatment	No response	Response	Remission	No response	Response	Remission	Post surgery[a]
Conventional management	0.41	0.76	0.87	0.41	0.76	0.87	0.70
IFX	0.41	0.76	0.87	0.41	0.76	0.87	0.70
ADA	0.41	0.76	0.87	0.41	0.76	0.87	0.70
GOL	0.41	0.76	0.87	0.41	0.76	0.87	0.70
Colectomy	0.41	0.76	0.87	0.41	0.76	0.87	0.70

a Including a proportion of patients with chronic pouchitis.

TABLE 72 Dosing regimens and costs for biological options

Treatment group	Mean doses and frequency within cycle	Cycle cost (£)
Induction phase (8-week duration)		
5 mg/kg of IFX	12 × 100 mg of IFX (3 outpatient appointments)	5035.44 (acquisition) + 893.18 (administration) = 5928.44
160 mg/80 mg of ADA	4 × 40 mg ofADA + 2 × 40 mg of ADA (self-administered)	2817.12
200 mg/100 mg of GOL	4 × 50 mg of GOL + 2 × 50 mg of GOL (self-administered)	4577.82
Maintenance phase (26-week duration)		
5 mg/kg of IFX	13.04 × 100 mg of IFX (3.26 outpatient appointments)	5473.79 (acquisition) + 970.94 (administration) = 6444.73
40 mg of ADA EOW dosing (72.6% patients)	13.04 × 40 mg of ADA	4593.54
40 mg of ADA EW dosing (27.4% patients)	26.08 × 40 mg of ADA	9187.08
100 mg of GOL (body mass > 80 kg, 31.60% patients)	13.04 × 50 mg of GOL	9952.67
50 mg of GOL (body mass < 80 kg, 68.40% patients)	6.52 × 50 mg of GOL	4976.34

EOW, every other week; EW, every week.

(after two doses). The costs and benefits of GOL induction are modelled in line with the design of the PURSUIT-SC trial and, therefore, the costs within the induction phase relate only to the first two doses of GOL. The dose adjustments for ADA were based on the estimate reported within the AbbVie submission.[62]

Non-biological drug resource use

The costs of conventional therapies in each UC state are shown in *Table 73*. These resource costs were assumed to be the same for all biological options and for the conventional management group. The treatments, doses and their frequencies were based on expert opinion (Professor Alan Lobo, Sheffield Teaching Hospitals, April 2014, personal communication) and BNF dosing recommendations. When multiple products were available, the least expensive was included in the analysis. The model assumes that all patients would receive 5-ASAs using Ipocol® (Sandoz Ltd) at a dose of 2.4 mg/day during induction and 1.2 mg/day during maintenance. Ninety per cent of patients are also assumed to receive topical 5-ASAs (80% enemas, 10% suppositories) during induction; these are assumed to be given for a maximum of 28 days per cycle. Following loss of response, the same therapies may also be used to reinduce response/remission; these same assumptions are applied during each maintenance cycle to the conventional management active UC state only. Eighty per cent of patients are assumed to receive 2.5 mg/kg of AZA daily, with the remaining 20% receiving 6-MP at a dose of 1.5 mg/kg daily (note: it is likely that a lower proportion of patients will actually fulfil the criteria for treatment hence this may be an overestimate). All patients are also assumed to require one course of oral prednisolone during induction with the dose starting at 40 mg being tapered by 5 mg each week until the dose is zero (again, the same assumption is made with respect to reinduction of response/remission in patients in the conventional management active UC state during each maintenance cycle). The model does not include estimates of uncertainty around drug usage.

Other ulcerative colitis health state resource use

Health state costs relating to the use of elective and emergency endoscopy, hospitalisations, consultant visits and blood tests were taken from the previous economic analysis reported by Tsai *et al.*[82] (*Table 74*). As Tsai *et al.*[82] did not report any uncertainty around these resource-use estimates, the standard error was arbitrarily assumed to be equal to 10% of the mean.

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TABLE 73 Conventional drug regimen costs per induction/maintenance cycle

Drug, brand	Regimen assumed (% use)	Unit cost	Cost per cycle (for those receiving treatment)
Induction phase (8 weeks)			
5-ASAs (oral), Ipocol®	2.4 mg/day for 56 days (100% patients)	400 mg (120 tablets) = £17.68	£49.50
5-ASAs (enema), Asacol® (Warner Chilcott UK Ltd)	1 metered application/day for 28 days (80% patients)	1 mg (14 application canister) = £26.72	£53.44
5-ASAs (suppository), Asacol	1.5 g/day for 28 days (10% patients)	250 mg (20 suppository pack) = £4.82	£20.24
AZA, non-proprietary	2.5 mg/kg daily for 56 days (80% patients)	50 mg (56 tablets) = £3.85	£14.82
6-MP, Puri-Nethol® (Teva Pharmaceuticals)	1.5 mg/kg daily for 56 days (20% patients)	50 mg (25 tablets) = £50.47	£261.15
Prednisolone (oral), non-proprietary	40 mg tapered by 5 mg/week until dose is zero after 56 days (100% patients)	5 mg (28 tablets) = £1.03	£9.27
Maintenance phase (26 weeks)			
5-ASAs (oral), Ipocol®	1.2 g/day for 182.63 days (100% patients)	400 mg (120 tablets) = £17.68	£80.72
5-ASAs (enema), [a]Asacol®	1 metered application/day for 28 days (80% patients)	1 mg (14 application canister) = £26.72	£53.44
5-ASAs (suppository),[a] Asacol®	1.5 g/day for 28 days (10% patients)	250 mg (20 suppository pack) = £4.82	£20.24
AZA, non-proprietary	2.5 mg/kg daily for 182.63 days (80% patients)	50 mg (56 tablets) = £3.85	£48.34
6-MP, Puri-Nethol®	1.5 mg/kg daily for 182.63 days (20% patients)	50 mg (25 tablets) = £50.47	£851.66
Prednisolone (oral), non-proprietary[a]	40 mg tapered by 5 mg/week until dose is zero after 56 days (100% patients)	5 mg (28 tablets) = £1.03	£9.27

a Costs included for patients in conventional management active UC state only to reinduce response/remission.

TABLE 74 Ulcerative colitis resource use per year[82]

Resource item	Remission	Response	No response	Post-surgery remission	Post-surgery complications
Consultant visit	2.00	4.50	6.50	1.50	1.75
Hospitalisation episode	0.30	0.30	0.30	0.00	3.25
Blood tests	3.25	3.90	6.50	1.50	3.25
Elective endoscopy	0.20	0.50	2.00	1.25	0.65
Emergency endoscopy	0.00	0.25	0.75	0.50	0.13

The MSD submissions to NICE included a meta-analysis in which relative risks were derived for hospitalisations for 160 mg/80 mg/40 mg of ADA and 5 mg/kg of IFX versus conventional treatment.[64,66] The MSD NMA did not include estimates of the relative risk of hospitalisation for GOL versus conventional treatment as this was not measured in the PURSUIT-Maintenance trial. The relative risk for GOL was assumed to be the same as that for ADA (the least favourable option); this assumption favours GOL compared with the other options included in the economic analysis. The relative risks used in the model are shown in *Table 75*.

Unit costs for ulcerative colitis health state resource use, surgery and complications

The unit costs for UC health state resource use, surgery and complications were taken from NHS Reference Costs[130] and are shown in *Table 76*.

Methods for model evaluation

The base-case analysis relates to use of IFX, ADA and GOL within an adult population, based on the expectation of the mean. The cost-effectiveness of competing options are evaluated within a fully incremental analysis according to standard cost-effectiveness decision rules.[77] Results of the probabilistic analyses are presented separately for patients for whom colectomy is a potential option and those for whom it is not. Decision uncertainty is represented using cost-effectiveness planes and CEACs.

TABLE 75 Relative risks of hospitalisation for IFX, ADA and GOL[64,66]

Drug	Relative risk of hospitalisation	Estimated standard error	Comment
IFX	0.64	0.13	Taken from MSD submission NMA[64,66]
ADA	0.70	0.12	
GOL	0.70	0.12	Assumed to be the same as relative risk for ADA

TABLE 76 Unit costs for UC health state resource use, surgery and complications

Item	Unit cost (£)	Standard error (£)	Source
Consultant visit	123.43	3.30	NHS Reference Costs 2013,[130] WF01 A, Gastroenterology, Non-Admitted Face to Face Attendance, Follow-up
Hospitalisation	2722.96	101.66	NHS Reference Costs 2013,[130] FZ37 N, Gastroenterology, Inflammatory Bowel Disease, with Single Intervention, with CC score 0–3
Elective endoscopy	462.36	14.96	NHS Reference Costs 2013,[130] FZ51Z, Gastroenterology, Diagnostic Colonoscopy, 19 years and over
Emergency endoscopy	512.62	26.20	NHS Reference Costs 2013,[130] FZ51Z, Gastroenterology, Diagnostic Colonoscopy, 19 years and over
Blood tests	1.94	0.26	NHS Reference Costs 2013,[130] DAPS03, Integrated Blood Services
Colectomy	13,451.60	1345.16	Buchanan *et al.*[143]
Stoma care per maintenance cycle	214.95	21.49	Buchanan *et al.*[143]
Surgical management of complications	8792.85	473.03	NHS Reference Costs 2013,[130] FZ73F, Colorectal Surgery, Very Complex Large Intestine Procedures with CC Score 0–2
Medical management of complications[a]	4170.95	464.59	NHS Reference Costs 2013,[130] WA12D, Colorectal Surgery, Complications of Procedures, with CC score 0

a Assumes a length of stay of 7 days.

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A secondary analysis is presented for the paediatric population; this analysis compares IFX with standard non-biological treatments versus colectomy. Given the absence of head-to-head trials of IFX versus any other therapy, this analysis is exactly the same as the base-case analysis except that the patients' starting age is set to 15 years (the median age within Hyams *et al.*[52]).

In addition to the main analyses, a number of secondary scenario analyses and sensitivity analyses are presented (*Box 5*). It should be noted that although the base-case economic analysis utilises the results of the NMA models, sensitivity analysis number 4 presents pairwise estimates of cost-effectiveness using direct head-to-head transition probabilities sourced from the individual clinical trials of IFX, ADA and GOL. The pairwise analysis of IFX uses simple pooling of the ACT1 and ACT2 trial data. The pairwise analysis of ADA is based on the anti-TNF-α-naive subgroup from ULTRA2. The GOL analysis is based on the data from the PURSUIT-SC[47] trial and the PURSUIT-Maintenance[48] trial.

Unless otherwise stated, all results are discounted at a rate of 3.5%.

BOX 5 Sensitivity/scenario analyses undertaken using the Assessment Group model

- Base-case analysis: NMA using anti-TNF-α-naive subgroup from ULTRA2[45,126] and excluding Suzuki *et al.*[46] (probabilistic).
- Sensitivity analysis 1: NMA using ITT population from ULTRA2[45] and excluding Suzuki *et al.*[46] (probabilistic).
- Sensitivity analysis 2: NMA using anti-TNF-α-naive subgroup from ULTRA2[45,126] and including Suzuki *et al.*[46] (probabilistic).
- Sensitivity analysis 3: NMA using ITT population from ULTRA2[45,126] and including Suzuki *et al.*[46] (probabilistic).
- Sensitivity analysis 4: pairwise head-to-head comparisons of IFX, GOL and ADA vs. conventional management using direct trial evidence from ACT1 and ACT2, ULTRA2 and PURSUIT[45,47,49,126] (deterministic).
- Sensitivity analysis 5: base case using point estimates of parameters (deterministic).
- Sensitivity analysis 6: time horizon = 20 years (deterministic).
- Sensitivity analysis 7: time horizon = 10 years (deterministic).
- Sensitivity analysis 8: time horizon = 5 years (deterministic).
- Sensitivity analysis 9: all utilities except post-surgical complications drawn from Swinburn *et al.*[139] (deterministic).
- Sensitivity analysis 10: utilities of response/remission drawn from ACT1 trial[49] (deterministic).
- Sensitivity analysis 11: utilities of response/remission drawn from PURSUIT-Maintenance trial[47] (deterministic).
- Sensitivity analysis 12: relative risk of hospitalisation for GOL vs. conventional treatment assumed to be 1.0 (deterministic).
- Sensitivity analysis 13: UC health state costs doubled (deterministic).
- Sensitivity analysis 14: UC health state costs halved (deterministic).
- Sensitivity analysis 15: probability of chronic pouchitis doubled (deterministic).
- Sensitivity analysis 16: probability of chronic pouchitis halved (deterministic).
- Sensitivity analysis 17: cost of surgery doubled (deterministic).
- Sensitivity analysis 18: cost of surgery halved (deterministic).
- Sensitivity analysis 19: probability of surgery in drug groups halved (deterministic).
- Sensitivity analysis 20: probability of surgery in drug groups based on Gower-Rousseau *et al.*[151] (deterministic).
- Sensitivity analysis 21: disutility of pouchitis doubled (deterministic).
- Sensitivity analysis 22: disutility of pouchitis tripled (deterministic).

Model verification and validation

The Assessment Group undertook a number of measures to ensure the credibility of the model (author/advisor initials are shown in brackets).

- Peer review of economic analysis by two internal clinical advisors (SH, AL), one external clinical expert (MH) and one external methodological expert (SD).
- Verification of executable model by a second modeller not involved in its implementation (HB).
- Double programming of separate Markov models for all five treatment options by the lead modeller (PT).
- Scrutiny of implemented model coding and formulae by lead modeller (PT).
- Double-checking of accuracy of all model inputs against sources.
- Comparison of model results using point estimates of parameters and expectation of the mean.
- Comparison of mean of all parameter samples against point estimates of parameters.
- Examination of all identified sources of discrepancy.
- Model testing using sensitivity analysis and use of extreme parameter values.
- Comparison of model results against manufacturers' models (see *Systematic review of existing cost-effectiveness evidence*).

Assessment Group model results

Central estimates of cost-effectiveness (base-case analysis: adults)

Table 77 presents the base-case results generated using the probabilistic version of the model within an adult population in whom colectomy is an acceptable option. The base-case analysis of the model suggests that colectomy is expected to produce 14.71 QALYs at a cost of approximately £56,268 over the patient's remaining lifetime. All medical options are expected to produce substantially fewer QALYs at a greater cost than colectomy, hence colectomy is expected to dominate IFX, ADA, GOL and conventional non-biological treatments.

Figure 89 presents CEACs for IFX, ADA, GOL, conventional treatment and colectomy for the adult population. Assuming a willingness-to-pay threshold of £20,000 per QALY gained, the probability that colectomy produces the greatest amount of expected net benefit is approximately 1.0. The probability that any of the biological treatments produce the greatest amount of expected net benefit at this threshold is approximately zero. Assuming a willingness-to-pay threshold of £30,000 per QALY gained, the probability that colectomy produces the greatest amount of expected net benefit is approximately 1.0. The probability that any of the biological treatments produce the greatest amount of expected net benefit at this threshold is approximately zero.

Table 78 presents the probabilistic base-case model results within an adult population in whom colectomy is not an acceptable option, thus relevant treatment options are restricted to medical treatments only (IFX, ADA, GOL and conventional non-biological treatments). The model results suggest that within this population, IFX is expected to be dominated by ADA (note: the difference in QALYs is very small), while GOL is expected to be ruled out because of extended dominance. The incremental cost-effectiveness of ADA versus conventional treatment is expected to be £50,278 per QALY gained.

TABLE 77 Probabilistic cost-effectiveness results, base-case analysis, adult patients in whom colectomy is an option (medical and surgical treatments)

Option	QALYs	Costs (£)	Incremental QALYs	Incremental cost	ICER
Colectomy	14.71	56,267.73	–	–	Dominating
ADA	10.82	91,221.71	–	–	Dominated
IFX	10.81	96,594.62	–	–	Dominated
GOL	10.63	90,086.69	–	–	Dominated
Conventional treatment	10.47	73,619.77	–	–	Dominated

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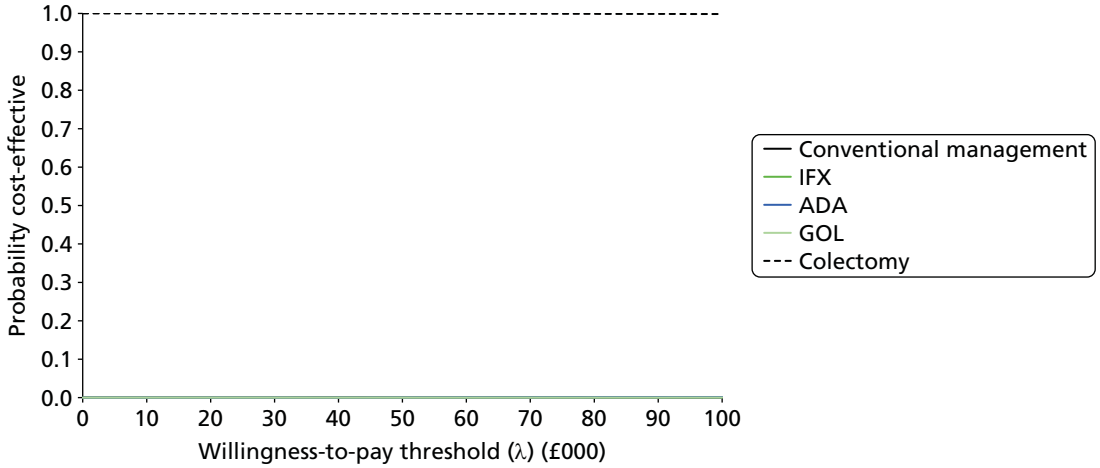

FIGURE 89 Cost-effectiveness acceptability curves, base-case analysis, adult patients in whom colectomy is an option (medical and surgical treatments).

TABLE 78 Probabilistic cost-effectiveness results, base-case analysis, adult patients in whom colectomy is not an option (medical treatments only)

Option	QALYs	Costs (£)	Incremental QALYs	Incremental cost (£)	ICER
ADA	10.82	91,221.71	0.35	17,601.94	£50,278
IFX	10.81	96,594.62	–	–	Dominated
GOL	10.63	90,086.69	–	–	Ext dom
Conventional treatment	10.47	73,619.77	–	–	–

Ext dom, extendedly dominated.

Figure 90 presents CEACs for IFX, ADA, GOL and conventional treatment within a population in whom colectomy is not an option. Assuming a willingness-to-pay threshold of £20,000 per QALY gained, the probability that conventional non-biological treatment produces the greatest expected net benefit is approximately 1.0. Assuming a WTP threshold of £30,000 per QALY gained, the probability that conventional management produces the greatest expected net benefit is approximately 0.98.

Central estimates of cost-effectiveness (base-case analysis: paediatric population)

Table 79 presents the base-case results generated using the probabilistic version of the model within a paediatric population in whom colectomy is an acceptable option. The base-case analysis of the model suggests that colectomy is expected to produce 17.54 QALYs at a cost of approximately £64,097 over the patient's remaining lifetime. IFX and conventional management are expected to produce substantially fewer QALYs at a greater cost than colectomy, hence colectomy is expected to dominate these medical options.

Figure 91 presents CEACs for IFX, conventional treatment and colectomy for the paediatric population. Assuming a willingness-to-pay threshold of £20,000 per QALY gained, the probability that colectomy produces the greatest amount of expected net benefit is approximately 1.0. Assuming a willingness-to-pay threshold of £30,000 per QALY gained, the probability that colectomy produces the greatest amount of expected net benefit is approximately 1.0. The probability that IFX produces the greatest amount of expected net benefit at these thresholds is approximately zero.

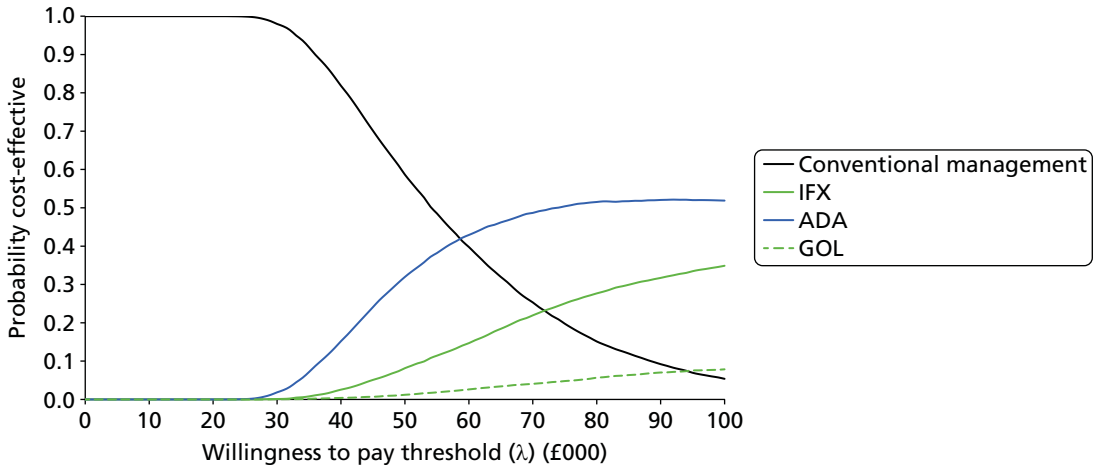

FIGURE 90 Cost-effectiveness acceptability curves, base-case analysis, adult patients in whom colectomy is not an option (medical treatments only).

TABLE 79 Probabilistic cost-effectiveness results, base-case analysis, paediatric patients in whom colectomy is an option (medical and surgical treatments)

Option	QALYs	Costs (£)	Incremental QALYs	Incremental cost (£)	ICER
Colectomy	17.54	64,097.18	–	–	Dominating
IFX	13.00	109,438.73	–	–	Dominated
Conventional treatment	12.65	86,280.28	–	–	Dominated

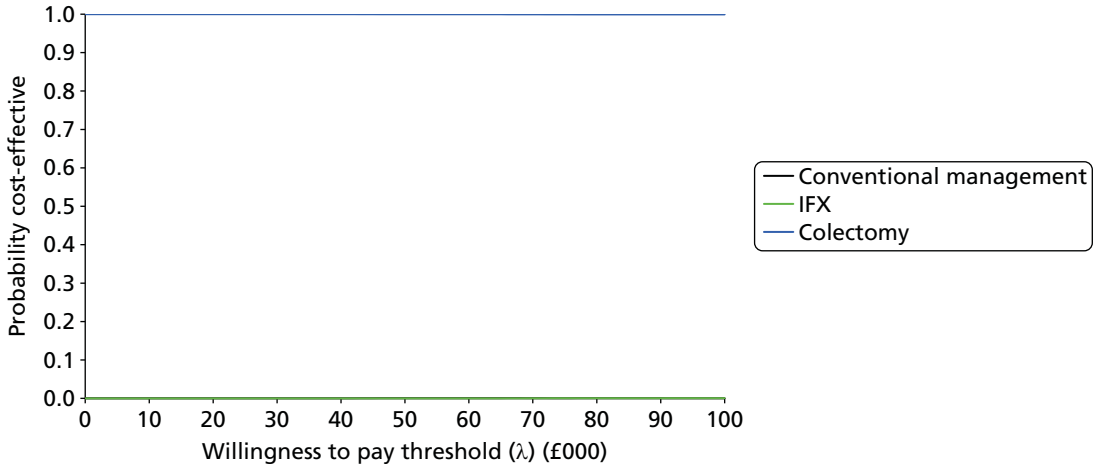

FIGURE 91 Cost-effectiveness acceptability curves, base-case analysis, paediatric patients in whom colectomy is an option (medical and surgical treatments).

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Table 80 presents the probabilistic base-case model results within a paediatric population in whom colectomy is not an acceptable option, thus relevant treatment options are restricted to IFX and conventional non-biological treatments. The model indicates that within this population, IFX is expected to produce an additional 0.34 QALYs at an additional cost of £23,158 over the patient's remaining lifetime; the ICER for IFX versus conventional management is expected to be £68,007 per QALY gained.

Figure 92 presents CEACs for IFX and conventional treatment for the paediatric population. Assuming willingness-to-pay thresholds of £20,000 and £30,000 per QALY gained, the probability that conventional management produces the greatest amount of expected net benefit is approximately 1.0. The probability that IFX produces the greatest amount of expected net benefit at these thresholds is approximately zero.

Network meta-analysis sensitivity analyses (sensitivity analyses 1–3, probabilistic)

Table 81 summarises the results of the economic analysis for the adult population based on the three alternative sensitivity analyses.

In the circumstances for which colectomy is an option, the three NMA sensitivity analyses produce very similar results to the base-case analysis. In all three analyses, colectomy is consistently expected to dominate all medical treatment options. Assuming a WTP threshold of £20,000 per QALY gained, the probability that colectomy produces the greatest amount of net benefit is expected to be approximately 1.0. Assuming a WTP threshold of £30,000 per QALY gained, the probability that colectomy produces the greatest amount of net benefit is expected to be approximately 1.0. When colectomy is not an acceptable option, the results are influenced by which studies are included in the NMA, as the difference in effectiveness between ADA and IFX is very small. GOL is consistently expected to be ruled out of the analysis because of extended dominance. In sensitivity analyses 1 and 2, IFX is expected to produce slightly more QALYs than ADA; however, the ICER for IFX versus ADA is expected to be > £236,000 per QALY gained. In these sensitivity analyses, the ICER for ADA versus conventional non-biological treatment is

TABLE 80 Probabilistic cost-effectiveness results, base-case analysis, paediatric patients in whom colectomy is not an option (medical treatments only)

Option	QALYs	Costs (£)	Incremental QALYs	Incremental cost (£)	ICER (£)
IFX	13.00	109,438.73	0.34	£23,158.45	68,007
Conventional treatment	12.65	86,280.28	–	–	–

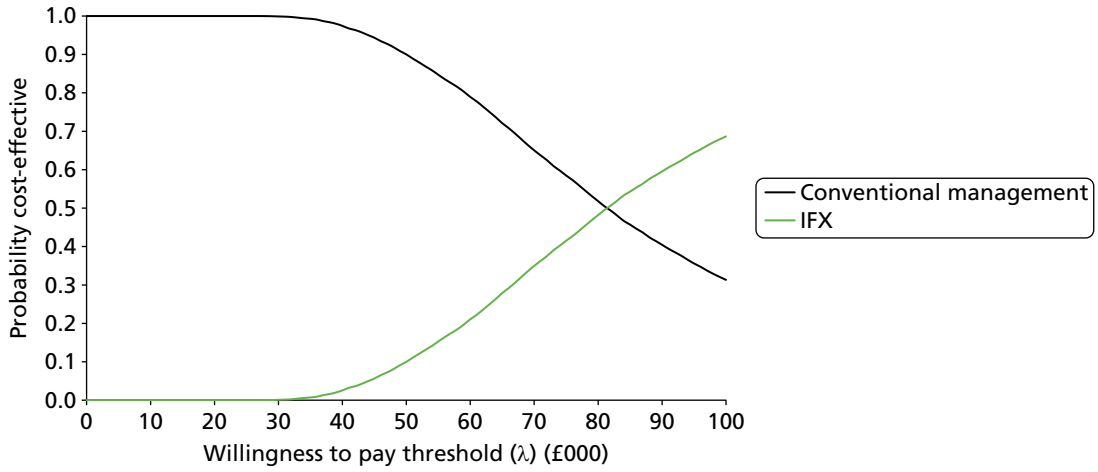

FIGURE 92 Cost-effectiveness acceptability curves, base-case analysis, paediatric patients in whom colectomy is not an option (medical options only).

TABLE 81 Results of probabilistic NMA sensitivity analyses

	Colectomy	IFX	ADA	GOL	Conventional management
Adult population in whom colectomy is an option					
NMA sensitivity analysis number 1: ULTRA2 ITT population, excluding Suzuki et al.[46]					
ICER	Dominating	Dominated	Dominated	Dominated	Dominated
P(optimal £20,000/QALY)	1.00	0.00	0.00	0.00	0.00
P(optimal £30,000/QALY)	1.00	0.00	0.00	0.00	0.00
NMA sensitivity analysis number 2: ULTRA2 anti-TNF-α-naive subgroup, including Suzuki et al.[46]					
ICER	Dominated	Dominated	Dominated	Dominated	Dominated
P(optimal £20,000/QALY)	1.00	0.00	0.00	0.00	0.00
P(optimal £30,000/QALY)	1.00	0.00	0.00	0.00	0.00
NMA sensitivity analysis number 3: ULTRA2 ITT population, including Suzuki et al.[46]					
ICER	Dominated	Dominated	Dominated	Dominated	Dominated
P(optimal £20,000/QALY)	1.00	0.00	0.00	0.00	0.00
P(optimal £30,000/QALY)	1.00	0.00	0.00	0.00	0.00
Adult population in whom colectomy is an not option					
NMA sensitivity analysis number 1: ULTRA2 ITT population, excluding Suzuki et al.[46]					
ICER	N/A	£236,340 (1)	£54,066 (2)	Ext dom(3)	–(4)
P(optimal £20,000/QALY)	N/A	0.00	0.00	0.00	1.00
P(optimal £30,000/QALY)	N/A	0.00	0.01	0.00	0.99
NMA sensitivity analysis number 2: ULTRA2 anti-TNF-α-naive subgroup, including Suzuki et al.[46]					
ICER	N/A	£546,051 (1)	£56,284 (2)	Ext dom(3)	–(4)
P(optimal £20,000/QALY)	N/A	0.00	0.00	0.00	1.00
P(optimal £30,000/QALY)	N/A	0.00	0.00	0.00	1.00
NMA sensitivity analysis number 3: ULTRA2 ITT population, including Suzuki et al.[46]					
ICER	N/A	Dominated (2)	£55,637 (1)	Ext dom(3)	–(4)
P(optimal £20,000/QALY)	N/A	0.00	0.00	0.00	1.00
P(optimal £30,000/QALY)	N/A	0.00	0.00	0.00	1.00

Ext dom, extendedly dominated; N/A, not applicable.
When different from the base-case analysis, the QALY rank is shown in parentheses.

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expected to be > £54,000 per QALY gained. In sensitivity analysis 3, IFX is expected to be ruled out owing to simple dominance; the ICER for ADA versus conventional non-biological treatments is expected to be approximately £55,637 per QALY gained.

Head-to-head analyses (sensitivity analysis 4)

Table 82 presents the results of the economic analysis using the direct head-to-head trial data.

The head-to-head analyses indicate that colectomy is expected to dominate all medical options. Within a population in whom colectomy is not an acceptable option, the incremental cost-effectiveness of IFX versus conventional non-biological treatments is estimated to be £96,403 per QALY gained, the ICER for ADA versus conventional non-biological treatments is estimated to be £69,782 per QALY gained and the ICER for GOL versus conventional non-biological treatments is estimated to be £90,413 per QALY gained.

Sensitivity analyses 5–22: other deterministic sensitivity analyses (medical and surgical options)

Table 83 presents the results of the remaining deterministic sensitivity analysis (analyses 5–22).

The analyses indicate that the model results remain largely unaffected by changes in the model time horizon, assumed patient age, utilities for remission and response, assumptions regarding UC resource use, and the colectomy rate. However, the model is very sensitive to assumptions regarding the relative utilities of remission, response, active UC and postsurgery. Within the sensitivity analysis in which utility values are drawn from Swinburn *et al.*[139] (analysis number 9), the rank ordering of QALY gains is altered such that colectomy moves from being the most effective option to the least effective option. In this scenario, GOL and conventional non-biological treatments are expected to be ruled out of the analysis, the ICER for ADA versus colectomy is estimated to be approximately £79,714 per QALY gained while the ICER for IFX versus ADA is estimated to be approximately £178,982 per QALY gained.

TABLE 82 Head-to-head analysis: adult population, IFX versus conventional management

Option	QALYs	Costs (£)	Incremental QALYs	Incremental cost (£)	ICER
IFX versus conventional management and colectomy					
Colectomy	14.69	56,342.42	–	–	Dominating
IFX	11.62	86,609.58	–	–	Dominated
Conventional treatment	11.44	69,583.06	–	–	Dominated
ADA versus conventional management and colectomy					
Colectomy	14.69	56,342.42	–	–	Dominating
ADA	10.23	90,538.92	–	–	Dominated
Conventional treatment	10.02	75,416.12	–	–	Dominated
GOL versus conventional management and colectomy					
Colectomy	14.69	56,342.42	–	–	Dominating
GOL	10.16	91,395.09	–	–	Dominated
Conventional treatment	9.99	75,541.49	–	–	Dominated

TABLE 83 Other deterministic sensitivity analyses

Sensitivity analysis	Incremental cost per QALY gained				
	IFX	ADA	GOL	Conventional management	Colectomy
SA5: base case using point estimates of parameters	Dominated	Dominated	Dominated	Dominated	Dominating
SA6: time horizon = 20 years	Dominated	Dominated	Dominated	Dominated	Dominating
SA7: time horizon = 10 years	Dominated	Dominated	Dominated	–	£886.44
SA8: time horizon = 5 years	Dominated	Dominated	Dominated	–	£8840.14
[a]SA9: all utilities except post-surgical complications drawn from Swinburn *et al.*[139]	£178,982 (1)	£79,714 (2)	Dominated (3)	Ext dom (4)	–
SA10: utilities of response/remission drawn from ACT1 trial[49] (0.88, 0.82 for remission and response respectively)	Dominated	Dominated	Dominated	Dominated	Dominating
SA11: utilities of response/remission drawn from PURSUIT-Maintenance trial[47] (0.89, 0.80 for remission and response respectively)	Dominated	Dominated	Dominated	Dominated	Dominating
SA12: relative risk of hospitalisation for GOL vs. conventional treatment assumed to be 1.0	Dominated	Dominated	Dominated	Dominated	Dominating
SA13: UC health state resource use doubled	Dominated	Dominated	Dominated	Dominated	Dominating
SA14: UC health state resource use halved	Dominated	Dominated	Dominated	Dominated	Dominating
SA15: probability of chronic pouchitis doubled	Dominated	Dominated	Dominated	Dominated	Dominating
SA16: probability of chronic pouchitis halved	Dominated	Dominated	Dominated	Dominated	Dominating
SA17: cost of surgery doubled	Dominated	Dominated	Dominated	Dominated	Dominating
SA18: cost of surgery halved	Dominated	Dominated	Dominated	Dominated	Dominating
SA19: probability of undergoing surgery in drug groups halved	Dominated	Dominated	Dominated	Dominated	Dominating
SA20: colectomy rate based on Gower-Rousseau *et al.*[151]	Dominated	Dominated	Dominated	Dominated	Dominating
SA21: disutility of pouchitis doubled	Dominated	Dominated	Dominated	Dominated	Dominating
SA22: disutility of pouchitis tripled	Dominated	Dominated	Dominated	Dominated	Dominating

Ext dom, extendedly dominated.
a QALY rank shown in parentheses.

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Budget impact analysis

This section presents an analysis of the expected net budget impact of introducing IFX, ADA and GOL for the treatment of moderate to severe UC in England and Wales. Budget impact estimates are presented annually for a 5-year period. The analysis makes the following assumptions:

- The prevalence of UC is 240 per 100,000 population.
- The incidence of UC is 10 per 100,000 population.
- The population of England and Wales is approximately 56 million.
- A total of 14.5% of all UC patients would be eligible to receive biological treatments.[80]
- All patients who are eligible for treatment with biologicals will receive these therapies.
- Discounting is not applied.

These assumptions suggest an eligible prevalent UC cohort of approximately 19,488 patients and an eligible incident cohort of approximately 812 patients per year. Based on the cost distribution over time estimated for each treatment using the Assessment Group model, combined with the estimated eligible prevalent and incident cohorts in each year, this gives rise to the budget impact estimates presented in *Table 84*. Assuming full uptake of these drugs, the estimated net budget impact of IFX, ADA and GOL for the treatment of moderate to severe UC is estimated to be between £269M and £434M.

TABLE 84 Estimated absolute and net budgetary impact of introducing biologicals for the treatment of moderate to severe UC in England and Wales

Year	IFX	ADA	GOL	Conventional non-biological treatments
Absolute budget impact for each treatment				
Year 1	£320,465,072	£212,829,031	£274,600,660	£75,051,491
Year 2	£145,622,769	£114,284,053	£130,417,738	£69,748,947
Year 3	£124,230,659	£108,603,021	£109,713,744	£74,396,609
Year 4	£113,140,687	£105,994,793	£101,177,679	£77,850,322
Year 5	£107,896,081	£104,691,559	£98,410,165	£80,753,619
Net budget impact for costs of biological less costs of conventional treatments				
Year 1	£245,413,582	£137,777,540	£199,549,169	–
Year 2	£75,873,822	£44,535,106	£60,668,791	–
Year 3	£49,834,050	£34,206,412	£35,317,135	–
Year 4	£35,290,365	£28,144,472	£23,327,357	–
Year 5	£27,142,461	£23,937,940	£17,656,546	–
Total cost over 5 years	£433,554,281	£268,601,470	£336,518,999	–

Discussion

The manufacturers of ADA, IFX and GOL submitted economic models to assess the cost-effectiveness of biological therapies versus conventional treatment. The MSD IFX submission model indicates that the estimated ICER for IFX versus standard non-biological treatment (colectomy) is £37,682 per QALY gained.[64] The MSD GOL submission reports an estimated ICER of £27,322 per QALY gained.[66] The AbbVie submission reports a base-case ICER for ADA versus conventional therapy of £34,590 per QALY gained.[62] The Assessment Group scrutinised these models and critiqued the evidence and assumptions which underpin the cost-effectiveness estimates reported by the manufacturers. A number of problems with these models were identified by the Assessment Group, particularly with respect to the exclusion of relevant treatment options specified in the final NICE scope[36] and the use of a short time horizon. In addition, the MSD model does not include a fully incremental analysis, confuses evidence from populations with varying degrees of UC severity and inadequately reflects likely UK treatment pathways. As a consequence of these problems, the Assessment Group do not consider that the cost-effectiveness evidence produced by either manufacturer adequately addresses the specified decision problem.

In light of the problems with the manufacturers' submitted economic analyses, the Assessment Group developed a de novo cost-effectiveness model to assess IFX, ADA, GOL, conventional non-biological treatments and elective surgery within the moderate to severe UC population. The Assessment Group model differs from both the manufacturers' models in that all relevant medical and surgical options are evaluated over a lifetime horizon, as specified in the final NICE scope. Underpinning the Assessment Group model is a series of complex NMAs, which synthesise all relevant evidence relating to IFX, ADA, GOL and conventional non-biological therapies. A summary of the key differences between the Assessment Group model and the manufacturers' models is presented in *Table 85*.

TABLE 85 Summary of key differences between the Assessment Group model and the manufacturers' models

Element of evaluation	Assessment Group model (base case)	MSD models[64,66]	AbbVie model[62]
Options evaluated	• IFX • ADA • GOL • Conventional non-biological treatments • Colectomy	• IFX • ADA • GOL • Conventional non-biological treatments	• ADA • Conventional non-biological treatments
Time horizon	Lifetime	10 years	10 years
Source of efficacy evidence	NMA using unpublished ordered categorical data	NMA using published binomial data (includes manipulation of PURSUIT-Maintenance trial data)	Unpublished data from ULTRA2 and ULTRA1 and ULTRA2 extension study supplemented using estimates from Kane *et al.*[133] and Odes *et al.*[121]
Treatment options following failure of biologic	Conventional non-biological treatments and possible colectomy	Relapse management and imminent colectomy	Conventional non-biological treatments and possible colectomy
Possible transitions between active UC states (remission, response, no response)	All transitions in matrix allowed	Patients losing remission transit to response, patients achieving response cannot achieve remission	All transitions in matrix allowed
Source of health utilities	Woehl *et al.*[145] (chronic pouchitis valued using Arseneau *et al.*[110])	ACT1/PURSUIT-Maintenance, Woehl *et al.*,[145] complications valued using Arseneau *et al.*[110]	Swinburn *et al.*,[139] Tsai *et al.*,[82] complications valued using weighted average of Arseneau *et al.*,[110] Hu *et al.*[140] and Smith and Roberts[141]

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The base-case analysis of the Assessment Group model suggests that within an adult UC population, colectomy is expected to produce 14.71 discounted QALYs at a discounted cost of approximately £56,300 over the patient's remaining lifetime. All medical options are expected to produce substantially fewer QALYs at a greater cost than colectomy, hence colectomy is expected to dominate IFX, ADA, GOL and conventional non-biological treatments. Importantly however, elective colectomy may not be considered an acceptable or preferable option for some patients. In circumstances whereby only drug options are considered acceptable, the base-case version of the Assessment Group model suggests that IFX and GOL are expected to be ruled out because of dominance, while the incremental cost-effectiveness of ADA versus conventional non-biological treatment is expected to be approximately £50,300 per QALY gained.

The Assessment Group also undertook a separate probabilistic economic analysis of IFX, conventional non-biological treatments and colectomy within a paediatric population (mean age = 15 years). When colectomy is an acceptable treatment option, the economic analysis suggests that this option dominates IFX and conventional non-biological treatments. When colectomy is not an acceptable option, the economic analysis suggests that the incremental cost-effectiveness of IFX versus conventional treatments is approximately £68,000 per QALY gained. However, this analysis is based on adult efficacy evidence, hence it should be interpreted with some degree of caution.

Three separate PSAs were undertaken using data from the Japanese trial reported by Suzuki *et al.*[46] and using the ITT data rather than anti-TNF-α-naive patients from ULTRA2.[45] Across these three scenarios, the general conclusions of the economic analysis remain unchanged. The Assessment Group also undertook separate comparisons of (1) IFX versus colectomy and conventional treatments; (2) ADA versus colectomy and conventional treatments; and (3) GOL versus colectomy and conventional treatments using the head-to-head trials rather than the NMA models. These analyses indicate that where colectomy is an acceptable option, it is expected to dominate the drug options. When colectomy is not an acceptable option, the ICERs produced from these analyses are all in excess of £69,000 per QALY gained.

A number of simple sensitivity analyses were also undertaken using the point estimates of model parameters. Across these scenarios, the model results appear to be insensitive to changes in these assumptions, with the exception of the HRQoL values assumed. Within the scenario whereby utilities from Swinburn *et al.*[139] are used in the model (rather than those reported by Woehl *et al.*[145] as per the base-case analysis), colectomy produces the lowest QALY gain and conventional management and GOL are ruled out because of extended dominance. Within this scenario, the incremental cost-effectiveness of ADA versus elective colectomy is estimated to be £79,714 per QALY gained, while the incremental cost-effectiveness of IFX versus ADA is estimated to be £178,982 per QALY gained. Although these results are very different from the Assessment Group's base-case analysis, the economic conclusions that should be drawn from this sensitivity analysis are not.

Chapter 5 Assessment of factors relevant to the NHS and other parties

Surgery and patient choice

Surgery may be considered as an option for patients with UC for a number of reasons including complications of disease, perceived risk of or identified dysplasia/neoplasia or lack or loss of efficacy of medical treatments. For a proportion of patients without emergency symptoms, surgery may not represent an acceptable treatment option.

Administration route: intravenous infusions versus subcutaneous injection

The method of drug administration differs between the interventions included in this appraisal. IFX is given via i.v. infusion while ADA and GOL are administered via subcutaneous injection. IFX therefore requires outpatient attendances, additional nursing care and monitoring. These resources are not required for the administration of ADA or GOL. Pre-infusion prophylaxis may be required to minimise the risk of infusion reactions associated with IFX.

Training for subcutaneous injections

When considered appropriate (by the physician), patients, family members and/or carers require training for the administration of subcutaneous injections. This training is associated with additional resource use and costs.

Screening for tuberculosis and other infectious diseases (e.g. hepatitis B)

All of the biological therapies considered in this assessment report may be associated with the reactivation of TB. Patients should be screened for TB (and other infectious disease, e.g. hepatitis B) before initiation of treatment.

Off-license use in children for golimumab and adalimumab

Currently, IFX is the only biological treatment option that is licensed for the treatment of moderate to severe UC in children in the UK.

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Chapter 6 Discussion

Statement of principal findings

Principal findings: clinical effectiveness

A total of 10 RCTs were identified in the clinical effectiveness systematic review, of which nine[44–51] related to adults and one[52] was conducted in a paediatric population. All of the adult RCTs were performed against PBO (with the exception of UC-SUCCESS) and were a maximum of 1 year in duration. No head-to-head RCTs were identified in which interventions of interest were assessed against each other.

The risks of bias associated with included RCTs were assessed using the Cochrane risk of bias instrument. Only three RCTs could be considered as being at overall low risk of bias (as allocation concealment, blinded outcome assessment and completeness of outcome data were all judged as low risk). It should be noted that one of the maintenance trials (PURSUIT- Maintenance) rerandomised patients who had previously responded to GOL induction therapy in two previous trials; the extent of this potential bias on patient outcomes is unclear.

The outcome measures pre-specified in the final NICE scope were all addressed by the included trial evidence, with the exception of rates of relapse. Clinical response and remission data based on complete Mayo scores were well reported across trials. Evidence was identified to demonstrate that patients receiving IFX, ADA or GOL were more likely than patients receiving PBO to achieve clinical response and remission at induction and maintenance time points. Patients in the UC-SUCCESS trial who received combination treatment with IFX and AZA experienced the most favourable rates of steroid-free remission compared with IFX and AZA treatment groups. Seven RCTs performed in adult populations contributed data on clinical response and remission at induction or maintenance time points to NMAs.[44–49]

Based on the NMA, in the induction phase, all treatments were associated with statistically significant beneficial effects relative to PBO with the greatest effect being associated with IFX. IFX was also associated with the highest probability of moving from no response to response and from no response to remission. The effects of ADA and GOL on these two probabilities were broadly comparable.

For patients classified as responders at the end of the induction phase, treatment effects were not statistically significant, although the greatest effect was associated with 100 mg of GOL at 8–32 weeks. A treatment of 100 mg of GOL was associated with the highest probability of moving from response to remission and staying in response and the smallest probability of moving from response to no response. However, at 32–52 weeks, only IFX and 50 mg of GOL were associated with beneficial effects on clinical response, although the effects were not statistically significant. IFX was associated with the highest probability of moving from response to remission and staying in response and the smallest probability of moving from response to no response at 32–52 weeks. The probabilities of staying in response were comparable among treatments at both 8–32 weeks and 32–52 weeks.

For patients classified as being in remission at the end of the induction phase, all treatments except for ADA were associated with beneficial treatment effects relative to PBO with the greatest effect being associated with 50 mg and 100 mg of GOL, although the effects were not statistically significant at 8–32 weeks. A treatment of 50 mg and 100 mg of GOL were associated with the highest probability of staying in remission and the smallest probability of moving from remission to response and from remission to no response. At 32–52 weeks, all treatments except 50 mg of GOL were associated with beneficial treatment effects relative to PBO, with the greatest effect being associated with ADA (the only treatment with statistically significant effect). ADA was associated with the highest probability of staying in remission and the smallest probability of moving from remission to response and from remission to no response.

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Available data on hospitalisation outcomes were very limited, but suggested that outcomes may be more favourable for ADA-treated and IFX-treated patients than PBO (with no data available from GOL trials). Data on surgical intervention were also very sparse, with a potential inconclusive benefit for intervention-treated patients compared with PBO. No trials reported whether surgical outcomes were elective or emergency in nature; however, more data are required to demonstrate the impact of interventions on hospitalisation and surgical intervention more conclusively. Data were available from a single trial to support the use of IFX in induction and maintenance treatment in a paediatric population.

The main safety issues highlighted in the RCT evidence appeared to be generally consistent with those previously discussed in the respective SmPC (including serious infections, malignancies and administration site reactions). Deaths occurring during and after the study period were described in some trials evaluating GOL (PURSUIT-Maintenance) and IFX (ACT1 and ACT2), of which infection or malignancy was most commonly implicated. This underlines the importance of monitoring and treating serious infections and malignancies in patients receiving immunosuppressive treatment.

The trials included in the clinical effectiveness systematic review typically excluded patients with ulcerative proctitis, patients with fulminant/acute severe disease, those with a history of or at imminent risk of bowel surgery, pregnant or lactating women, and patients with diseases of the central nervous system (e.g. demyelinating disease). Furthermore, patients with a history of serious infection and/or immunodeficiency were also typically excluded, as were individuals with a history of malignancy or signs of dysplasia. Therefore, the effects of ADA, GOL or IFX in these UC populations are unknown.

Two biosimilars (Remsima and Inflectra) to Remicade were considered as part of the evidence base for IFX as part of this assessment. The sponsor submission received from the manufacturers of Remsima and the EPAR reports for Remsima and Inflectra indicated that both biosimilars were approved by the EMA on the basis of reported similar pharmacokinetic and efficacy (demonstrated in AS and RA patients) profiles to Remicade. No further trials of Remsima or Inflectra were identified over the course of this assessment.

Principal findings: cost-effectiveness

The manufacturers of ADA, IFX and GOL submitted economic models to assess the cost-effectiveness of biological therapies versus conventional treatment. The MSD IFX submission model indicates that the estimated ICER for IFX versus standard non-biological treatment (colectomy) is £37,682 per QALY gained.[64] The MSD GOL submission reports an estimated ICER of £27,322 per QALY gained.[66] The AbbVie submission reports a base-case ICER for ADA versus conventional therapy of £34,590 per QALY gained.[62]

The Assessment Group identified several issues with the manufacturers' submitted models, in particular, the exclusion of relevant treatment options specified in the final NICE scope[36] and the use of a short time horizon. Given the missing comparators within each of the manufacturers' submitted economic analyses, it is unclear how these models should be used to inform NICE decision-making.

The Assessment Group developed a de novo cost-effectiveness model to assess IFX, ADA, GOL, conventional non-biological treatments and elective surgery within the moderate to severe UC population. The base-case analysis of the Assessment Group model suggests that within an adult UC population, colectomy is expected to produce 14.71 discounted QALYs at a discounted cost of approximately £56,300 over the patient's remaining lifetime. All medical options are expected to produce substantially fewer QALYs at a greater cost than colectomy, hence colectomy is expected to dominate IFX, ADA, GOL and conventional non-biological treatments. When colectomy is not considered to be an acceptable option, the base-case analysis of the Assessment Group model suggests that IFX and GOL are expected to be ruled out because of dominance, while the incremental cost-effectiveness of ADA versus conventional non-biological treatment is expected to be approximately £50,300 per QALY gained.

The Assessment Group also undertook a separate probabilistic economic analysis of IFX, conventional non-biological treatments and colectomy within a paediatric population (mean age = 15 years). When colectomy is an acceptable treatment option, the economic analysis suggests that this option dominates IFX and conventional non-biological treatments. When colectomy is not an acceptable option, the economic analysis suggests that the incremental cost-effectiveness of IFX versus conventional treatments is approximately £68,000 per QALY gained.

The results of the Assessment Group model were largely insensitive to changes in model parameter values with the exception of the HRQoL values for each state. The use of utility estimates from Swinburn *et al.*[139] results in a situation whereby colectomy produces the lowest QALY gain and conventional management and GOL are ruled out because of extended dominance. Within this scenario, the incremental cost-effectiveness of ADA versus elective colectomy is estimated to be £79,714 per QALY gained, while the incremental cost-effectiveness of IFX versus ADA is estimated to be £178,982 per QALY gained.

Strengths and limitations of the assessment

The systematic review was based on rigorous methods, with comprehensive searches for evidence, a good level of consistency between reviewers in study selection and double-checking of data extraction. Clinical response and remission data were widely reported across included trials and study authors were consistent in their use of the complete Mayo score, which aided the comparison of trials. Although no head-to-head RCT evidence was available, NMAs were performed to permit a comparison of the efficacy of interventions in terms of clinical response and remission.

The economic analysis presented by the Assessment Group has several strengths:

- The treatment pathway represented within the model was based on considerable expert opinion of several leading UC experts.
- The Assessment Group model is underpinned by a complex NMA across all drug options thereby synthesising relevant efficacy outcomes data within a single network of evidence.
- The model generally adheres to the NICE reference case and fully addresses the decision problem set out in the final NICE scope.
- When appropriate and possible, systematic search methods have been used to identify, select and use evidence to inform the model's parameters (efficacy, HRQoL and colectomy rates).
- The Assessment Group have undertaken extensive sensitivity analyses to examine the impact of alternative assumptions and sources of evidence on the robustness of the results of the model.

The Assessment Group model is also subject to a number of limitations:

- There is considerable uncertainty associated with Assessment Group's extrapolation of short-term trial data (maximum 54 weeks) to a lifetime horizon.
- The model does not consider an explicit sequential pathway of non-biological treatments; rather, during any cycle, a proportion of patients are assumed to receive 5-ASAs, immunomodulators and prednisolone.
- Evidence relating to complications of colectomy was identified through consideration of approaches used within previous models rather than through a full systematic review; however, these assumptions were tested within the sensitivity analyses.

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Uncertainties

Key uncertainties in this assessment include:

- the optimal duration of intervention treatment in responding patients
- the maintenance of efficacy outcomes and safety of interventions beyond the limited study lengths available
- the maintenance of outcomes in responding patients following cessation of anti-TNF-α treatment
- the relationship between post-surgical outcomes and HRQoL.

Chapter 7 Conclusions

Based on the NMA for clinical response and remission in the induction phase, all treatments were associated with statistically significant beneficial effects relative to PBO, with the greatest effect being associated with IFX. For patients classified as responders at the end of the induction phase, treatment effects were not statistically significant, although the greatest effect at 8–32 weeks was associated with 100 mg of GOL. At 32–52 weeks, only 50 mg of IFX and GOL were associated with beneficial effects on clinical response. For patients classified as being in remission at the end of the induction phase, all treatments except for ADA were associated with beneficial treatment effects relative to PBO with the greatest effect being associated with 50 mg and 100 mg of GOL, although the effects were not statistically significant at 8–32 weeks. At 32–52 weeks, all treatments except 50 mg of GOL were associated with beneficial treatment effects relative to PBO, with the greatest effect being associated with ADA (the only treatment with statistically significant effect). ADA was associated with the highest probability of staying in remission and the smallest probability of moving from remission to response and from remission to no response.

Available data on hospitalisation outcomes were very limited, but suggested that outcomes may be more favourable for ADA-treated and IFX-treated patients than PBO (with no data available from GOL trials). Data on surgical intervention were also very sparse, with a potential inconclusive benefit for intervention-treated patients compared with PBO. No trials reported whether surgical outcomes were elective or emergency in nature; however, further data are required to demonstrate the impact of interventions on hospitalisation and surgical intervention more conclusively. Data were available from a single trial to support the use of IFX in induction and maintenance treatment in a paediatric population.

The main safety issues highlighted in the RCT evidence appeared to be generally consistent with those previously discussed in the respective SmPCs for each product (including serious infections, malignancies and administration site reactions). Deaths occurring during and after the study period were described in some trials evaluating GOL (PURSUIT-Maintenance) and IFX (ACT1 and ACT2), of which infection or malignancy commonly appeared to be implicated. This underlines the importance of monitoring and treating serious infections and malignancies in patients receiving immunosuppressive treatment.

The base-case analysis of the Assessment Group model suggests that within an adult UC population, colectomy is expected to dominate IFX, ADA, GOL and conventional non-biological treatments. When elective colectomy is not an acceptable option, the Assessment Group model suggests that IFX and GOL are expected to be ruled out because of dominance, while the incremental cost-effectiveness of ADA versus conventional non-biological treatment is expected to be approximately £50,300 per QALY gained. The base-case analysis of the Assessment Group model suggests that within a paediatric UC population, colectomy is expected to dominate IFX and conventional non-biological treatments. When colectomy is not an acceptable option, the incremental cost-effectiveness of IFX versus conventional treatments is approximately £68,000 per QALY gained.

Implications for service provision

The Assessment Group is unaware of any further implications for service provision beyond those addressed in *Chapter 5* of this report.

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Suggested research priorities

- Assessment of maintenance of outcomes in responding patients following cessation of anti-TNF-α treatment.
- Assessment of efficacy, safety and immunogenicity following reintroduction of interventions after interruption in treatment.
- Assessment of efficacy of interventions under assessment in specific subgroups (e.g. according to disease duration, as specified in the appraisal scope).
- Head-to-head RCTs of interventions under assessment against each other in the treatment of moderate to severe UC after the failure of conventional therapy.
- RCTs evaluating use of interventions under assessment in biological switching (i.e. after failure of first anti-TNF-α agent).
- RCTs of longer duration of follow-up to assess maintenance of outcomes over the longer term.
- RCTs assessing the clinical effectiveness of biologicals in paediatric patients.
- Surgical intervention and hospitalisation to be incorporated as outcomes in future RCTs and associated extension studies of interventions in the treatment of moderately to severely active UC after the failure of conventional therapy.
- Definition of factors that predict an improved patient response to anti-TNF-α treatment.
- Further exploration of comparative clinical and economic outcomes (including the use of a preference-based utility instrument) associated with medical versus surgical treatments for patients with moderate to severe UC.
- Consideration of unified universally agreed primary end points in future UC RCTs.

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About ScHARR: ScHARR is one of the nine departments that comprise the Faculty of Medicine, Dentistry and Health at the University of Sheffield. ScHARR specialises in health services and public health research, and the application of health economics and decision science to the development of health services and the improvement of public health.

The ScHARR Technology Assessment Group (ScHARR-TAG) synthesises research on the clinical effectiveness and cost-effectiveness of health-care interventions for the NIHR HTA programme on behalf of a range of policy makers, including NICE. ScHARR-TAG is part of a wider collaboration of a number of units from other regions including Health Economics Research Unit and Health Services Research Unit, University of Aberdeen; Southampton Health Technology Assessment Centre, University of Southampton; Liverpool Reviews and Implementation Group, University of Liverpool; Peninsular Technology Assessment Group, University of Exeter; the NHS Centre for Reviews and Dissemination, University of York; Warwick Evidence, University of Warwick; the BMJ Technology Assessment Group, BMJ Evidence Centre and Kleijnen Systematic Reviews Ltd.

Contributions of authors

Rachel Archer acted as principal investigator for this assessment.

Paul Tappenden and **Hasan Basarir** undertook the health economic review and developed the Assessment Group model.

Shijie Ren, Rebecca Harvey and **John Stevens** conducted the NMAs.

Rachel Archer, Marrissa Martyn-St James and **Christopher Carroll** undertook the clinical effectiveness systematic review.

Anna Cantrell carried out the electronic searches.

Alan Lobo (Sheffield Teaching Hospitals NHS Foundation Trust) and **Sami Hoque** (Barts Health NHS Trust) provided clinical advice and commented on the draft assessment report.

Data sharing statement

Requests for data should be addressed to the corresponding author.

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Appendix 1 MEDLINE search for clinical effectiveness evidence

Database: MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations (via Ovid).

Searched: 1946 to December 2013.

URL: Gateway.ovid.com.

Search strategy

1. Colitis, Ulcerative/
2. ulcerative colitis.tw.
3. colitis ulcerosa.tw.
4. uc.tw.
5. colitis ulcerative.tw.
6. Colitis/
7. colitis.tw.
8. colitides.tw.
9. Inflammatory Bowel Diseases/
10. inflammatory bowel disease$.tw.
11. ibd.tw.
12. (col* and ulcer*).tw.
13. colitis gravis.tw.
14. proctocolitis.tw.
15. or/1-14
16. adalimumab.af.
17. humira.af.
18. d 2e7.af.
19. d2e7.af.
20. 331731-18-1.rn.
21. infliximab.af.
22. remicade.af.
23. 170277-31-3.rn.
24. ta650.af.
25. ta 650.af.
26. inx.af.
27. remsima.af.
28. inflectra.af.
29. ct p13.af.
30. ctp13.af.
31. golimumab.af.
32. simponi.af.
33. cnto148.af.
34. cnto 148.af.
35. 476181-74-5.rn.
36. tnf inhibitor$.tw.
37. anti tnf.tw.
38. antitnf.tw.

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39. tnf antagonist$.tw.
40. tnf-alpha blocker$.tw.
41. antitumo?r necrosis factor.tw.
42. Biosimilar Pharmaceuticals/
43. (biosimilar$ or biologic$).tw.
44. or/16-43
45. 15 and 44

Terms 1–14 are terms for the condition (ulcerative colitis) which are then combined using OR in term 15. Terms 16–43 are terms for the interventions (infliximab, adalimumab and golimumab) which are then combined using OR in term 44. Terms 15 and 44 are then combined using AND to find studies on the condition and interventions in term 45.

To retrieve RCTs and systematic reviews specially designed highly sensitive search filter were combined with term 45. RCT filter and systematic review filter below.

Randomised controlled trial filter

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. 49 placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. or/1-8
10. exp animals/ not humans.sh.
11. 9 not 10

Systematic review filter

1. Meta-Analysis/
2. meta analy$.tw.
3. metaanaly$.tw.
4. meta analysis.pt.
5. (systematic adj (review$1 or overview$1)).tw.
6. exp Review Literature/
7. or/1-6
8. cochrane.ab.
9. embase.ab.
10. (psychlit or psyclit).ab.
11. (psychinfo or psycinfo).ab.
12. (cinahl or cinhal).ab.
13. science citation index.ab.
14. bids.ab.
15. cancerlit.ab.
16. or/8-15
17. reference list$.ab.
18. bibliograph$.ab.
19. hand-search$.ab.
20. relevant journals.ab.
21. manual search$.ab.

22. or/17-78
23. selection criteria.ab.
24. data extraction.ab.
25. 23 or 24
26. review.pt.
27. 25 and 26
28. comment.pt.
29. letter.pt.
30. editorial.pt.
31. animal/
32. human/
33. 31 not (31 and 32)
34. or/28-30,33
35. 7 or 16 or 22 or 27
36. 35 not 34

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Appendix 2 Table of excluded studies

Author and year/NCT number	Reason for exclusion
Actis *et al.*, 2002[161]	Not a RCT
Actis, 2003[162]	Not a RCT
Afif *et al.*, 2009[163]	Not a RCT
Allez *et al.*, 2010[164]	Not a RCT
(No authors listed) 2007[165]	Not a RCT
Armuzzi *et al.*, 2004[166]	Not protocol-eligible population. No prior immunosuppressant use reported
Baert *et al.*, 2007[167]	Not a RCT
Barbato *et al.*, 2006[168]	Not a RCT
Barreiro-de *et al.*, 2009[169]	Not a RCT
Baumgart, 2010[170]	Not a RCT
Ben-Horin, 2012[171]	Not treatment of interest (rituximab)
Bengi and Akpinar, 2012[172]	Not a RCT
Biancone *et al.*, 2009[173]	Not a RCT
(No authors listed) 2012[174]	Not a RCT
Bordeianou, 2009[175]	Not a RCT
Borruel *et al.*, 2013[176]	Not a RCT
Brooklyn *et al.*, 2006[177]	Not UC trial population
Bujanover and Weiss, 2008[178]	Not a RCT
Busquets and Aldeguer, 2013[179]	Not a RCT
Carbone *et al.*, 2009[180]	Not a RCT
Cariñanos *et al.*, 2011[181]	Not a RCT
Casteele *et al.*, 2012[182,183]	Evaluation of two IFX dosing strategies
Charles *et al.*, 2010[184]	Not a RCT
Chen *et al.*, 2013[185]	Not a RCT
Chey and Shah, 2005[186]	Not a RCT
Chowers *et al.*, 2010[187]	Not a RCT
Chuang *et al.*, 2010[188]	Not a RCT
Cohen, 2003[189]	Not a RCT
Colombel *et al.*, 2011[190]	No protocol-eligible outcome data
Colombel *et al.*, 2011[190]	Not a RCT
Colombel *et al.*, 2012[191]	Parallel publication, duplicate outcome data
Cottone, *et al.*, 2008[192]	Not a RCT
Croft *et al.*, 2013[193]	Population outside scope of appraisal (use of biological in acute severe UC following failure of i.v. steroids)
Cross *et al.*, 2008[194]	Not a RCT
Danese, 2013[195]	Unable to obtain

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Author and year/NCT number	Reason for exclusion
De Vos *et al.*, 2012[196]	Not a RCT
de Vries *et al.*, 2009[197]	Not a RCT
D'Haens, 2005[198]	Not a RCT
Dean *et al.*, 2012[199]	Not a RCT
Dignass *et al.*, 2012[200]	Not a RCT
Domènech *et al.*, 2010[201]	Not a RCT
Dranitsaris *et al.*, 2012[202]	Not a RCT
Eidelwein *et al.*, 2005[203]	Not a RCT
Erikkson *et al.*, 2012[204]	Not a RCT
Esteve *et al.*, 2011[205]	Not a RCT
EUCTR2007–006692–37-GB[206]	Not UC trial population
EUCTR2007–007702–30-IT[206]	Not a RCT
EUCTR2007–000842–11-AT[206]	Not a RCT
EUCTR2008–007519–34-SE[206]	Not a RCT
EUCTR2011–002411–29-SE[206]	Not a RCT
EUCTR2011–006084–22-GB[206]	Not a RCT
Fanjiang *et al.*, 2007[207]	Not a RCT
Fasanmade *et al.*, 2009[208]	No protocol-eligible outcome data
Fasanmade *et al.*, 2010[209]	No protocol-eligible outcome data
Feagan *et al.*, 2005[210]	Not a RCT
Feagan, 2006[211]	Not a RCT
Florholmen *et al.*, 2011[212]	Population outside scope of appraisal (use of biological in acute severe UC following failure of i.v. steroids)
Ford *et al.*, 2013[3]	Not a RCT
Gao and Jiang, 2013[213]	Not available in English language
Gavalas *et al.*, 2007[214]	Population outside scope of appraisal (use of biological in acute severe UC)
Gearry and Falvey, 2012[215]	Not a RCT
Gies *et al.*, 2010[216]	Not a RCT
Ginard *et al.*, 2008[217]	Not a RCT
Grosen *et al.*, 2013[218]	Not a RCT
Gustavsson *et al.*, 2010[219]	Follow-on study to excluded Järnerot *et al.*, 2005[112]
Ha *et al.*, 2011[220]	Not a RCT
Halpin *et al.*, 2010[221]	Not a RCT
Halpin and Hamlin, 2012[222]	Not a RCT
Hämäläinen *et al.*, 2011[223]	Not a RCT
Hanauer, 2005[224]	Not a RCT
Hanauer *et al.*, 2008[225]	Not a RCT
Hanauer *et al.*, 2008[226]	Not a RCT
Heraganahally *et al.*, 2009[227]	Not a RCT

Author and year/NCT number	Reason for exclusion
Herrlinger *et al.*, 2010[228]	Not a RCT
Honeywell *et al.*, 2007[229]	Unable to obtain
Hyams *et al.*, 2010[230]	Not a RCT
Hyams *et al.*, 2011[231]	Unable to obtain
Assasi, 2009[232]	Not a RCT
Jackson, 2007[233]	Not a RCT
Järnerot *et al.*, 2005[112]	Population outside scope of appraisal (use of biological in acute UC following failure of i.v. steroids)
Järnerot, 2006[234]	Not a RCT
Jiménez, 2004[235]	Not a RCT
Joob and Wiwanikit, 2013[236]	Not a RCT
JPRN-UMIN000006169[206]	Not a RCT
JPRN-UMIN000007256[206]	Not a RCT
JPRN-UMIN000007806[206]	Not a RCT
JPRN-UMIN000010205[206]	Not a RCT
JPRN-UMIN000013033[206]	Not a RCT
Kaser and Tilg, 2008[237]	Not a RCT
Kaur and Targan, 2013[238]	Not a RCT
Kerbleski and Gottlieb, 2009[239]	Not a RCT
Klotz, *et al.*, 2007[240]	Not a RCT
Kohn *et al.*, 2004[241]	Not a RCT
Kohn *et al.*, 2007[242]	Not a RCT
Kohn, 2008[243]	Not a RCT
Laharie *et al.*, 2012[244,245]	Population outside scope of appraisal (use of biological in acute severe UC following failure of i.v. steroids)
Leal *et al.*, 2012[246]	Not a RCT
LeBlanc *et al.*, 2013[247]	Not a RCT
Leblanc *et al.*, 2011[248]	Not a RCT
Levesque and Sandborn, 2012[249]	Not a RCT
Levy, 2009[250]	Not a RCT
Li *et al.*, 2013[251]	No protocol-eligible outcome data
Lichtenstein, 2001[252]	Not a RCT
Lichtenstein, 2009[253]	Not a RCT
Liu *et al.*, 2013[254]	Not a RCT
Löfberg *et al.*, 2012[255]	Not UC trial population
Lorenzo-Zúñiga *et al.*, 2013[256]	Not a RCT
Mallow *et al.*, 2013[257]	Not a RCT
Mallow *et al.*, 2013[258]	Not a RCT
Maser *et al.*, 2008[259]	Not a RCT
Matsumoto, 2007[260]	Not a RCT

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Author and year/NCT number	Reason for exclusion
Mazumdar and Greenwald, 2009[261]	Not a RCT
McCann and Smith, 2013[262]	Not a RCT
Molnár *et al.*, 2010[263]	Not a RCT
Molnár *et al.*, 2011[264]	Not a RCT
Molnár *et al.*, 2011[265]	Not a RCT
Moss and Farrell, 2006[266]	Not a RCT
Nakase *et al.*, 2010[267]	Not a RCT
National Institute for Health Research, 2011[268]	Not a RCT
National Institute for Health Research, 2011[269]	Not a RCT
National Institute for Health Research, 2013[270]	Not a RCT
NCT00207688[206]	Not a RCT
NCT00421642[206]	Not a RCT
NCT00488774[271]	Unlicensed route of administration for intervention
NCT00573794[271]	Not a RCT
NCT00586599[271]	Not a RCT
NCT00586807[271]	Not a RCT
NCT00606346[271]	Not a RCT
NCT00705484[271]	Not a RCT
NCT00745329[271]	Not a RCT
NCT00791557[271]	Not a RCT
NCT00955123[271]	Not a RCT
NCT00984568[271]	Evaluation of different IFX treatment strategies
NCT01346826[271]	Evaluation of accelerated IFX infusions
NCT01408810[271]	Not a RCT
NCT01417728[271]	Not a RCT
NCT01494857[271]	Not a RCT
NCT01550965[271]	Not a RCT
NCT01585155[271]	Not a RCT
NCT01670240[271]	Evaluation of biological in treatment of chronic pouchitis (trial currently recruiting)
NCT01716039[271]	Study evaluating ADA–MTX interaction
NCT01787786[271]	Not a RCT
NCT01846026[271]	Not protocol-eligible intervention
NCT01848561[271]	Not a RCT
NCT01851343[206]	Not a RCT
NCT01900574[271]	Not a RCT
NCT01947816[271]	Not a RCT
NCT01960426[271]	Evaluation of two dosing methods
NCT01971814[271]	Not a RCT
NCT01988961[271]	Not a RCT

Author and year/NCT number	Reason for exclusion
NCT02057016[206]	Not a RCT
NCT02073526[206]	Not a RCT
Nguyen and Prather, 2009[272]	Not a RCT
Nielsen and Jess, 2013[273]	Unable to obtain
Ochsenkühn *et al.*, 2004[274]	Population outside scope of appraisal: (1) use of biological in acute severe UC, (2) no patients were receiving immunosuppressants/immunomodulators > 10 mg/day prednisolone at baseline and, therefore, not inadequate responders/stated intolerant to conventional therapy options
Orlando *et al.*, 2012[275]	Not UC trial population
Oussalah *et al.*, 2008[276]	Not a RCT
Oussalah *et al.*, 2010[277]	Not a RCT
Panncione *et al.*, 2011[278]	Parallel publication, duplicate outcome data
Panncione *et al.*, 2013[279]	Parallel publication, duplicate outcome data
Pardi and Sandborn, 2008[280]	Not a RCT
Pastore *et al.*, 2010[281]	Not a RCT
Pastorelli *et al.*, 2009[282]	Not a RCT
Pearce and Lawrance, 2007[283]	Not a RCT
Peyrin-Biroulet *et al.*, 2007[284]	Not a RCT
Pola *et al.*, 2013[285]	Not a RCT
Reinisch and Sandborn 2012[286]	No protocol-eligible outcome data
Rizzello *et al.*, 2013[287]	Not a RCT
Rostholder *et al.*, 2012[288]	Not a RCT
Rubin *et al.*, 2012[289]	Not UC trial population
Russell and Katz, 2004[290]	Not a RCT
Rutgeerts, 2002[291]	Not a RCT
Rutgeerts *et al.*, 2010[292]	Not a RCT
Rutgeerts *et al.*, 2013[293]	Parallel publication, duplicate outcome data
Rutgeerts *et al.*, 2013[294]	Parallel publication, duplicate outcome data
Salvana and Salata, 2009[295]	Not a RCT
Sandborn *et al.*, 2007[296]	Not a RCT
Sandborn *et al.*, 2009[67]	Not a RCT
Sandborn, 2012[297]	Not a RCT
Sandborn *et al.*, 2011[298]	Parallel publication, duplicate outcome data
Sandborn *et al.*, 2011[299]	Parallel publication, duplicate outcome data
Sandborn *et al.*, 2012[300]	Parallel publication, duplicate outcome data
Sandborn *et al.*, 2012[301]	Parallel publication, duplicate outcome data
Sandborn *et al.*, 2012[302]	Parallel publication, duplicate outcome data
Sandborn *et al.*, 2012[60]	Parallel publication, duplicate outcome data
Sandborn *et al.*, 2012[303]	Unable to obtain
Sandborn *et al.*, 2012[304]	Unable to obtain

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Author and year/NCT number	Reason for exclusion
Sandborn and Loftus, 2004[305]	Not a RCT
Sands *et al.*, 2001[306]	Population outside scope of appraisal (use of biological in acute severe UC following failure of i.v. steroids)
Scholmerich, 2009[307]	Not a RCT
Sciaudone *et al.*, 2010[308]	Not a RCT
Sciaudone *et al.*, 2011[309]	Not a RCT
Seirafi *et al.*, 2011[310]	Not a RCT
Siemanowski and Regueiro, 2007[311]	Not a RCT
Simmons and Jewell, 2002[312]	Not a RCT
Singh and Loftus, 2013[313]	Not a RCT
Sjöberg *et al.*, 2012[314]	Not a RCT
Smith, 2013[315]	Unable to obtain
Sokol *et al.*, 2010[316]	Not a RCT
Stein and Stein 2013[317]	Unable to obtain
Su *et al.*, 2002[318]	Not a RCT
Taxonera *et al.*, 2011[319]	Not a RCT
Thorlund *et al.*, 2013[320]	Not a RCT
Toedter *et al.*, 2010[321]	No protocol-eligible outcome data
Toedter *et al.*, 2011[322]	No protocol-eligible outcome data
Travis, 2011[323]	Not a RCT
Tursi *et al.*, 2010[324]	Not a RCT
Van Assche, 2008[325]	Not a RCT
Van Assche, *et al.*, 2008[326]	Not a RCT
van Casteren-Messidoro *et al.*, 2012[327]	Not a RCT
Velayos and Mahadevan, 2007[328]	Not a RCT
Vermeire *et al.*, 2011[329]	Not treatment of interest (antibody PF-00547,659)
Warner and Harris, 2012[330]	Not a RCT
Waters *et al.*, 2008[331]	Unable to obtain
Waters *et al.*, 2009[332]	Not a RCT
Willert and Lawrance, 2008[333]	Not a RCT
Wolf *et al.*, 2007[334]	Not a RCT
Wolf *et al.*, 2012[335]	Parallel publication, duplicate outcome data
Yamamoto and Shiraki, 2012[336]	Not a RCT
Yamamoto-Furusho and Uzcanga, 2008[337]	Not a RCT
Yapali and Hamzaoglu, 2007[338]	Not a RCT

NCT, National Clinical Trial.

Appendix 3 Table of numbers withdrawing and reasons for withdrawal

Participants withdrawing from treatment arms, reasons for withdrawal and risk of attrition bias assessment judgement

Study number	Treatment arm	Number completing: *n/N* (%)	Reasons for withdrawal	Attrition bias judgement
ULTRA1[44]	PBO	ITT-A3 (amendment): 121/130 (93%)	ITT-A3 (amendment): AE, 5/130 (4%); lack of efficacy, 4/130 (3%) – overall, 9/130 (7%)	Low risk: ≤ 10% attrition in each group, numbers balanced across groups, ITT analysis presented
ULTRA1[44]	160 mg/80 mg of ADA	ITT-A3 (amendment): 118/130 (91%)	ITT-A3 (amendment): AE, 6/130 (5%); withdrew consent, 2/130 (1.5%); lost to follow-up, 2/130 (1.5%); lack of efficacy, 2/13 (1.5%) – overall, 12/130 (9%)	
ULTRA2[45]	PBO	135/260 (52%) switched to open label of which *n* = 84 dose escalated to 40 mg per week overall, 131/260 (50.4%); completed on 16 mg/80 mg/40 mg dosing, 56/260 (21.5%); switched to open label 40 mg every other week at week 12 (*n* = 135), 30/260 (11.5%); dose escalated to 40 mg weekly (*n* = 68), 45/260 (17.3%)	Site non-compliance, 10/258 (4%); lack of efficacy, 63/258 (24%); AE, 12/258 (5%); withdrew consent, 8/258 (3%); lost to follow-up, 1/258 (< 1%); protocol violation, 1/258 (< 1%); other, 9/258 (3%)	High risk: although ITT analysis was undertaken, there was a high level of attrition and an imbalance between treatment groups (PBO, 50%; ADA, 59%)
ULTRA2[45]	160 mg of ADA at week 0, 80 mg at week 2 and then 40 mg EOW beginning at week 4	116/258 (45%) switched to open label of which *n* = 68 dose escalated to 40 mg week overall, 154/258 (59.7%); completed on 16 mg/80 mg/40 mg dosing, 82/258 (31.7%); switched to open label 40 mg every other week at week 12 (*n* = 116), 32/258 (12.4%); dose escalated to 40 mg weekly (*n* = 68), 40/258 (15.5%)	Site non-compliance, 14/260 (5%); lack of efficacy, 70/260 (27%); AE, 25/260 (10%); withdrew consent, 4/260 (1.5%); protocol violation, 5/260 (2%); other, 11/260 (4%)	
Suzuki[46]	PBO	Week 8: 92/96 (96%), week 52: 73/96 (77%)	Week 8: total discontinued, 4/96 (4%) – lack of efficacy *n* = 2, AE *n* = 2. Week 52: total discontinued, 23/96 (23%) – withdrew consent *n* = 2, lack of efficacy *n* = 14, AE *n* = 7; moved to rescue therapy *n* = 63	Induction: low risk – < 10% attrition in each group and numbers reasonably balanced across groups. All patients accounted for in the primary outcome analysis

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Study number	Treatment arm	Number completing: *n/N* (%)	Reasons for withdrawal	Attrition bias judgement
Suzuki[46]	80 mg/40 mg of ADA	Week 8: 85/87 (98%) (unlicensed), week 52: 58/87 (67%)	Week 8: total discontinued, 2/87 (2%) – withdrew consent $n = 1$, lack of efficacy $n = 1$. Week 52: total discontinued, 29/87 (33%) – withdrew consent $n = 3$, lack of efficacy $n = 17$, AE $n = 9$; moved to rescue therapy $n = 50$	Maintenance: high risk – PBO, 23%; ADA, 33%
Suzuki[46]	160 mg/80 mg of ADA	Week 8: 86/90 (96%), week 52: 60/90 (67%)	Week 8: total discontinued, 4/90 (4%) – lack of efficacy $n = 1$, AE $n = 3$. Week 52: total discontinued, 30/90 (33%) – lack of efficacy $n = 16$, AE $n = 13$, other $n = 1$; moved to rescue therapy $n = 46$	
ULTRA3[54]	PBO	91/121 (75%)	Lack of efficacy, 21/121 (17%); AE, 16/121 (13%); withdrew consent, 3/121 (2%); protocol violation, 1/121 (1%)	Extension study not included in risk of bias assessment
ULTRA3[54]	80 mg/40 mg of ADA	86/118 (73%)	Lack of efficacy, 17/118 (14%); AE, 12/118 (10%); withdrew consent, 5/118 (4%); lost to follow-up, 1/118 (1%); protocol violation, 1/118 (1%); other, 4/118 (3%)	
ULTRA3[54]	160 mg/80 mg of ADA	95/121 (79%)	Lack of efficacy, 15/121 (%); AE, 10/121 (%); withdrew consent, 4/121 (%); lost to follow-up, 1/121 (%); protocol violation, 1/121 (%)	
PURSUIT-SC[47]	Phase II PBO	41/42 plus 26/31 enrolled while Phase II data being analysed	2/42 'other' reasons	Low risk: ITT reported and withdrawal < 10% across all groups and *n* balanced
PURSUIT-SC[47]	Phase II 200 mg/100 mg of GOL all randomised	41/42 plus 31/31 enrolled while Phase II data being analysed	1/42 withdrew consent	
PURSUIT-Maintenance[48]	PBO	PBO 115/156 (73%) randomised completed through week 54	Discontinued treatment prior to week 52 ($n = 43$): 17 AE, 19 unsatisfactory therapeutic effect, 1 lost to follow-up, 6 other. Terminated study before week 54 ($n = 18$): 5 withdrew consent, 3 lost to follow-up, 10 other	High risk: although ITT reported, withdrawal > 10% across all groups

Study number	Treatment arm	Number completing: *n/N* (%)	Reasons for withdrawal	Attrition bias judgement
PURSUIT-Maintenance[48]	50 mg of GOL	50 mg of GOL. 120/154 (78%) randomised completed through week 54	Discontinued treatment prior to week 52 ($n = 43$): 12 AE, 17 unsatisfactory therapeutic effect, 2 lost to follow-up, 12 other. Terminated study before week 54 ($n = 18$): 10 withdrew consent, 2 lost to follow-up, 6 other	
PURSUIT-Maintenance[48]	100 mg of GOL	100 mg of GOL. 116/154 (75%) randomised completed through week 54	Discontinued treatment prior to week 52 ($n = 45$): 12 AE, 22 unsatisfactory therapeutic effect, 1 lost to follow-up, 10 other. Terminated study before week 54 ($n = 21$): 11 withdrew consent, 2 lost to follow-up, 8 other	
UC-SUCCESS[51]	AZA	53/79 (66%)	AE, 11/80 (14%); withdrew consent, 8/80 (10%); non-compliance with protocol, 5/80 (6%); protocol ineligible, 3/80 (4%)	High risk: although ITT analysis was undertaken, there was a high level of attrition and an imbalance between treatment groups (AZA, 34%; IFX, 18%; IFX/AZA, 21%)
UC-SUCCESS[51]	IFX	65/78 (82%)	AE, 7/79 (9%); clinical event, 1/79 (1%); lost to follow-up, 1/79 (1%); withdrew consent, 3/79 (4%); non-compliance with protocol, 1/79 (1%); protocol ineligible, 1/79 (1%)	
UC-SUCCESS[51]	IFX/AZA	63/80 (79%)	AE, 8/80 (10%); withdrew consent, 4/80 (5%); non-compliance with protocol, 1/80 (1%); protocol ineligible, 2/80 (3%); administrative reasons, 2/80 (3%)	
Probert *et al.*[50]	PBO	20/20 (100%)	No withdrawals reported	Low risk: all patients accounted for in the primary outcome analysis
Probert *et al.*[50]	IFX	23/23 (100%)		
Hyams *et al.*[52]	5 mg of IFX every 8 weeks	18/22 (82%) completed infusions and follow-up	AE, 3/22 (14%); lack of efficacy, 1/22 (5%)	High risk: numbers withdrawing > 10% and unbalanced across groups (every 8 weeks, 21%; every 12 weeks, 51%)
Hyams *et al.*[52]	5 mg of IFX every 12 weeks	12/23 (52%) complete infusions; 11/23 (49%) completed follow-up	AE, 6/23 (26%); lack of efficacy, 4/23 (17%); other, 1/23 (4%)	

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APPENDIX 3

Study number	Treatment arm	Number completing: *n/N* (%)	Reasons for withdrawal	Attrition bias judgement
ACT1[49]	PBO	47 completed study infusions, of whom 46/121 completed follow-up. 74 discontinued study infusions, of whom 18 completed follow-up	In ACT1, similar numbers of patients in each group discontinued treatment because of an AE	High risk: although ITT reported, > 50% in PBO and > 30% in IFX 5 and 10 mg did not complete
ACT1[49]	5 mg/kg of IFX	76/121 completed study infusions, of whom 76 completed follow-up. 45 discontinued study infusions, of whom six completed follow-up		
ACT2[49]	PBO	67 completed study infusions, of whom 64/123 completed follow-up. 56 discontinued study infusion, nine completed follow-up	In ACT2, more patients in the PBO group than in the two IFX groups discontinued treatment because of an AE	High risk: although ITT reported, > 50% in PBO and > 30% in IFX 5 mg and 10 mg did not complete
ACT2[49]	5 mg/kg of IFX	97 completed study infusions, of whom 94/121 completed follow-up. 24 discontinued study infusions, of whom three completed follow-up		

EOW, every other week; ITT-A3, intention to treat-amendment 3.

Appendix 4 Additional efficacy outcomes tables

Additional efficacy outcomes (adult population trials)

Study name	Treatment arm	Time point	Outcome measure
ULTRA1[44]	PBO	Week 8	Subgroup analysis results: remission *n*/*N* (%): Mayo score < 10: 10/83 (12.0%) Mayo score ≥ 10: 2/47 (4.3%); extensive colitis: 11/73 (15.1%); no extensive colitis: 1/57 (1.8%); CS (without IMM%): 6/55 (10.9%); IMM (AZA and 6-MP without CS%): 0/18 (0%) 2/25 (8.0%) 6/28 (21.4%); IMM + CS: 2/34 (5.9%); no CS + no IMM: 4/23 aminosalicylates: 11/98 (11.2%); no aminosalicylates: 1/32 (3.1%); CRP < 10 mg/l: 7/95 (7.4%); CRP ≥ 10 mg/l: 4/32 (12.5%); weight < 70.0 kg: 5/35 (14.3%); weight ≥ 70.0 kg, < 82.0 kg: 3/43 (7.0%); weight ≥ 82.0 kg: 4/52 (7.7%) Change from baseline in CRP mg/l: median –0.09 (range –274.79 to 88.71) Rectal bleeding subscore of ≤ 1, 86/130 (66.2%) PGA subscore of ≤ 1, 61/130 (46.9%) Stool frequency subscore, 49/130 (37.7%) Reinisch *et al.*[61] Change from baseline: Haemoglobin g/l, 4.4; *p*-value vs. PBO < 0.001 Haematocrit fraction, 0.014; *p*-value vs. PBO < 0.001 Red blood cells × 10^{12}/l, 0.16; *p*-value vs. PBO < 0.01 Total protein g/l, 1.5; *p*-value vs. PBO < 0.05 Albumin g/l, 1.3 CRP mg/l, –0.47

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Study name	Treatment arm	Time point	Outcome measure
ULTRA1	160 mg/80 mg of ADA	Week 8	Reinisch *et al.*[44] Subgroup analysis results: remission *n*/N (%): Mayo score < 10: 17/85 (20.0%), difference from PBO (95% CI) 1.5 (–8.7 to 11.8) 8.0 (–3.1 to 19.0) Mayo score ≥ 10: 7/45 (15.6%), difference from PBO (95% CI) 11.3 (–0.8 to 23.4); extensive colitis: 12/60 (20.0%), difference from PBO (95% CI) 4.9 (–8.1 to 18.0); no extensive colitis: 12/70 (17.1%), difference from PBO (95% CI) 15.4 (5.9 to 24.9); CS (without IMM%): 10/48 (20.8%), difference from PBO (95% CI) 11.3 (–3.0 to 25.7) IMM (AZA and 6-MP without CS%): 6/28 (21.4%), difference from PBO (95% CI) 20.7 (5.9 to 35.4); IMM + CS: 2/23 (8.7%), difference from PBO (95% CI) 4.1 (–11.2 to 19.5); no CS + no IMM: 6/31 (19.4%), difference from PBO (95% CI) –1.0 (–20.5 to 18.5); aminosalicylates: 18/105 (17.1%), difference from PBO (95% CI) 5.9 (–3.6 to 15.5); no aminosalicylates: 6/25 (24.0%), difference from PBO (95% CI) 20.9 (3.1 to 38.7); CRP < 10 mg/l: 21/101 (20.8%), difference from PBO (95% CI) 13.4 (3.9 to 22.9); CRP ≥ 10 mg/l: 2/25 (8.0%), difference from PBO (95% CI) –4.5 (–20.1 to 11.1); weight < 70.0 kg: 11/45 (24.4%), difference from PBO (95% CI) 10.2 (–6.9 to 27.2); weight ≥ 70.0 kg, < 82.0 kg: 8/33 (24.2%), difference from PBO (95% CI) 17.3 (0.8 to 33.8); weight ≥ 82.0 kg: 5/52 (9.6%), difference from PBO (95% CI) 1.9 (–8.9 to 12.7) Change from baseline in CRP mg/l: median –0.77 (range –95.09 to 130.41) Rectal bleeding subscore of ≤ 1, 101/130 (77.7%) PGA subscore of ≤ 1, 78/130 (60.0%) Stool frequency subscore, 63/130 (48.5%) Reinisch *et al.*[61] Change from baseline: Haemoglobin g/l, 4.9; *p*-value vs. PBO < 0.001 Haematocrit fraction, 0.014; *p*-value vs. PBO < 0.001 Red blood cells × 10^{12}/l, 0.19; *p*-value vs. PBO < 0.001 Total protein g/l, 1.7; *p*-value vs. PBO < 0.01 Albumin g/l, 1.7; *p*-value vs. PBO < 0.01 CRP mg/l, –0.87; *p*-value vs. PBO < 0.001
ULTRA2	PBO	Week 8	Sandborn *et al.*[45] No prior anti-TNF-α treatment: PGA ≤ 1, 63/145 (43.4%); SFS ≤ 1, 43/145 (29.7%); RBS ≤ 1, 86/145 (59.3%); prior anti-TNF-α treatment: PGA ≤ 1, 29/101 (28.7%); SFS ≤ 1, 27/101 (26.7%); RBS ≤ 1, 57/101 (56.4%)

Study name	Treatment arm	Time point	Outcome measure
ULTRA2	PBO	Week 32	EPAR (Humira)[34] Number and percentage of subjects taking CSs at baseline who discontinued CS use and achieved clinical remission per Mayo score at week 32 (ITT analysis): clinical remission at week 32 – discontinued CS at any time prior to week 32, 10/140 (7.1%) clinical remission at week 32 – discontinued CS for ≥ 90 days prior to week 32, 9/140 (6.4%)
ULTRA2	PBO	Week 52	Sandborn *et al.*[45] Discontinued CS use before week 52 and achieved clinical remission at week 52 among patients with baseline CS use, 5/81 (6.2%); discontinued CS use for ≥ 90 days before week 52 and achieved remission at week 52 among patients with baseline CS use, 5/81 (6.2%); discontinued CS use and achieved sustained clinical remission at both weeks 32 and 52 among patients with baseline CS use, 1/81 (1.2%); IBDQ responders at week 52, 31/145 (21.4%); prior anti-TNF-α treatment: discontinued CS use before week 52 and achieved clinical remission at week 52 among patients with baseline CS use, 3/59 (5.1%); discontinued CS use for ≥ 90 days before week 52 and achieved remission at week 52 among patients with baseline CS use, 3/59 (5.1%); discontinued CS use and achieved sustained clinical remission at both weeks 32 and 52 among patients with baseline CS use, 1/59 (1.7%); IBDQ responders at week 52, 9/101 (8.9%) EPAR (Humira)[34] Discontinued corticosteroid use for ≥ 90 days before week 52 and achieved remission at week 52, 8/246 (5.7%); discontinued corticosteroid use and sustained remission at both week 32 and week 52, 2/246 (1.4%); IBDQ responders at week 52, 40/246 (16.3%); number and percentage of subjects taking CSs at baseline who discontinued CS use and achieved clinical remission per Mayo score at week 52 (ITT analysis): clinical remission at week 52 – discontinued CS at any time prior to week 52, 8/140 (5.7%); clinical remission at week 52 – discontinued CS for ≥ 90 days prior to week 52, 8/140 (5.7%) Sandborn *et al.*[304] Week 52 CS-free remission: all PBO, 8/140 (5.7%); anti-TNF-α-naive PBO, 5/81 (6.2%); anti-TNF-α-exposed PBO, 3/59 (5.1%) week 52 CS-free: all PBO, 32/140 (22.9%); anti-TNF-α-naive PBO, 20/81 (24.7%); anti-TNF-α-exposed PBO, 12/59 (20.3%) Sandborn *et al.*[60] Post-hoc analysis, week 52 $n = 246$: mean days in IBDQ remission (IBDQ score of ≥ 170), 79.00; mean SAE adjusted days in clinical remission, 48.23

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Study name	Treatment arm	Time point	Outcome measure
ULTRA2	160 mg of ADA at week 0, 80 mg at week 2 and then 40 mg EOW	Week 8	Sandborn *et al.*[45] Serum trough concentrations over time by remission status, mean (SD) [min., max.], N_{nmiss}: 40 mg EOW patients who were remitters ($n = 43$): 11.4 (5.15) [0.000, 22.8], 41 40 mg EOW patients who were non-remitters ($n = 153$): 8.49 (4.35) [0.000, 21.8], 110 No prior anti-TNF-α treatment: PGA ≤ 1, 88/150 (58.7%); *p*-value vs. PBO, 0.009SFS ≤ 1, 69/150 (46.0%); *p*-value vs. PBO, 0.004RBS ≤ 1, 116/150 (77.3%); *p*-value vs. PBO, 0.001 IBDQ responders, 102/150 (68.0%); *p*-value vs. PBO, 0.004 Prior anti-TNF-α treatment: PGA ≤ 1, 26/98 (26.5%); *p*-value vs. PBO, 0.731SFS ≤ 1, 25/98 (25.5%); *p*-value vs. PBO, 0.844 RBS ≤ 1, 58/98 (59.2%); *p*-value vs. PBO, 0.695IBDQ responders, 42/98 (42.9%); *p*-value vs. PBO, 0.370
ULTRA2	160 mg of ADA at week 0, 80 mg at week 2 and then 40 mg EOW	Week 32	Sandborn *et al.*[45] Serum trough concentrations over time by remission status, mean (SD) [min., max.], N_{nmiss}: 40 mg EOW patients who were remitters ($n = 43$), 10.6 (5.64) [0.000, 26.9], 39 40 mg EOW patients who were non-remitters ($n = 153$), 6.95 (3.98) [0.000, 18.1], 70
ULTRA2	160 mg of ADA at week 0, 80 mg at week 2 and then 40 mg EOW	Week 52	Sandborn *et al.*[45] Serum trough concentrations over time by remission status, mean (SD) [min., max.], N_{nmiss}: 40 mg EOW patients who were remitters ($n = 43$), 10.8 (7.45) [0.000, 39.3], 39 40 mg EOW patients who were non-remitters ($n = 153$), 6.18 (4.22) [0.000, 16.1], 62 No prior anti-TNF-α treatment: discontinued CS use before week 52 and achieved clinical remission at week 52 among patients with baseline CS use, 15/110 (13.6%); *p*-value vs. PBO, 0.096 discontinued CS use for ≥ 90 days before week 52 and achieved remission at week 52 among patients with baseline CS use, 15/110 (13.6%); *p*-value vs. PBO, 0.096; discontinued CS use and achieved sustained clinical remission at both weeks 32 and 52 among patients with baseline CS use, 11/110 (10.0%); *p*-value vs. PBO, 0.014; IBDQ responders at week 52, 48/150 (32.0%); *p*-value vs. PBO, 0.039; prior anti-TNF-α treatment: discontinued CS use before week 52 and achieved clinical remission at week 52 among patients with baseline CS use, 5/40 (12.5%); *p*-value vs. PBO, 0.263; discontinued CS use for ≥ 90 days before week 52 and achieved remission at week 52 among patients with baseline CS use, 5/40 (12.5%); *p*-value vs. PBO, 0.263; discontinued CS use and achieved sustained clinical remission at both weeks 32 and 52 among patients with baseline CS use, 4/40 (10.0%); *p*-value vs. PBO, 0.155; IBDQ responders at week 52, 17/98 (17.3%); *p*-value vs. PBO, 0.078 EPAR (Humira)[34] Discontinued CS use before week 52 and achieved remission at week 52, 20/248 (13.3%); *p*-value vs. PBO, 0.035; discontinued corticosteroid use for ≥ 90 days before week 52 and achieved remission at week 52, 20/248 (13.3%); *p*-value vs. PBO, 0.035; discontinued corticosteroid use and sustained remission at both week 32 and week 52, 15/248 (10.0%); *p*-value vs. PBO, 0.002; IBDQ responders at week 52, 65/248 (26.2%); *p*-value vs. PBO, 0.007

Study name	Treatment arm	Time point	Outcome measure
			Number and percentage of subjects taking CSs at baseline who discontinued CS use and achieved clinical remission per Mayo score (ITT analysis): clinical remission at week 52 – discontinued CS at any time prior to week 52, 20/150 (13.3%); *p*-value vs. PBO, 0.035; clinical remission at week 52 – discontinued CS for ≥ 90 days prior to week 52, 20/150 (13.3%); *p*-value vs. PBO, 0.035 Van *et al.*[59] Week 52 CS-free remission – full Mayo: all ADA, 18/90 (20.0%); *p*-value vs. PBO, < 0.05; anti-TNF-α-naive ADA, 14/69 (20.3%); *p*-value vs. PBO, < 0.05; anti-TNF-α-exposed ADA, 4/21 (19.0%). Week 52 CS-free remission – partial Mayo: all ADA, 19/90 (21.1%); *p*-value vs. PBO, < 0.001; anti-TNF-α-naive ADA, 14/68 (20.6%); *p*-value vs. PBO, < 0.05; anti-TNF-α-exposed ADA, 5/22 (22.7%); *p*-value vs. PBO, < 0.05 week 52 CS-free – full Mayo: all ADA, 4/90 (45.6%); *p*-value vs. PBO, < 0.001; anti-TNF-α-naive ADA, 31/69 (44.9%); *p*-value vs. PBO, < 0.05; anti-TNF-α-exposed ADA, 10/21 (47.6%); *p*-value vs. PBO, < 0.05 week 52 CS-free – partial Mayo: all ADA, 43/90 (47.8%); *p*-value vs. PBO, < 0.001; anti-TNF-α-naive ADA, 31/68 (45.6%); *p*-value vs. PBO, < 0.05; anti-TNF-α-exposed ADA, 12/22 (54.5%); *p*-value vs. PBO, < 0.05 Sandborn *et al.*[60] Post-hoc analysis, week 52 *n* = 248: mean days in IBDQ remission (IBDQ score of ≥ 170), 103.93; *p*-value vs. PBO, 0.025; mean SAE adjusted days in clinical remission, 81.21; *p*-value vs. PBO, < 0.001
ULTRA3	40 mg of ADA EOW or EW	Week 52	Sandborn *et al.*[339] Clinical remission at week 52 in patients who responded per partial Mayo score at week 8 – ITT-A3 protocol: non-responder imputation, 76/196 (38.8%); modified non-responder imputation, 84/196 (42.9%); as observed 76/131 (58.0%) clinical response at week 52 in patients who responded per partial Mayo score at week 8 – ITT-A3 protocol: non-responder imputation, 113/196 (57.7%); modified non-responder imputation, 131/196 (66.8%); as observed 113/131 (86.3%) proportion of patients in the ITT-A3 population with Mayo subscores indicative of mild disease or remission at week 52: rectal bleeding subscore of ≤ 1: non-responder imputation, 185/390 (47.4%); modified non-responder imputation, 246/390 (63.1%); as observed, 185/279 (67.0%) stool frequency subscore of ≤ 1: non-responder imputation, 145/390 (37.2%); modified non-responder imputation, 175/390 (44.9%); as observed, 145/276 (52.5%); physician's global assessment ≤ 1: non-responder imputation, 169/390 (43.3%); modified non-responder imputation, 215/390 (55.1%); as observed, 169/276 (61.2%) proportion of patients in the ITT-A3 and ITT-E populations with Mayo subscores indicative of mild disease or remission at week 52: rectal bleeding subscore of ≤ 1: non-responder imputation, 270/575 (47.0%); modified non-responder imputation, 348/575 (60.5%); as observed, 270/290 (93.1%); stool frequency subscore of ≤ 1: non-responder imputation, 210/575 (36.5%); modified non-responder imputation, 251/575 (43.7%); as observed, 210/290 (72.4%); physician's global assessment ≤ 1: non-responder imputation, 240/575 (41.7%); modified non-responder imputation, 299/575 (52.0%) 240/290 (82.8%); steroid-free remission at week 52; patients using steroids at baseline in the ITT-A3 population (modified non-responder imputation): steroid-free at week 52, 131/234 (56.0%); remission at week 52, 66/234 (28.2%); steroid-free for ≥ 90 days at week 52, 118/234 (50.4%); remission at week 52, patients who were steroid-free for ≥ 90 days, 61/234 (26.1%)

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Study name	Treatment arm	Time point	Outcome measure
ULTRA3	ADA 40 mg EOW or EW	Weeks 0 to 156	Sandborn *et al.*[339] Remission per partial Mayo score presented graphically for weeks 0, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144 and 156. Samples below from: Week 0: All non-responder imputation, 307/588 (52.2%) Entered ULTRA 3 on EOW modified non-responder imputation, 252/447 (56.4%) Week 36: All non-responder imputation, 334/588 (56.8%) Entered ULTRA 3 on EOW modified non-responder imputation, 254/447 (56.8%) Week 60: All non-responder imputation, 325/588 (55.3%) Entered ULTRA 3 on EOW modified non-responder imputation, 229/447 (51.2%) Week 156: All non-responder imputation, 273/588 (46.4%) Entered ULTRA 3 on EOW modified non-responder imputation, 187/447 (41.8%)
Suzuki	PBO	Week 8	Suzuki *et al.*[46] Rectal bleeding subscore of ≤ 1, 65/96 (67.7%); PGA subscore of ≤ 1, 43/96 (44.8%);stool frequency subscore of ≤ 1, 31/96 (32.3%); IBDQ response (increase in IBDQ score of ≥ 16 points from baseline), 38/96 (39.6%); remission by baseline CS use, 10/58 (17.2%); non-use, 1/38 (2.6%); remission by baseline immunomodulator use, 1/52 (1.9%); non-use, 10/44 (22.7%)
Suzuki	PBO	Week 32	Suzuki *et al.*[46] Rectal bleeding subscore of ≤ 1, 27/96 (28.1%) PGA subscore of ≤ 1, 27/96 (28.1%); stool frequency subscore of ≤ 1, 20/96 (20.8%); IBDQ response (increase in IBDQ score of ≥ 16 points from baseline), 2196 (21.9%); steroid-free, 12/58 (*n* at baseline) (20.7%); steroid-free remission, 5/58 (*n* at baseline) (8.6%)
Suzuki	PBO	Week 52	Suzuki *et al.*[46] Rectal bleeding subscore of ≤ 1, 22/96 (22.9%) PGA subscore of ≤ 1, 19/96 (19.8%); stool frequency subscore of ≤ 1, 13/96 (13.5%); IBDQ response (increase in IBDQ score of ≥ 16 points from baseline), 12/96 (12.5%); steroid-free, 12/58 (*n* at baseline) (20.7%); steroid-free remission, 4/58 (*n* at baseline) (6.9%); remission by baseline CS use, 4/58 (6.9%); non-use, 3/38 (7.9%); remission by baseline immunomodulator use, 1/52 (1.9%); non-use, 6/44 (13.6%)

Study name	Treatment arm	Time point	Outcome measure
Suzuki	160 mg/80 mg of ADA	Week 8	Suzuki *et al.*[46] Rectal bleeding subscore of ≤ 1, 64/90 (71.1%); PGA subscore of ≤ 1, 55/90 (61.1%); *p*-value vs. PBO ≤ 0.05; stool frequency subscore of ≤ 1, 36/90 (40.0%); IBDQ response (increase in IBDQ score of ≥ 16 points from baseline), 38/90 (42.2%); remission by baseline CS use, 5/57 (8.8%); non-use, 4/33 (12.1%); remission by baseline immunomodulator use, 6/41 (14.6%), *p*-value vs. PBO ≤ 0.05; non-use, 3/49 (6.1%)
Suzuki	80 mg/40 mg of ADA or 160 mg/80 mg of ADA to week 8 then 40 mg ADA EOW	Week 32	Suzuki *et al.*[46] Rectal bleeding subscore of ≤ 1, 74/177 (41.8%); PGA subscore of ≤ 1, 66/177 (37.3%); stool frequency subscore of ≤ 1, 57/177 (32.2%); *p*-value vs. PBO, ≤ 0.05; IBDQ response (increase in IBDQ score of ≥ 16 points from baseline), 55/177 (31.1%); steroid-free, 35/120 (*n* at baseline) (29.2%); steroid-free remission, 12/120 (*n* at baseline) (10.0%)
Suzuki	80 mg/40 mg of ADA or 160 mg/80 mg of ADA to week 8 then 40 mg ADA EOW	Week 52	Suzuki *et al.*[46] Rectal bleeding subscore of ≤ 1, 59/177 (33.3%); PGA subscore of ≤ 1, 57/177 (32.2%); *p*-value vs. PBO, ≤ 0.05; stool frequency subscore of ≤ 1, 51/177 (28.8%); *p*-value vs. PBO, ≤ 0.05; IBDQ response (increase in IBDQ score of ≥ 16 points from baseline), 45/177 (25.4%); *p*-value vs. PBO, ≤ 0.01; steroid-free; *p*-value vs. PBO, ≤ 0.05; *p*-value vs. PBO, ≤ 0.05, 39/120 (*n* at baseline) (32.5%); steroid-free remission; *p*-value vs. PBO, ≤ 0.05; *p*-value vs. PBO, ≤ 0.05, 17/120 (*n* at baseline) (14.2%); remission by baseline CS use, 24/120 (20.0%); non-use, 17/57 (29.8%); *p*-value vs. PBO use and non-use, ≤ 0.05; remission by baseline immunomodulator use, 24/79 (30.4%), *p*-value vs. PBO ≤ 0.001; non-use, 17/98 (17.3%)
PURSUIT-SC	Phase II PBO	Week 6	Sandborn *et al.*[47] Mean change (SD) –1.8 (2.96), median change from baseline in Mayo score (IQR) –1.0 (–4.0 to 1.0)
PURSUIT-SC	Phase II 200 mg/100 mg of GOL all randomised	Week 6	Sandborn *et al.*[47] Mean (SD) –2.6 (2.73), median change from baseline in Mayo score (IQR) –2.0 (–4.0 to 0.0); $p = 0.219$
PURSUIT-SC	Phase III PBO	Week 6	Sandborn *et al.*[47] Phase III: mean change in CRP concentration at week 6 (mg/l) PBO = 1.59 Phase III: week 6 Mayo score change from baseline PBO, mean (SD) = –1.6 (2.53), median (IQR) = –1.0 (–3.0 to 0.0) Phase III: normal or inactive mucosal disease (endoscopy score = 0) at week 6 PBO = 10/251 (4.0)
PURSUIT-SC	Phase III 200 mg/100 mg of GOL phase III	Week 6	Sandborn *et al.*[47] Phase III: mean change in CRP concentration at week 2 (mg/l) 200 mg/100 mg of GOL = – 6.57 ($p < 0.0001$) Phase III: mean change in CRP concentrationat week 6 (mg/l) 200 mg/100 mg of GOL = – 3.35 ($p < 0.0001$) Phase III: week 6 Mayo score change from baseline 200 mg/100 mg of GOL, mean (SD) = –3.1 (2.90), median (IQR) = –3.0 (–6.0 to 0.0) ($p < 0.0001$) Phase III: normal or inactive mucosal disease (endoscopy score = 0) at week 6 200 mg/100 mg of GOL = 21/253 (8.3) ($p = 0.0437$)

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Study name	Treatment arm	Time point	Outcome measure
PURSUIT-SC	PBO	Weeks 0 to 6	Sandborn *et al.*[340] Stool frequency at week 0 [all mean (SD)] PBO = 2.3 (0.8) Stool frequency at week 2 PBO = 2.1 (0.9) Stool frequency at week 4 PBO = 1.9 (0.9) Stool frequency at week 6 PBO = 2 (1) (as reported) Rectal bleeding score at week 0 [all mean (SD)] PBO = 1.50 (0.86) Rectal bleeding score at week 2 PBO = 1.20 (0.91) Rectal bleeding score at week 4 PBO = 1.04 (0.94) Rectal bleeding score at week 6 PBO = 1.04 (0.94)
PURSUIT-M	PBO	Week 54	Sandborn *et al.*[48] PBO: 18.4% ($n = 87$) were in CS-free clinical remission at week 54 (among those who were receiving CSs at baseline) 31.2% ($n = 154$) maintained clinical response through week 54. 169 (37.1%) patients in primary analysis population had dose adjustment. PBO = 75 (48.7%) Reduction in median partial Mayo scores observed at baseline of PURSUIT-Maintenance among GOL-induction responders (i.e. decrease of 4 points from induction baseline) maintained in 100 mg and 50 mg groups through weeks 52 and 48, respectively, (but in PBO group increased after week 8 and increased to value approaching that an induction baseline at week 54 Proportion of patients with normal or inactive mucosal disease (i.e. endoscopy score = 0) at week 54 = 13.0%
PURSUIT-M	50 mg of GOL	Week 54	Sandborn *et al.*[48] 28.2% ($n = 78$, $p = 0.279$) were in CS-free clinical remission at week 54. 47.0% ($n = 151$, $p < 0.001$) maintained clinical response through week 54. 51 (33.8%) had dose adjustment Proportion of patients with normal or inactive mucosal disease (i.e. endoscopy score = 0) at week 54 = 25.8% ($p = 0.011$)
PURSUIT-M	100 mg of GOL	Week 54	Sandborn *et al.*[48] 23.3% were in CS-free clinical remission at week 54 ($n = 82$; $p = 0.423$). 49.7% ($n = 151$, $p < 0.001$) maintained clinical response through week 54. 43 (28.5%) had dose adjustment Proportion of patients with normal or inactive mucosal disease (i.e. endoscopy score = 0) at week 54 = 21.9% ($p = 0.033$)

Study name	Treatment arm	Time point	Outcome measure
UC-SUCCESS	AZA	Week 8	Panaccione *et al.*[51] Patients with partial Mayo score decrease of ≥ 1: 50/76 (65.79%); *p*-value between IFX, 0.002 and IFX/AZA, 0.003; patients with partial Mayo score decrease of ≥ 2: 28/76 (36.84%) Change (SD) in partial Mayo scores from baseline –2.81 (2.46) Faecal calprotectin ≤ 50 µg/g, 12/62 (19.4%); ≤ 250 µg/g, 24/62 (38.7%) ≥ 251 µg/g
UC-SUCCESS	AZA	Week 16	Panaccione *et al.*[51] Patients with Mayo score response: 38/76 (50.00%); *p*-value between IFX, 0.018 and IFX/AZA, 0.001; total Mayo score change from baseline, mean; $n = 71$: –3.00 (baseline 8.50); *p*-value between IFX, 0.013 and IFX/AZA, 0.001 Change (SD) in partial Mayo scores from baseline–2.34 (2.70) A post-hoc analysis was conducted to determine the proportion of patients who achieved a Mayo endoscopy subscore of 0 only at week 16. A greater proportion of patients treated with IFX/AZA combination therapy (29.5%) achieved a Mayo endoscopy subscore of 0 than patients given monotherapy with IFX (11.7%; $p = 0.006$) and AZA (13.2%; $p = 0.014$). The difference between the IFX group and the AZA group was not statistically significant ($p = 0.783$) Faecal calprotectin ≤ 50 µg/g, 12/66 (18.2%); ≤ 250 µg/g, 29/66 (43.9%) Panaccione *et al.*[341] Change from baseline (assume mean): stool frequency –0.97, rectal bleeding –0.77, physician global assessment –0.59, total Mayo score –3.00
UC-SUCCESS	IFX	Week 8	Panaccione *et al.*[51] Patients with partial Mayo score decrease of ≥ 1: 68/77 (88.31%); *p*-value IFX/AZA, 0.654; patients with partial Mayo score decrease of ≥ 2: 38/77 (49.35%) Change (SD) in partial Mayo scores from baseline –3.52 (2.25) Faecal calprotectin ≤ 50 µg/g, 15/66 (22.7%); ≤ 250 µg/g, 33/66 (50.7%) ≥ 251 µg/g
UC-SUCCESS	IFX	Week 16	Panaccione *et al.*[51] Patients with Mayo score response: 53/77 (68.83%); *p*-value IFX/AZA, 0.514; total Mayo score change from baseline, mean; $n = 70$: –4.27 (baseline 8.08); *p*-value IFX/AZA, 0.001 Change (SD) in partial Mayo scores from baseline –3.43 (2.26) Faecal calprotectin ≤ 50 µg/g, 11/62 (17.7%); ≤ 250 µg/g, 19/62 (30.6%) Panaccione *et al.*[341] Change from baseline (assume mean): stool frequency –1.23; rectal bleeding –1.14; *p*-value vs. AZA < 0.05; physician global assessment –1.06; *p*-value vs. AZA< 0.05; total Mayo –4.27; *p*-value vs. AZA < 0.05

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Study name	Treatment arm	Time point	Outcome measure
UC-SUCCESS	IFX/AZA	Week 8	Panaccione *et al.*[51] Patients with partial Mayo score decrease of ≥ 1: 67/78 (85.90%); patients with partial Mayo score decrease of ≥ 2: 41/78 (52.56%) Change (SD) in partial Mayo scores from baseline –4.01 (SD 2.04); *p*-value vs. AZA 0.005 Faecal calprotectin ≤ 50 µg/g, 26/63 (41.3%); ≤ 250 µg/g, 42/63 (66.7%) ≥ 251 µg/g
UC-SUCCESS	IFX/AZA	Week 16	Panaccione *et al.*[51] Patients with Mayo score response: 60/78 (76.92%); total Mayo score change from baseline, mean (SD); $n = 76$: –5.28 (baseline 8.54) Change (SD) in partial Mayo scores from baseline –4.09 (SD 2.18); *p*-value vs. IFX < 0.001 Faecal calprotectin ≤ 50 µg/g, 22/70 (31.4%); ≤ 250 µg/g, 41/70 (58.6%) Panaccione *et al.*[341] Change from baseline (assume mean): stool frequency –1.54; *p*-value vs. AZA < 0.05; rectal bleeding –1.25; *p*-value vs. AZA < 0.05; physician global assessment –1.30; *p*-value vs. AZA and IFX < 0.05; total Mayo score –5.28; *p*-value vs. AZA and IFX < 0.05
Probert	PBO	Week 6	Probert *et al.*[50] UCSS mean (SD), 5 (3); improvement in UCSS, 4 (SD 3); median improvement, 3. Median between-group difference, $p = 0.82$; Baron score mean (SD), 1 (1); proportion of patients with a Baron score of 0, 6/20 (30%). 95% CI for difference, –30% to 23%; $p = 0.96$. Mean (SD) improvement in Baron score, 1 (SD 1). Baron score improved by a decrease in score of at least 1 in 3/20 (13%); seven (37%) remained the same and one underwent colectomy; $p = 0.67$. When remission rates of patients with total disease in each of the two groups were compared, no significant difference was found ($p = 0.9$). Remission rate in patients receiving AZA, 2/6 (33%). 95% CI for difference, –79% to 45%; $p = 0.89$ Mean reduction in daily dose of glucocorticoid was equivalent to 14 mg prednisolone (SD 12); $p = 0.037$ compared with IFX Week 6: CRP median value did not change (data not reported); *p*-value 0.96 but unclear if change from baseline or between IFX
Probert	IFX	Week 6	Probert *et al.*[50] UCSS mean (SD), 5 (3); improvement in UCSS ($n = 18$), 4 (SD 3); median improvement, 2.5 for the 18 assessable patients; Baron score mean (SD), 1 (1); proportion of patients with a Baron score of 0, 6/23 (26%). Mean (SD) improvement in Baron score, 1 (1). Baron score improved by a decrease in score of at least 1 in 13/23 (57%); seven (30%) remained the same, and three (13%) deteriorated 5/14 (36%) with total colitis went into remission, 3/5 (60%) with left-sided colitis and 1/4 (25%) with distal colitis ($p = 0.5$). Remission rate in patients receiving AZA, 4/6 (67%) Mean reduction in daily dose of glucocorticoid was equivalent to 19 mg prednisolone (SD 15) Week 6: CRP median levels rose from 6.5 mg/l to 10 mg/l

Study name	Treatment arm	Time point	Outcome measure
ACT1	PBO	Week 2	Rutgeerts *et al.*[49]
			Partial Mayo score median (IQR) at baseline, 6.0 (5.0–7.0)
			Partial Mayo score median (IQR) at week 2, 5.0 (4.0–6.0)
ACT1	PBO	Week 6	Rutgeerts *et al.*[49]
			Partial Mayo score median (IQR) at week 6, 5.0 (3.0–6.0)
ACT1	PBO	Week 8	Rutgeerts *et al.*[49]
			Refractory to CS therapy, 35.3 (12/34)
			Not refractory to CS therapy, 37.9 (33/87)
			Partial Mayo score median (IQR) at week 8, 5.0 (3.0–6.0)
			Daily CS dose in mg (median, IQR) at baseline, 20.0 (10.0–30.0) Daily CS dose in mg (median, IQR) at week 8, 20.0 (10.0–30.0)
ACT1	PBO	Week 30	Rutgeerts *et al.*[49]
			Partial Mayo score median (IQR) at week 30, 5.0 (3.0–6.0)
			Daily CS dose in mg, median (IQR), 10.0 (0.8–30.0)
ACT1	PBO	Week 54	Rutgeerts *et al.*[49]
			Partial Mayo score median (IQR) at week 54, 5.0 (4.0–7.0)
			Clinical remission and discontinued use of CSs at week 54, 7/79 (8.9)
			Daily CS dose in mg, median (IQR), 20.0 (0.0–30.0)
			Lichtenstein *et al.*[342]
			Clinical response: baseline IMM use: 26% (14/53), no baseline IMM use: 15% (10/68)
			Clinical remission: baseline IMM use: 21% (11/53), no baseline IMM use: 13% (9/68)
ACT1	5 mg/kg of IFX	Week 2	Rutgeerts *et al.*[49]
			Partial Mayo score median (IQR) at baseline, 6.0 (5.0–7.0)
			Partial Mayo score median (IQR) at week 2, 3.0 (2.0–5.0)
ACT1	5 mg/kg of IFX	Week 6	Rutgeerts *et al.*[49]
			Partial Mayo score median (IQR) at week 6, 3.0 (2.0–5.0)
ACT1	5 mg/kg of IFX	Week 8	Rutgeerts *et al.*[49]
			Refractory to CS therapy, 77.4 (24/31) ($p < 0.001$)
			Not refractory to CS therapy, 66.7 (60/90) ($p < 0.001$)
			Partial Mayo score median (IQR) at week 8, 2.0 (1.0–4.0)
			Daily CS dose in mg, median (IQR), at baseline, 20.0 (10.0–25.0)
			Daily CS dose in mg, median (IQR), at week 8, 20.0 (10.0–25.0)

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Study name	Treatment arm	Time point	Outcome measure
ACT1	5 mg/kg of IFX	Week 30	Rutgeerts *et al.*[49] Partial Mayo score median (IQR) at week 30, 3.0 (1.0–6.0) Clinical remission and discontinued use of CSs at week 30, 17/70 (24.3) ($p = 0.030$) Daily CS dose in mg, median (IQR), at week 30, 5.6 (0.0–20.0)
ACT1	5 mg/kg of IFX	Week 54	Rutgeerts *et al.*[49] Partial Mayo score median (IQR) at week 54, 3.0 (1.0–6.0) Clinical remission and discontinued use of CSs at week 54, 18/70 (25.7) ($p = 0.006$) Daily CS dose in mg (median, IQR) at week 54, 5.0 (0.0–20.0) Rutgeerts *et al.*[49] Clinical response: baseline IMM use: 48% (32/66), OR 2.62 (95% CI 1.20 to 5.71); no baseline IMM use: 42% (23/55), OR 4.17 (95% CI 1.77 to 9.84) Clinical remission: baseline IMM use: 35% (23/66), OR 2.04 (95% CI 0.89 to 4.71); no baseline IMM use: 35% (19/55), OR 3.46 (95% CI 1.41 to 8.47)
ACT1	IFX combined	Week 54	Rutgeerts *et al.*[49] Clinical response: baseline IMM use: 45% (56/125), OR 2.26 (95% CI 1.12 to 4.58); no baseline IMM use: 45% (53/118), OR 4.73 (95% CI 2.21 to 10.1) Clinical remission: baseline IMM use: 34% (42/125), OR 1.93 (95% CI 0.90 to 4.13); no baseline IMM use: 36% (42/118), OR 3.62 (95% CI 1.63 to 8.03)
ACT2	PBO	Week 2	Rutgeerts *et al.*[49] Partial Mayo score median (IQR) at baseline, 6.0 (5.0–7.0) Partial Mayo score median (IQR) at week 2, 5.0 (4.0–7.0)
ACT2	PBO	Week 6	Rutgeerts *et al.*[49] Partial Mayo score median (IQR) at week 6, 5.0 (4.0–7.0)
ACT2	PBO	Week 8	Rutgeerts *et al.*[49] Refractory to CS therapy, 37.5 (12/32); not refractory to CS therapy, 37.5 (12/32); partial Mayo score median (IQR) at week 8, 5.0 (3.0–7.0) Daily CS dose in mg, median (IQR), at baseline, 20.0 (15.0–30.0) Daily CS dose in mg, median (IQR), at week 8, 20.0 (15.0–30.0)

Study name	Treatment arm	Time point	Outcome measure
ACT2	PBO	Week 30	Rutgeerts *et al.*[49]
			Partial Mayo score median (IQR) at week 30, 6.0 (3.0–7.0)
			Daily CS dose in mg, median (IQR), 20.0 (5.6–30.0)
			Clinical remission and discontinued use of CSs, 2/60 (3.3)
			Rutgeerts *et al.*[49]
			Clinical response: baseline IMM use: 26% (14/54); no baseline IMM use: 26% (18/69)
			Clinical remission: baseline IMM use: 9% (5/54); no baseline IMM use: 12% (8/69)
ACT2	PBO	Week 54	Rutgeerts *et al.*[49]
			Partial Mayo score median (IQR) at week 54, NR
			Daily CS dose in mg, median (IQR), at week 54, NR
			Rutgeerts *et al.*[49]
			Clinical response at week 54 with baseline immunomodulator use OR = 3.09 (95% CI 1.36 to 6.98)
ACT2	5 mg/kg of IFX	Week 2	Rutgeerts *et al.*[49]
			Partial Mayo score median (IQR) at baseline, 6.0 (5.0–7.0)
			Partial Mayo score median (IQR) at week 2, 4.0 (2.0–5.0)
ACT2	5 mg/kg of IFX	Week 6	Rutgeerts *et al.*[49]
			Partial Mayo score median (IQR) at week 6, 3.0 (1.0–5.0)
ACT2	5 mg/kg of IFX	Week 8	Rutgeerts *et al.*[49]
			Refractory to CS therapy, 63.3 (19/30) ($p = 0.053$); not refractory to CS therapy, 63.3 (19/30) ($p = 0.053$)
			Partial Mayo score median (IQR) at week 8, 2.0 (1.0–4.0)
			Daily CS dose in mg, median (IQR), at baseline, 5 mg/kg of IFX = 20.0 (10.0–30.0)
			Daily CS dose in mg, median (IQR), at week 8, 5 mg/kg of IFX = 20.0 (10.0–30.0)
ACT2	5 mg/kg of IFX	Week 30	Rutgeerts *et al.*[49]
			Partial Mayo score median (IQR) at week 30, 4.0 (1.0–6.0)
			Daily CS dose in mg, median (IQR), 7.5 (0.0–20.0)
			Clinical remission and discontinued use of CSs, 11/60 (18.3) ($p = 0.010$)
			Rutgeerts *et al.*[49]
			Clinical response: baseline IMM use: 52% (27/52), OR 3.09 (95% CI 1.36 to 6.98); no baseline IMM use: 43% (30/69), OR 2.18 (95% CI 1.06 to 4.47)
			Clinical remission: baseline IMM use: 35% (18/52), OR 5.19 (95% CI 1.76 to 15.3); no baseline IMM use: 19% (13/69), OR 1.77 (95% CI 0.68 to 4.59)

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Study name	Treatment arm	Time point	Outcome measure
ACT2	5 mg/kg of IFX	Week 54	Rutgeerts *et al.*[49] Partial Mayo score median (IQR) at week 54, NR Daily CS dose in mg, median (IQR), NR Rutgeerts *et al.*[49] Clinical response without baseline immunomodulator use, OR = 2.18 (95% CI 1.06 to 4.47)
ACT2	IFX combined	Week 54	Rutgeerts *et al.*[49] Clinical remission with baseline immunomodulator use, OR = 5.19 (95% CI 1.76 to 15.3) Rutgeerts *et al.*[49] Clinical remission without baseline immunomodulator use, OR = 1.77 (95% CI 0.68 to 4.59)
ACT1 and ACT2 extension studies	Randomised patients in the IFX group of the ACT1 or ACT2 trials who entered the extension studies	Weeks 0 to 152	Reinisch *et al.*[55] Patients with no disease activity (PGA assessment of no disease): Week E0: ACT1, 55.7% (64/115); ACT2, 27.9% (31/111) Week E24: ACT1, 66.4% (73/110); ACT2, 43.3% (42/97) Week E48: ACT1, 70.8% (75/106); ACT2, 52.3% (46/88) Week E72: ACT1, 72.7% (72/99); ACT2, 52.9% (45/85) Week E104: ACT1, 69.5% (57/82); ACT2, 66.2% (51/77) Week E128: ACT1, 79.5% (35/44); ACT2, 66.0% (35/53) Week E152: ACT1, 88.9% (8/9); ACT2, 45.5% (5/11) Patients with no or mild disease activity (PGA assessment of no or mild disease): Week E0: ACT1, 84.3% (97/115); ACT2, 68.5% (76/111) Week E24: ACT1, 90.9% (100/110); ACT2, 91.8% (89/97) Week E48: ACT1, 96.2% (102/106); ACT2, 92.0% (81/88) Week E72: ACT1, 94.9% (94/99); ACT2, 88.2% (75/85) Week E104: ACT1, 96.3% (79/82); ACT2, 92.2% (71/77) Week E128: ACT1, 95.5% (42/44); ACT2, 90.6% (48/53) Week E152: ACT1, 100.0% (9/9); ACT2, 81.8% (9/11) Randomised patients in the IFX group of the extension studies with and without a gap in treatment of > 8 weeks between the last infusion of the main studies and the extension studies week 0 infusions ($n = 134$) Patients with no disease activity: Week E0: patients without treatment gap ($n = 134$), 52.3% (69/132); patients with treatment gap ($n = 95$), 27.7% (26/94)

Study name	Treatment arm	Time point	Outcome measure
			Week E8: patients without treatment gap ($n = 134$), 59.4% (76/128); patients with treatment gap ($n = 95$), 44.6% (41/92) Week E24: patients without treatment gap ($n = 134$), 55.6% (69/124); patients with treatment gap ($n = 95$), 55.4% (46/83) Week E48: patients without treatment gap ($n = 134$), 64.8% (79/122); patients with treatment gap ($n = 95$), 58.3% (42/72) Week E72: patients without treatment gap ($n = 134$), 64.6% (73/113); patients with treatment gap ($n = 95$), 62.0% (44/71) Week E104: patients without treatment gap ($n = 134$), 70.5% (67/95); patients with treatment gap ($n = 95$), 64.1% (41/64) Week E128: patients without treatment gap ($n = 134$), 72.5% (37/51); patients with treatment gap ($n = 95$), 71.7% (33/46) Week E152: patients without treatment gap ($n = 134$), 62.5% (5/8); patients with treatment gap ($n = 95$), 66.7% (8/12) Patients with no or mild disease activity: Week E0: patients without treatment gap ($n = 134$), 84.1% (111/132); patients with treatment gap ($n = 95$), 66.0% (62/94) Week E8: patients without treatment gap ($n = 134$), 87.5% (112/128); patients with treatment gap ($n = 95$), 81.5% (75/92) Week E24: patients without treatment gap ($n = 134$), 92.7% (115/124); patients with treatment gap ($n = 95$), 89.2% (74/83) Week E48: patients without treatment gap ($n = 134$), 94.3% (115/122); patients with treatment gap ($n = 95$), 94.4% (68/72) Week E72: patients without treatment gap ($n = 134$), 91.2% (103/113); patients with treatment gap ($n = 95$), 93.0% (66/71) Week E104: patients without treatment gap ($n = 134$), 90.5% (86/95); patients with treatment gap ($n = 95$), 100% (64/64) Week E128: patients without treatment gap ($n = 134$), 94.1% (48/51); patients with treatment gap ($n = 95$), 91.3% (42/46) Week E152: patients without treatment gap ($n = 134$), 87.5% (7/8); patients with treatment gap ($n = 95$), 91.7% (11/12) All randomised patients in the IFX group who entered the extension studies ($n = 229$): Week E8: patients with no disease activity (PGA assessment of no disease), 46.4% (102/220); patients with no or mild disease activity (PGA assessment of no or mild disease), 70.9% (156/220) Week E24: patients with no disease activity (PGA assessment of no disease), 50.7% (105/207); patients with no or mild disease activity (PGA assessment of no or mild disease), 80.7% (167/207) Week E48: patients with no disease activity (PGA assessment of no disease), 56.7% (110/194); patients with no or mild disease activity (PGA assessment of no or mild disease), 82.0% (159/194) Week E72: patients with no disease activity (PGA assessment of no disease), 58.7% (108/184); patients with no or mild disease activity (PGA assessment of no or mild disease), 83.2% (153/184)

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Study name	Treatment arm	Time point	Outcome measure
			Week E104: patients with no disease activity (PGA assessment of no disease), 66.0% (105/159); patients with no or mild disease activity (PGA assessment of no or mild disease), 88.1% (140/159) Week E128: patients with no disease activity (PGA assessment of no disease), 69.1% (67/97); patients with no or mild disease activity (PGA assessment of no or mild disease), 87.6% (85/97) Week E152: patients with no disease activity (PGA assessment of no disease), 65.0% (13/20); patients with no or mild disease activity (PGA assessment of no or mild disease), 90.0% (18/20) Number of randomised patients in the extension studies ($n = 229$) who used CSs in the past 8 weeks for UC: Week E8: 0 days, 179/223 (80.3%); 1 to 7 days, 4/223 (1.8%); 8 to 30 days, 8/223 (3.6%); > 30 days, 32/223 (14.3%) Week E24: 0 days, 179/208 (86.1%); 1 to 7 days, 1/208 (0.5%); 8 to 30 days, 2/208 (1.0%); > 30 days, 26/208 (12.5%) Week E48: 0 days, 167/194 (86.1%); 1 to 7 days, 2/194 (1.0%); 8 to 30 days, 4/194 (2.1%); > 30 days, 21/194 (10.8%) Week E72: 0 days, 165/188 (87.8%); 1 to 7 days, 3/188 (1.6%); 8 to 30 days, 4/188 (2.1%); > 30 days, 16/188 (8.5%) Week E104: 0 days, 149/161 (92.5%); 1 to 7 days, 0/161 (0.0%); 8 to 30 days, 1/161 (0.6%); > 30 days, 11/161 (6.8%) Week E128: 0 days, 92/99 (92.9%); 1 to 7 days, 0/99 (0.0%); 8 to 30 days, 0/99 (0.0%); > 30 days, 7/99 (7.1%) Week E152: 0 days, 20/20 (100.0%); 1 to 7 days, 0/20 (0.0%); 8 to 30 days, 0/20 (0.0%); > 30 days, 0/20 (0.0%)

CS, corticosteroid; E, extension; EOW, every other week; EW, every week; IMM, immunomodulator; IQR, interquartile range; ITT-A3, intention to treat-amendment 3; ITT-E, intention to treat original population prior to protocol amendment; max., maximum; min., minimum; NR, not reported.

Additional efficacy outcomes (paediatric population trial)

Study name	Treatment arm	Time point	Outcome measure
Hyams	5 mg/kg of IFX q8w	Week 8	Hyams *et al.*[52] Median reduction in partial Mayo score 4 points median corticosteroid use mg/kg/day: 0
Hyams	5 mg/kg of IFX q8w	Week 30	Hyams *et al.*[52] Median reduction in partial Mayo score: approximately 2.5 points (read from source graph). Remission (PUCAI) without CSs: 5/12 (41.7%) EPAR[73] Remission (PUCAI) by age ($n = 20$ evaluable): 6 years, 0/0 (0%); 7 years, 2/2 (100%); 8 years, 0/0 (0%); 9 years, 1/1 (100%); 10 years, 0/1 (0%); 11 years, 1/1 (100%); 12 years, 0/1 (0%); 13 years, 2/4 (50%); 14 years, 0/0 (0%); 15 years, 1/3 (33.3%); 16 years, 0/3 (0%); 17 years, 1/4 (25%)

Study name	Treatment arm	Time point	Outcome measure
Hyams	5 mg/kg of IFX q8w	Week 54	Hyams *et al.*[52] Median reduction in partial Mayo score: approximately 2.5 points (read from source graph). Remission (PUCAI) without CSs: 5/13 (38.5%). Efficacy after step-up decrease of ≥ 2 points in partial Mayo score – patients with data at week 54: 9/10 (90%). Unclear if this value is for IFX 5 mg/q8d group or both groups median corticosteroid use mg/kg/day: 0.04 EPAR[73] Clinical response: 3/4 patients who had endoscopy at week 54 (optional) Remission (PUCAI) by age ($n = 20$ evaluable): 6 years, 0/0 (0%); 7 years, 1/2 (50%); 8 years, 0/0 (0%); 9 years, 1/1 (100%); 10 years, 0/1 (0%); 11 years, 1/1 (100%); 12 years, 0/1 (0%); 13 years, 3/4 (75%); 14 years, 0/0 (0%); 15 years, 1/4 (25.3%); 16 years, 0/3 (0%); 17 years, 1/4 (25%)
Hyams	5 mg/kg of IFX q12w	Week 8	Hyams *et al.*[52] Median reduction in partial Mayo score: 4 points median corticosteroid use mg/kg/day: 0.15
Hyams	5 mg/kg of IFX q12w	Week 30	Hyams *et al.*[52] Median reduction in partial Mayo score: approximately 1 point (read from source graph). Remission (PUCAI) without CSs: 1/13 (7.7%) EPAR[73] Remission (PUCAI) by age ($n = 21$ evaluable): 6 years, 0/1 (0%); 7 years, 0/0 (0%); 8 years, 0/1 (0%); 9 years, 0/0 (0%); 10 years, 0/1 (0%); 11 years, 0/1 (0%); 12 years, 0/0 (0%); 13 years, 0/0 (0%); 14 years, 0/2 (0%); 15 years, 3/4 (75%); 16 years, 1/5 50 (20%); 17 years, 0/5 (0%)
Hyams	5 mg/kg of IFX q12w	Week 54	Hyams *et al.*[52] Median reduction in partial Mayo score: approximately 1 point (read from source graph). Remission (PUCAI) without CSs: 0/13 (0%) Median CS use mg/kg/day: same as baseline 4 EPAR[73] Clinical response: 3/4 patients who had endoscopy at week 54 (optional) Remission (PUCAI) by age ($n = 22$ evaluable): 6 years, 0/1 (0%); 7 years, 0/0 (0%); 8 years, 0/1 (0%); 9 years, 0/0 (0%); 10 years, 0/1 (0%); 11 years, 0/1 (0%); 12 years, 0/2 (0%); 13 years, 0/0 (0%) 3/4 (75%); 14 years, 0/2 (0%); 15 years, 2/4 (50%); 16 years, 1/5 (20%) 1/8 (12.5%); 17 years, 1/5 (20%) 2/9 (22.2%)
Hyams	All patients ($n = 60$)	Week 8	Hyams *et al.*[52] Disease activity was more severe at the last visit for patients who discontinued after week 8 [no disease, 1 of 10 (10%); mild, 1 of 10 (10%); moderate, 6 of 10 (60%); severe, 2 of 10 (20%)] than for patients who discontinued before week 8 [mild, 4 of 13 (30.8%); moderate, 4 of 13 (30.8%); and severe disease, 5 of 13 (38.5%)]

CS, corticosteroid; q8w, every 8 weeks; q12w, every 12 weeks.

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Hospitalisation, surgery and mortality data (adult population trials)

Study acronym	Treatment arm	Rates of hospitalisation	Rates of surgical intervention	Death
ADA				
ULTRA1	PBO	From submission[62] Week 8 ($n = 222$, PYs = 19.6) Physician visits number of events (visits) (events/PY), 21 (0.619) Emergency room visits number of events (visits) (events/PY), 8 (0.236) Hospital admissions number of events (admissions) (events/PY), 7 (0.206) Days in hospital number of events (days) (events/PY), 73 (2.153)	Colectomy, 8/130 (3.6%) during induction, week 8 Elective/emergency NR	0/223 (0%)
ULTRA1	160 mg/80 mg of ADA	From submission[62] Week 8 ($n = 223$, PYs = 34.0) Physician visits number of events (visits) (events/PY), 15 (0.441); *p*-value 0.559 Emergency room visits number of events (visits) (events/PY), 2 (0.059); *p*-value NA Hospital admissions number of events (admissions) (events/PY), 5 (0.147); *p*-value NA Days in hospital number of events (days) (events/PY), 26 (0.764); *p*-value 0.297	Colectomy, 5/130 (1.4%) during induction, week 8 Elective/emergency NR	0/223 (0%)

Study acronym	Treatment arm	Rates of hospitalisation	Rates of surgical intervention	Death
ULTRA2	PBO	From submission[62] ($n = 246$, PYs = 101.6) Physician visits number of events (visits) (events/PY), 169 (1.663) Emergency room visits number of events (visits) (events/PY), 10 (0.098) Hospital admissions number of events (admissions) (events/PY), 13 (0.128) Days in hospital number of events (days) (events/PY), 105 (0.837)	Colectomy, 12/246 (4.9%) during follow-up week 52 Elective/emergency NR	0/260 (0%)
ULTRA2	160 mg/80 mg of ADA	From submission[62] ($n = 248$, person years = 125.5) Physician visits number of events (visits) (events/PY), 169 (1.347); *p*-value vs. PBO 0.035 Emergency room visits number of events (visits) (events/PY), 12 (0.096); *p*-value vs. PBO 0.847 Hospital admissions number of events (admissions) (events/PY), 13 (0.104); *p*-value vs. PBO 0.418 Days in hospital number of events (days) (events/PY), 120 (1.181); *p*-value vs. PBO 0.467	Colectomy, 10/248 (4%) during follow-up, week 52 Elective/emergency NR	0/257 (0%)
ULTRA1 and ULTRA2	ADA	Feagan *et al.*[63] ADA Hospitalisation and Colectomy Rates in ULTRA 1 and 2: week 8 ADA responders: All-cause hospitalisation (*n*/PYs at risk), 46/260.4 All-cause hospitalisation incidence rate (*n*/PYs at risk), 0.18; All-cause hospitalisation *p*-value vs. PBO, 0.047 UC-related hospitalisation (*n*/PYs at risk), 29/266.5 UC-related hospitalisation incidence rate (*n*/PYs at risk), 0.11 UC-related hospitalisation *p*-value vs. PBO, 0.002 Colectomy (*n*/PYs at risk), 6/271.9 Elective/emergency, NR Colectomy incidence rate (*n*/PYs at risk), 0.02		

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Study acronym	Treatment arm	Rates of hospitalisation	Rates of surgical intervention	Death
		Colectomy *p*-value vs. PBO, 0.122 Hospitalisations – all-cause events/PYs, 55/272.7 Hospitalisations – all-cause incidence rate (events/PYs), 0.20 Hospitalisations – all-cause relative risk ADA/PBO, 0.65 $p = 0.021$ Hospitalisations – UC-related events/PYs, 32/272.7 Hospitalisations – UC-related incidence rate (events/person years), 0.12 Hospitalisations – UC-related relative risk ADA/PBO, 0.48 $p < 0.001$ Feagan *et al.*[65] Non-UC-related hospitalisation categories week 52: General disorder; gastroestinal tract disorder, 3 (0.63%); gynaecological disorder and pregnancy, 1 (0.21%); musculoskeletal and connective tissue disorder; hepatobiliary disorder, 1 (0.21%); neurological disorder, 1 (0.21%); urogenital tract disorder, 3 (0.63%); cardiovascular disorder, 2 (0.42%); endocrine and metabolic disorder; hematologic disorder, 1 (0.21%); infection, 11 (2.28%) 9 (1.88%); malignancy, 1 (0.21%); skin disorder, 2 (0.42%); trauma and surgical/medical procedure, 3 (0.63%) Feagan *et al.*[65] UC-related hospitalisation categories week 52: UC flare, 47 (9.73%) 31 (6.46%); UC leading to colectomy, 19 (3.93%) 15 (3.13%); extraintestinal complication of UC, 6 (1.25%); sequelae of colectomy, 1 (0.21%) Feagan *et al.*[65] Hospitalisation and colectomy analysis: induction period (8 weeks) All-cause hospitalisation, 22 (4.6) UC-related hospitalisation, 17 (3.5%) UC- or drug-related hospitalisation, 19 (4.0%) Colectomy, 5 (1.0%). Elective/emergency, NR Feagan *et al.*[65] Hospitalisation and colectomy analysis: 52-week period, *n*/PYs at risk (incident rate); RR (relative risk) (95% CI): All-cause hospitalisation, 69/387.5 (0.18); RR, 0.7 (95% CI 0.5 to 1.0); $p = 0.03$ UC-related hospitalisation, 47/398.1 (0.12); RR, 0.5 (95% CI 0.4 to 0.8); $p = 0.002$		

Study acronym	Treatment arm	Rates of hospitalisation	Rates of surgical intervention	Death
		UC- or drug-related hospitalisation, 55/393.8 (0.14); RR, 0.6 (0.4 to 0.9); $p = 0.005$ Colectomy, 15/408.1 (0.04) Sensitivity analysis 1: all events that occurred during the open-label period (during ADA therapy) were excluded for the PBO group All-cause hospitalisation, 69/387.5 (0.18); RR, 0.6 (0.4 to 0.9); $p = 0.007$ UC-related hospitalisation, 47/398.1 (0.12); RR, 0.5 (0.3 to 0.7); $p < .0001$ UC- or drug-related hospitalisation, 55/393.8 (0.14); RR, 0.5 (0.4 to 0.8); $p = 0.001$ Colectomy, 15/408.1 (0.04) Elective/emergency, NR Sensitivity analysis 2: all events were attributed to the randomised groups regardless of whether or not patients treated with PBO had switched to open-label ADA therapy All-cause hospitalisation, 69/387.5 (0.18); RR, 0.8 (0.6 to 1.0); $p = 0.08$ UC-related hospitalisation, 47/398.1 (0.12) 0.7; RR, (0.5 to 1.0); $p = 0.03$ UC- or drug-related hospitalisation, 55/393.8 (0.14); RR, 0.7 (0.5 to 1.0); $p = 0.045$ Colectomy, 15/408.1 (0.04) Elective/emergency, NR		
		Reinisch *et al.*[343] Incidence rates for all-cause and UC-related hospitalisations for ADA-treated patients by Mayo subscores at week 8: Mayo subscore 0 ($n = 433$): stool frequency – all-cause, 0.08 UC-related, 0.05; rectal bleeding – all-cause, 0.13 UC-related, 0.06; PGA – all-cause, 0.11 UC-related, 0.05; endoscopy – all-cause, 0.14 UC-related, 0.06 Mayo subscore 1 ($n = 433$): stool frequency – all-cause, 0.11 UC-related, 0.05; rectal bleeding – all-cause, 0.13 UC-related, 0.10; PGA – all-cause, 0.11 UC-related, 0.06; endoscopy – all-cause, 0.11 UC-related, 0.06 Mayo subscore 2 ($n = 433$): stool frequency – all-cause, 0.15 UC-related, 0.11; rectal bleeding – all-cause, 0.22 UC-related, 0.13; PGA – all-cause, 0.20 UC-related, 0.14; endoscopy – all-cause, 0.16 UC-related, 0.10 Mayo subscore 3 ($n = 422$): stool frequency – all-cause, 0.22 UC-related, 0.16; rectal bleeding – all-cause, 0.29 UC-related, 0.29; PGA – all-cause, 0.23 UC-related, 0.19; endoscopy – all-cause, 0.27 UC-related, 0.21		

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Study acronym	Treatment arm	Rates of hospitalisation	Rates of surgical intervention	Death
ULTRA 1 and 2	PBO	Feagan *et al.*[63] PBO hospitalisation and colectomy rates in ULTRA 1 and 2: week 8 ADA responders: All-cause hospitalisation (*n*/PYs at risk), 58/222.3 All-cause hospitalisation incidence rate (*n*/PYs at risk), 0.26 UC-related hospitalisation (*n*/PYs at risk), 49/223.6 UC-related hospitalisation incidence rate (*n*/PYs at risk), 0.22 Colectomy (*n*/PYs at risk), 11/231.7 Elective/emergency, NR Colectomy incidence rate (*n*/PYs at risk), 0.05 Hospitalisations – all-cause events/PYs, 71/232.8 Hospitalisations – all-cause incidence rate (events/PYs), 0.31 Hospitalisations – UC-related events/PYs, 59/232.8 Hospitalisations – UC-related incidence rate (events/PYs), 0.25 Feagan *et al.*[65] Non-UC-related hospitalisation categories week 52: General disorder, 1 (0.21%); gastrointestinal tract disorder, 1 (0.21%); gynaecological disorder and pregnancy, 2 (0.41%); musculoskeletal and connective tissue disorder, 1 (0.21%); hepatobiliary disorder, 0 (0%); neurological disorder, 0 (0%); urogenital tract disorder, 3 (0.62%); cardiovascular disorder, 1 (0.21%); endocrine and metabolic disorder, 1 (0.21%); hematologic disorder, 0 (0%); infection, 11 (2.28%); malignancy, 1 (0.21%); skin disorder, 1 (0.21%); trauma and surgical/medical procedure, 3 (0.62%) Feagan *et al.*[65] UC-related hospitalisation categories week 52: UC flare, 47 (9.73%); UC leading to colectomy, 19 (3.93%); extraintestinal complication of UC, 8 (1.66%); sequelae of colectomy, 1 (0.21%) Feagan *et al.*[65] Hospitalisation and colectomy analysis: induction period (8 weeks) All-cause hospitalisation, 37 (7.7%); $p = 0.46$ UC-related hospitalisation, 34 (7.0%); $p = 0.02$ UC- or drug-related hospitalisation, 36 (7.5); $p = 0.02$ Colectomy, 6 (1.2%); $p = 0.77$		

Study acronym	Treatment arm	Rates of hospitalisation	Rates of surgical intervention	Death
		Feagan *et al.*[65] Hospitalisation and colectomy analysis: 52-week period, *n*/PYs at risk (incident rate): All-cause hospitalisation, 58/222.3 (0.26) UC-related hospitalisation, 49/223.6 (0.22) UC- or drug-related hospitalisation, 53/223.2 (0.24) Colectomy, 11/231.7 (0.05) Elective/emergency, NR Sensitivity analysis 1: all events that occurred during the open-label period (during ADA therapy) were excluded for the PBO group All-cause hospitalisation, 47/159.2 (0.30) UC-related hospitalisation, 40/159.8 (0.25) UC- or drug-related hospitalisation, 43/159.5 (0.27) Colectomy, 7/166.3 (0.04) Elective/emergency, NR Sensitivity analysis 2: all events were attributed to the randomised groups regardless of whether or not patients treated with PBO had switched to open-label ADA therapy All-cause hospitalisation, 89/377.7 (0.24) UC-related hospitalisation, 68/384.2 (0.18) UC- or drug-related hospitalisation, 76/382.2 (0.20) Colectomy, 19/400.0 (0.05) Elective/emergency NR		
Suzuki	PBO	NR	NR	NR
Suzuki	80 mg/40 mg of ADA	NR	NR	NR
Suzuki	160 mg/80 mg of ADA	NR	NR	NR
Suzuki	40 mg of ADA EOW	NR	NR	NR
Suzuki	Rescue arm	NR	NR	NR
PURSUIT-SC	All randomised PBO	NR	NR	NR
PURSUIT-SC	All randomised 200 mg/100 mg of GOL	NR	NR	NR
PURSUIT-SC	Phase II PBO	NR	NR	NR
PURSUIT-SC	Phase II 200 mg/100 mg of GOL all randomised	NR	NR	NR
PURSUIT-SC	Phase III PBO	NR	NR	NR

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Study acronym	Treatment arm	Rates of hospitalisation	Rates of surgical intervention	Death
PURSUIT-SC	Phase III 200 mg/100 mg of GOL phase III	NR	NR	NR
PURSUIT-Maintenance	PBO randomised	NR	NR	Deaths reported through week 54. PBO = 0 deaths reported after week 54. PBO SC induction and maintenance = 1 (pneumonia and heart failure)
PURSUIT-Maintenance	50 mg of GOL randomised	NR	From submission In the PURSUIT trial, only 2–3% of GOL induction responders re-randomised to 50 mg or 100 mg of GOL had a colectomy at the end of maintenance	Deaths reported through week 54. 50 mg of GOL = 0 deaths reported after week 54. s.c. 100 mg/50 mg of GOL induction, 50 mg maintenance = 1 (heart dysfunction in the presence of pronounced atherosclerosis and stenosis affecting aorta, large arteries and coronary arteries)
PURSUIT-Maintenance	100 mg of GOL randomised	NR	NR	Deaths reported through week 54. 100 mg of GOL = 3 (causes = malnutrition and sepsis (GOL 2 mg/kg i.v. induction), cardiac failure with history of thrombosis (400 mg/200 mg of GOL s.c. induction), disseminated TB in patient who tested positive for latent TB on induction study entry and was receiving isoniazid at time of event (200 mg/100 mg of GOL s.c. induction) Deaths reported after week 54. PBO SC induction, 100 mg of GOL maintenance = 1 (myocardial infarction in patient with history of myocardial infarction). 2 mg/kg of GOL i.v. induction, 100 mg of GOL maintenance = 2 (gallbladder adenocarcinoma with liver metastasis), (sepsis). 200 mg/100 mg of GOL s.c. induction, 100 mg of GOL maintenance = 1 (accidental nitrous oxide overdose)
ACT1	PBO	From submission[64] UC-related hospitalisation, mean (SD): 0.22 (0.57)	From submission[64] Colectomy *n* (%), 9 (7.4) Ostomy *n* (%), 5 (4.1)	NR

Study acronym	Treatment arm	Rates of hospitalisation	Rates of surgical intervention	Death
ACT1	5 mg/kg of IFX	From submission[64] UC-related hospitalisation, mean (SD): 0.11 (0.34); *p*-value (assume vs. PBO), 0.061	From submission[64] Colectomy *n* (%), 7 (5.8) Ostomy *n* (%), 3 (2.5)	1 during ACT2 extension
ACT2	PBO	From submission[64] UC-related hospitalisation, mean (SD): 0.21 (0.55)	From submission[64] Colectomy *n* (%), 1 (0.7) Ostomy *n* (%), 1 (0.7)	NR
ACT2	5 mg/kg of IFX	From submission[64] UC-related hospitalisation, mean (SD): 0.07 (0.29); *p*-value (assume vs. PBO), 0.009	From submission[64] Colectomy *n* (%), 0 (0.0) Ostomy *n* (%), 0 (0.0)	NR
UC-SUCCESS	AZA	NR	NR	NR
UC-SUCCESS	IFX	NR	NR	NR
UC-SUCCESS	IFX/AZA	NR	NR	NR
Probert	PBO		One PBO patient underwent colectomy during the intervention period and was recorded as a treatment failure. One patient (unclear which group) refused sigmoidoscopic assessment but by other clinical measures was deemed to be a treatment failure	NR
Probert	IFX	NR	NR	NR

EOW, every other week; NR, not reported; s.c., subcutaneous.

Hospitalisation, surgery and mortality data (paediatric population trial)

Study acronym	Treatment arm	Rates of hospitalisation	Rates of surgical intervention	Death
IFX				
Hyams	5 mg/kg of IFX q8w	NR	Patients requiring colectomy in the 54-week period: 1/22 (4.5%)	NR
Hyams	5 mg/kg of IFX q12w	NR	Patients requiring colectomy in the 54-week period: 2/23 (8.7%)	NR
Hyams	All patients to week 8 ($n = 60$)	NR	Patients requiring colectomy in the 54-week period: 5/60 (8%) (2 out of 15 non-randomised)	NR

q8w, every 8 weeks; q12w, every 12 weeks; NR, not reported.

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Appendix 5 Safety data tables

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Safety: participants experiencing adverse events, serious adverse events and withdrawal due to adverse events (adult population trials)

Trial name	Treatment arm	Length of safety follow-up/mean number of administrations	Time point	Number of patients experiencing one or more AE, *n*/*N*(%)	Number of patients experiencing one or more SAE, *n*/*N* (%) (including definition)	Discontinuation owing to AE(s), *n*/*N* (%)
ULTRA1	PBO	NR	Week 8	Reinisch *et al.*[44] Any severe (not defined) 17/223 (7.6%); any serious [not defined, 17/223 (7.6%)] Submission[62] 17/223 (7.6%); drug-related SAE, 4/223 (1.8%)	Reinisch *et al.*[44] 108/223 (48.4%) Submission[62] 108/223 (48.1%); possibly drug related, 48/223 (21.5%)	Reinisch *et al.*[44] 12/223 (5.4%) Submission[62] 12/223 (5.4%)
ULTRA1	160 mg/80 mg of ADA	NR	Week 8	Reinisch *et al.*[44] Any severe (not defined) 19/223 (8.5%); any serious (not defined, 9/223 (4.0%)	Reinisch *et al.*[44] 112/223 (50.2%)	Reinisch *et al.*[44] 12/223 (5.4%)
ULTRA1	160 mg/80 mg of ADA	NR	Week 8	Submission[62] 97/223 (4.0%); drug-related SAE, 1/223 (0.4%)	Submission[62] 112/223 (50.2%); possibly drug related, 43/223 (19.3%)	Submission[62] 12/223 (5.4%)
ULTRA2	PBO	NR	Week 52	Sandborn *et al.*[45] Any severe (not defined) 37/260 (14.2%); any serious [not defined, 32/260 (12.3%)] Submission[62] 32/260 (12.3%)	Sandborn *et al.*[45] 218/260 (83.8%); possibly drug-related, 86/260 (33.1%) Submission[62] 218/260 (83.8%)	Sandborn *et al.*[45] 34/260 (13.1%) Submission[62] 34/260 (13.1%)

Trial name	Treatment arm	Length of safety follow-up/mean number of administrations	Time point	Number of patients experiencing one or more AE, *n*/*N*(%)	Number of patients experiencing one or more SAE, *n*/*N* (%) (including definition)	Discontinuation owing to AE(s), *n*/*N* (%)
ULTRA2	160 mg of ADA at week 0, 80 mg at week 2 and then 40 mg EOW beginning at week 4	NR	Week 52	Sandborn *et al.*[45] Any severe (not defined) 41/257 (16.0%); any serious [not defined, 31/257 (12.1%)] Submission[62] 31/257 (12.1%)	Sandborn *et al.*[45] 213/257 (82.9%); possibly drug-related, 101/257 (39.3%) Submission[62] 213/257 (82.9%)	Sandborn *et al.*[45] 23/257 (8.9%) Submission[62] 23/257 (8.9%)
ULTRA3	40 mg of ADA EOW or EW	NR	Week 52	Reinisch *et al.*[54] 76/577 (13.6%) events, 93 (events per 100 PY, 21.8)	Reinisch *et al.*[54] 421/577 (75.6%) events, 2187 (events per 100 PY, 512.3)	Reinisch *et al.*[54] 78/577 (14.0%) events, 90 (events per 100 PY, 21.1)
ULTRA3	40 mg of ADA EOW or EW	NR	Week 52	Submission[62] 40 mg of ADA EOW/EW $n = 1010$; PYs, 2338 events (events/100 PYs): 414 (17.7)	Submission[62] 40 mg of ADA EOW/EW $n = 1010$; PYs, 2338 events (events/100 PYs): 8057 (344.6)	Submission[62] 40 mg of ADA EOW/EW $n = 1010$; PYs, 2338 events (events/100 PYs): 249 (10.7)
Suzuki	PBO	52 weeks	Week 8	Suzuki *et al.*[46] Week 8: 7/96 (7.3%)	Suzuki *et al.*[46] Week 8: 45/96 (46.9%)	Suzuki *et al.*[46] Week 8: 4/96 (4.2%)
Suzuki	PBO	52 weeks	Week 52	Suzuki *et al.*[46] Week 52 ($n = 96$, PYs = 44.8): events, 273 (events/100 PYs, 609.4)	Suzuki *et al.*[46] Week 52 ($n = 96$, PYs = 44.8): events, 14 (events/100 PYs, 31.3)	Suzuki *et al.*[46] Week 52 ($n = 96$, PYs = 44.8): events, 6 (events/100 PYs, 13.4)
Suzuki	160 mg/80 mg of ADA	52 weeks	Week 8	Suzuki *et al.*[46] Week 8: 4/90 (4.4%)	Suzuki *et al.*[46] Week 8: 40/90 (44.4%)	Suzuki *et al.*[46] Week 8: 6/90 (6.7%)

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Trial name	Treatment arm	Length of safety follow-up/mean number of administrations	Time point	Number of patients experiencing one or more AE, *n*/*N*(%)	Number of patients experiencing one or more SAE, *n*/*N* (%) (including definition)	Discontinuation owing to AE(s), *n*/*N* (%)
Suzuki	80 mg/40 mg of ADA or 160 mg/80 mg of ADA to week 8 then 40 mg of ADA EOW	52 weeks	Week 52	Suzuki *et al.*[46] Week 52 ($n = 177$, PYs, 98.2): events, 33 (events/100 PYs, 33.6) ADA week 8 responders per full Mayo score ($n = 82$, PYs, 68.7): 20 (events/100 PYs, 29.1)	Suzuki *et al.*[46] Week 52 ($n = 177$, PYs, 98.2): events, 538 (events/100 PYs, 547.9); ADA week 8 responders per full Mayo score ($n = 82$, PYs, 68.7): 343 (events/100 PYs, 499.3)	Suzuki *et al.*[46] Week 52 ($n = 177$, PYs, 98.2): events, 22 (events/100 PYs, 22.4); ADA week 8 responders per full Mayo score ($n = 82$, PYs, 68.7): 11 (events/100 PYs, 16.0)
PURSUIT-SC	PBO	6.05 weeks Mean 1.98	Week 6	Sandborn *et al.*[47] Patients with ≥ 1 SAE (not defined) 20/330 (6.1)	Sandborn *et al.*[47] 126/330 (38.2) Headache, 17/330 (5.2); nasophayngitis, 11/330 (3.3); pyrexia 7/330, (2.1); nausea 7/330, (2.1); exacerbation of UC, 13/330 (3.9)	Sandborn *et al.*[47] 3/330 (0.9) (viral infection = erythema nodosum, exacerbation of UC)
PURSUIT-SC	200 mg/100 mg of GOL	6.08 weeks Mean 1.99	Week 6	Sandborn *et al.*[47] 9/331 (2.7)	Sandborn *et al.*[47] 124/331 (37.5) Headache, 10/331 (3.0); nasophayngitis, 11/331 (3.3); pyrexia, 6/331 (1.8); nausea, 3/331 (0.9); exacerbation of UC 7/331, (2.1)	Sandborn *et al.*[47] 1/331 (0.3) (worsening of UC/clostridia infection)

Trial name	Treatment arm	Length of safety follow-up/mean number of administrations	Time point	Number of patients experiencing one or more AE, *n*/*N*(%)	Number of patients experiencing one or more SAE, *n*/*N* (%) (including definition)	Discontinuation owing to AE(s), *n*/*N* (%)
PURSUIT-M	PBO, $n = 156$	32.7 weeks 8.2 Total number of study agent injections. PBO, 3333	Week 54	Sandborn *et al.*[48] ≥ 1 SAE. PBO,12 (7.7)	Sandborn *et al.*[48] 103 (66.0) (all are treatment-emergent AEs) Exacerbation of UC, 29 (18.6); nasopharyngitis, 11 (7.1); headache, 14 (9.0); arthralgia, 12 (7.7); abdominal pain = 4 (2.6); upper respiratory tract infection, 4 (2.6); rash, 3 (1.9); pharyngitis, 4 (2.6); cough, 5 (3.2)	Sandborn *et al.*[48] PBO, 10 (6.4)
PURSUIT-M	50 mg of GOL, $n = 154$	44.3 Total number of study agent injections, 11.1. GOL 50 mg, 4392	Week 54	Sandborn *et al.*[48] 50 mg of GOL, 13 (8.4)	Sandborn *et al.*[48] 112 (72.7) Exacerbation of UC, 27 (17.5); nasopharyngitis, 14 (9.1); headache, 12 (7.8); arthralgia, 11 (7.1); abdominal pain = 11 (7.1); upper respiratory tract infection = 8 (5.2); rash, 9 (5.8); pharyngitis, 8 (5.2); cough, 5 (3.2)	Sandborn *et al.*[48] 50 mg of GOL, 8 (5.2)
PURSUIT-M	100 mg of GOL, $n = 154$	46.3 Total number of study agent injections, 11.3. GOL 100 mg, 4440	Week 54	Sandborn *et al.*[48] 100 mg of GOL, 22 (14.3)	Sandborn *et al.*[48] 113 (73.4) Exacerbation of UC, 24 (15.6); nasopharyngitis, 21 (13.6); headache, 12 (7.8); arthralgia, 8 (5.2); abdominal pain = 11 (7.1); upper respiratory tract infection = 9 (5.8); rash, 7 (4.5); pharyngitis, 5 (3.2); cough, 9 (5.8)	Sandborn *et al.*[48] 100 mg of GOL, 14 (9.1)

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Trial name	Treatment arm	Length of safety follow-up/mean number of administrations	Time point	Number of patients experiencing one or more AE, *n*/*N*(%)	Number of patients experiencing one or more SAE, *n*/*N* (%) (including definition)	Discontinuation owing to AE(s), *n*/*N* (%)
UC-SUCCESS	AZA	Week 8 and week 8 to 16	Week 8 and week 8 to 16	Panaccione *et al.*[51] Week 8: 6/79 (8%) no definition Week 8 to 16: 0/42 (0%); AFX to IFX/AZA, 1/20 (5%)	Panaccione *et al.*[51] Week 8: 41/79 (52%) Week 8 to 16: 11/42 (26%); AFX to IFX/AZA, 7/20 (35%) Week 8: abdominal pain, 4/79 (5%); abdominal pain, upper 4/79 (5%); anaemia, 4/79 (5%); fatigue, 4/79 (5%); headache, 8/79 (10%); nausea, 10/79 (13%); pyrexia, 3/79 (4%); vomiting, 6/79 (8%) Week 8 to 16: arthralgia 3/42 (7%); aspergillosis, chest discomfort, conjunctival haemorrhage, drug hypersensitivity, dyspnoea, leucopoenia, nasopharyngitis, painful defecation = pyrexia, UC – all 0/42 (0%); pain in extremity 2/42 (5%) Week 8 to 16: AFX to IFX/AZA: arthralgia, 0/20 (0%); aspergillosis, 1/20 (5); chest discomfort, 1/20 (5); conjunctival haemorrhage, 1/20 (5); drug hypersensitivity, 1/20 (5); dyspnoea, 1/20 (5); leucopoenia, 1/20 (5); nasopharyngitis, 1/20 (5); painful defecation, 1/20 (5); pain in extremity, 0; pyrexia, 1/20 (5); UC, 1/20 (5)	Panaccione *et al.*[51] Week 8: 6/79 (8%) Week 8 to 16: 1/42 (2%); AFX to IFX/AZA, 3/20 (15%)

Trial name	Treatment arm	Length of safety follow-up/mean number of administrations	Time point	Number of patients experiencing one or more AE, *n*/*N*(%)	Number of patients experiencing one or more SAE, *n*/*N* (%) (including definition)	Discontinuation owing to AE(s), *n*/*N* (%)
UC-SUCCESS	IFX	NR	Week 8 and week 8 to 16	Panaccione *et al.*[51]	Panaccione *et al.*[51]	Panaccione *et al.*[51]
				Week 8: 2/78 (3%)	Week 8: 26/78 (33%)	Week 8: 2/79 (3%)
				Week 8 to 16: 4/74.5	Week 8 to 16: 22/30 (29%)	Week 8 to 16: 3/74 (4%)
					Week 8: abdominal pain, 3/78 (4%); abdominal pain, upper 0/78 (0%); anaemia, 3/78 (4%); fatigue, 0/78 (0%); headache, 4/78 (5%); nausea, 1/78 (1%); pyrexia, 5/78 (6%); vomiting, 0/78 (0%)	
					Week 8 to 16: Arthralgia, 2/74 (3%); aspergillosis, chest discomfort, conjunctival haemorrhage, drug hypersensitivity, dyspnoea, leucopoenia, painful defecation = pain in extremity – all 0/74 (0%); nasopharyngitis 1/74 (1%); pyrexia, 2/74 (3%); UC, 4/74 (5%)	
UC-SUCCESS	IFX/AZA	NR	Week 8 and week 8 to 16	Panaccione *et al.*[51]	Panaccione *et al.*[51]	Panaccione *et al.*[51]
				Week 8: 3/80 (4%)	Week 8: 30/80 (38%)	Week 8: 3/79 (4%)
				Week 8 to 16: 1/72 (1%)	Week 8 to 16: 21/72 (29%)	Week 8 to 16: 3/72 (4%)
					Week 8: abdominal pain, 0/80 (0%); abdominal pain, upper 0/80 (0%); anaemia, 1/80 (1%); fatigue, 1/80 (1%); headache, 4/80 (5%); nausea, 7/80 (9%); pyrexia, 2/80 (3%); vomiting, 1/80 (1%)	

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Trial name	Treatment arm	Length of safety follow-up/mean number of administrations	Time point	Number of patients experiencing one or more AE, *n*/*N*(%)	Number of patients experiencing one or more SAE, *n*/*N* (%) (including definition)	Discontinuation owing to AE(s), *n*/*N* (%)
					Week 8 to 16: Arthralgia, 2 (3); aspergillosis, chest discomfort, conjunctival haemorrhage, drug hypersensitivity, dyspnoea, leucopoenia, painful defecation = pain in extremity, pyrexia – all 0/72 (0%); nasopharyngitis, 1/72 (1%); UC, 3/72 (4%)	
Probert	PBO	Week 6	Week 6		2/20 (10%); 1 septic complication, 1 colectomy due to toxic exacerbation and spontaneous perforation	
ACT1	PBO	36.2 weeks (all mean = SD NR) 24.2 weeks treatment (mean = SD NR for all)	Week 54	Rutgeerts *et al.*[49] 31/121 (25.6) states SAEs most commonly related to gastrointestinal system in both studies (no further details)	Rutgeerts *et al.*[49] 103/121 (85.1) AEs occurring in ≥ 10% of any treatment group only reported. Worsening UC, 40/121 (33.1); abdominal pain, 16/121 (13.2 nausea, 14/121 (11.6); upper RTI, 28/121 (23.1); pharyngitis, 10/121 (8.3); sinusitis, 4/121 (3.3); pain = 19/121 (15.7); rash, 16/121 (13.2); arthralgia, 18/121 (14.9); headache, 27/121 (22.3); fever, 10/121 (8.3); anaemia, 12/121 (9.9); fatigue, 11/121 (9.1)	Rutgeerts *et al.*[49] 11/121 (9.1)
ACT1	PBO	Mean duration of treatment, 23 weeks (no SD reported) mean duration of follow-up, 32 weeks (no SD reported) NR	Week 54	Sandborn *et al.*[67] 57/244 (23) patients with long-term follow-up (mean 30 weeks) patients with ≥ 1 SAE (%), 6/14 (43); UC, 6/14 (43); fever, 1/14 (7)	Sandborn *et al.*[67] Any AE (%) 196/244 (80) AEs occurring in > 10% of any treatment group: worsening UC 61/244 (25); abdominal pain, 31/244 (13); nausea, 23/244 (9); upper RTI, 43/244 (18); pharyngitis, 16/244 (7); sinusitis, 12/244 (5); pain, 30/244 (12); fatigue, 19/244 (8); arthralgia, 26/244 (11); fever, 22/244 (9); headache, 45/244 (18); anaemia, 25/244 (10)	Sandborn *et al.*[67] 23/244 (9)

Trial name	Treatment arm	Length of safety follow-up/mean number of administrations	Time point	Number of patients experiencing one or more AE, *n*/*N*(%)	Number of patients experiencing one or more SAE, *n*/*N* (%) (including definition)	Discontinuation owing to AE(s), *n*/*N* (%)
ACT1	5 mg/kg of IFX	44.9 weeks 34.8 weeks	Week 54	Rutgeerts *et al.*[49] 26/121 (21.5)	Rutgeerts *et al.*[49] 106/121 (87.6) Worsening UC, 23/121 (19.0); abdominal pain, 11/121 (9.1); nausea, 14/121 (11.6); upper RTI, 20/121 (16.5); pharyngitis, 12/121 (9.9); sinusitis, 8/121 (6.6); pain = 14/121 (11.6); rash, 14/121 (11.6); arthralgia, 21/121 (17.4); headache, 22/121 (18.2); fever, 14/121 (11.6); anaemia, 4/121 (3.3); fatigue, 14/121 (11.6)	Rutgeerts *et al.*[49] 10/121 (8.3)
ACT1	5 mg/kg of IFX	Mean duration of treatment, 33 weeks (no SD reported); mean duration of follow-up, 41 weeks (no SD reported) NR	Week 54	Sandborn *et al.*[67] 43/242 (18) patients with long-term follow-up (mean 25 weeks) patients with 1 or more SAEs (%) (AEs included, IFX-related AEs or those requiring hospitalisation for treatment of UC (including colectomy) 5/15 (33); UC 5/15 (33); fever 0	Sandborn *et al.*[67] Any AE (%) 208/242 (86) AEs occurring in > 10% of any treatment group: worsening UC 36/242 (15) abdominal pain 22/242 (9) nausea 21 (242 (9) upper RTI 39/16 (16) pharyngitis 23/242 (10) sinusitis 20/242 (8) pain 25/242 (10) fatigue 21/242 (9) arthralgia 40/242 (17) fever 27/242 (11) headache 44/242 (18) anaemia 11/242 (5)	Sandborn *et al.*[67] 14/242 (6)
ACT2	PBO	21.9 weeks (Mean for all, SD NR) 14.4 weeks Duration of treatment (Mean for all, SD NR)	Week 54	Rutgeerts *et al.*[49]	Rutgeerts *et al.*[49] AEs selected as for ACT1: PBO 90/123 (73.2) worsening UC, 20/123 (16.3) abdominal pain = 14/123 (11.4) nausea, 9/123 (7.3) upper RTI, 14/123 (11.4) pharyngitis, 3/123 (2.4) sinusitis, 7/123 (5.7) pain = 11/123 (8.9) rash, 3/123 (2.4) arthralgia, 6/123 (4.9) headache, 18/123 (14.6) fever, 12/123 (9.8) anaemia, 13/123 (10.6) fatigue, 6/123 (4.9)	Rutgeerts *et al.*[49] 12/123 (9.8)

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Trial name	Treatment arm	Length of safety follow-up/mean number of administrations	Time point	Number of patients experiencing one or more AE, *n*/*N*(%)	Number of patients experiencing one or more SAE, *n*/*N* (%) (including definition)	Discontinuation owing to AE(s), *n*/*N* (%)
ACT2	5 mg/kg of IFX	27.5 weeks 99/121 (81.8)	Week 54	Rutgeerts *et al.*[49] 5 mg/kg of IFX 99/121 (81.8); worsening UC, 11/121 (9.1); abdominal pain, mg/kg of IFX 10/121 (8.3); nausea, 6/121 (5.0); upper RTI, 16/121 (13.2); pharyngitis, 7/121 (5.8); sinusitis, 11/121 (9.1); pain, 9/121 (7.4); rash, 2/121 (1.7); arthralgia, 16/121 (13.2); headache, 19/121 (15.7); fever, 13/121 (10.7); anaemia, 6/121 (5.0); fatigue, 6/121 (5.0)	Rutgeerts *et al.*[49] 2/121 (1.7)
ACT1, ACT2 extension studies	IFX combined group, $n = 230$	Mean (SD) duration of follow-up of 113 (642) weeks (range, 4–184 weeks; median, 128 weeks; 25–75 interquartile range, 96–144 weeks). Mean 2.16 years (no SD) Treatment duration mean (no SD) 1.99 years		Reinisch *et al.*[55] 49/230 (21.3%) experienced SAE. Number SAEs, 21 per 100 PYs. SAE experienced by > 1 patient: UC flare, $n = 11$; (4.8%), pneumonia; $n = 5$, (2.2%); gastrointestinal bleeding, $n = 4$ (1.7%); nausea, $n = 3$ (1.3%); bone fracture, $n = 3$ (1.3%); abdominal pain, $n = 2$ (0.9%); intestinal obstruction, $n = 2$ (0.9%); fever, $n = 2$ (0.9%)	Reinisch *et al.*[55] Number of AEs, 506 per 100 PYs	Reinisch *et al.*[55] 4.63 per 100 PYs

EOW, every other week; EW, every week.

Safety: participants experiencing adverse events, serious adverse events and withdrawal owing to adverse events (paediatric population trial)

Trial name	Treatment arm	Length of safety follow-up/mean number of administrations	Time point	Discontinuation due to AE(s), *n*/*N* (%)	Number of patients experiencing 1 or more AE, *n*/*N*(%)	Number of patients experiencing 1 or more SAE, *n*/*N* (%) (including definition)
Hyams	5 mg of IFX q8w	Mean weeks, 50.4	Week 8	Hyams *et al.*[52]	Hyams *et al.*[52]	Hyams *et al.*[52]
		Mean exposure weeks, 41.0. Total infusions, 165		22/22 (100)	4/22 (18.2) (1, serious infection; 1, pancreatitis and UC flare during induction plus viral infection after step-up; 1, UC flare after step-up; 1, anaemia during maintenance)	3/22 (13.6)
				22/22 (100)		
Hyams	5 mg of IFX q12w	Mean weeks, 44.6	Week 8	Hyams *et al.*[52]	Hyams *et al.*[52]	Hyams *et al.*[52]
		Mean exposure weeks, 34.3. Total infusions, 135		23/23 (100)	5/23 (21.7) [1, pharyngitis during induction; 1, urinary tract infection during induction; 1, UC flare during induction (× 1) and UC flare during maintenance (× 1); 1, UC flares during induction (× 2); 1, UC flare after step-up (× 1)]	6/23 (26.1)
Hyams	All patients to week 8 ($n = 60$)	Mean weeks, 38.0	Week 8	Hyams *et al.*[52]	Hyams *et al.*[52]	Hyams *et al.*[52]
				57/60 (95)	14/60 (23.3)	13/60 (21.7)

q8w, every 8 weeks; q12w, every 12 weeks.

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Safety: infections, serious infections, infections requiring treatment, reactivation of TB or hepatitis, injection site reactions, infusion reactions, serious allergic reactions (adult population trials)

Trial name	Treatment arm	Time point	Infections	Infections requiring treatment	Serious infections	Reactivation of TB	Reactivation of hepatitis B	Injection site reactions (relevant to ADA and GOL)	Infusion reactions (relevant to IFX)	Serious allergic reactions (e.g. anaphylaxis)
ULTRA1	PBO	Week 8	Reinisch *et al.*[44] 35/223 (15.7%)	NR	Reinisch *et al.*[44] 3/223 (1.3%) (pneumonia, 1; sepsis, 1; wound infection staphylococcal, 1)	NR	NR	Reinisch *et al.*[44] 7/223 (3.1%)	NR	NR
ULTRA1	80 mg/ 40 mg of ADA	Week 8	Reinisch *et al.*[44] 26/130 (20.0%)	NR	Reinisch *et al.*[44] 2/130 (1.5%) (abscess rupture, 1; perirectal abscess, 1)	NR	NR	Reinisch *et al.*[44] 7/130 (5.4%)	NR	NR
ULTRA1	160 mg/ 80 mg ADA	Week 8	Reinisch *et al.*[44] 32/223 (14.3%); opportunist infection (oesophageal candidiasis) 1/223 (0.4%)	NR	Reinisch *et al.*[44] 0/223 (0%)	NR	NR	Reinisch *et al.*[44] 13/223 (5.8%)	NR	NR
ULTRA2	PBO	Week 52	Sandborn *et al.*[45] 103/260 (39.6%); opportunistic infection-related AE (excluding TB) 3/260 (1.2%)	NR	Sandborn *et al.*[45] 5/260 (1.9%)	NR	NR	Sandborn *et al.*[45] 10/260 (3.8%)	NR	NR

Trial name	Treatment arm	Time point	Infections	Infections requiring treatment	Serious infections	Reactivation of TB	Reactivation of hepatitis B	Injection site reactions (relevant to ADA and GOL)	Infusion reactions (relevant to IFX)	Serious allergic reactions (e.g. anaphylaxis)
ULTRA2	160 mg/ 80 mg ADA	Week 52	Sandborn *et al.*[45] 116/257 (45.1%); opportunistic infection-related AE (excluding TB) 5/257 (1.9%)	NR	Sandborn *et al.*[45] 4/257 (1.6%)	NR	NR	Sandborn *et al.*[45] 31/257 (12.1%)	NR	NR
ULTRA3	80 mg/ 40 mg ADA		Reinisch *et al.*[54] 213/577 (38.2%) events, 382 (events per 100 PY, 89.5) opportunistic infection: 5/577 (0.9%) events, 6 (events per 100 PY, 1.4)	NR	Reinisch *et al.*[54] 17/577 (3.1%) events, 17 (events per 100 PY, 4.0)	NR	NR	Reinisch *et al.*[54] 8/577 (1.4%) events, 8 (events per 100 PY, 1.9)	NR	NR
ULTRA3	160 mg/ 80 mg ADA	Week 52	NR	NR	Submission[62] ADA 40 mg EOW/EW $n = 1010$; PYs, 2338events (events/100 PYs): serious infection = 79 (3.4); opportunistic infection excluding TB, 6 (0.3)	ADA 40 mg EOW/EW $n = 1010$; PYs, 2338 events (events/100 PYs): 1 (< 0.1)	NR	Submission[62] ADA 40 mg EOW/EW $n = 1010$; PYs, 2338 events (events/100 PYs): 246 (10.5)	NR	NR
Suzuki	PBO	Week 8	Suzuki *et al.*[46] Week 8: 15/96 (15.6%) opportunistic infection (excluding TB); Week 8: 0/96 (0%)	NR	Suzuki *et al.*[46] Week 8: 0/96 (0%)	Suzuki *et al.*[46] Week 8: 0/96 (0%)	NR	Suzuki *et al.*[46] Week 8: 2/96 (2.1%)	NR	NR

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Trial name	Treatment arm	Time point	Infections	Infections requiring treatment	Serious infections	Reactivation of TB	Reactivation of hepatitis B	Injection site reactions (relevant to ADA and GOL)	Infusion reactions (relevant to IFX)	Serious allergic reactions (e.g. anaphylaxis)
Suzuki	PBO	Week 52	Suzuki *et al.*[46] Week 52 ($n = 96$, PYs, 44.8): events, 70 (events/100 PYs, 156.3). Opportunistic infection (excluding TB); week 52 ($n = 96$, PYs, 44.8): events, 0 (events/100 PYs, 0)	NR	Suzuki *et al.*[46] Week 52 ($n = 96$, PYs, 44.8): events, 2 (events/100 PYs, 4.5)	Suzuki *et al.*[46] Week 52 ($n = 96$, PYs, 44.8): events, 0 (events/100 PYs, 0)	NR	Suzuki *et al.*[46] Week 52 ($n = 96$, PYs, 44.8): events, 4 (events/100 PYs, 8.9)	NR	NR
Suzuki	80 mg/ 40 mg of ADA	Week 8	Week 8: 11/87 (12.6%). Opportunistic infection (excluding TB); week 8: 0/87 (0%)[46]	NR	Week 8: 0/87 (0%)[46]	Week 8: 0/87 (0%)[46]	NR	Week 8: 5/87 (5.7%)[46]	NR	NR
Suzuki	160 mg/ 80 mg ADA	Week 8	Week 8: 17/90 (18.9%). Opportunistic infection (excluding TB); week 8: 1/90 (1.1%)[46]	NR	Week 8: 3/90 (3.3%)[46]	Week 8: 1/90 (1.1%)[46]	NR	Week 8: 7/90 (7.8%)[46]	NR	NR

Trial name	Treatment arm	Time point	Infections	Infections requiring treatment	Serious infections	Reactivation of TB	Reactivation of hepatitis B	Injection site reactions (relevant to ADA and GOL)	Infusion reactions (relevant to IFX)	Serious allergic reactions (e.g. anaphylaxis)
Suzuki	40 mg of ADA EOW	Week 52	Week 52 ($n = 177$, PYs, 98.2): events, 134 (events/100 PYs, 136.5). ADA week 8 responders per full Mayo score ($n = 82$, PYs, 68.7): 90 (events/100 PYs, 131.0). Opportunistic infection (excluding TB); week 52 ($n = 177$, PYs, 98.2): events, 2 (events/100 PYs, 2.0). ADA week 8 responders per full Mayo score ($n = 82$, PYs, 68.7): 2 (events/100 PYs, 2.9)[46]	Suzuki *et al.*[46]	Week 52 ($n = 177$, PYs, 98.2): events, 8 (events/100 PYs, 8.1). ADA week 8 responders per full Mayo score ($n = 82$, PYs, 68.7): 6 (events/100 PYs, 8.7)[46]	Week 52 ($n = 177$, PYs, 98.2): events, 1 (events/100 PYs, 1.0). ADA week 8 responders per full Mayo score ($n = 82$, PYs, 68.7): 0 (events/100 PYs, 0)[46]		Week 52 ($n = 177$, PYs, 98.2): events, 20 (events/100 PYs, 20.4). ADA week 8 responders per full Mayo score ($n = 82$, PYs, 68.7): 9 (events/100 PYs, 13.1)[46]		NR
PURSUIT-SC	PBO	Week 6	Patients with ≥ 1 infection 40/330 (12.1). 1 opportunistic infection (cytomegalovirus infection) (not reported as serious)[47]	Patients with ≥ 1 infection requiring treatment 23/330 (7.0)[47]	Patients with ≥ 1 serious infection 6/330 (1.8) (1 pneumonia)[47]	NR	NR	Patients with ≥ 1 injection site reaction 5/330 (1.5)[47]	NR	NR
PURSUIT-SC	100 mg/ 50 mg of GOL		8/71 (11.3)[47]	0[47]	0[47]	NR	NR	4/71 (5.6)[47]	NR	NR
PURSUIT-SC	200 mg/ 100 mg of GOL	Week 6	39/331 (11.8)[47]	15/331 (4.5)[47]	1/331 (0.3) (1 pneumonia)[47]	NR	NR	11/331 (3.3)[47]	NR	NR

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Trial name	Treatment arm	Time point	Infections	Infections requiring treatment	Serious infections	Reactivation of TB	Reactivation of hepatitis B	Injection site reactions (relevant to ADA and GOL)	Infusion reactions (relevant to IFX)	Serious allergic reactions (e.g. anaphylaxis)
PURSUIT-SC	400 mg/ 200 mg of GOL	Week 6	41/332 (12.3); 1 opportunistic infection (oesophageal candidiasis) (not reported as serious)[47]	25/332 (7.5)[47]	3/332 (0.9)[47]	NR	NR	10/332 (3.0)[47]	NR	NR
PURSUIT-M	PBO. $n = 156$	Week 54	≥ 1 infection (as assessed by investigator), 44 (28.2)[48]	24 (15.4)[48]	3 (1.9) serious opportunistic infection; 200 mg/ 100 mg of GOL s.c. induction = PBO maintenance, 1 (cytomegalovirus infection approximately 3 months after last GOL dose)[48]	TB reported through week 54. GOL 4 mg/kg i.v. induction = PBO maintenance, 1[48]	NR	Injections with injection site reactions, 18 (0.5) ≥ 1; injection site reactions, 3 (1.9)[48]	NR	NR
PURSUIT-M	50 mg of GOL, $n = 154$	Week 54	60 (39.0)[48]	39 (25.3)[48]	5 (3.2) serious opportunistic infection; 50 mg of GOL maintenance, 0[48]	0	NR	Injections with injection site reactions, 18 (0.4) ≥ 1; injection site reactions, 3 (1.9)[48]	NR	NR
PURSUIT-M	100 mg of GOL, $n = 154$	Week 54	60 (39.0)[48]	44 (28.6)[48]	5 (3.2) serious opportunistic infection; 200 mg/ 100 mg of GOL induction = 100 mg of GOL maintenance, 1 (*Staphylococcus aureus* and *Nocardia* cultured from a brain abscess)[48]	3 (1.9) 100 mg of GOL maintenance (1 each 400 mg/ 200 mg of GOL s.c., 4 mg/kg i.v. and 200 mg/ 100 mg s.c. induction) (including fatal case reported previously)[48]	NR	Injections with injection site reactions, 28 (0.6) ≥ 1; injection site reactions, 11 (7.1)[48]	NR	NR

Trial name	Treatment arm	Time point	Infections	Infections requiring treatment	Serious infections	Reactivation of TB	Reactivation of hepatitis B	Injection site reactions (relevant to ADA and GOL)	Infusion reactions (relevant to IFX)	Serious allergic reactions (e.g. anaphylaxis)
UC-SUCCESS	AZA	Week 8	NR	NR	1/79 (1%)[51]	NR	NR	NR	1/79 (1%)[51]	NR
UC-SUCCESS	IFX	Week 8	NR	NR	1/78 (1%)[51]	NR	NR	NR	0/78 (0%)[51]	NR
UC-SUCCESS	IFX/AZA	Week 8	NR	NR	0/80 (0%)[51]	NR	NR	NR	0/80 (0%)[51]	NR
ACT1	PBO	Week 54	47/121 (38.8); fungal dermatitis, 8/121 (6.6); pneumonia, 0; varicella-zoster virus infection, 1/121 (0.8); herpes zoster, 0[49]	25/121 (20.7)[49]	Serious infections, 5/121 (4.1); bacterial infection = 1/121 (0.8); upper RTI, 1/121 (0.8); pneumonia, 0; TB, 0; abscess, 1/121 (0.8); pharyngitis, 1/121 (0.8); gastroenteritis, 0; earache, 0; fever, 0; vaginitis, 0; appendicitis, 0; colitis, 0; surgical wound infection, 1/121 (0.8); pancreatitis, 0; pleurisy, 0; sinusitis, 1/121 (0.8)[49]	NR	NR	NR	Acute infusion reaction (any AE occurring ≤ 2 hours after start of infusion), 13/121 (10.7)	NR

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Trial name	Treatment arm	Time point	Infections	Infections requiring treatment	Serious infections	Reactivation of TB	Reactivation of hepatitis B	Injection site reactions (relevant to ADA and GOL)	Infusion reactions (relevant to IFX)	Serious allergic reactions (e.g. anaphylaxis)
ACT1	PBO	ACT1 and ACT2, and ACT2 extension through 54 weeks	80/244 (33)[67]	NR	Serious infections (%), 6/244 (2); bacterial infection, 1/244 (0.4); upper RTI, 1/244 (0.4); pneumonia, 0; TB, 0; abscess, 2/244 (1); pharyngitis, 1/244 (0.4); gastroenteritis, 0; earache, 0; fever, 0; vaginitis, 0; appendicitis, 0; colitis, 0; infection, 1/244 (0.4); (no further details); pancreatitis, 0; pericarditis, 0; pleurisy, 0; pyelonephritis, 0; sinusitis, 1/244 (0.4)[67]	NR	NR	NR	Possible delayed hypersensitivity reactions (%), 2/242 (1)	NR

Trial name	Treatment arm	Time point	Infections	Infections requiring treatment	Serious infections	Reactivation of TB	Reactivation of hepatitis B	Injection site reactions (relevant to ADA and GOL)	Infusion reactions (relevant to IFX)	Serious allergic reactions (e.g. anaphylaxis)
ACT1	5 mg/kg of IFX	Week 54	53/121 (43.8); fungal dermatits, 1/121 (0.8);[49] pneumonia, 2/121 (1.7); varicella-zoster virus infection, 1/121 (0.8); herpes zoster, 1/121 (0.8) *n* = 121 all infections baseline IMM: 32/66 (48.5%); all infections no baseline IMM: 21/55 (38.2%)[342]	39/121 (32.2)[49]	Serious infections, 3/121 (2.5); bacterial infection, 0; upper RTI, 0; pneumonia, 0; TB, 0; abscess, 0; pharyngitis, 0; gastroenteritis, 1/121 (0.8); earache, 0; fever, 0; vaginitis, 0; appendicitis, 1/121 (0.8); colitis, 0; surgical wound infection, 0 (0.8); pancreatitis, 1/121 (0.8); pleurisy, 0; sinusitis, 0[49] *n* = 121 serious infections baseline IMM: 3/66 (4.5%); serious infections no baseline IMM: 0/55 (0.0%)[49]	NR	NR	NR	121 (9.9); possible delayed hypersensitivity reactions 2/121 (1.7) [49] *n* = 121: infusions *n* with reactions baseline IMM: 7/423 (1.7%); infusions *n* with reactions no baseline IMM: 8/364 (2.2%); patients *n* with any infusion reactions baseline IMM: 6/66 (9.1%); patients *n* with any infusion reactions no baseline IMM: 6/55 (10.9%); *n* = 121: infusions *n* with serious reactions baseline IMM: 0/364 (0.0%); infusions *n* with serious reactions no baseline IMM: 0/423 (0.0%); patients *n* with serious infusion reactions baseline IMM: 0/66 (0.0%); patients *n* with serious infusion reactions no baseline IMM: 0/55 (0.0%)	NR

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Trial name	Treatment arm	Time point	Infections	Infections requiring treatment	Serious infections	Reactivation of TB	Reactivation of hepatitis B	Injection site reactions (relevant to ADA and GOL)	Infusion reactions (relevant to IFX)	Serious allergic reactions (e.g. anaphylaxis)
ACT1	5 mg/kg of IFX	ACT1 and ACT2, and ACT2 extension through 54 weeks	94/242 (39)[67]	Sandborn *et al.*[67]	Serious infections, (%) 7/242 (3); bacterial infection, 0; upper RTI, 0; pneumonia, 2/242 (1); TB, 0; abscess, 0; pharyngitis, 0; gastroenteritis, 2/242 (1); earache, 1/242 (0.4); fever, 1/242 (0.4); vaginitis, 0; appendicitis, 1/242 (0.4); colitis, 0; infection, 0; pancreatitis, 1/242 (0.4); pericarditis, 0; pleurisy, 0; pyelonephritis, 0; sinusitis [67]	NR	NR	NR	Possible delayed hypersensitivity reactions (%), 2/242 (1)[342]	NR

Trial name	Treatment arm	Time point	Infections	Infections requiring treatment	Serious infections	Reactivation of TB	Reactivation of hepatitis B	Injection site reactions (relevant to ADA and GOL)	Infusion reactions (relevant to IFX)	Serious allergic reactions (e.g. anaphylaxis)
ACT1	10 mg/kg of IFX	Week 54	60/122 (49.2); fungal dermatitis, 3/122 (2.5); pneumonia, 4/122 (3.3); varicella-zoster virus infection, IFX 10 mg 0; herpes zoster, 0[49] *n* = 122 all infections baseline IMM: 32/59 (54.2%); all infections no baseline IMM: 28/63 (44.4%)[342]	43/122 (35.2)[49]	Serious infections, 8/122 (6.6); bacterial infection, 0; upper RTI, 0; pneumonia, 3/122 (2.5); TB, 1 (0.8); abscess, 2/122 (1.6); pharyngitis, 1/122 (0.8); gastroenteritis, 1/122 (0.8); earache, 0; fever, 1/122 (0.8); vaginitis, 0; appendicitis, 0; colitis, 1/122 (0.8); surgical wound infection, 1/122 (0.8); pancreatitis, 0; pleurisy, 1/122 (0.8); sinusitis, 0[49] *n* = 122 serious infections baseline IMM: 6/59 (10.2%); serious infections no baseline IMM: 2/63 (3.2%)[342]	NR	NR	NR	15/122 (12.3); possible delayed hypersensitivity reactions, 2/121 (1.7)[49] *n* = 122: infusions *n* with reactions no baseline IMM: 8/403 (2.0%); infusions *n* with reactions baseline IMM: 8/367 (2.2%); patients *n* with any infusion reactions baseline IMM: 8/59 (13.6%);[342] patients *n* with any infusion reactions no baseline IMM: 7/63 (11.1%); *n* = 122: infusions *n* with serious reactions baseline IMM: 0/367 (0.0%); infusions *n* with serious reactions no baseline IMM: 0/403 (0.0%); serious infusion reactions baseline IMM: 0/59 (0.0%); serious infusion reactions no baseline IMM: 0/63 (0.0%)	NR

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Trial name	Treatment arm	Time point	Infections	Infections requiring treatment	Serious infections	Reactivation of TB	Reactivation of hepatitis B	Injection site reactions (relevant to ADA and GOL)	Infusion reactions (relevant to IFX)	Serious allergic reactions (e.g. anaphylaxis)
ACT1	IFX comb	Week 54	*n* = 243. All infections baseline IMM: 64/125 (51.2%); all infections no baseline IMM: 49/118 (41.5%); ACT2 week 30 *n* = 241 all infections baseline IMM: 30/102 (29.4%); all infections no baseline IMM: 37/139 (26.6%)[342]	Lichtenstein *et al.*[342]	*n* = 243 serious infections baseline IMM: 9/125 (7.2%); serious infections no baseline IMM: 2/118 (1.7%); ACT2 week 30 *n* = 241 serious infusion reactions baseline IMM: 0/102 (0.0%); serious infusion reactions no baseline IMM: 0/139 (0.0%)[342]	NR	NR	NR	*n* = 243: infusions *n* with reactions baseline IMM: 15/790 (1.9%); infusions *n* with reactions no baseline IMM: 16/767 (2.1%); patients *n* any infusion reactions baseline IMM: 14/125 (11.2%); patients *n* any infusion reactions no baseline IMM: 13/118 (11.0%) *n* = 243: infusions *n* with serious reactions baseline IMM: 0/790 (0.0%); infusions *n* with serious reactions no baseline IMM: 0/767 (0.0%); serious infusion reactions baseline IMM: 0/125 (0.0%); serious infusion reactions no baseline IMM: 0/118 (0.0%)[342]	NR

Trial name	Treatment arm	Time point	Infections	Infections requiring treatment	Serious infections	Reactivation of TB	Reactivation of hepatitis B	Injection site reactions (relevant to ADA and GOL)	Infusion reactions (relevant to IFX)	Serious allergic reactions (e.g. anaphylaxis)
ACT2	PBO	Week 30	29/123 (23.6); fungal dermatitis, 0; IFX pneumonia, 0; IFX varicella-zoster virus infection, 0; herpes zoster, 1/123 (0.8); IFX 5[49]	15/123 (12.2)[49]	1/123 (0.8); bacterial infection, 0; upper RTI, 0; pneumonia, OTB, 0; abscess, 1/123 (0.8); pharyngitis, 0; gastroenteritis, PBO 0; earache, 0; fever, 0; vaginitis, 0; appendicitis, 0; colitis, 0; surgical wound infection, 0; pancreatitis, 0; pleurisy, 0; sinusitis, 0[49]	NR	NR	NR	Defined as for ACT1: 10/123 (8.1) possible delayed hypersensitivity 0[49]	NR

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Trial name	Treatment arm	Time point	Infections	Infections requiring treatment	Serious infections	Reactivation of TB	Reactivation of hepatitis B	Injection site reactions (relevant to ADA and GOL)	Infusion reactions (relevant to IFX)	Serious allergic reactions (e.g. anaphylaxis)
ACT2	5 mg/kg of IFX	Week 30	18/121 (14.9); fungal dermatitis, 0; pneumonia, 0; varicella-zoster virus infection, 1/121 (0.8); herpes zoster, 2/121 (0.8)[49] *n* = 121 all infections baseline IMM: 17/52 (32.7%); all infections no baseline IMM: 16/69 (23.2%)[342]		2/121 (1.7); bacterial infection, 0; upper RTI, 0; pneumonia, 0; TB, 0; abscess, 0; pharyngitis, 0; gastroenteritis, 1/121 (0.8); earache, 1/121 (0.8); fever, 1/121(0.8); vaginitis, 0; appendicitis, 0; colitis, 0; surgical wound infection = 0; pancreatitis, 0; pleurisy, 0; sinusitis, 0[49] *n* = 121 serious infections[342] baseline IMM: 1/52 (1.9%); serious infections no baseline IMM: 1/69 (1.4%)				14/121 (11.6) possible delayed hypersensitivity 0[49] *n* = 121; infusions *n* with reactions baseline IMM: 4/242 (1.7%); infusions *n* with reactions no baseline IMM: 12/316 (3.8%); patients *n* with any infusion reactions baseline IMM: 3/52 (5.8%); patients *n* with any infusion reactions no baseline IMM: 11/69 (15.9%). *n* = 121; infusions *n* with serious reactions baseline IMM: 0/242 (0.0%); infusions *n* with serious reactions no baseline IMM: 0/316 (0.0%); patients *n* with serious infusion reactions baseline IMM: 0/52 (0.0%); patients *n* with serious infusion reactions no baseline IMM: 0/69 (0.0%)	NR

Trial name	Treatment arm	Time point	Infections	Infections requiring treatment	Serious infections	Reactivation of TB	Reactivation of hepatitis B	Injection site reactions (relevant to ADA and GOL)	Infusion reactions (relevant to IFX)	Serious allergic reactions (e.g. anaphylaxis)
ACT2	10 mg/kg of IFX	Week 30	17/120 (14.2); fungal dermatitis, 10 mg/kg 1 (0.8); pneumonia, 10 mg/kg 2/120 (1.7); varicella-zoster virus infection, 0; herpes zoster, 1/120 (0.8)[49]	Rutgeerts *et al.*[49]	3/120 (2.5); bacterial infection, 0; upper RTI, 0; pneumonia, 0; TB, 0; abscess, 1/120 (0.8); pharyngitis, 0; gastroenteritis, 0; earache, 0; fever, 0; vaginitis, 1/120 (0.8); appendicitis, 0; colitis, 0; surgical wound infection, 1/120 (0.8); pancreatitis, 0; pleurisy, 0; sinusitis, 0[49]	NR	NR	Rutgeerts *et al.*[49]	14/120 (11.7); possible delayed hypersensitivity 1/120 (0.8)[342]	NR
ACT2	All treated patients, safety at week 30, $n = 121$	Week 30	5 mg/kg of IFX WITH immunomodulators, 17/52 (32.7); 5 mg/kg of IFX WITHOUT immunomodulators, 16/69 (23.2)[342] $n = 120$. All infections baseline IMM: 13/50 (26.0%); all infections no baseline IMM: 21/70 (30.0%)[342]	NR	5 mg/kg of IFX WITH immunomodulators, 1/52 (1.9)[342] $n = 120$ serious infections baseline IMM: 1/50 (2.0%); serious infections no baseline IMM: 2/70 (2.9%)[342]	NR	NR	NR	5 mg/kg of IFX WITH immunomodulators, 3/52 (5.8); 5 mg/kg of IFX WITHOUT immunomodulators, 11/69 (15.9); serious infusion reactions. 5 mg/kg of IFX WITH immunomodulators, 0/52 (0); serious infusion reactions. 5 mg/kg of IFX WITHOUT immunomodulators, 0/69 (0);[342] $n = 120$:[342] infusions	NR

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Trial name	Treatment arm	Time point	Infections	Infections requiring treatment	Serious infections	Reactivation of TB	Reactivation of hepatitis B	Injection site reactions (relevant to ADA and GOL)	Infusion reactions (relevant to IFX)	Serious allergic reactions (e.g. anaphylaxis)
									n with reactions baseline IMM: 6/224 (2.7%); infusions *n* with reactions no baseline IMM: 15/318 (4.7%); patients *n* with any infusion reactions baseline IMM: 5/50 (10.0%); patients *n* with any infusion reactions no baseline IMM: 9/70 (12.9%); *n* = 120: infusions *n* with serious reactions baseline IMM: 0/224 (0.0%); infusions *n* with serious reactions no baseline IMM: 0/318 (0.0%); serious infusion reactions baseline IMM: 0/50 (0.0%); serious infusion reactions no baseline IMM: 0/70 (0.0%)	

Trial name	Treatment arm	Time point	Infections	Infections requiring treatment	Serious infections	Reactivation of TB	Reactivation of hepatitis B	Injection site reactions (relevant to ADA and GOL)	Infusion reactions (relevant to IFX)	Serious allergic reactions (e.g. anaphylaxis)
ACT2	IFX combined group	Week 30	ACT1 week 54 $n = 243$ all infections baseline IMM: 64/125 (51.2%); all infections no baseline IMM: 49/118 (41.5%); ACT2 week 30 $n = 241$ all infections baseline IMM: 30/102 (29.4%); all infections no baseline IMM: 37/139 (26.6%)[342]	NR	ACT1 week 54 $n = 243$ serious infections baseline IMM: 9/125 (7.2%); serious infections no baseline IMM: 2/118 (1.7%); ACT2 week 30 $n = 241$ serious infusion reactions baseline IMM: 0/102 (0.0%); serious infusion reactions no baseline IMM: 0/139 (0.0%)[342]	NR	NR	NR	$n = 241$: infusions n with reactions baseline IMM: 10/466 (2.2%); infusions n with reactions no baseline IMM: 27/634 (4.3%); n patients any infusion reactions baseline IMM: 8/102 (7.82%); n patients any infusion reactions no baseline IMM: 20/139 (14.4%); $n = 241$: n infusions with reactions no baseline IMM: 27/634 (4.3%); n infusions with serious reactions baseline IMM: 0/466 (0.0%); serious infusion reactions baseline IMM: 0/102 (0.0%); serious infusion reactions no baseline IMM: 0/139 (0.0%)[342]	NR
ACT1, ACT2 extension studies	IFX combined group $n = 230$	NR	Number infections, 99 per 100 PYs[55]	Number infections requiring antimicrobial treatment, 41 per 100 PYs[55]	Patients (4.3%) had serious infection. Number serious infections 3.4 per 100 PYs. During extension studies, no reports of TB or other opportunistic infections[55]	NR	NR	NR	NR	NR

EOW, every other week; EW, every week; IMM, immunomodulator; RTI, respiratory tract infection; s.c. subcutaneous.

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Safety: infections, serious infections, infections requiring treatment, reactivation of tuberculosis or hepatitis, injection site reactions, infusion reactions, serious allergic reactions (paediatric population trial)

Trial name	Treatment arm	Time point	Infections	Infections requiring treatment	Serious infections	Reactivation of TB	Reactivation of hepatitis B	Injection site reactions (relevant to ADA and GOL)	Infusion reactions (relevant to IFX)	Serious allergic reactions (e.g. anaphylaxis)
Hyams	5 mg of IFX q8w	Week 8	13/22 (59.1%)[52]	NR	NR	NR	NR	NR	4/22 (18.2%)[52]	NR
Hyams	5 mg of IFX q12w	Week 8	14/23 (60.9%)[52]	NR	NR	NR	NR	NR	3/23 (13.0%)[52]	NR
Hyams	All patients to week 8 ($n = 60$)	Week 8	31/60 (51.7%)[52]	NR	NR	NR	NR	NR	8/60 (13.3%)[52]	NR

q8w, every 8 weeks; q12w, every 12 weeks.

Safety: heart failure, malignancies, hepatobiliary events, autoimmune processes, neurological events, haematological reactions (adult population trials)

Trial name	Treatment arm	Time point	Heart failure	Malignancies and lymphoproliferative disorders	Hepatobiliary events/liver enzyme changes	Autoimmune processes (e.g. lupus-like syndrome)	Neurological events	Haematological reactions	Other
ULTRA1	PBO	Week 8	0/223 (0%)[44]	2/223 (0.9%) – basal cell carcinoma, 1; breast cancer, 1[44]	NR	Demyelinating disease, 0/223 (0%)[44]	Demyelinating disease, 0/223 (0%)	NR	Submission MedDRA System Organ Class and Preferred Term: any AE, 218/223 (83.8%); colitis ulcerative, 21/223 (9.4%)
ULTRA1	160 mg/80 mg of ADA	Week 8	0/130 (0%)	0/130 (0%)[44]	NR	Lupus-like syndrome, 0/130 (0%)[44]	Demyelinating disease, 0/130 (0%)[44]	NR	Submission MedDRA System Organ Class and Preferred Term: any AE, 213/223 (82.9%); colitis ulcerative, 13/223 (5.8%)
ULTRA2	PBO	Week 52	0/260 (0%)[45]	0/260 (0%)[45]	NR	Lupus-like syndrome, 0/260 (0%)[45]	Demyelinating disease, 0/260 (0%)[45]	0/260 (0%)[45]	NR

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Trial name	Treatment arm	Time point	Heart failure	Malignancies and lymphoproliferative disorders	Hepatobiliary events/liver enzyme changes	Autoimmune processes (e.g. lupus-like syndrome)	Neurological events	Haematological reactions	Other
ULTRA2	160 mg of ADA at week 0, 80 mg at week 2 and then 40 mg EOW beginning at week 4	Week 52	1/257 (0.4%)[45]	Malignancies: 2/257 (0.8%)[45]	NR	Lupus-like syndrome, 1/257 (0.4%)[45]	Demyelinating disease, 0/257 (0%)[45]	5/257 (1.9%)[45]	Submission MedDRA System Organ Class and Preferred Term: any AE, 213/257 (82.9%); anaemia, 10/257 (3.9%); iron deficiency anaemia, 7/257 (2.7%); colitis ulcerative, 58/257 (22.6%); abdominal pain, 20/257 (7.8%); nausea, 15/257 (5.8%); fatigue, 16/257 (6.2%); pyrexia, 11/257 (4.3%); gastroenteritis, 9/257 (3.5%); nasopharyngitis, 45/257 (17.5%); pharyngitis, 9/257 (3.5%); URTI, 11/257 (4.3%); arthralgia, 20/257 (7.8%); headache, 22/257 (8.6%); oropharyngeal pain, 15/257 (5.8%)
ULTRA3	40 mg ofADA EOW or EW	Week 52	1/577 (0.2%) events, 1 (events per 100 PY, 0.2)	3/577 (0.5%) events, 3 (events per 100 PY, 0.7)	NR	Demyelinating disease: 1/557 (0.2%); 1 event (events per 100 PY, 0.2)	NR	11/577 (2.0%) events, 13 (events per 100 PY, 3.0)	NR

Trial name	Treatment arm	Time point	Heart failure	Malignancies and lymphoproliferative disorders	Hepatobiliary events/liver enzyme changes	Autoimmune processes (e.g. lupus-like syndrome)	Neurological events	Haematological reactions	Other
ULTRA3	40 mg of ADA EOW or EW	Week 52	Submission $n = 1010$; PYs, 2338; events (events/100 PYs): 4 (0.2)	Submission PYs, 2338; events (events/100 PYs): excluding lymphoma, 23 (1.0); lymphoma, 3 (0.1)	Submission $n = 1010$; PYs, 2338; events (events/100 PYs): 12 (0.5)	Submission $n = 1010$; PYs, 2338; events (events/100 PYs): demyelinating disease, 3 (0.1)	NR	NR	Submission $n = 1010$; PYs, 2338; events (events/100 PYs): UC worsening, 588 (25.2); flare, 588 (25.2)
Suzuki	PBO	Week 8	NR	Week 8: 0/96 (0%)[46]	Week 8: 1/96 (1.0%)[46]	NR	NR	Week 8: 1/96 (1.0%)[46]	UC worsening/flare: Week 8: 8/96 (8.3%)[46]
Suzuki	PBO	Week 52	NR	Week 52 ($n = 96$, PYs, 44.8): events, 0 (events/100 PYs, 0)[46]	Week 52 ($n = 96$, PYs, 44.8): events, 3 (events/100 PYs, 6.7)[46]	NR	NR	Week 52 ($n = 96$, PYs, 44.8): events, 4 (events/100 PYs, 8.9)[46]	Week 52 ($n = 96$, PYs, 44.8): events, 15 (events/100 PYs, 33.5)[46]
Suzuki	160 mg/80 mg of ADA only	Week 8	NR	1/90 (1.1%)[46]	1/90 (1.1%)[46]	NR	NR	1/90 (1.1%)[46]	UC worsening/flare: week 8: 2/90 (2.2%)[46]
Suzuki	80 mg/40 mg of ADA or 160 mg/80 mg of ADA to week 8 then 40 mg of ADA EOW	Week 52	NR	Week 52 ($n = 177$, PYs, 98.2): events, 2 (events/100 PYs, 2.0) ADA Week 8 responders per full Mayo score ($n = 82$, PYs, 68.7): 1 (events/100 PYs, 1.5)	Week 52 ($n = 177$, PYs, 98.2): events, 5 (events/100 PYs, 5.1) ADA Week 8 responders per full Mayo score ($n = 82$, PYs, 68.7): 3 (events/100 PYs, 4.4)	NR	NR	Week 52 ($n = 177$, PYs, 98.2): events, 6 (events/100 PYs, 6.1) ADA Week 8 responders per full Mayo score ($n = 82$, PYs, 68.7): 4 (events/100 PYs, 5.8)	UC worsening/flare: week 52 ($n = 177$, PYs, 98.2): events, 18 (events/100 PYs, 18.3) ADA Week 8 responders per full Mayo score ($n = 82$, PYs, 68.7): 7 (events/100 PYs, 10.2)
PURSUIT-SC	Phase III PBO	Week 6	NR	NR	NR	NR	NR	NR	Proportion of patients reporting AEs through week 6, 38.2[47]
PURSUIT-SC	Phase III 200 ml/100 mg of GOL Phase III	Week 6	NR	NR	NR	NR	NR	NR	Proportion of patients reporting AEs through week 6, 37.5[47]

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Trial name	Treatment arm	Time point	Heart failure	Malignancies and lymphoproliferative disorders	Hepatobiliary events/liver enzyme changes	Autoimmune processes (e.g. lupus-like syndrome)	Neurological events	Haematological reactions	Other
PURSUIT-M	PBO	Week 54	NR	Neoplasm benign = malignant and unspecified. PBO, 1 (0.6). Breast cancer was reported in a patient who had received only PBO during induction and maintenance[48]	NR	NR	NR	NR	NR
PURSUIT-M	50 mg of GOL	Week 54	NR	50 mg of GOL, 4 (2.6)[48]	NR	NR	NR	NR	NR
PURSUIT-M	100 mg of GOL	Week 54	NR	100 mg of GOL, 4 (2.6).[48] Three malignancies were reported through week 54 in patients receiving 100 mg of GOL maintenance; two of these (rectal cancer and thyroid cancer) presented with symptoms while the patients were receiving SC PBO induction and one (lung adenocarcinoma) occurred in a patient with a 40-year smoking history who received 200 mg/100 mg GOL s.c. induction therapy	NR	NR	NR	0	NR
UC-SUCCESS	AZA	Week 8	NR	NR	13/79 (16%)[51]	NR	NR	NR	NR
UC-SUCCESS	IFX	Week 8	NR	NR	3/78 (4%)[51]	NR	NR	NR	NR
UC-SUCCESS	IFX/AZA	Week 8	NR	NR	5/80 (6%)[51]	NR	NR	NR	NR

Trial name	Treatment arm	Time point	Heart failure	Malignancies and lymphoproliferative disorders	Hepatobiliary events/liver enzyme changes	Autoimmune processes (e.g. lupus-like syndrome)	Neurological events	Haematological reactions	Other
ACT1	PBO	Week 54	NR	One (basal cell carcinoma) one colonic dysplasia through week 54 in RESULTS-UC[67]	NR	NR	NR	NR	AEs of particular interest (%): fungal dermatitis, 8/244 (3); pneumonia, 0; varicella zoster virus infection, 1/244 (0.4); herpes zoster, 1/244 (0.4)[67]
ACT1	5 mg/kg ofIFX i.v.	Week 54	NR	$n = 2$. One patient with prostatic adenocarcinoma with 2-year history of elevated PSA concentration. One patient with colonic dysplasia. Two (prostate adenocarcinoma, rectal adenocarcinoma) through 54 weeks in RESULTS-UC, one new cancer (squamous cell skin carcinoma) developed in 5 mg/kg of IFX group patient, plus one colonic dysplasia[67]	NR	0	One patient with optic neuritis[67]	NR	AEs of particular interest (%): fungal dermatitis, pneumonia, varicella zoster virus infection = herpes zoster[67]
ACT2	PBO	Week 30	NR	$n = 1$. Basal-cell carcinoma[49]	NR	0	0	NR	At week 30 proportion with positive tests for antibodies to IFX who had infusion reaction 50.0 (6/12)[49]
ACT2	IFX	Week 30	NR	$n = 1$. Rectal adenocarcinoma[49]	NR	$n = 1$. One patient with lupus-like reaction (considered SAE)[49]	$n = 1$. One patient with optic neuritis[49]	NR	NR

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Trial name	Treatment arm	Time point	Heart failure	Malignancies and lymphoproliferative disorders	Hepatobiliary events/liver enzyme changes	Autoimmune processes (e.g. lupus-like syndrome)	Neurological events	Haematological reactions	Other
ACT2	IFX	Week 30	NR	0	NR	0	$n = 1$. One patient with multifocal motor neuropathy[49]	NR	NR
ACT1, ACT2 extension studies	IFX all		NR	Malignancy 1.01 per 100 PYs. Five malignancies reported during extension studies for IFX-treated patients. 19-year-old patient with adenocarcinoma of lung diagnosed (receiving 5 mg/kg of IFX) 1 month after E128 infusion. Patient was non-smoker and died approximately 18 months after completing extension study. One patient each developed breast cancer and prostate cancer, both receiving 5 mg/kg of IFX. Breast cancer diagnosed after week E72 infusion	NR	NR	No cases of optic neuritis or multifocal motir neuropathy were reported during extension studies[55]	NR	NR

Trial name	Treatment arm	Time point	Heart failure	Malignancies and lymphoproliferative disorders	Hepatobiliary events/liver enzyme changes	Autoimmune processes (e.g. lupus-like syndrome)	Neurological events	Haematological reactions	Other
				in 33-year-old patient with no family history of breast cancer. IFX discontinued and patient treated. Prostate cancer diagnosed approximately 2 weeks after E72 infusion in 64-year-old patient with pre-existing prostatitis (elevated PSA levels) at week E32. IFX discontinued and patient treated. Two patients, each on 10 mg/kg of IFX, developed a skin neoplasm. Neither resulted in discontinuation of treatment. One patient with extensive disease and 10-year UC history at main study baseline received 5 mg/kg of IFX and demonstrated colonic dysplasia during extension studies[55]				

EOW, every other week; EW, every week; URTI, upper respiratory tract infection.

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Safety: heart failure, malignancies, hepatobiliary events, autoimmune processes, neurological events, haematological reactions (paediatric population trial)

Trial name	Treatment arm	Time point	Heart failure	Malignancies and lymphoproliferative disorders	Hepatobiliary events/liver enzyme changes	Autoimmune processes (e.g. lupus-like syndrome)	Neurological events	Haematological reactions	Other
Hyams	IFX q8w	NR	NR	NR	NR	NR	NR	NR	NR
Hyams	IFX q12w	NR	NR	NR	NR	NR	NR	NR	NR

q8w, every 8 weeks; q12w, every 12 weeks.

Appendix 6 Quality-of-life tables

Quality-of-life outcomes

Study name	Treatment group	HRQoL instrument and domain, time point, mean (SD) [median] values, *n/N* (%) reporting improvement
ULTRA1	PBO	Reinisch *et al.*[344] Change from baseline at week 4: IBDQ overall, 146 SF-36 mental and physical component summary, 43[344] Change from baseline value at week 8: IBDQ overall, 152 SF-36 mental and physical component summary, 44 Reinisch *et al.*[61] IBDQ mean response (SD) at week 8 ($n = 130$): 75 (57.7)
ULTRA1	ADA 160/80 mg	Reinisch *et al.*[344] Change from baseline at week 4: IBDQ overall, 149 SF-36 mental and physical component summary, 45; *p*-value vs. PBO, < 0.05[344] Change from baseline value at week 8: IBDQ overall, 153 SF-36 mental and physical component summary, 46 Reinisch *et al.*[61] IBDQ mean response (SD) at week 8 ($n = 130$): 70 (53.8); *p*-value vs. PBO, 0.532
ULTRA2	PBO	Sandborn *et al.*[339] IBDQ (domain NR) Value at week 8: 20 (36), value at week 32: 20 (41), value at week 52: 19 (41) Sandborn *et al.*[339] Increase in IBDQ ≥ 16 points from baseline: value at week 8: 112/246 (45.5%), value at week 32: 54/246 (22.0%), value at week 52: 40/246 (16.3%), value at week 8, 32 and 52: 30/246 (12.2%)
ULTRA2	ADA 160/80 mg	Sandborn *et al.*[339] IBDQ (domain NR) value at week 8: 29 (36); *p*-value vs. PBO < 0.05, value at week 32: 28 (41); *p*-value vs. PBO < 0.05, value at week 52: 27 (42); *p*-value vs. PBO < 0.05 Sandborn *et al.*[339] Increase in IBDQ ≥ 16 points from baseline: value at week 8: 144/248 (58.1%); *p*-value vs. PBO, $p < 0.05$, value at week 32: 86/248 (34.7%); *p*-value vs. PBO, $p < 0.05$, value at week 52: 65/248 (26.2%); *p*-value vs. PBO, $p < 0.05$, value at week 8, 32 and 52: 58/248 (23.4%); *p*-value vs. PBO, $p < 0.05$

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Study name	Treatment group	HRQoL instrument and domain, time point, mean (SD) [median] values, *n/N* (%) reporting improvement
ULTRA3		Sandborn *et al.*[339] Value at week 12: IBDQ overall, 178.2 (34.60); SF-36 physical, NASF-36 mental, N/A[339] Value at week 48: IBDQ overall, 177.2 (34.94); SF-36 physical, 49.6 (8.24); SF-36 mental, 46.1 (10.77)[339] Value at week 108: IBDQ overall, 176.3 (37.15); SF-36 physical, 49.4 (8.13); SF-36 mental, 46.0 (11.00)
PURSUIT-SC	Phase II PBO	Sandborn *et al.*[47] Phase II PBO change from baseline in IBDQ overall, $n = 41$, mean (SD) 14.8 (37.16), median (IQR) 14.0 (–2.0 to 34.0) Read from source graph: Randomised in Phase II, 13 Randomised while Phase II data analysed, 12.5 Randomised in Phase III, 12.5
PURSUIT-SC	Phase II GOL 100/50 mg (regimen discontinued after Phase II)	Sandborn *et al.*[47] Phase II 100 mg/50 mg of GOL change from baseline in IBDQ overall, $n = 40$, mean (SD) 26.2 (39.71), median (IQR) 24.5 (–5.5 to 55.0) $p = 0.287$)
PURSUIT-SC	Phase II GOL 200/ 100 mg all randomised	Sandborn *et al.*[47] Phase II 200 mg/100 mg of GOL change from baseline in IBDQ overall, $n = 40$, mean (SD) 24.9 (36.89), median (IQR) 16.0 (–2.5 to 49.5) ($p = 0.318$) Read from source graph: Randomised in Phase II, 14 Randomised while Phase II data analysed, 25 Randomised in Phase III, 27
PURSUIT-SC	Phase II GOL 400/ 200 mg all randomised	Sandborn *et al.*[47] Phase II 400 mg/200 mg of GOL change from baseline in IBDQ, $n = 40$, mean (SD) 31.6 (26.21), median (IQR) 33.0 (9.0–54.0) ($p = 0.021$) Read from source graph: Randomised in Phase II, 32 Randomised while Phase II data analysed,30 Randomised in Phase III, 25
PURSUIT-SC	Phase III PBO	Sandborn *et al.*[47] Phase III change from baseline IBDQ PBO, $n = 251$, mean (SD) 14.8 (31.25), median (IQR) = 11.0 (–3.0 to 29.0)

Study name	Treatment group	HRQoL instrument and domain, time point, mean (SD) [median] values, *n/N* (%) reporting improvement
PURSUIT-SC	Phase III GOL 200/ 100 mg phase III	Sandborn *et al.*[47] Phase III change from baseline 200 mg/100 mg of GOL, $n = 252/253$, mean (SD) 27.0 (33.72), median (IQR) 22.5 (0.5–48.5) ($p < 0.0001$)
PURSUIT-SC	Phase III GOL 400/ 200 mg phase III	Sandborn *et al.*[47] Phase III change from baseline IBDQ 400 mg/200 mg of GOL, $n = 255/257$, mean (SD) 26.9 (34.28), median (IQR) 21.0 (0.0–50.0) ($p < 0.0001$)
PURSUIT-SC		Feagan *et al.*[345] Compared with PBO, significantly greater improvements experienced in combined GOL-treated group in IBDQ (27.2 vs. 14.6; $p < 0.001$), SF-36 physical component summary (4.14 vs. 2.46; $p < 0.01$) and mental component summary (4.89 vs. 1.60; $p < 0.001$) at week 6. Mean improvements in IBDQ (27.4 and 27.0), physical component summary (4.51 and 3.78) and mental component summary (4.69 and 5.10) comparable for 200 mg/100 mg of GOL and 400 mg/200 mg of GOL groups. Distributions of IBDQ score changed from mean of 129.4 (SD 33.9) at baseline to 156.5 (SD 39.8) at week 6 in GOL-treated patients, with 45.2% patients achieving IBDQ remission vs. PBO group mean of 144.2 (SD 37.1) with 28.1% achieving IBDQ remission ($p < 0.001$ vs. combined GOL group) Feagan *et al.*[345] In cumulative percentage curve vs. PBO, greater proportions of patients in each GOL group achieved 'any improvement' to 'clinically meaningful improvement' in IBDQ (51.1% vs. 35.2%; $p < 0.001$), SF-36 physical component summary (41.0% vs. 31.6; $p = 0.01$) and mental component summary (42.7% vs. 28.5%; $p < 0.001$) at week 6
PURSUIT-SC and PURSUIT-M		Sandborn *et al.*[340] GOL-treated patients achieving clinical remission at week 6 displayed greater mean improvement in SF-36 physical component summary, mental component summary, EQ-5D and IBDQ than those not achieving remission [physical component summary 8.0 vs. 2.9 ($p < 0.001$), mental component summary 10.7 vs. 2.6 ($p < 0.001$), EQ-5D 21.4 vs. 7.2 ($p < 0.001$) and IBDQ 54.7 vs. 17.7 ($p < 0.001$)] Sandborn *et al.*[340] Patients in clinical remission more likely to achieve normalised SF-36 physical component summary, normalised mental component summary and IBDQ remission than those not achieving clinical remission [physical component summary 53.6% vs. 25.3% ($p < 0.001$), mental component summary 63.6% vs. 31.6% ($p < 0.001$), IBDQ 85.5% vs. 32.2% ($p < 0.001$)]. Furthermore, GOL-treated patients achieving clinical remission during induction and maintained clinical remission at week 54 in maintenance were also more likely to achieve normalised physical component summary, mental component summary and IBDQ remission than those not [physical component summary 73.5% vs. 22.7% ($p < 0.001$), mental component summary 63.3% vs. 28.4% ($p < 0.001$), IBDQ remission 89.8% vs. 22.7 ($p < 0.001$)]

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Study name	Treatment group	HRQoL instrument and domain, time point, mean (SD) [median] values, *n/N* (%) reporting improvement
UC-SUCCESS	AZA	Panaccione *et al.*[51] Change from baseline at week 8: IBQD overall, $n = 50$: 37.84; *p*-value between IFX, 0.539 and IFX/AZA, 0.070. Change from baseline at week 8: SF-36 physical function, $n = 58$: 3.45; *p*-value between IFX, 0.422 and IFX/AZA, 0.044 Change from baseline at week 16: IBQD overall, $n = 53$: 32.51; *p*-value between IFX, 0.482 and IFX/AZA, < 0.001. Change from baseline at week 16: SF-36 physical function, $n = 54$: 4.13; *p*-value between IFX, 0.522 and IFX/AZA, 0.052
UC-SUCCESS	IFX	Panaccione *et al.*[51] Change from baseline at week 8: IBQD, $n = 53$: 33.42; *p*-value between IFX/AZA, 0.003. Change from baseline at week 8: SF-36 physical function, $n = 63$: 3.24; *p*-value between IFX/AZA, 0.010 Change from baseline at week 16: IBQD, $n = 58$: 38.55; *p*-value between IFX/AZA, 0.004. Change from baseline at week 16: SF-36 physical function, $n = 59$: 4.10; *p*-value between IFX/AZA, 0.022
UC-SUCCESS	IFX/AZA	Panaccione *et al.*[51] Change from baseline at week 8: IBQD, $n = 53$: 49.83. Change from baseline at week 8: SF-36 physical function, $n = 59$: SF-36 vitality, 16.6 (22.0); 6.42 Change from baseline at week 16: IBQD, $n = 57$: 57.70. Value at week 16: SF-36 physical function, $n = 59$: SF-36 vitality, 16.6 (22.0); 7.70
Probert	PBO	Probert *et al.*[50] Change from baseline at week 6: IBQD (domain NR), 25 (28) Change from baseline at week 6: European quality of life (domain NR) 4 (16)
Probert	IFX	Probert *et al.*[50] Change from baseline at week 6: IBQD (domain NR), 36 (49); *p*-value vs. PBO, 0.22 Change from baseline at week 6: European quality of life (domain NR) 7 (17); *p*-value vs. PBO, 0. 3
ACT1	PBO	Feagan *et al.*[346] Change from baseline at week 8: SF-36 physical component summary, 4.5 (6.8) SF-36 mental component summary, 3.1 (9.7) Feagan *et al.*[346] Change from baseline at week 8: SF-36 physical component summary, 2.9 (6.0) SF-36 mental component summary, 3.1 (9.7)
ACT1	PBO	Metz *et al.*[347] Mean IBDQ scores (read from source graph): Week 8, 20.70 Week 30, 17.83 Week 54, 12.33

Study name	Treatment group	HRQoL instrument and domain, time point, mean (SD) [median] values, *n/N* (%) reporting improvement
ACT1	5 mg/kg of IFX	Feagan *et al.*[346] Change from baseline at week 8: SF-36 physical component summary, 6.8 (7.8); *p*-value vs. PBO < 0.05; SF-36 mental component summary, 5.6 (10.2); *p*-value vs. PBO < 0.05 Feagan *et al.*[346] Change from baseline at week 8: SF-36 physical component summary, 6.8 (7.4); *p*-value vs. PBO < 0.05; SF-36 mental component summary, 6.1 (10.8); *p*-value vs. PBO < 0.05
ACT1	5 mg/kg of IFX	Metz *et al.*[347] Mean IBDQ scores (read from source graph): Week 8, 41.72 Week 30, 33.31 Week 54, 32.38
ACT1	10 mg/kg of IFX	Metz *et al.*[347] Mean IBDQ scores (read from source graph): Week 8, 34.71 Week 30, 35.01 Week 54, 31.42
ACT1	10 mg/kg of IFX	Feagan *et al.*[346] Change from baseline at week 8: SF-36 physical component summary, 5.6 (7.8); SF-36 mental component summary, 6.6 (12.0); *p*-value vs. PBO < 0.05 Feagan *et al.*[346] Change from baseline at week 8: SF-36 physical component summary, 6.2 (7.9); *p*-value vs. PBO < 0.05; SF-36 mental component summary, 6.2 (10.7); *p*-value vs. PBO < 0.05
ACT1	IFX combined	Feagan *et al.*[346] Change from baseline at week 8: SF-36 physical component summary, 6.2 (7.8); *p*-value vs. PBO < 0.05; SF-36 mental component summary, 6.1 (11.1); *p*-value vs. PBO < 0.05 Feagan *et al.*[346] Change from baseline at week 8: SF-36 physical component summary, 6.5 (7.7); *p*-value vs. PBO < 0.05; SF-36 mental component summary, 6.2 (10.7); *p*-value vs. PBO < 0.05
ACT1	IBDQ: responders who were not in remission ($n = 150$)	Reinisch *et al.*[348] Change from baseline at week 8 IBDQ (domain NR), 47 ($p < 0.001$ vs. non-responders)
ACT1	IBDQ: responders who were in remission ($n = 206$)	Reinisch *et al.*[348] Change from baseline at week 8 IBDQ (domain NR), 65

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Study name	Treatment group	HRQoL instrument and domain, time point, mean (SD) [median] values, *n/N* (%) reporting improvement
ACT1	Patients who had not discontinued CSs at week 30 ($n = 21$)	Reinisch *et al.*[348] Change from baseline at week 30: IBDQ 55.2 (58.0), SF-36 physical component summary 5.9 (7.4), SF-36 mental component summary 11.4 (9.6)
ACT1	Patients who had discontinued CSs at week 30 ($n = 70$)	Reinisch *et al.*[348] Change from baseline at week 30: IBDQ (domain NR), 64.7 (65.5), SF-36 physical component summary 9.8 (10.4), SF-36 mental component summary 11.0 (9.2)
ACT2	PBO	Metz *et al.*[347] Mean IBDQ scores (read from source graph): Week 8, 19.81 Week 30, 17.87
ACT2	IFX 5 mg/kg	Metz *et al.*[347] Mean IBDQ scores (read from source graph): Week 8, 38.65 Week 30, 31.64
ACT2	IFX 10 mg/kg	Metz *et al.*[347] Mean IBDQ scores (read from source graph): Week 8, 35.75 Week 30, 35.99
ACT1 and ACT2 combined	IBDQ: non-responders ($n = 137$)	Reinisch *et al.*[348] Mean change from baseline IBDQ (no SD for all), 12 Reinisch *et al.*[348] Significantly greater proportions of patients in responder and remission subgroups achieved at least a 16-point increase (87% and 96%, respectively) or a 32-point increase (68% and 87%, respectively) in total IBDQ score vs. patients classed as non-responders (39% and 26% respectively; $p < 0.001$ for all comparisons)
ACT1 and ACT2 combined	PBO	Feagan *et al.*[346] Change from baseline at week 8, $n = 244$: IBDQ bowel, 7.9 (9.7); IBDQ emotional, 6.2 (10.6); IBDQ systemic, 3.0 (4.8); IBDQ social, 3.8 (6.0); SF-36 physical functioning, 6.0 (17.3); SF-36 role-physical, 22.4 (39.7); SF-36 bodily pain, 13.1 (24.7); SF-36 general health, 5.6 (15.8); SF-36 vitality, 11.5 (20.7); SF-36 social functioning, 15.8 (24.8); SF-36 role-emotional, 12.4 (47.6); SF-36 mental health, 5.0 (18.4); SF-36 physical component summary, 3.7 (6.5); SF-36 mental component summary, 3.0 (9.6) Feagan *et al.*[346] Percentage of patients who achieved clinically meaningful improvement at value at week 8: IBDQ change ≥ 16, 49.6%; IBDQ change ≥ 32, 32.6%; SF-36 physical component summary change ≥ 3, 40.6%; SF-36 mental component summary change ≥ 3, 32.4%; SF-36 physical component summary change ≥ 5, 34.0%; SF-36 mental component summary change ≥ 5, 29.2%

Study name	Treatment group	HRQoL instrument and domain, time point, mean (SD) [median] values, *n/N* (%) reporting improvement
ACT1 and ACT2 combined	IFX 5 mg/kg	Feagan *et al.*[346] Change from baseline week to 8 $n = 242$: IBDQ bowel, 14.5 (11.7); *p*-value vs. PBO < 0.05; IBDQ emotional, 12.7 (12.6); *p*-value vs. PBO < 0.05; IBDQ systemic, 5.7 (5.9); *p*-value vs. PBO < 0.05; IBDQ social, 7.4 (8.0); *p*-value vs. PBO < 0.05; SF-36 physical functioning, 12.8 (19.3); *p*-value vs. PBO < 0.05; SF-36 role-physical, 29.6 (41.0); SF-36 bodily pain, 20.2 (22.5); *p*-value vs. PBO < 0.05; SF-36 general health, 10.0 (16.9); *p*-value vs. PBO < 0.05; SF-36 vitality, 16.6 (22.0); *p*-value vs. PBO < 0.05; SF-36 social functioning, 21.2 (24.8); *p*-value vs. PBO < 0.05; SF-36 role-emotional, 15.5 (46.1); SF-36 mental health, 10.6 (17.5); *p*-value vs. PBO < 0.05; SF-36 physical component summary, 6.8 (7.6); *p*-value vs. PBO < 0.05; SF-36 mental component summary, 5.9 (10.5); *p*-value vs. PBO < 0.05 Feagan *et al.*[346] Percentage of patients who achieved clinically meaningful improvement at value at week 8: IBDQ change ≥ 16, 69.7%; *p*-value vs. PBO < 0.05; IBDQ change ≥ 32, 56.8%; *p*-value vs. PBO < 0.05; SF-36 physical component summary change ≥ 3, 62.0%; *p*-value vs. PBO < 0.05; SF-36 mental component summary change ≥ 3, 52.1%; *p*-value vs. PBO < 0.05; SF-36 physical component summary change ≥ 5, 48.8%; *p*-value vs. PBO < 0.05; SF-36 mental component summary change ≥ 5, 40.9%; *p*-value vs. PBO < 0.05
ACT1 and ACT2 combined	IFX combined	Feagan *et al.*[346] Change from baseline week to 8 $n = 484$: IBDQ bowel, 13.7 (11.8); *p*-value vs. PBO < 0.05; IBDQ emotional, 12.0 (12.6); *p*-value vs. PBO < 0.05; IBDQ systemic, 5.4 (5.9); *p*-value vs. PBO < 0.05; IBDQ social, 6.8 (7.5); *p*-value vs. PBO < 0.05; SF-36 physical functioning, 11.0 (18.9); *p*-value vs. PBO < 0.05; SF-36 role-physical, 31.1 (42.5); *p*-value vs. PBO < 0.05; SF-36 bodily pain, 20.0 (23.4); *p*-value vs. PBO < 0.05; SF-36 general health, 10.4 (18.1); *p*-value vs. PBO < 0.05; SF-36 vitality, 18.3 (22.3); *p*-value vs. PBO < 0.05; SF-36 social functioning, 21.0 (25.9); *p*-value vs. PBO < 0.05; SF-36 role-emotional, 18.2 (45.4) SF-36 mental health, 10.5 (18.2); *p*-value vs. PBO < 0.05; SF-36 physical component summary, 6.4 (7.7); *p*-value vs. PBO < 0.05; SF-36 mental component summary, 6.1 (10.9); *p*-value vs. PBO < 0.05 Feagan *et al.*[346] Percentage of patients who achieved clinically meaningful improvement at value at week 8: IBDQ change ≥ 16, 68.7%; *p*-value vs. PBO < 0.05; IBDQ change ≥ 32, 54.7%; *p*-value vs. PBO < 0.05; SF-36 physical component summary change ≥ 3, 59.1%; *p*-value vs. PBO < 0.05; SF-36 mental component summary change ≥ 3, 49.0%; *p*-value vs. PBO < 0.05; SF-36 physical component summary change ≥ 5, 50.0%; *p*-value vs. PBO < 0.05; SF-36 mental component summary change ≥ 5, 43.0%; *p*-value vs. PBO < 0.05

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Study name	Treatment group	HRQoL instrument and domain, time point, mean (SD) [median] values, *n/N* (%) reporting improvement
ACT1 and ACT2 combined	IFX combined	Reinisch *et al.*[348] Mean change in PCS and MCS and individual SF-36 scale scores from baseline to week 30 by response status (read from source graph): Physical component summary: non-responders ($n = 137$), 40.00; responders who were not in remission ($n = 150$), 44.78; remission ($n = 206$), 49.77 Physical functioning: non-responders ($n = 137$), 44.18; responders who were not in remission ($n = 150$), 48.54; remission ($n = 206$), 51.66 Role-physical: non-responders ($n = 137$), 39.24; responders who were not in remission ($n = 150$), 44.85; remission ($n = 206$), 50.76 Bodily pain: non-responders ($n = 137$), 42.07; responders who were not in remission ($n = 150$), 47.05; remission ($n = 206$), 52.35 General health: non-responders ($n = 137$), 36.19; responders who were not in remission ($n = 150$), 40.24; remission ($n = 206$), 45.54 Vitality: non-responders ($n = 137$), 41.20; responders who were not in remission ($n = 150$), 47.11; remission ($n = 206$), 51.48 Social functioning: non-responders ($n = 137$), 40.61; responders who were not in remission ($n = 150$), 48.39; remission ($n = 206$), 52.13 Role-emotional: non-responders ($n = 137$), 44.06; responders who were not in remission ($n = 150$), 48.42; remission ($n = 206$), 51.58 Mental health: non-responders ($n = 137$), 45.02; responders who were not in remission ($n = 150$), 48.76; remission ($n = 206$), 50.95 Mental component summary: non-responders ($n = 137$), 44.12; responders who were not in remission ($n = 150$), 49.1; remission ($n = 206$), 51.6
ACT1 and ACT2 combined	PBO/IFX combined	Metz *et al.*[347] Mean baseline and change at week 8 scores per question for each IBDQ dimension (read from source graph): Bowel: baseline, 3.33; week 8, 4.48 Emotional: baseline, 3.62; week 8, 4.44 Systemic: baseline, 2.89; week 8, 3.83 Social: baseline, 3.41; week 8, 4.57 Mean baseline and change at week 8 in norm-based SF-36 scale scores (read from source graph): Physical functioning: baseline, 42.78; week 8, 45.97 Role-physical: baseline, 33.89; week 8, 41.23 Bodily pain: baseline, 39.03; week 8, 45.10 General health: baseline, 34.28; week 8, 37.16 Vitality: baseline, 36.88; week 8, 42.30

Study name	Treatment group	HRQoL instrument and domain, time point, mean (SD) [median] values, *n/N* (%) reporting improvement
		Social functioning: baseline, 34.68; week 8, 41.07
		Role-emotional: baseline, 41.42; week 8, 45.26
		Mental health: baseline, 41.14; week 8, 44.34
		Mean baseline and change at week 8 scores per question for each IBDQ dimension (read from source graph):
		Bowel: baseline, 3.34; week 8, 5.12
		Emotional: baseline, 3.80; week 8, 5.00
		Systemic: baseline, 3.00; week 8, 4.22
		Social: baseline, 3.74; week 8, 5.47
		Mean baseline and change at week 8 in norm-based SF-36 scale scores (read from graph):
		Physical functioning: baseline, 44.07; week 8, 49.49
		Role-physical: baseline, 35.81; week 8, 45.07
		Bodily pain: baseline, 39.68; week 8, 48.30
		General health: baseline, 35.89; week 8, 40.68
		Vitality: baseline, 37.84; week 8, 46.14
		Social functioning: baseline, 36.93; week 8, 46.82
		Role-emotional: baseline, 42.39; week 8, 48.14
		Mental health: baseline, 42.11; week 8, 47.85

CS, corticosteroid; IQR, interquartile range; N/A, not applicable; NR, not reported.

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Appendix 7 Network meta-analysis tables

Induction phase

	Treatments		Treatment 1				Treatment 2			
	1	2	No response	Response	Remission	Total	No response	Response	Remission	Total
Base-case data										
ULTRA 1	PBO	ADA	72	46	12	130	59	47	24	130
ULTRA 2 (anti-TNF-α-naive)	PBO	ADA	89	40	16	145	61	57	32	150
PURSUIT-SC Phases II + III	PBO	GOL	218	79	23	320	162	104	58	324
ACT1	PBO	IFX	76	27	18	121	37	37	47	121
ACT2	PBO	IFX	87	29	7	123	43	37	41	121
Sensitivity analysis 1										
ULTRA 1	PBO	ADA	72	46	12	130	59	47	24	130
ULTRA 2 (ITT)	PBO	ADA	161	62	23	246	123	84	41	248
PURSUIT-SC Phases II + III	PBO	GOL	218	79	23	320	162	104	58	324
ACT1	PBO	IFX	76	27	18	121	37	37	47	121
ACT2	PBO	IFX	87	29	7	123	43	37	41	121
Sensitivity analysis 2										
ULTRA 1	PBO	ADA	72	46	12	130	59	47	24	130
ULTRA 2 (anti-TNF-α-naive)	PBO	ADA	89	40	16	145	61	57	32	150
PURSUIT-SC Phases II + III	PBO	GOL	218	79	23	320	162	104	58	324
ACT1	PBO	IFX	76	27	18	121	37	37	47	121
ACT2	PBO	IFX	87	29	7	123	43	37	41	121
Suzuki *et al.*	PBO	ADA	62	23	11	96	45	36	9	90
Sensitivity analysis 3										
ULTRA 1	PBO	ADA	72	46	12	130	59	47	24	130
ULTRA 2 (ITT)	PBO	ADA	161	62	23	246	123	84	41	248
PURSUIT-SC Phases II + III	PBO	GOL	218	79	23	320	162	104	58	324
ACT1	PBO	IFX	76	27	18	121	37	37	47	121
ACT2	PBO	IFX	87	29	7	123	43	37	41	121
Suzuki *et al.*	PBO	ADA	62	23	11	96	45	36	9	90

Further maintenance NMA data removed owing to commercial-in-confidence status. Commercial-in-confidence information has been removed.

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Appendix 8 Network meta-analysis figures

Results when using conventional reference prior for the between study standard deviation

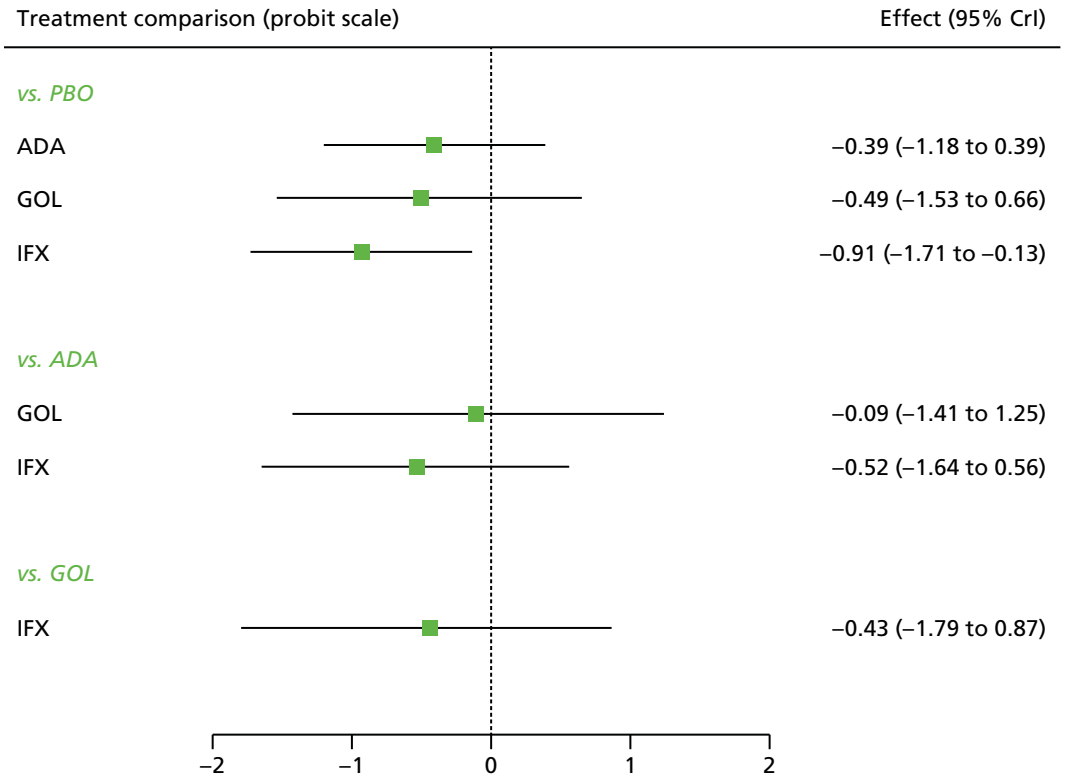

FIGURE 93 Base case: comparative effect of anti-TNF-α treatment on clinical response/remission in the induction phase [SD ~ U(0,2)].

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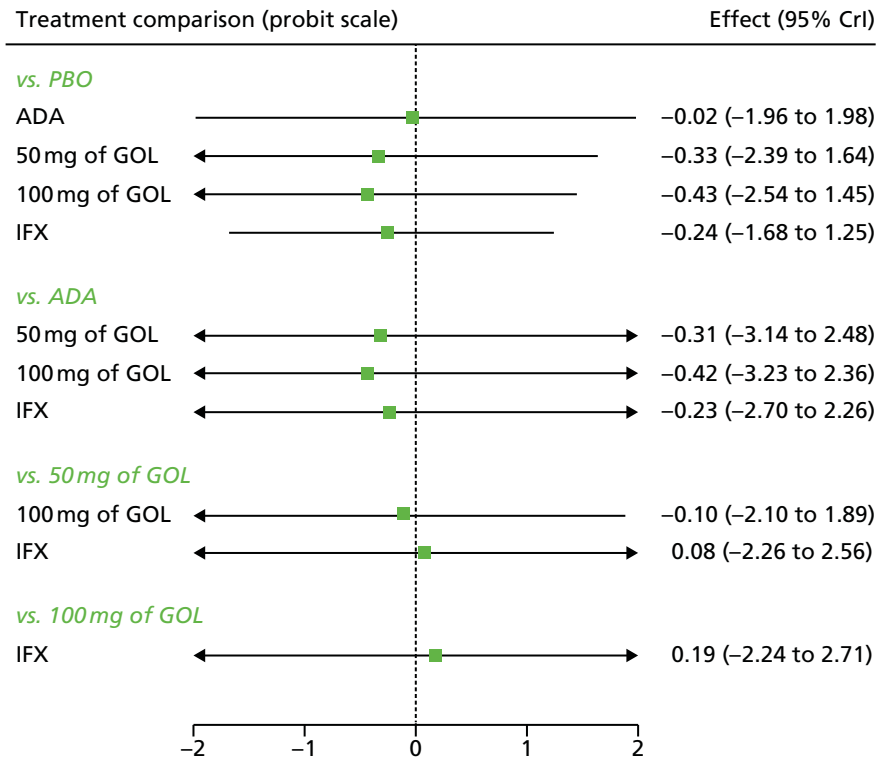

FIGURE 94 Base case: comparative effect of anti-TNF-α treatment on clinical response/remission in the maintenance phase at 8–32 weeks for patients starting in response [SD ~ U(0,2)].

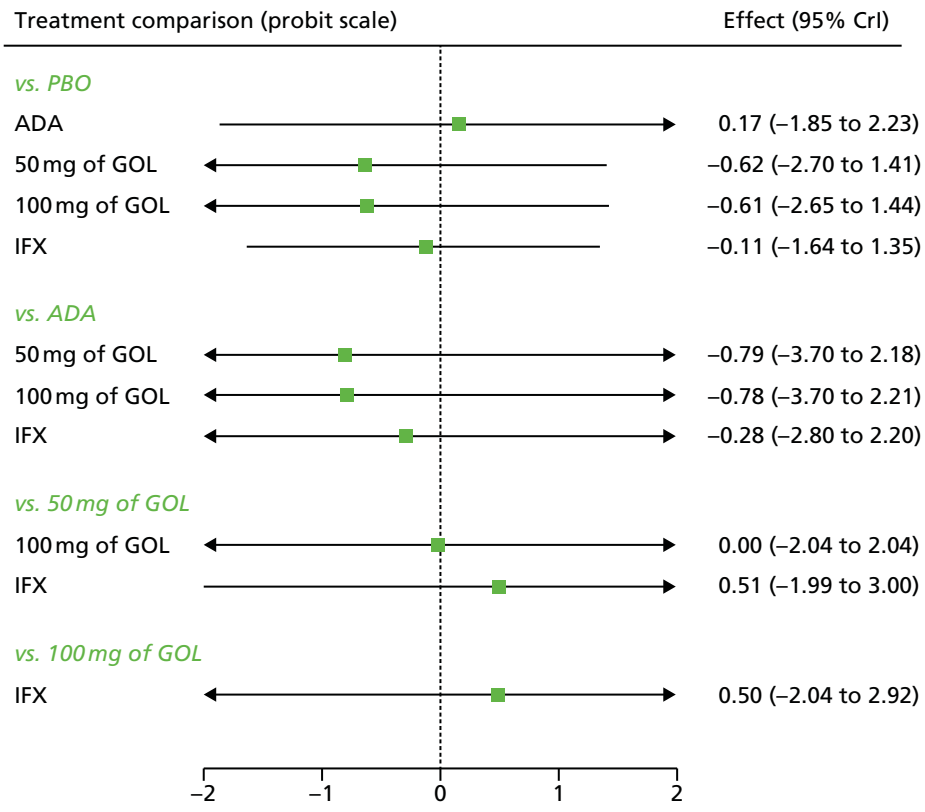

FIGURE 95 Base case: comparative effect of anti-TNF-α treatment on clinical response/remission in the maintenance phase at 8–32 weeks for patients starting in remission [SD ~ U(0,2)].

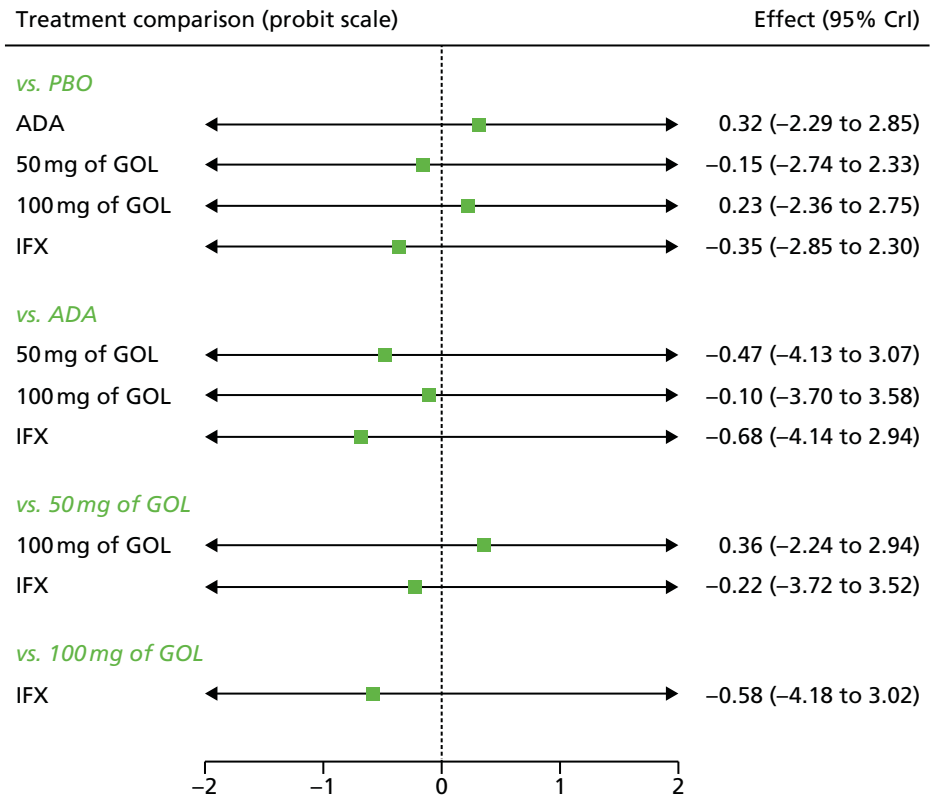

FIGURE 96 Base case: comparative effect of anti-TNF-α treatment on clinical response/remission in the maintenance phase at 32–52 weeks for patients starting in response [SD ~ U(0,2)].

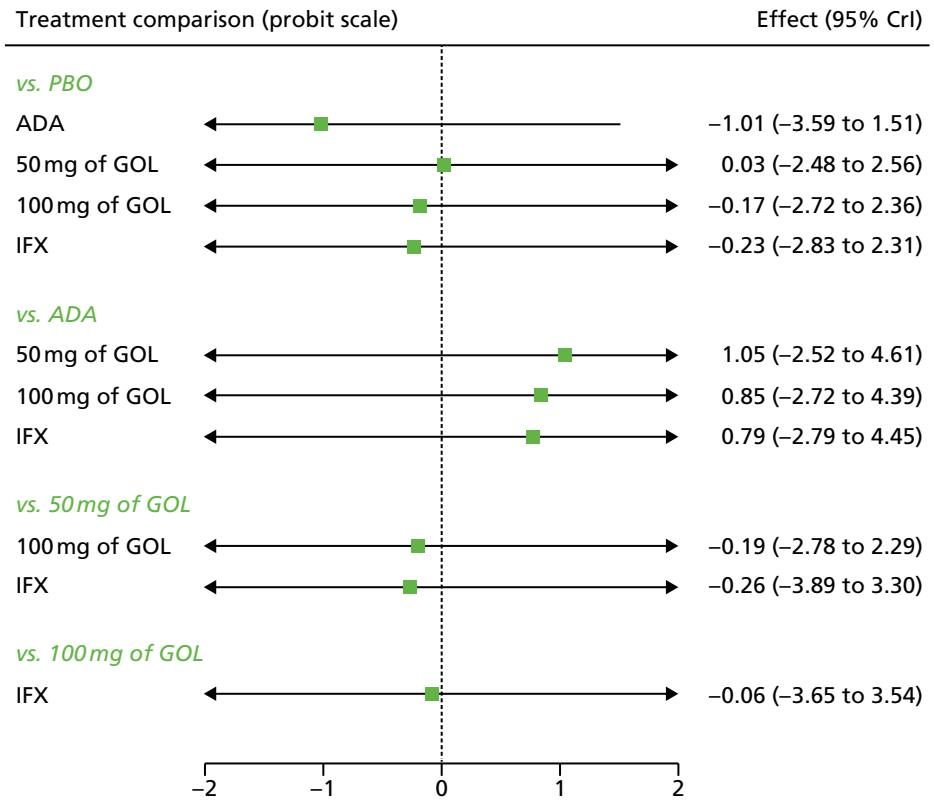

FIGURE 97 Base case: comparative effect of anti-TNF-α treatment on clinical response/remission in the maintenance phase at 32–52 weeks for patients starting in remission [SD ~ U(0,2)].

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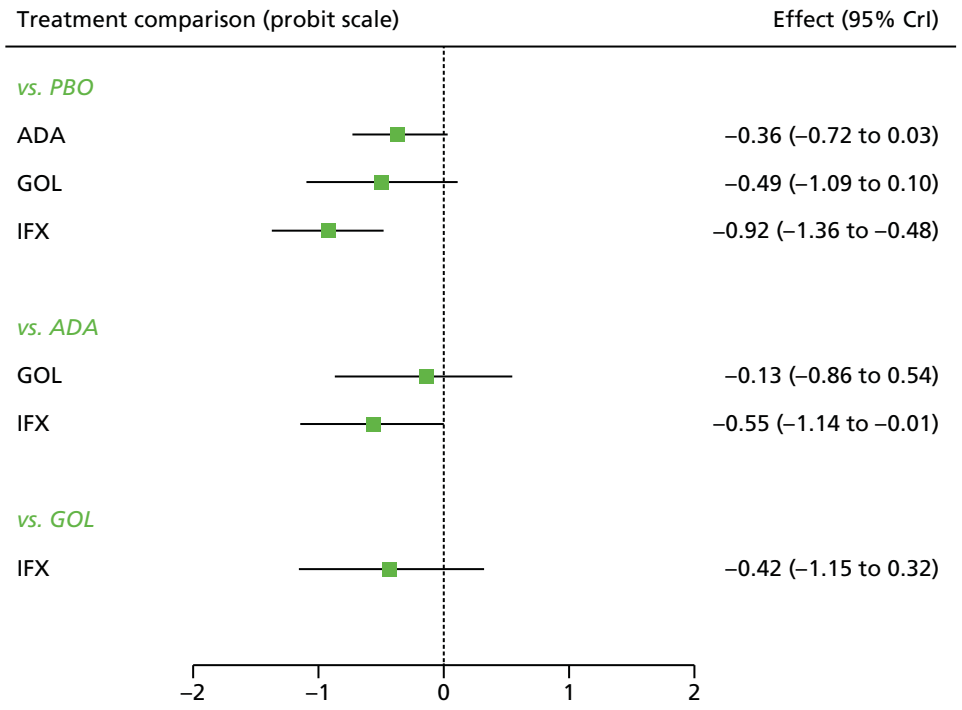

FIGURE 98 Sensitivity analysis 1: comparative effect of anti-TNF-α treatment on clinical response/remission in the induction phase [SD ~ U(0,2)].

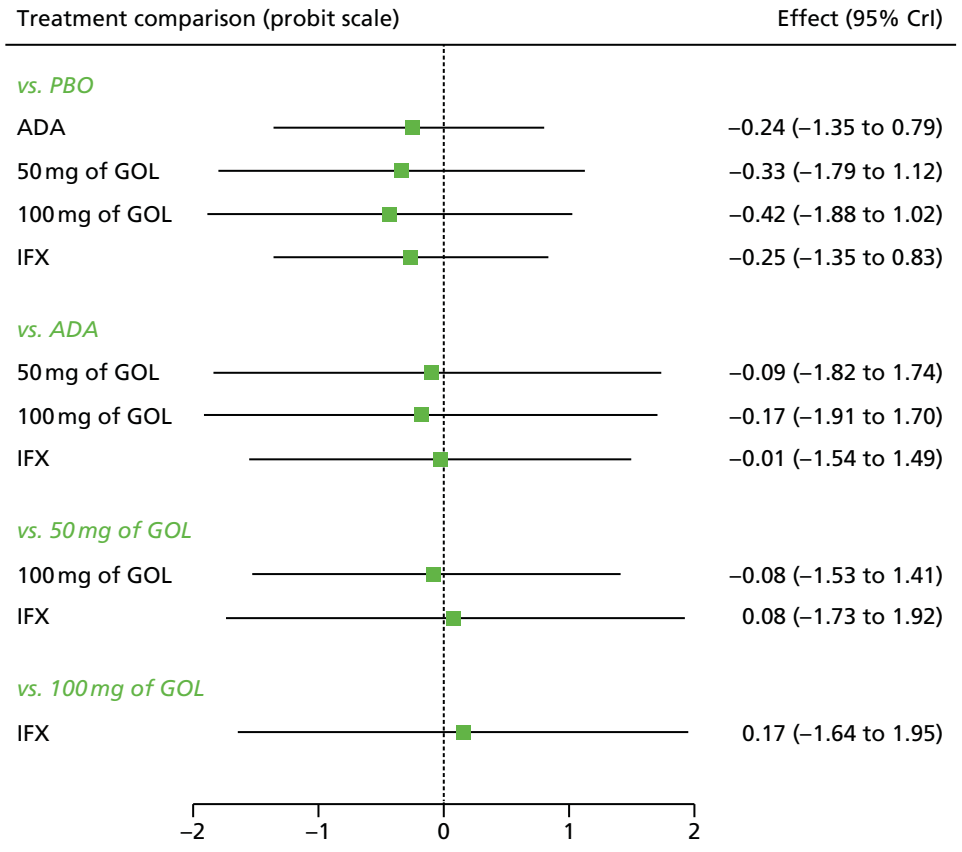

FIGURE 99 Sensitivity analysis 1: comparative effect of anti-TNF-α treatment on clinical response/remission in the maintenance phase at 8–32 weeks for patients starting in response [SD ~ U(0,2)].

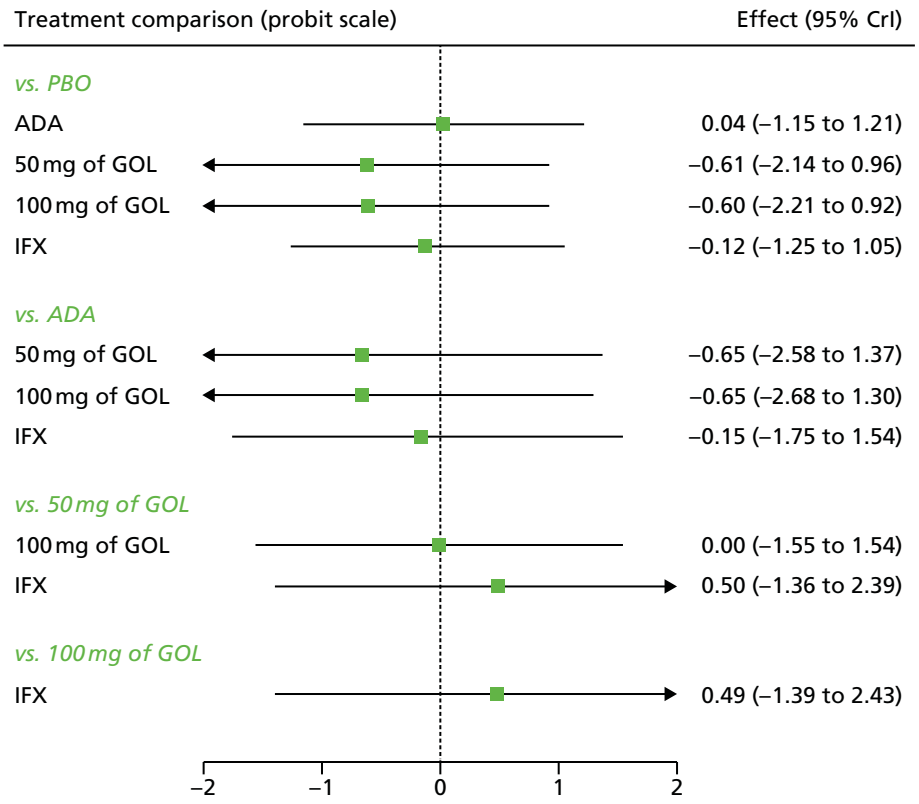

FIGURE 100 Sensitivity analysis 1: comparative effect of anti-TNF-α treatment on clinical response/remission in the maintenance phase at 8–32 weeks for patients starting in remission [SD ~ U(0,2)].

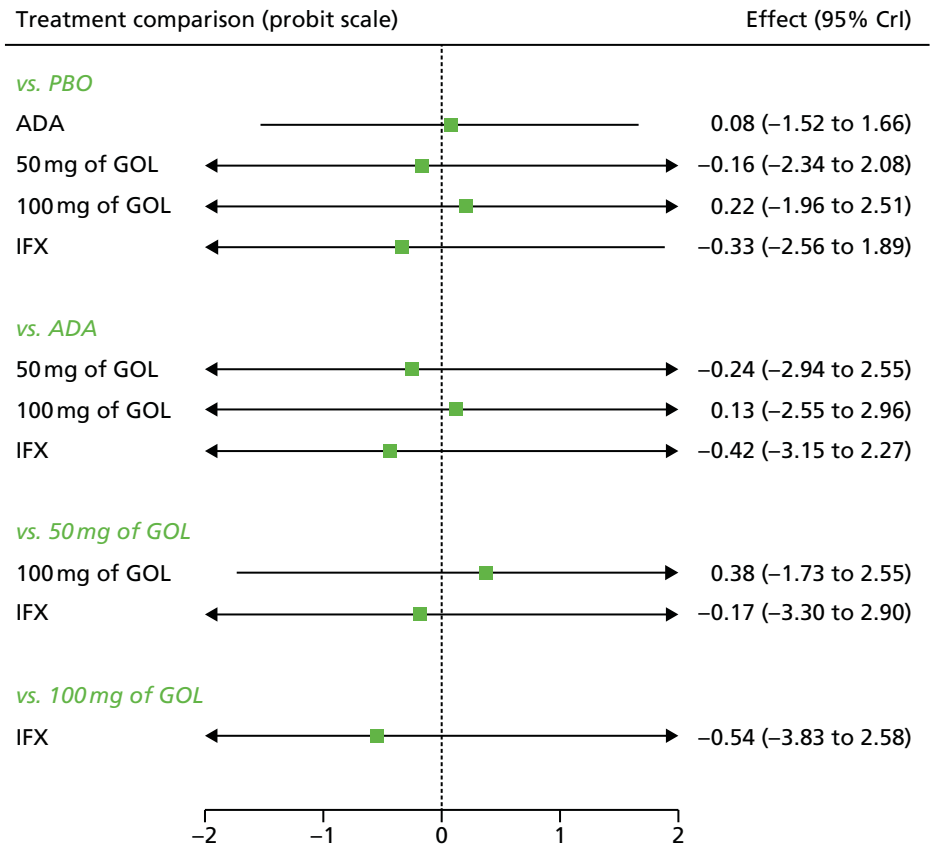

FIGURE 101 Sensitivity analysis 1: comparative effect of anti-TNF-α treatment on clinical response/remission in the maintenance phase at 32–52 weeks for patients starting in response [SD ~ U(0,2)].

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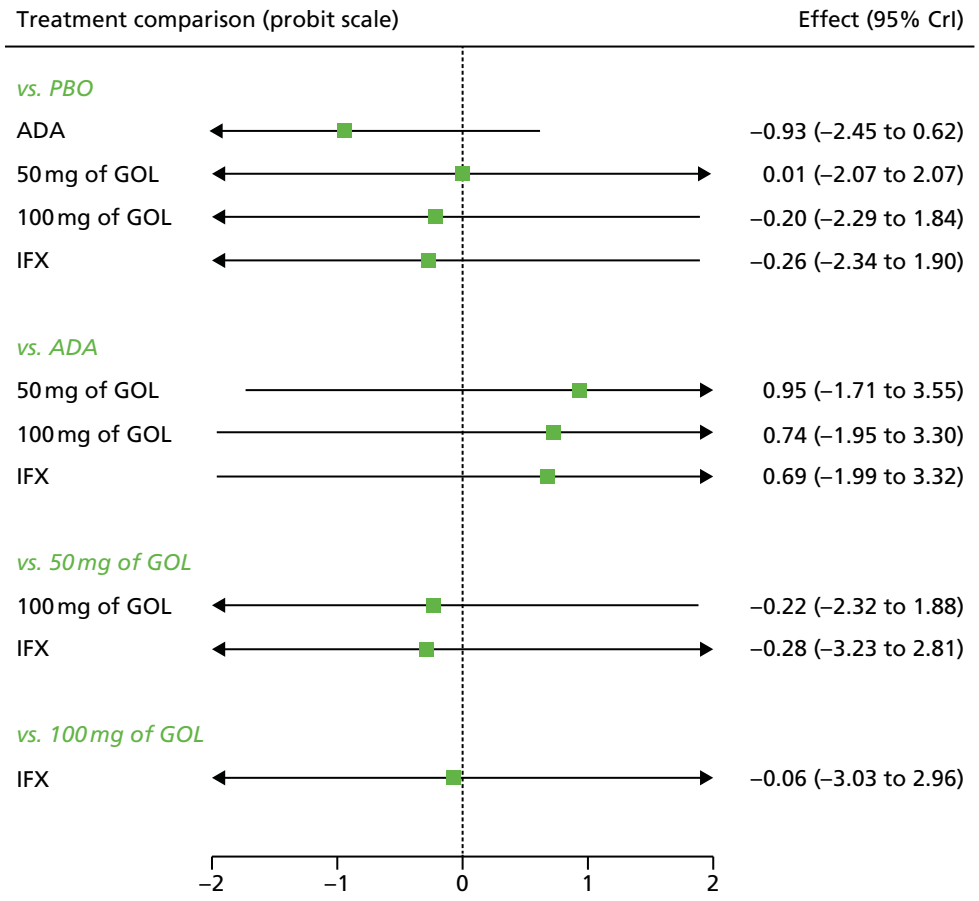

FIGURE 102 Sensitivity analysis 1: comparative effect of anti-TNF-α treatment on clinical response/remission in the maintenance phase at 32–52 weeks for patients starting in remission [SD ~ U(0,2)].

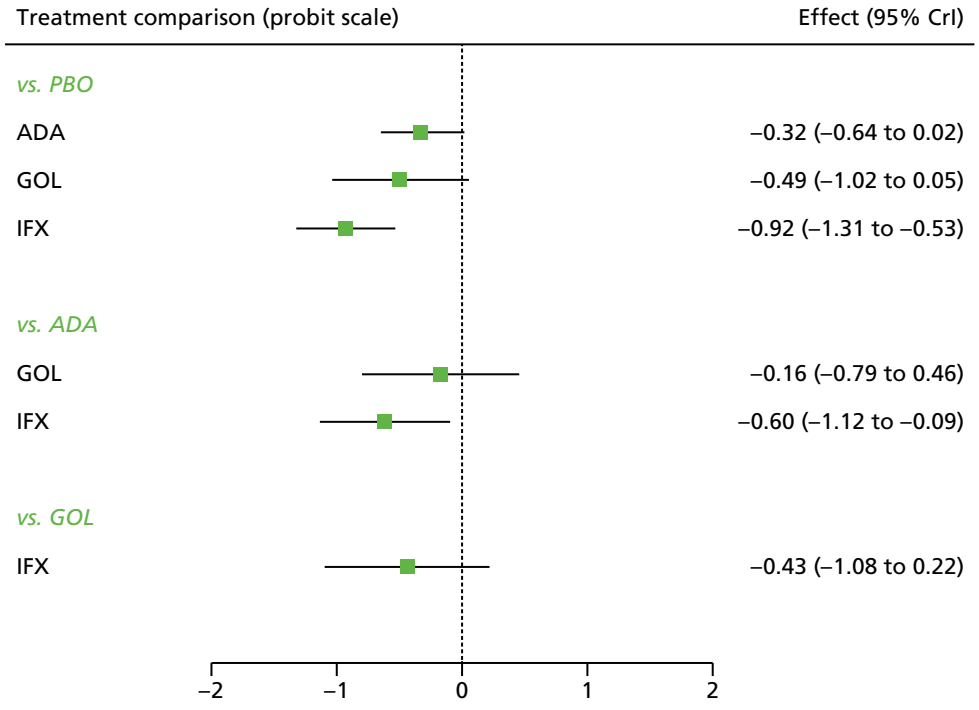

FIGURE 103 Sensitivity analysis 2: comparative effect of anti-TNF-α treatment on clinical response/remission in the induction phase [SD ~ U(0,2)].

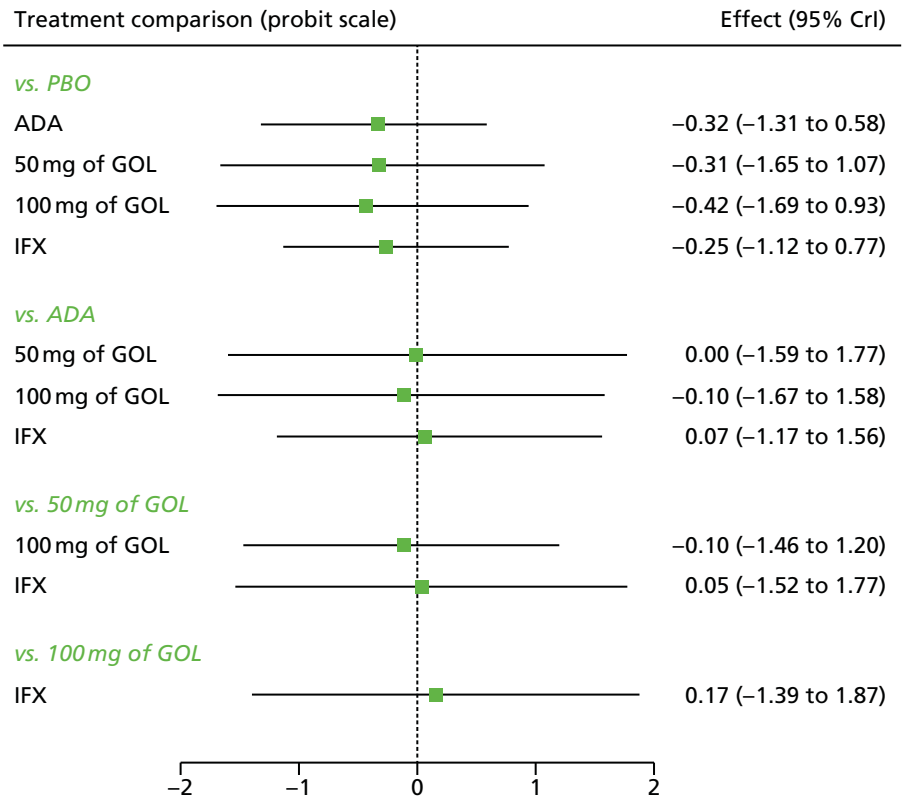

FIGURE 104 Sensitivity analysis 2: comparative effect of anti-TNF-α treatment on clinical response/remission in the maintenance phase at 8–32 weeks for patients starting in response [SD ~ U(0,2)].

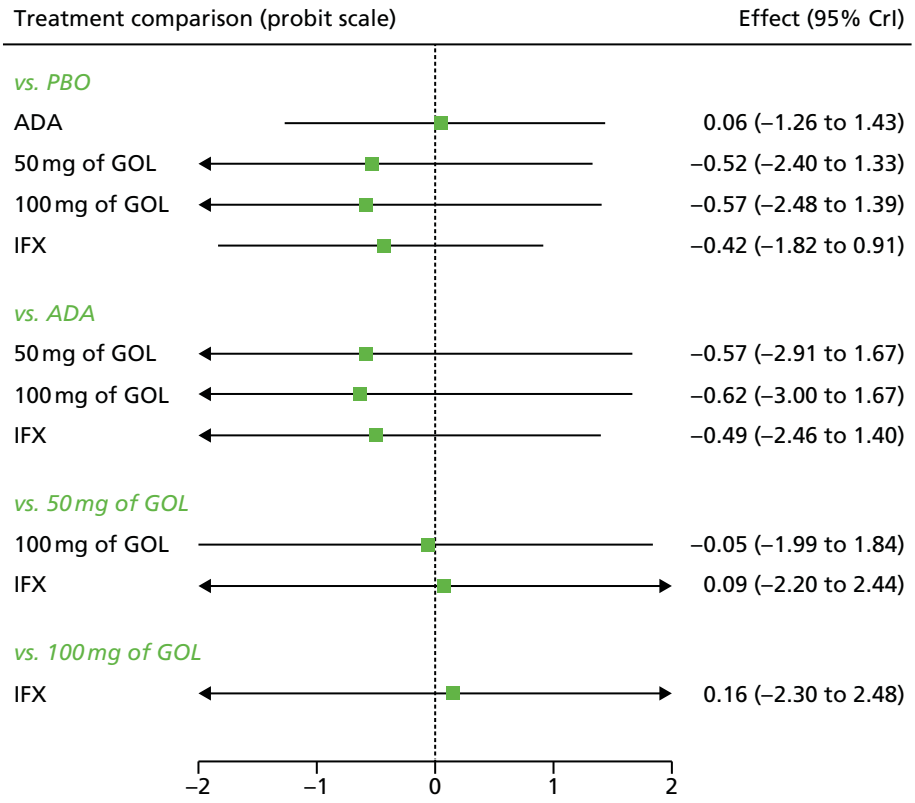

FIGURE 105 Sensitivity analysis 2: comparative effect of anti-TNF-α treatment on clinical response/remission in the maintenance phase at 8–32 weeks for patients starting in remission [SD ~ U(0,2)].

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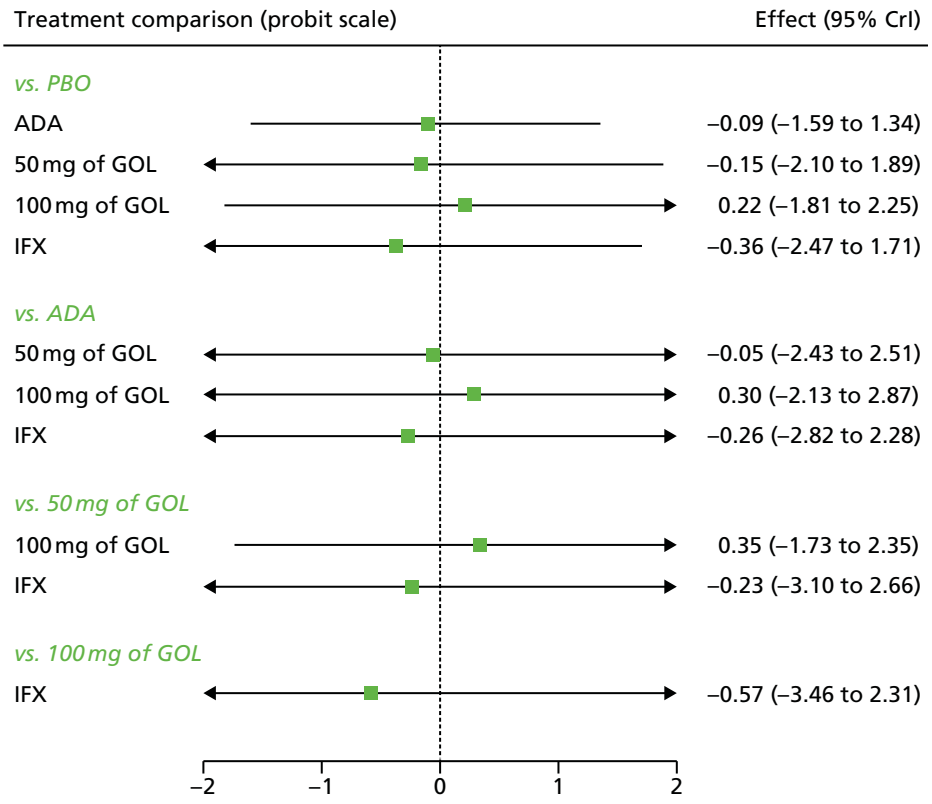

FIGURE 106 Sensitivity analysis 2: comparative effect of anti-TNF-α treatment on clinical response/remission in the maintenance phase at 32–52 weeks for patients starting in response [SD ~ U(0,2)].

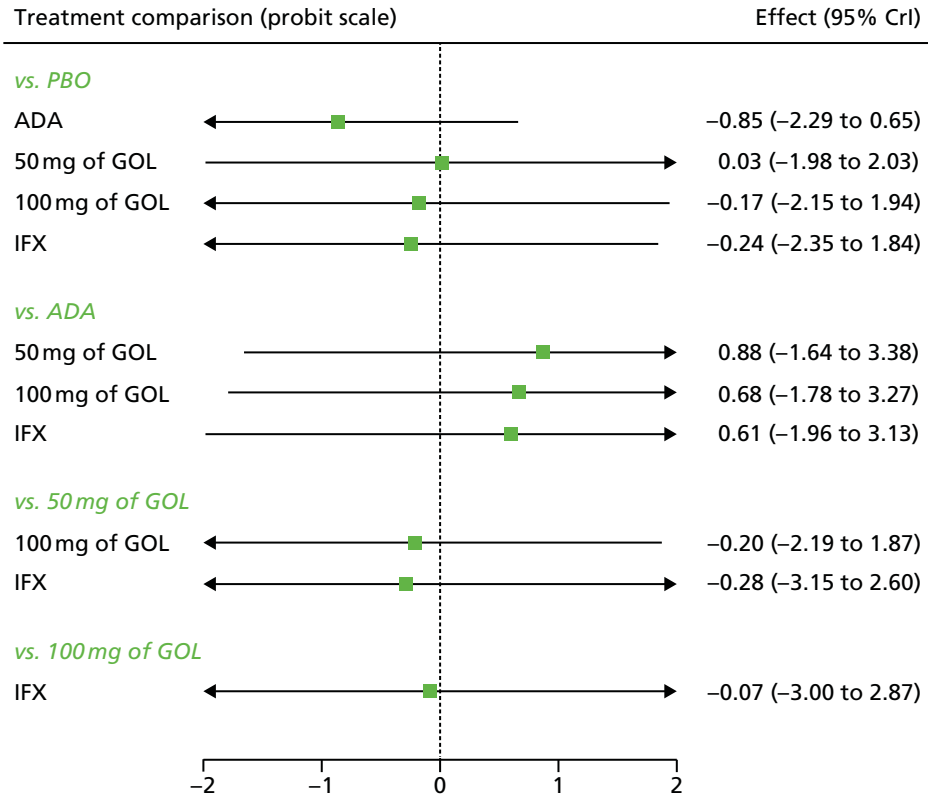

FIGURE 107 Sensitivity analysis 2: comparative effect of anti-TNF-α treatment on clinical response/remission in the maintenance phase at 32–52 weeks for patients starting in remission [SD ~ U(0,2)].

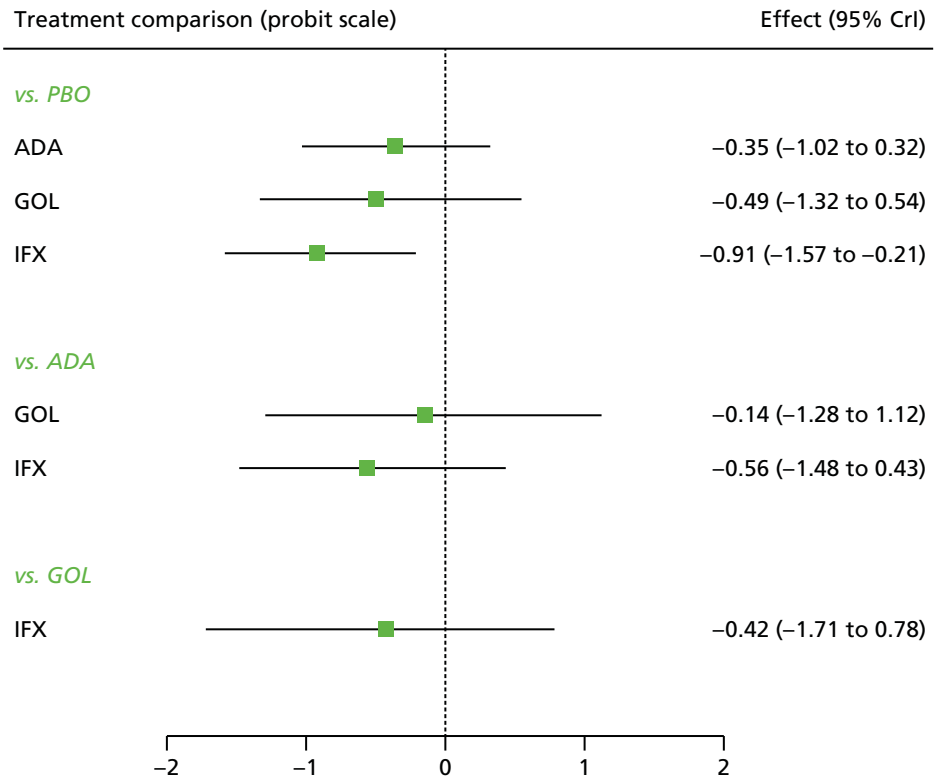

FIGURE 108 Sensitivity analysis 3: comparative effect of anti-TNF-α treatment on clinical response/remission in the induction phase [SD ~ U(0,2)].

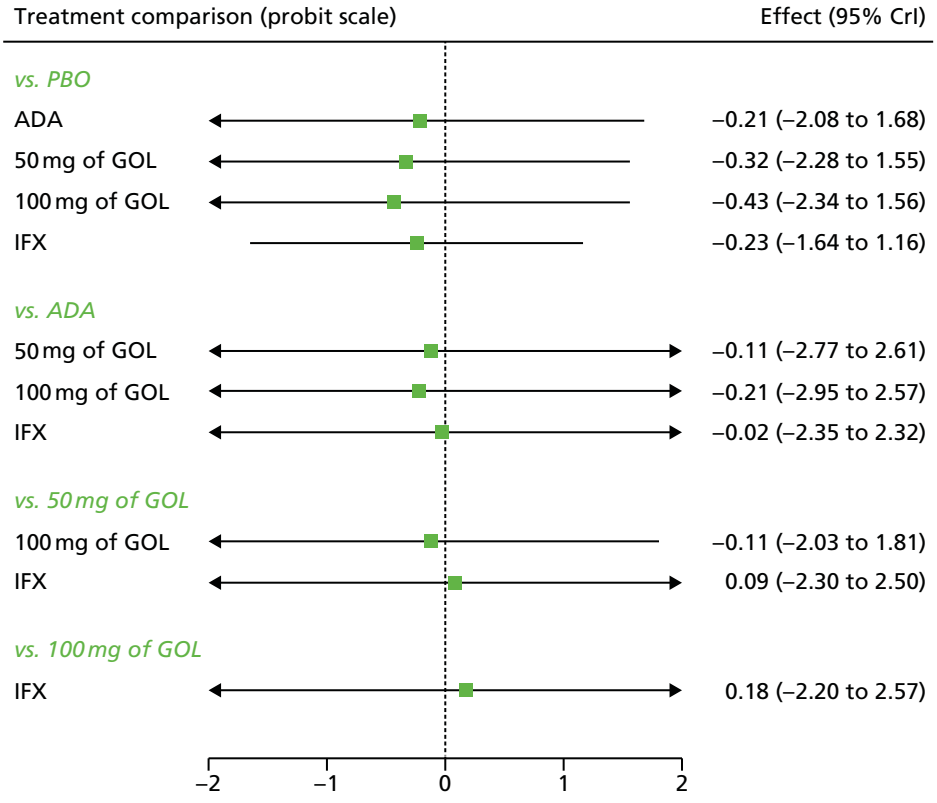

FIGURE 109 Sensitivity analysis 3: comparative effect of anti-TNF-α treatment on clinical response/remission in the maintenance phase at 8–32 weeks for patients starting in response [SD ~ U(0,2)].

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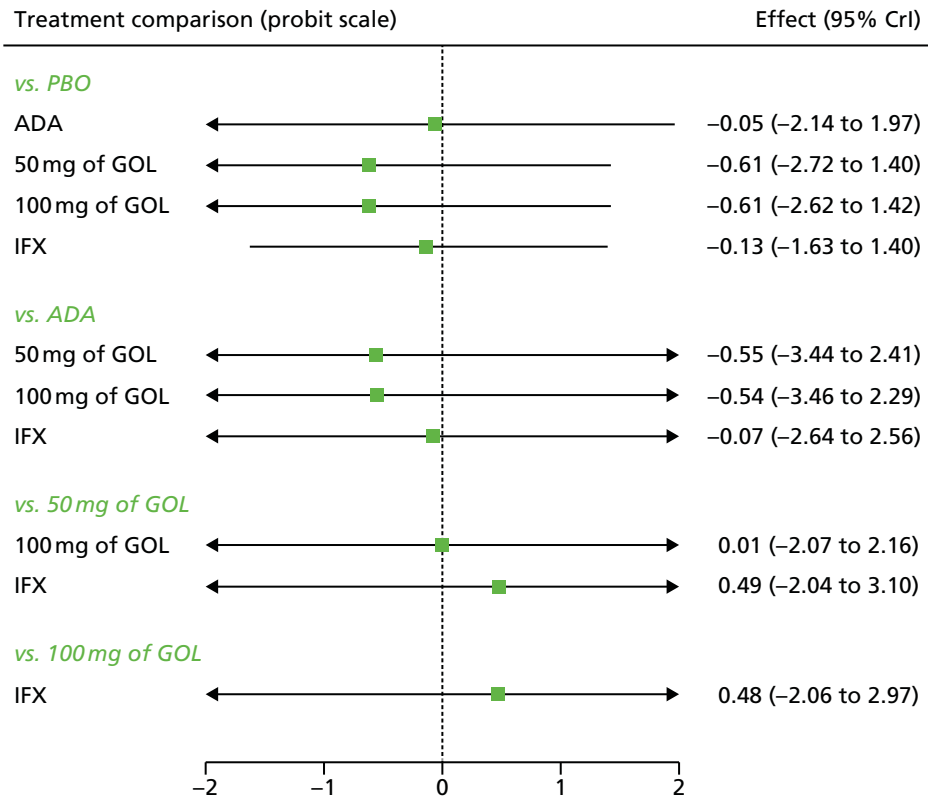

FIGURE 110 Sensitivity analysis 3: comparative effect of anti-TNF-α treatment on clinical response/remission in the maintenance phase at 8–32 weeks for patients starting in remission [SD ~ U(0,2)].

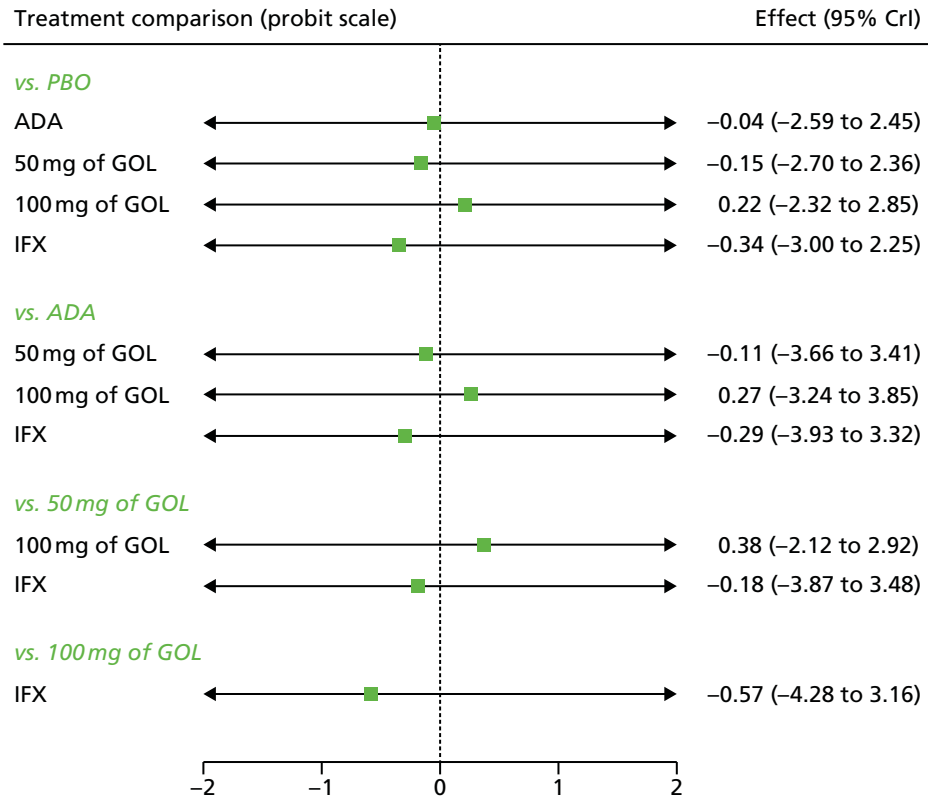

FIGURE 111 Sensitivity analysis 3: comparative effect of anti-TNF-α treatment on clinical response/remission in the maintenance phase at 32–52 weeks for patients starting in response [SD ~ U(0,2)].

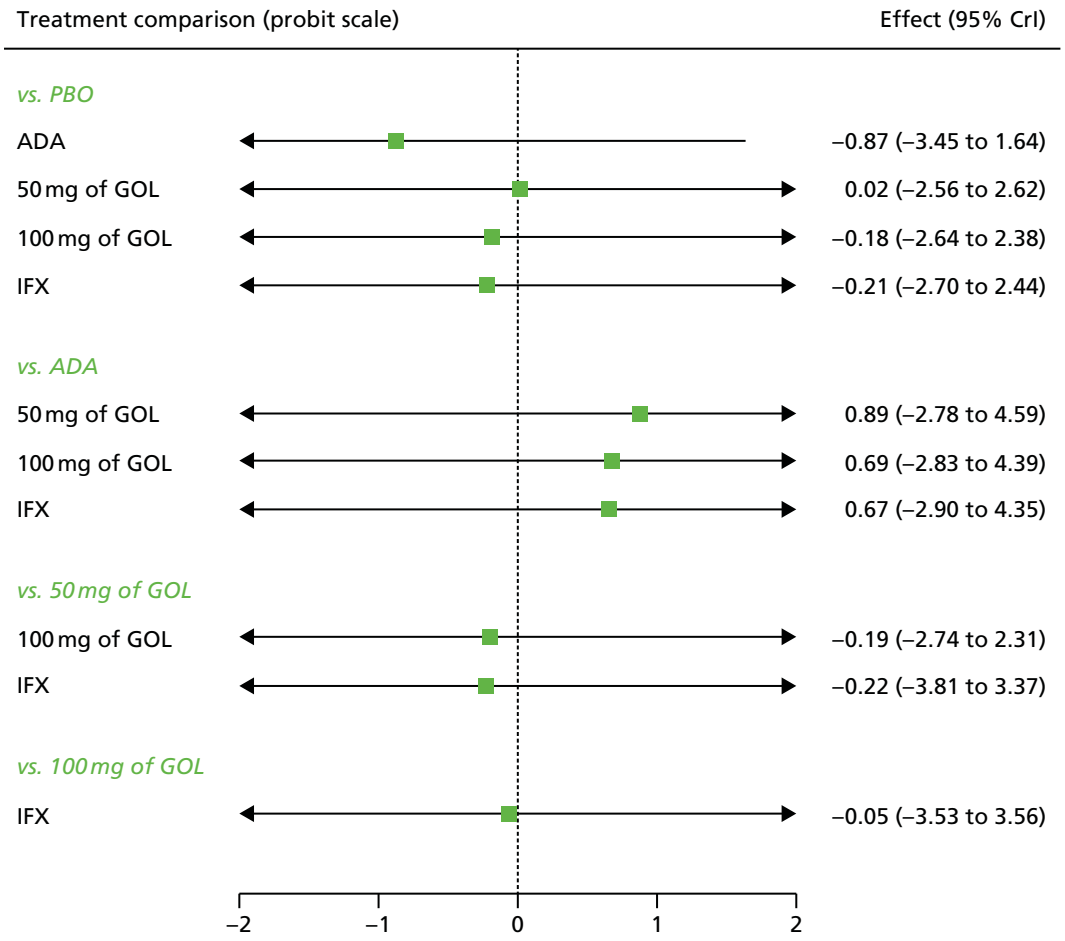

FIGURE 112 Sensitivity analysis 3: comparative effect of anti-TNF-α treatment on clinical response/remission in the maintenance phase at 32–52 weeks for patients starting in remission [SD ~ U(0,2)].

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Appendix 9 Searches for cost-effectiveness studies

Database: MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations (via Ovid).

Searched: 1946 to January 2014.

Search strategy

1. Colitis, Ulcerative/
2. ulcerative colitis.tw.
3. colitis ulcerosa.tw.
4. uc.tw.
5. colitis ulcerative.tw.
6. Colitis/
7. colitis.tw.
8. colitides.tw.
9. Inflammatory Bowel Diseases/
10. inflammatory bowel disease$.tw.
11. ibd.tw.
12. (col* and ulcer*).tw.
13. colitis gravis.tw.
14. proctocolitis.tw.
15. or/1-14
16. adalimumab.af.
17. humira.af.
18. d 2e7.af.
19. d2e7.af.
20. 331731-18-1.rn.
21. infliximab.af.
22. remicade.af.
23. 170277-31-3.rn.
24. ta650.af.
25. ta 650.af.
26. inx.af.
27. remsima.af.
28. inflectra.af.
29. ct p13.af.
30. ctp13.af.
31. golimumab.af.
32. simponi.af.
33. cnto148.af.
34. cnto 148.af.
35. 476181-74-5.rn.
36. tnf inhibitor$.tw.
37. anti tnf.tw.
38. antitnf.tw.
39. tnf antagonist$.tw.
40. tnf-alpha blocker$.tw.
41. antitumo?r necrosis factor.tw.

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42. Biosimilar Pharmaceuticals/
43. (biosimilar$ or biologic$).tw.
44. or/16-43
45. 15 and 44

Terms 1–14 are terms for the condition (ulcerative colitis) which are then combined using OR in term 15. Terms 16–43 are terms for the interventions (infliximab, adalimumab and golimumab) which are then combined using OR in term 44. Terms 15 and 44 are then combined using AND to find studies on the condition and interventions in term 45.

To retrieve economic evaluations specially designed highly sensitive search filter were combined with term 45. Economics filter below.

Economic filter

1. exp "costs and cost analysis"/
2. economics/
3. exp economics, hospital/
4. exp economics, medical/
5. economics, nursing/
6. exp models, economic/
7. economics, pharmaceutical/
8. exp "fees and charges"/
9. exp budgets/
10. budget$.tw.
11. ec.fs.
12. cost$.ti.
13. (cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).ab.
14. (economic$ or pharmacoeconomic$ or pharmaco-economic$).ti.
15. (price$ or pricing$).tw.
16. (financial or finance or finances or financed).tw.
17. (fee or fees).tw.
18. (value adj2 (money or monetary)).tw.
19. quality-adjusted life years/
20. (qaly or qalys).af.
21. (quality adjusted life year or quality adjusted life years).af.
22. or/1-22

Appendix 10 European Quality of Life-5 Dimensions search

Database: MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations (via Ovid).

Searched: 1946 to January 2014.

Search strategy

1. Colitis, Ulcerative/
2. ulcerative colitis.tw.
3. colitis ulcerosa.tw.
4. uc.tw.
5. colitis ulcerative.tw.
6. Colitis/
7. colitis.tw.
8. colitides.tw.
9. Inflammatory Bowel Diseases/
10. inflammatory bowel disease$.tw.
11. ibd.tw.
12. (col* and ulcer*).tw.
13. colitis gravis.tw.
14. proctocolitis.tw.
15. or/1-14
16. (euroqol or euro qol or eq5d or eq 5d).tw.
17. 15 and 16

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