



UNIVERSITY OF LEEDS

This is a repository copy of *Efficacy of biological therapies and small molecules in induction and maintenance of remission in luminal Crohn's disease: systematic review and network meta-analysis*.

White Rose Research Online URL for this paper:

<https://eprints.whiterose.ac.uk/id/eprint/190295/>

Version: Accepted Version

Article:

Barberio, B, Gracie, DJ, Black, CJ et al. (1 more author) (2023) Efficacy of biological therapies and small molecules in induction and maintenance of remission in luminal Crohn's disease: systematic review and network meta-analysis. *Gut*, 72 (2). pp. 264-274. ISSN 0017-5749

<https://doi.org/10.1136/gutjnl-2022-328052>

© Author(s) (or their employer(s)) 2022. . This manuscript version is made available under the CC BY-NC 4.0 license <https://creativecommons.org/licenses/by-nc/4.0/>

Reuse

This article is distributed under the terms of the Creative Commons Attribution-NonCommercial (CC BY-NC) licence. This licence allows you to remix, tweak, and build upon this work non-commercially, and any new works must also acknowledge the authors and be non-commercial. You don't have to license any derivative works on the same terms. More information and the full terms of the licence here: <https://creativecommons.org/licenses/>

Takedown

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.



eprints@whiterose.ac.uk
<https://eprints.whiterose.ac.uk/>

Accepted for publication 22nd July 2022

TITLE PAGE

Title: Efficacy of Biological Therapies and Small Molecules in Induction and Maintenance of Remission in Luminal Crohn's Disease: Systematic Review and Network Meta-analysis.

Short title: Network Meta-analysis of Biological Therapies and Small Molecules for Luminal CD.

Authors: Brigida Barberio¹, David J Gracie^{2,3}, Christopher J. Black^{2,3*}, Alexander C. Ford^{2,3*}.

*Joint last author

¹Department of Surgery, Oncology and Gastroenterology (DISCOG), Gastroenterology Unit, University of Padova-Azienda Ospedaliera di Padova, Padova, Italy.

²Leeds Gastroenterology Institute, St. James's University Hospital, Leeds, UK.

³Leeds Institute of Medical Research at St. James's, University of Leeds, Leeds, UK.

Abbreviations:	CD	Crohn's disease
	CDAI	Crohn's disease activity index
	CI	confidence interval
	RCT	randomised controlled trial
	RR	relative risk
	TNF	tumour necrosis factor

Correspondence: Professor Alex Ford
Leeds Gastroenterology Institute
Room 125
4th Floor
Bexley Wing
St. James's University Hospital
Beckett Street
Leeds
United Kingdom
LS9 7TF
Email: alex12399@yahoo.com
Telephone: +441132684963
ORCID ID: 0000-0001-6371-4359
Twitter: @alex_ford12399

Key words: Crohn's disease
RCT comparison
efficacy
drugs

Word count: 5342

ABSTRACT

Objective: There are numerous biological therapies and small molecules licensed for luminal Crohn's disease (CD), but these are often studied in placebo-controlled trials, meaning relative efficacy is uncertain. We examined this in a network meta-analysis.

Design: We searched the literature to 1st July 2022, judging efficacy according to induction of clinical remission, clinical response, and maintenance of clinical remission, and according to previous exposure or non-exposure to biologics. We used a random effects model and reported data as pooled relative risks (RRs) with 95% confidence intervals (CIs), ranking drugs according to P-score.

Results: We identified 25 induction of remission trials (8720 patients). Based on failure to achieve clinical remission, infliximab 5mg/kg ranked first versus placebo (RR = 0.67; 95% CI 0.56 to 0.79, P-score 0.95), with risankizumab 600mg second, and upadacitinib 45mg o.d. third. However, risankizumab 600mg ranked first for clinical remission in biologic-naïve (RR = 0.66; 95% CI 0.52 to 0.85, P-score 0.78) and in biologic-exposed patients (RR = 0.74; 95% CI 0.67 to 0.82, P-score 0.92). In 15 maintenance of remission trials (4016 patients), based on relapse of disease activity, upadacitinib 30mg o.d. ranked first (RR = 0.61; 95% CI 0.52 to 0.72, P-score 0.93) with adalimumab 40mg weekly second, and infliximab 10mg/kg 8-weekly third. Adalimumab 40mg weekly ranked first in biologic-naïve patients (RR = 0.59; 95% CI 0.48 to 0.73, P-score 0.86), and vedolizumab 108mg 2-weekly first in biologic-exposed (RR = 0.70; 95% CI 0.57 to 0.86, P-score 0.82).

Conclusion: In a network meta-analysis, infliximab 5mg/kg ranked first for induction of clinical remission in all patients with luminal CD, but risankizumab 600mg was first in biologic-naïve and biologic-exposed patients. Upadacitinib 30mg o.d. ranked first for maintenance of remission.

STUDY HIGHLIGHTS

What is already known about this subject

- Crohn's disease (CD) is a chronic inflammatory bowel disease, leading to progressive intestinal damage, and a high likelihood of requiring surgery within 10 years of first diagnosis.
- Although immunomodulators are often used to reduce need for treatment with corticosteroids, evidence for their efficacy is limited.
- In the last 20 years, multiple biological therapies and small molecules have been developed and licensed for luminal CD.
- Although previous network meta-analyses have compared their efficacy and safety, trials of newer drugs have been published.

What are the new findings

- In terms of induction of clinical remission, although infliximab 5mg/kg ranked first in all patients, risankizumab 600mg ranked first in both biologic-naïve patients and biologic-exposed patients.
- In terms of clinical response, infliximab 5mg/kg ranked first in all patients, but risankizumab 1200mg was first in both biologic-naïve and biologic-exposed patients.
- In terms of maintenance of clinical remission, upadacitinib 30mg o.d. ranked first, with adalimumab 40mg weekly ranked first in biologic-naïve patients, and vedolizumab 108mg 2-weekly first in biologic-exposed patients.
- None of the drugs studied were more likely to lead to adverse events, serious adverse events, or infections than placebo in either induction of remission or maintenance of remission trials.

How might it impact on clinical practice in the foreseeable future

- These data can be used to facilitate treatment decisions for patients with moderate to severe luminal CD to induce remission, and for patients with luminal CD that has responded to therapy to reduce likelihood of relapse.
- They can be used to update future evidence-based management guidelines and could inform health economic analyses to help guide cost-effective treatment selection.
- It is important to point out that the trials of upadacitinib are yet to be published in full.

INTRODUCTION

Crohn's disease (CD) is a chronic disorder involving any region of the intestine, although most commonly the ileo-caecum, and causing transmural inflammation.[1] Contemporaneous prevalence data demonstrate that CD affects almost 300 per 100,000 people in Europe.[2] Due to the fact that incidence of CD exceeds mortality,[3] prevalence is likely to rise for the foreseeable future. Although some patients will have a mild disease course, for the majority the condition follows a relapsing and remitting course, with progressive intestinal damage.[4] Up to 50% of patients will require surgery within 10 years from first diagnosis.[5] Unlike in ulcerative colitis, where 5-aminosalicylates are the mainstay of treatment,[6] there is little evidence for use of these drugs in luminal CD.[7] Many patients, therefore, require immunomodulator drugs, such as azathioprine or methotrexate, to avoid the need for repeated courses of corticosteroids. However, evidence for efficacy of these drugs is not strong, with few randomised controlled trials (RCTs).[8]

Since the advent of infliximab, a drug targeting the pro-inflammatory cytokine tumour necrosis factor- α (TNF- α), which demonstrated efficacy in clinical trials for induction of remission of active luminal CD,[9] prevention of relapse of quiescent luminal CD,[10] and healing and prevention of recrudescence of fistulizing CD,[11, 12] multiple novel drugs have been developed. These include other drugs targeting TNF- α , such as adalimumab or certolizumab, and drugs acting on integrins or other pro-inflammatory cytokines implicated in the pathogenesis of CD, such as vedolizumab, ustekinumab, or risankizumab. More recently, small molecules, which can be administered orally, and on a daily basis, have been evaluated in inflammatory bowel disease.[13] These include janus kinase inhibitors, such as tofacitinib, filgotinib, and upadacitinib.

The relative efficacy and safety of some of these drugs have been assessed previously using network meta-analysis.[14, 15] These have, for the most part, demonstrated that anti-

TNF- α drugs, such as infliximab and adalimumab, are the most efficacious, in all patients, and in those with previous anti-TNF- α exposure. However, even since the most recent of these network meta-analyses, there have been new trials published of risankizumab,[16] an interleukin-23 p-19 inhibitor, and upadacitinib,[17] a preferential janus kinase-1 inhibitor, in luminal CD. In addition, there are other studies that were not included in previous network meta-analyses. We, therefore, performed a contemporaneous network meta-analysis to evaluate the efficacy of all biological therapies and small molecules that have progressed on to phase III trials in luminal CD, compared with each other or placebo, in terms of induction of clinical remission, clinical response, and maintenance of clinical remission, as well as safety.

METHODS

Search Strategy and Selection Criteria

We searched MEDLINE (1946 to 1st July 2022), EMBASE and EMBASE Classic (1947 to 1st July 2022), and the Cochrane central register of controlled trials. We also searched clinicaltrials.gov for recently completed trials or supplementary data for potentially eligible RCTs. In addition, we hand-searched conference proceedings (Digestive Diseases Week, American College of Gastroenterology, United European Gastroenterology Week, and the Asian Pacific Digestive Week) between 2001 and 2022 to identify trials published only in abstract form. Finally, we performed a recursive search of the bibliographies of all eligible articles.

To be eligible, RCTs had to examine efficacy of biological therapies (anti-TNF α antibodies (infliximab, adalimumab, or certolizumab), anti-integrin antibodies (vedolizumab or etrolizumab), anti-interleukin-12/23 antibodies (ustekinumab), or anti-interleukin-23 antibodies (risankizumab)) or janus kinase inhibitors (tofacitinib, filgotinib, upadacitinib) at the doses taken through into phase III clinical trials. Studies needed to recruit adults (≥ 18 years) with luminal CD (Supplementary Table 1), and compare biological therapies or small molecules with placebo, or each other. Trials conducted only in patients with perianal CD were ineligible. We required a minimum follow-up duration of 4 weeks for induction of remission trials in moderately to severely active luminal CD and 20 weeks for maintenance of remission in luminal CD. Maintenance of remission trials had to re-randomise patients at baseline; run-through trials of active drug or placebo from baseline that reported both induction of remission and maintenance of remission were ineligible.

Two investigators (BB and ACF) conducted independent literature searches. We identified studies on CD with the terms: *inflammatory bowel disease*, or *Crohn's disease*

(both as medical subject headings and free text terms). We used the set operator AND to combine these with studies identified with the following terms: *infliximab*, *remicade*, *adalimumab*, *humira*, *certolizumab*, *cimzia*, *vedolizumab*, *entyvio*, *etrolizumab*, *ustekinumab*, *stelara*, *risankizumab*, *tofacitinib*, *xeljanz*, *filgotinib*, or *upadacitinib*, applying a clinical trials filter. There were no language restrictions. Two investigators (BB and ACF) evaluated all abstracts identified, independently. We obtained potentially relevant papers and evaluated them in more detail, using pre-designed forms, to assess eligibility independently according to the pre-defined criteria. We translated foreign language papers, where required. We resolved disagreements between investigators by discussion.

Outcome Assessment

In induction of remission trials, we assessed efficacy of biological therapies or small molecules, compared with placebo or each other, in terms of failure to achieve clinical remission (Crohn's disease activity index (CDAI) <150) or failure to achieve clinical response (fall in CDAI of ≥ 70), at the point the primary endpoint was assessed in each trial. In maintenance of remission trials, we assessed efficacy in terms of occurrence of relapse of disease activity (CDAI ≥ 150) at the last point of follow-up. Other outcomes assessed included adverse events (total numbers of adverse events, as well as serious adverse events, infections, and adverse events leading to study withdrawal), if reported.

Data Extraction

Two investigators (BB and ACF) extracted data from all eligible studies independently onto a Microsoft Excel spreadsheet (XP professional edition; Microsoft Corp, Redmond, WA, USA) as dichotomous outcomes (clinical remission or no clinical remission; clinical response or no clinical response; relapse of disease activity or no relapse of disease

activity). We assessed efficacy according to the proportion of patients failing to achieve clinical remission or clinical response in induction of remission trials, and the proportion of patients having relapse of disease activity in maintenance of remission trials. We also extracted the following data for each trial, where available: country of origin, number of centres, disease distribution, proportion of patients naïve to biological therapy, dose and dosing schedule of active therapy and placebo, and source of patients in maintenance of remission trials. We extracted all data as intention-to-treat analyses, assuming all dropouts to be treatment failures (i.e., no remission or response to biological therapy, small molecule, or placebo, or relapse of disease activity with biological therapy, small molecule, or placebo), wherever trial reporting allowed. If this was not clear from the original article, we performed an analysis on all evaluable patients. When judging safety, we used the number of patients receiving at least one dose of the study drug, wherever possible. We compared results of the two investigators' data extraction with all discrepancies resolved by discussion.

Quality Assessment and Risk of Bias

We used the Cochrane risk of bias tool to assess this at the study level.[18] Two investigators (BB and ACF) performed this independently. We resolved disagreements by discussion. We recorded the method used to generate the randomisation schedule and conceal treatment allocation, as well as whether blinding was implemented for participants, personnel, and outcomes assessment, whether there was evidence of incomplete outcomes data, and whether there was evidence of selective reporting of outcomes.

Data Synthesis and Statistical Analysis

We performed a network meta-analysis using the frequentist model, with the statistical package “netmeta” (version 0.9-0, <https://cran.r->

project.org/web/packages/netmeta/index.html) in R (version 4.0.2). We explored direct and indirect treatment comparisons of efficacy and safety of each drug, with reporting according to the PRISMA extension statement for network meta-analyses.[19] Compared with standard, pairwise, analyses network meta-analysis results can give more precise estimates,[20, 21] and allows ranking of drugs to inform clinical decisions.[22]

We produced a network plot with node size corresponding to number of study subjects, and connection size corresponding to number of studies to examine the symmetry and geometry of the evidence. We assessed for publication bias or other small study effects, for all available comparisons, via comparison adjusted funnel plots, using Stata version 16 (Stata Corp., College Station, TX, USA). This is a scatterplot of effect size versus precision, measured via the inverse of the standard error. Absence of publication bias, or small study effects, is indicated by symmetry around the effect estimate line.[23] We judged efficacy of each comparison tested with a pooled relative risk (RR) with 95% confidence intervals (CIs), using a random effects model as a conservative estimate. We used a RR of failure to achieve clinical remission or clinical response, and a RR of relapse of disease activity. We checked the correlation between direct and indirect evidence across the network via consistency modelling, where there were direct comparisons between some active drugs,[24] generating network heat plots. These have grey squares representing the size of the contribution of the direct estimate of one study design in columns, compared with the network estimate in rows.[25] The coloured squares around these represent the change in inconsistency between direct and indirect evidence in a network estimate in the row after relaxing the consistency assumption for the effect of one design in the column. Blue squares indicate that the direct evidence of the design in the column supports the indirect evidence in the row, whereas red squares are “hotspots” of inconsistency between direct and indirect evidence.

Meta-analyses often use the I^2 statistic to measure heterogeneity, which ranges between 0% and 100%.[26] This statistic is easily interpretable and does not vary with number of studies. However, its value can increase with the number of patients included in the meta-analysis.[27] We, therefore, used the τ^2 measure from the “netmeta” statistical package to assess global statistical heterogeneity across all comparisons. We used estimates of τ^2 of approximately 0.04, 0.16, and 0.36 to represent low, moderate, and high levels of heterogeneity, respectively.[28]

We used the P-score, which is a value between 0 and 1, for all biological therapies and small molecules, versus placebo or each other, to rank them. P-scores are based solely on point estimates and standard errors from the network estimates and measure the mean extent of certainty that one intervention is better than another, averaged over all competing interventions.[29] Higher scores indicate a greater probability of the intervention being ranked as best,[29] but the magnitude of the P-score should be considered, as well as the rank. The mean value of the P-score is always 0.5. Therefore, if individual interventions cluster around this value they are likely to be similarly efficacious. However, it is also important to take the RR and corresponding 95% CI for each comparison into account when interpreting the results, rather than relying on rankings alone.[30] In our primary analyses, we pooled data for all patients, but we also performed *a priori* subgroup analyses for each efficacy endpoint according to whether or not patients had been exposed to biologics previously. For our analysis of achievement of clinical remission, we used the Confidence in Network Meta-Analysis (CINeMA) framework to evaluate confidence in the indirect and direct treatment estimates from the network,[31, 32] which is endorsed by the Cochrane Collaboration. This includes the Risk of Bias from Missing Evidence in Network Meta-Analysis tool for evaluation of reporting bias.[33]

RESULTS

The search strategy generated 4095 citations. In total, 100 appeared relevant and we retrieved these for further assessment. We excluded 67 that did not fulfil eligibility criteria, with reasons provided in Supplementary Figure 1, leaving 33 separate eligible articles. Agreement between investigators for study eligibility was excellent (kappa statistic = 0.85). Eighteen articles reported on 19 induction of remission RCTs only,[9, 16, 17, 34-47] (NCT00291668) five articles reported six induction of remission trials together with re-randomisation of patients in these RCTs into five subsequent maintenance of remission trials,[48-52] and 10 articles reported maintenance of remission RCTs only.[10, 53-61] In total, therefore, there were 23 articles reporting on 25 separate induction of remission RCTs,[9, 16, 17, 34-52] (NCT00291668) and 15 articles reporting on 15 separate maintenance of remission trials.[10, 48-61] All studies were funded by pharmaceutical companies.

Of the induction of remission RCTs, one was published in abstract form,[17] one was reported online,[46] and one was available on clinicaltrials.gov (NCT00291668). These 25 RCTs included 8720 patients, randomised to active drug or placebo (Supplementary Table 2). Characteristics of individual studies are provided in Supplementary Table 3 and risk of bias of all trials in Supplementary Table 4. Fifteen induction of remission RCTs, reported in 14 articles,[34-36, 38-40, 42, 43, 45, 47-50, 52] were low risk of bias across all domains. The 15 maintenance of remission trials included 4016 patients, randomised to active drug or placebo (Supplementary Table 5), one of which was reported online.[61] Characteristics of individual studies are provided in Supplementary Table 6. Risk of bias for maintenance of remission trials is reported in Supplementary Table 7, with five at low risk of bias across all domains.[48-50, 53, 55]

Achievement of Clinical Remission

All 25 induction of remission trials reported data for this endpoint at between 4 and 16 weeks.[9, 16, 17, 34-52] NCT00291668 The network plot is provided in Figure 1. When data were pooled, there was low heterogeneity ($\tau^2 = 0.0013$), and the funnel plot appeared symmetrical (Supplementary Figure 2). All drugs, other than infliximab 10mg/kg, adalimumab 80/40mg, and certolizumab 400mg, were superior to placebo. Infliximab 5mg/kg ranked first for efficacy (RR of failure to achieve clinical remission = 0.67; 95% CI 0.56 to 0.79, P-score 0.95) (Figure 2a), meaning that the probability of infliximab 5mg/kg being most efficacious was 95%. Risankizumab 600mg (RR = 0.73; 95% CI 0.66 to 0.80, P-score 0.85) and upadacitinib 45mg o.d. (RR = 0.75; 95% CI 0.68 to 0.83, P-score 0.77) ranked second and third, respectively. The network heat plot had no red “hotspots” of inconsistency (Supplementary Figure 3). After direct and indirect comparison, infliximab 5mg/kg was superior to ustekinumab 6mg/kg and 130mg, infliximab 10mg/kg, adalimumab 80/40mg, vedolizumab 300mg, and certolizumab 400mg (Table 1). Risankizumab 600mg was superior to ustekinumab 6mg/kg and 130mg, adalimumab 80/40mg, vedolizumab 300mg, and certolizumab 400mg, upadacitinib 45mg o.d. was superior to adalimumab 80/40mg, ustekinumab 130mg, vedolizumab 300mg, and certolizumab 400mg, and risankizumab 1200mg and adalimumab 160/80mg were both superior to ustekinumab 130mg, vedolizumab 300mg, and certolizumab 400mg. One trial of infliximab used a single infusion of drug or placebo at week 0.[9] Excluding this trial in a sensitivity analysis, infliximab 5mg/kg still ranked first (RR = 0.61; 95% CI 0.49 to 0.76, P-score 0.98), followed by risankizumab 600mg (P-score 0.83) and upadacitinib 45mg o.d. (P-score 0.76) (Supplementary Figure 4). Using the CINeMA framework to evaluate confidence in the results of this endpoint, all direct and indirect comparisons across the network were rated as either high or moderate confidence (Supplementary Table 8).

Table 1. League Table for Failure to Achieve Clinical Remission: All Patients with Moderate to Severe Luminal CD.

								0.86 (0.63-1.17)				0.67 (0.56-0.79)
0.92 (0.75-1.12)	RIS 600mg		0.95 (0.85-1.07)									0.73 (0.66-0.80)
0.89 (0.73-1.09)	0.97 (0.84-1.12)	UPA 45mg										0.75 (0.68-0.83)
0.88 (0.71-1.07)	0.95 (0.85-1.07)	0.98 (0.85-1.14)	RIS 1200mg									0.76 (0.69-0.84)
0.85 (0.70-1.03)	0.93 (0.82-1.06)	0.96 (0.84-1.09)	0.97 (0.86-1.11)	ADA 160/80mg	1.00 (0.84-1.18)	0.93 (0.73-1.19)		0.86 (0.73-1.03)				0.78 (0.72-0.85)
0.85 (0.66-1.10)	0.93 (0.75-1.15)	0.96 (0.77-1.18)	0.97 (0.78-1.20)	1.00 (0.84-1.18)	ADA 160/160mg							
0.79 (0.66-0.95)	0.86 (0.77-0.97)	0.89 (0.79-1.00)	0.90 (0.80-1.02)	0.93 (0.84-1.02)	0.93 (0.77-1.13)	UST 6mg/kg			0.94 (0.86-1.02)			0.84 (0.79-0.90)
0.77 (0.60-0.99)	0.84 (0.66-1.06)	0.86 (0.68-1.10)	0.88 (0.69-1.11)	0.90 (0.72-1.13)	0.90 (0.68-1.20)	0.97 (0.78-1.21)	IFX 10mg/kg					0.89 (0.72-1.11)
0.75 (0.60-0.93)	0.82 (0.69-0.96)	0.84 (0.72-0.99)	0.86 (0.73-1.01)	0.88 (0.77-1.01)	0.88 (0.71-1.10)	0.95 (0.82-1.09)	0.98 (0.76-1.25)	ADA 80/40mg				0.89 (0.78-1.02)
0.75 (0.62-0.90)	0.81 (0.72-0.92)	0.84 (0.74-0.95)	0.85 (0.75-0.97)	0.87 (0.79-0.97)	0.88 (0.72-1.07)	0.94 (0.87-1.02)	0.97 (0.77-1.22)	0.99 (0.86-1.15)	UST 130mg			0.89 (0.83-0.96)
0.73 (0.60-0.88)	0.79 (0.70-0.89)	0.82 (0.72-0.92)	0.83 (0.74-0.94)	0.85 (0.77-0.94)	0.86 (0.70-1.04)	0.92 (0.84-1.01)	0.95 (0.76-1.18)	0.97 (0.84-1.12)	0.97 (0.88-1.08)	VED 300mg		0.92 (0.86-0.98)
0.71 (0.59-0.86)	0.78 (0.69-0.88)	0.80 (0.71-0.91)	0.82 (0.72-0.93)	0.84 (0.75-0.93)	0.84 (0.69-1.03)	0.90 (0.82-0.99)	0.93 (0.74-1.17)	0.95 (0.82-1.10)	0.96 (0.86-1.06)	0.98 (0.89-1.08)	CER 400mg	0.93 (0.87-1.00)
0.67 (0.56-0.79)	0.73 (0.66-0.80)	0.75 (0.68-0.83)	0.76 (0.69-0.84)	0.78 (0.72-0.85)	0.78 (0.65-0.95)	0.84 (0.79-0.90)	0.87 (0.70-1.08)	0.89 (0.78-1.01)	0.89 (0.83-0.96)	0.92 (0.86-0.98)	0.93 (0.87-1.00)	Placebo

Relative risk with 95% confidence intervals in parentheses. Comparisons, column versus row, should be read from left to right, and are ordered relative to their overall efficacy. The intervention in the top left position is ranked as best after the network meta-analysis of direct and indirect effects. Direct comparisons are provided above the drug labels, and indirect comparisons are below. Boxes shaded green denote a statistically significant difference.

ADA; adalimumab, CER; certolizumab, IFX; infliximab, RIS; risankizumab, UPA; upadacitinib, UST; ustekinumab, VED; vedolizumab.

Seven trials reported clinical remission in a subset of patients naïve to biological therapies,[16, 39, 43, 44, 48, 50, 51] and another seven trials only recruited patients naïve to these drugs.[9, 34, 35, 37, 38, 42, 47] Therefore, in total, there were 14 separate RCTs, recruiting 2911 patients. When data were pooled, there was low heterogeneity ($\tau^2 = 0.0053$). In patients naïve to biologics, all drugs, other than infliximab 10mg/kg and certolizumab 400mg, were superior to placebo. Risankizumab 600mg ranked first for clinical remission (RR of failure to achieve clinical remission = 0.66; 95% CI 0.52 to 0.85, P-score 0.78) (Figure 2b), with infliximab 5mg/kg performing similarly in second (RR = 0.67; 95% CI 0.55 to 0.82, P-score 0.78), risankizumab 1200mg third (0.69; 95% CI 0.54 to 0.88, P-score 0.72), and adalimumab 160/80mg fourth (RR = 0.70; 95% CI 0.61 to 0.81, P-score 0.70). On direct and indirect comparison risankizumab 600mg, infliximab 5mg/kg, and adalimumab 160/80mg were superior to certolizumab 400mg, but there were no other significant differences (Supplementary Table 9). After excluding the trial of infliximab that only used a single infusion of drug or placebo at week 0,[9] infliximab 5mg/kg ranked first (RR = 0.61; 95% CI 0.48 to 0.78, P-score 0.86) and risankizumab 600mg second (P-score 0.74) (Supplementary Figure 5).

Seven RCTs reported on clinical remission in a subset of patients exposed to biological therapies previously,[16, 39, 43, 44, 48, 50, 51] and six trials recruited only patients with previous exposure to these drugs.[16, 17, 36, 45, 49, 52] There were 3785 patients included in these 13 trials, and low heterogeneity between them ($\tau^2 = 0$). In this analysis, all drugs other than adalimumab 160/160mg, vedolizumab 300mg, and adalimumab 80/40mg were superior to placebo, with risankizumab 600mg ranked first (RR of failure to achieve clinical remission = 0.74; 95% CI 0.67 to 0.82, P-score 0.92) (Figure 2c). On direct and indirect comparison risankizumab 600mg was superior to ustekinumab 6mg/kg and 130mg, vedolizumab 300mg, and adalimumab 80/40mg, upadacitinib 45mg and

risankizumab 1200mg were superior to ustekinumab 130mg, vedolizumab 300mg, and adalimumab 80/40mg, and adalimumab 160/160mg and ustekinumab 6mg/kg were superior to vedolizumab 300mg (Supplementary Table 10).

Achievement of Clinical Response

Clinical response was reported by 24 induction of remission trials at 6 to 12 weeks (Supplementary Figure 6).[9, 16, 17, 34-45, 47-52] NCT00291668 There was low heterogeneity between studies ($\tau^2 = 0.0109$), and the funnel plot appeared symmetrical (Supplementary Figure 7). All drugs, other than infliximab 10mg/kg and certolizumab 400mg were superior to placebo, but infliximab 5mg/kg ranked first (RR of no clinical response = 0.54; 95% CI 0.41 to 0.70, P-score 0.91), followed by risankizumab 1200mg (RR = 0.57; 95% CI 0.47 to 0.69, P-score 0.87), and adalimumab 160/160mg (0.59; 95% CI 0.41 to 0.87, P-score 0.76) (Figure 3a). The network heat plot had no red “hotspots” of inconsistency (Supplementary Figure 8). Infliximab 5mg/kg and risankizumab 1200mg were superior to ustekinumab 130mg, vedolizumab 300mg, and certolizumab 400mg (Table 2). Risankizumab 600mg and adalimumab 160/80mg were superior to vedolizumab 300mg and certolizumab 400mg, and ustekinumab 6mg/kg to certolizumab 400mg. All but four of these trials used a decrease in CDAI of ≥ 100 to define clinical response.[9, 38-40] Excluding these studies in a sensitivity analysis, infliximab 5mg/kg remained first (RR = 0.51; 95% CI 0.37 to 0.69, P-score 0.95), followed by risankizumab 1200mg (0.56; 95% CI 0.47 to 0.67, P-score 0.90), and risankizumab 600mg (0.63; 95% CI 0.54 to 0.74, P-score 0.76) (Supplementary Figure 9).

Eight trials reported on clinical response in a subset of patients naïve to biologics,[16, 41, 43, 44, 48, 50-52] and seven trials only recruited patients naïve to these drugs.[9, 34, 35, 37, 38, 42, 47] Therefore, data from 15 separate RCTs, recruiting 3392 patients, were pooled.

Table 2. League Table for Failure to Achieve Clinical Response: All Patients with Moderate to Severe Luminal CD.

IFX 5mg/kg									0.73 (0.45-1.17)			0.54 (0.41-0.70)
0.95 (0.68-1.31)	RIS 1200mg		0.92 (0.74-1.13)									0.56 (0.46-0.68)
0.90 (0.57-1.43)	0.95 (0.62-1.46)	ADA 160/160mg		0.88 (0.62-1.25)								
0.85 (0.62-1.16)	0.89 (0.73-1.10)	0.94 (0.62-1.43)	RIS 600mg									0.63 (0.53-0.75)
0.79 (0.59-1.07)	0.84 (0.66-1.07)	0.88 (0.62-1.25)	0.94 (0.75-1.18)	ADA 160/80mg		1.04 (0.71-1.52)	0.90 (0.68-1.20)					0.67 (0.57-0.78)
0.78 (0.55-1.13)	0.83 (0.60-1.14)	0.87 (0.55-1.38)	0.93 (0.68-1.26)	0.99 (0.74-1.33)	UPA 45mg							0.68 (0.53-0.88)
0.76 (0.57-1.02)	0.80 (0.63-1.01)	0.84 (0.57-1.25)	0.90 (0.72-1.11)	0.96 (0.79-1.15)	0.97 (0.73-1.28)	UST 6mg/kg		0.97 (0.81-1.17)				0.71 (0.62-0.82)
0.73 (0.51-1.03)	0.77 (0.56-1.04)	0.81 (0.52-1.24)	0.86 (0.64-1.15)	0.92 (0.71-1.17)	0.92 (0.66-1.30)	0.96 (0.73-1.25)	ADA 80/40mg					0.73 (0.57-0.93)
0.72 (0.53-0.98)	0.76 (0.59-0.98)	0.80 (0.53-1.21)	0.85 (0.67-1.08)	0.91 (0.73-1.13)	0.92 (0.68-1.24)	0.95 (0.80-1.13)	0.99 (0.74-1.32)	UST 130mg				0.76 (0.64-0.91)
0.67 (0.46-0.99)	0.71 (0.48-1.05)	0.75 (0.45-1.24)	0.80 (0.55-1.16)	0.85 (0.59-1.23)	0.86 (0.56-1.30)	0.89 (0.62-1.27)	0.93 (0.62-1.40)	0.94 (0.64-1.36)	IFX 10mg/kg			0.81 (0.58-1.14)
0.62 (0.46-0.84)	0.66 (0.52-0.84)	0.69 (0.46-1.04)	0.74 (0.59-0.92)	0.78 (0.64-0.97)	0.79 (0.59-1.06)	0.82 (0.67-1.00)	0.86 (0.65-1.13)	0.86 (0.69-1.08)	0.92 (0.64-1.33)	VED 300mg		0.86 (0.75-0.99)
0.61 (0.45-0.83)	0.65 (0.51-0.82)	0.68 (0.45-1.02)	0.72 (0.58-0.90)	0.77 (0.63-0.95)	0.78 (0.59-1.04)	0.81 (0.67-0.98)	0.84 (0.64-1.11)	0.85 (0.68-1.06)	0.91 (0.63-1.31)	0.98 (0.81-1.20)	CER 400mg	0.87 (0.76-1.01)
0.54 (0.41-0.70)	0.57 (0.47-0.69)	0.59 (0.41-0.87)	0.63 (0.53-0.75)	0.68 (0.58-0.78)	0.68 (0.53-0.88)	0.71 (0.62-0.81)	0.74 (0.58-0.93)	0.74 (0.63-0.88)	0.80 (0.57-1.11)	0.86 (0.75-0.99)	0.87 (0.76-1.01)	Placebo

Relative risk with 95% confidence intervals in parentheses. Comparisons, column versus row, should be read from left to right, and are ordered relative to their overall efficacy. The intervention in the top left position is ranked as best after the network meta-analysis of direct and indirect effects. Direct comparisons are provided above the drug labels, and indirect comparisons are below. Boxes shaded green denote a statistically significant difference.

ADA; adalimumab, CER; certolizumab, IFX; infliximab, RIS; risankizumab, UPA; upadacitinib, UST; ustekinumab, VED; vedolizumab.

There was low heterogeneity between studies ($\tau^2 = 0.0028$), and overall risankizumab 1200mg ranked first (RR = 0.51; 95% CI 0.37 to 0.71, P-score 0.88), followed by infliximab 5mg/kg (RR = 0.53; 95% CI 0.42 to 0.67, P-score 0.85), and adalimumab 160/80mg (0.57; 95% CI 0.48 to 0.69, P-score 0.76) (Figure 3b). Risankizumab 1200mg and infliximab 5mg/kg were superior to infliximab 10mg/kg, vedolizumab 300mg, and certolizumab 400mg, adalimumab 160/80mg and ustekinumab 6mg/kg were superior to vedolizumab 300mg and certolizumab 400mg, and ustekinumab 130mg was superior to certolizumab 400mg (Supplementary Table 11).

Eight RCTs reported on clinical response in a subset of patients exposed to biological therapy previously,[16, 41, 43, 44, 48, 50-52] and six trials recruited only patients previously exposed to these drugs.[16, 17, 36, 45, 49, 52] There were 4077 patients randomised in these 14 RCTs. Overall, there was low heterogeneity between studies ($\tau^2 = 0.0056$). All drugs, other than adalimumab 80/40mg, vedolizumab 300mg, and certolizumab 400mg were superior to placebo. Risankizumab 1200mg was again ranked first (RR = 0.58; 95% CI 0.48 to 0.69, P-score 0.93), with risankizumab 600mg second (RR = 0.63; 95% CI 0.54 to 0.74, P-score 0.83), and upadacitinib 45mg o.d. third (0.68; 95% CI 0.56 to 0.84, P-score 0.70) (Figure 3c). The league ranking is provided in Supplementary Table 12. Risankizumab 1200mg was superior to all drugs, other than risankizumab 600mg, upadacitinib 45mg o.d., and adalimumab 80/40mg. Risankizumab 600mg and upadacitinib 45mg o.d. were superior to vedolizumab 300mg and certolizumab 400mg.

Maintenance of Clinical Remission

The 15 maintenance of remission trials reported data between 22 and 60 weeks.[10, 48-61] The network plot is provided in Supplementary Figure 10. When data were pooled, there was low heterogeneity ($\tau^2 = 0$), and the funnel plot appeared symmetrical

(Supplementary Figure 11), although there were several small studies around the line of no effect. Running the pairwise data confirmed there was no funnel plot asymmetry (Egger test, $p = 0.85$). All drugs, other than infliximab 120-240mg 2-weekly, risankizumab 360mg 8-weekly, and ustekinumab 90mg 12-weekly were superior to placebo. Upadacitinib 30mg o.d. ranked first for efficacy (RR of relapse of disease activity = 0.61; 95% CI 0.52 to 0.72, P-score 0.93) (Figure 4a), with adalimumab 40mg weekly (RR = 0.66; 95% CI 0.57 to 0.76, P-score 0.84) and infliximab 10mg/kg 8-weekly (RR = 0.69; 95% CI 0.59 to 0.80, P-score 0.74) second and third, respectively. The network heat plot had no red “hotspots” of inconsistency (Supplementary Figure 12). After direct and indirect comparison, upadacitinib 30mg o.d. was superior to all drugs other than adalimumab 40mg weekly, infliximab 10mg/kg 8-weekly, adalimumab 40mg 2-weekly, infliximab 120-240mg 2-weekly, certolizumab 400mg 4-weekly, and risankizumab 180mg 8-weekly (Table 3). Adalimumab 40mg weekly was superior to vedolizumab 300mg 4-weekly and infliximab 5mg/kg 8-weekly. Two of these trials recruited patients irrespective of response to open-label treatment,[54, 57] so we excluded these in a sensitivity analysis. In this analysis, the top three ranked drugs were unchanged (Supplementary Figure 13).

Six trials reported on maintenance of clinical remission in a subset of patients naïve to biologics,[48, 50, 52, 55, 59, 60] and another four trials only recruited patients naïve to these drugs.[10, 53, 54, 56] Therefore, in total, there were 10 separate RCTs, recruiting 1523 patients. There was low heterogeneity between studies ($\tau^2 = 0$), with adalimumab 40mg weekly ranked first (RR = 0.59; 95% CI 0.48 to 0.73, P-score 0.86), adalimumab 40mg 2-weekly second (RR = 0.66; 95% CI 0.55 to 0.80, P-score 0.70), and ustekinumab 90mg 8-weekly third (0.67; 95% CI 0.47 to 0.97, P-score 0.65) (Figure 4b). Infliximab 10mg/kg and 5mg/kg 8-weekly and vedolizumab 300mg 8-weekly were also superior to placebo. After direct and indirect comparison, adalimumab 40mg weekly was superior to infliximab 5mg/kg

Table 3. League Table for Failure to Maintain Clinical Remission: All Re-randomised Patients with Luminal CD.

						0.82 (0.68 - 0.98)									0.61 (0.52 - 0.72)
0.93 (0.75 - 1.15)	ADA 40mg wkly		0.91 (0.77 - 1.09)												0.66 (0.57 - 0.76)
0.89 (0.71 - 1.10)	0.95 (0.77 - 1.17)	IFX 10mg/kg 8-wkly											0.86 (0.71 - 1.04)		0.69 (0.59 - 0.80)
0.85 (0.70 - 1.02)	0.91 (0.78 - 1.07)	0.96 (0.80 - 1.15)	ADA 40mg 2-wkly												0.72 (0.65 - 0.80)
0.91 (0.45 - 1.83)	0.98 (0.49 - 1.96)	1.03 (0.52 - 2.05)	1.08 (0.54 - 2.14)	IFX 120- 240mg 2- wkly									0.81 (0.42 - 1.58)		
0.84 (0.67 - 1.04)	0.90 (0.73 - 1.11)	0.94 (0.76 - 1.17)	0.99 (0.82 - 1.19)	0.92 (0.46 - 1.84)	CER 400mg 4-wkly										0.73 (0.63 - 0.85)
0.82 (0.68 - 0.98)	0.88 (0.73 - 1.07)	0.92 (0.76 - 1.13)	0.97 (0.82 - 1.14)	0.90 (0.45 - 1.79)	0.98 (0.80 - 1.20)	UPA 15mg o.d.									0.75 (0.65 - 0.85)
0.81 (0.62 - 1.06)	0.87 (0.67 - 1.13)	0.91 (0.70 - 1.19)	0.96 (0.75 - 1.21)	0.89 (0.44 - 1.81)	0.97 (0.74 - 1.26)	0.99 (0.77 - 1.27)	RIS 180mg 8-wkly				0.94 (0.73 - 1.20)				0.75 (0.61 - 0.94)
0.79 (0.64 - 0.98)	0.85 (0.69 - 1.04)	0.89 (0.72 - 1.10)	0.93 (0.78 - 1.11)	0.87 (0.43 - 1.73)	0.94 (0.77 - 1.17)	0.97 (0.79 - 1.18)	0.98 (0.75 - 1.27)	VED 300mg 8-wkly				0.96 (0.81 - 1.14)			0.77 (0.67 - 0.89)
0.79 (0.63 - 0.99)	0.85 (0.69 - 1.05)	0.89 (0.71 - 1.11)	0.93 (0.77 - 1.13)	0.87 (0.43 - 1.74)	0.94 (0.76 - 1.18)	0.96 (0.78 - 1.19)	0.97 (0.74 - 1.28)	1.00 (0.80 - 1.24)	UST 90mg 8-wkly				0.93 (0.73 - 1.18)		0.77 (0.66 - 0.91)
0.77 (0.61 - 0.97)	0.83 (0.67 - 1.03)	0.87 (0.70 - 1.09)	0.91 (0.75 - 1.11)	0.85 (0.42 - 1.71)	0.93 (0.74 - 1.16)	0.95 (0.77 - 1.17)	0.96 (0.73 - 1.25)	0.98 (0.79 - 1.22)	0.98 (0.78 - 1.24)	VED 108mg 2-wkly					0.79 (0.67 - 0.93)
0.76 (0.58 - 0.99)	0.82 (0.63 - 1.06)	0.86 (0.66 - 1.12)	0.90 (0.71 - 1.14)	0.83 (0.41 - 1.70)	0.91 (0.70 - 1.18)	0.93 (0.72 - 1.20)	0.94 (0.73 - 1.20)	0.96 (0.74 - 1.25)	0.96 (0.74 - 1.26)	0.98 (0.75 - 1.29)	RIS 360mg 8-wkly				0.80 (0.65 - 1.00)
0.75 (0.61 - 0.94)	0.81 (0.66 - 0.99)	0.85 (0.69 - 1.05)	0.89 (0.75 - 1.06)	0.83 (0.41 - 1.65)	0.90 (0.73 - 1.11)	0.92 (0.76 - 1.12)	0.93 (0.72 - 1.21)	0.95 (0.80 - 1.13)	0.96 (0.77 - 1.19)	0.97 (0.78 - 1.21)	0.99 (0.77 - 1.29)	VED 300mg 4-wkly			0.81 (0.70 - 0.94)
0.75 (0.58 - 0.96)	0.80 (0.63 - 1.03)	0.84 (0.66 - 1.08)	0.88 (0.71 - 1.10)	0.82 (0.40 - 1.66)	0.89 (0.69 - 1.15)	0.91 (0.72 - 1.16)	0.92 (0.69 - 1.24)	0.95 (0.74 - 1.21)	0.95 (0.76 - 1.18)	0.97 (0.74 - 1.25)	0.98 (0.73 - 1.32)	0.99 (0.77 - 1.27)	UST 90mg 12-wkly		0.81 (0.66 - 0.99)
0.74 (0.60 - 0.91)	0.80 (0.65 - 0.97)	0.84 (0.70 - 1.00)	0.87 (0.74 - 1.04)	0.81 (0.42 - 1.58)	0.89 (0.72 - 1.09)	0.91 (0.75 - 1.09)	0.91 (0.71 - 1.18)	0.94 (0.77 - 1.14)	0.94 (0.76 - 1.16)	0.96 (0.77 - 1.19)	0.97 (0.76 - 1.26)	0.98 (0.80 - 1.20)	0.99 (0.78 - 1.26)	IFX 5mg/kg 8-wkly	0.83 (0.72 - 0.95)

0.61 (0.52 - 0.72)	0.66 (0.57 - 0.76)	0.69 (0.59 - 0.80)	0.72 (0.65 - 0.80)	0.67 (0.34 - 1.32)	0.73 (0.63 - 0.85)	0.75 (0.65 - 0.85)	0.75 (0.61 - 0.94)	0.77 (0.67 - 0.89)	0.77 (0.66 - 0.91)	0.79 (0.67 - 0.93)	0.80 (0.65 - 1.00)	0.81 (0.70 - 0.94)	0.82 (0.67 - 1.00)	0.82 (0.72 - 0.95)	Placebo
--------------------------	--------------------------	--------------------------	--------------------------	-----------------------	--------------------------	--------------------------	--------------------------	--------------------------	--------------------------	--------------------------	--------------------------	--------------------------	-----------------------	--------------------------	----------------

Relative risk with 95% confidence intervals in parentheses. Comparisons, column versus row, should be read from left to right, and are ordered relative to their overall efficacy. The intervention in the top left position is ranked as best after the network meta-analysis of direct and indirect effects. Direct comparisons are provided above the drug labels, and indirect comparisons are below. Boxes shaded green denote a statistically significant difference.

ADA; adalimumab, CER; certolizumab, IFX; infliximab, RIS; risankizumab, UPA; upadacitinib, UST; ustekinumab, VED; vedolizumab.

8-weekly and vedolizumab 108mg 2-weekly, but there were no other significant differences (Supplementary Table 13).

Finally, six RCTs reported on maintenance of clinical remission in a subset of patients exposed to biological therapy previously,[48, 50, 52, 55, 59, 60] and one trial recruited only patients previously exposed to these drugs.[49] There were 1382 patients randomised in these seven RCTs, with low heterogeneity between studies ($\tau^2 = 0$). All drugs, other than risankizumab 360mg 8-weekly and ustekinumab 90mg 12-weekly were superior to placebo, but vedolizumab 108mg 2-weekly subcutaneously ranked first (RR = 0.70; 95% CI 0.57 to 0.86, P-score 0.82), with adalimumab 40mg weekly second (RR = 0.73; 95% CI 0.61 to 0.88, P-score 0.73), and adalimumab 40mg 2-weekly third (RR = 0.77; 95% CI 0.66 to 0.90, P-score 0.61) (Figure 4c). The league ranking is provided in Supplementary Table 14. There were no significant differences between any active drugs.

Adverse Events

Complete adverse events data for both induction and maintenance of remission trials are provided in the Supplementary Materials.

DISCUSSION

We report a contemporaneous systematic review and network meta-analysis of biological therapies and small molecules in luminal CD. We included data from more than 8700 patients in 25 induction of remission trials. Our analysis suggested that infliximab 5mg/kg was the most efficacious drug when data from all patients were pooled. All comparisons across this network were rated as either high or moderate confidence. However, when we analysed the data for biologic-naïve or exposed patients separately risankizumab 600mg ranked first for both groups, suggesting that the ranking of infliximab 5m/kg was driven by its use in biologic-naïve patients in all trials in which it was studied. In all trials, upadacitinib 45mg o.d. performed similarly to risankizumab 600mg and was ranked third. In biologic-naïve patients, infliximab 5mg/kg ranked second and risankizumab 1200mg third. In biologic-exposed patients, upadacitinib 45mg o.d. ranked second followed by risankizumab 1200mg. In terms of clinical response, infliximab 5mg/kg ranked first when all patients were considered, but risankizumab 1200mg was first in both biologic-naïve and exposed patients. Analysing data from 15 maintenance of remission trials, recruiting over 4000 patients, upadacitinib 30mg o.d. ranked first for efficacy, followed by adalimumab 40mg weekly and infliximab 10mg/kg 8-weekly. When data were pooled according to previous biologic exposure, adalimumab 40mg weekly ranked first in biologic-naïve patients, and vedolizumab 108mg 2-weekly first in biologic-exposed. Finally, there was no significant increase in total numbers of adverse events, serious adverse events, or infections with any drug over placebo, although withdrawals due to adverse events were significantly more likely with infliximab 10mg/kg 8-weekly in maintenance of remission trials.

Limitations of this network meta-analysis include the fact that only 15 of 25 induction of remission trials, and five of 15 maintenance of remission RCTs, were at low risk of bias across all domains. We identified no phase III trials of etrolizumab, tofacitinib, or filgotinib

in luminal CD, although the BERGAMOT trial of etrolizumab has now completed. However, the results of this study are reported as having led to the pharmaceutical company ceasing future development of the drug,[62] so incorporating the results from this trial is unlikely to have changed the ranking of the top therapies. The three trials of upadacitinib have yet to be published in full, and data for efficacy according to previous biologic exposure were unavailable for one of the induction of remission trials and for the maintenance of remission RCT, and there were no safety data available for the maintenance of remission trial. It may be, therefore, that when these data become available in full the ranking of upadacitinib will change in both biologic-naïve and exposed patients and safety signals may emerge. Although trials of newer drugs will have included patients with more refractory luminal CD who had failed multiple biologics, many of these recent trials also restricted their recruitment to biologic-naïve patients entirely or recruited a subset of biologic-naïve patients. This allowed subgroup analysis according to previous biologic exposure, although in the latter group of trials comparisons between subsets of biologic-naïve or biologic exposed patients according to treatment allocation may not be protected by randomisation. Endpoints were identical between all trials for both induction and maintenance of remission but differed slightly for clinical response. However, we performed a sensitivity analysis including only trials using a fall in CDAI of ≥ 100 to define this. Another issue is that there was a difference in duration of treatment between induction of remission trials, as well as the timepoints at which endpoints were assessed. It may not be fair to compare the efficacy of adalimumab at 4 weeks, which is when most trials reported data, with drugs like ustekinumab, risankizumab, and upadacitinib, where efficacy was assessed at 12 weeks of treatment. This is probably less of an issue in maintenance of remission trials, where most studies reported data at between 50 and 60 weeks of follow-up. Finally, efficacy of these drugs, in terms of endoscopic response and remission, which may be associated with improved prognosis and reductions in disability,[63,

64] cannot be judged as few trials reported rates of endoscopic improvement or healing. Despite these limitations, the results of our study may still be useful to inform treatment decisions for patients with luminal CD and can be used to update national and international evidence-based management guidelines.

A network meta-analysis by Singh *et al.*, published in 2018,[15] reported that infliximab and adalimumab were the most efficacious drugs for induction of remission in patients naïve to biological therapies, and for maintenance of remission after response to therapy. In this analysis, adalimumab and ustekinumab ranked highest for induction of remission in patients with previous anti-TNF- α exposure. In a recent update of this meta-analysis,[14] the ranking favoured infliximab combined with azathioprine, infliximab monotherapy, and adalimumab for induction of remission in 15 trials in biologic-naïve patients, and adalimumab and risankizumab in 10 trials in biologic-exposed patients. In 15 maintenance of remission trials, irrespective of previous biologic exposure and including treat-through studies without re-randomisation of patients, infliximab combined with azathioprine, and adalimumab, were the highest ranked. In contrast to these previous network meta-analyses, we identified studies from the “grey” literature,[46, 61] (NCT00291668) incorporated the more recent trials of newer drugs, conducted maintenance of remission analyses according to previous biologic exposure and only in trials re-randomising patients, and performed all our analyses according to dose, and dosing schedule, of each of the drugs of interest, rather than pooling individual drugs together irrespective of these issues. Our analyses, therefore, allow the selection of the optimal dose and treatment interval, as well as providing evidence that some novel drugs, which are likely to come to market soon, are potentially more efficacious than existing licensed therapies for both biologic-naïve and exposed individuals with luminal CD.

One of the core assumptions in any network meta-analysis relates to transitivity, where indirect comparisons between treatments assume that any patient included in the network could, theoretically, have been recruited to any of the trials and assigned to any of the treatments. Confounding due to underlying differences between RCTs, including previous failed therapies, disease duration, or concomitant medication use over the 25-year range these trials were conducted is possible. We had identified these issues *a priori*. Hence, our analyses including only biologic-naïve or exposed patients should address, to some extent, the concern that more refractory patients have been included in more recent trials. In fact, several of these studies restricted their recruitment to biologic-naïve patients. Disease duration was between 7 and 13 years in most studies. In addition, immunosuppressant use was similar between active drug and placebo arms across all induction of remission trials, although this was less well-balanced in maintenance of remission trials. It is also important to consider that there is a lack of real-world clinical experience for the use of newer drugs or routes of administration, such as risankizumab or subcutaneous vedolizumab. Although these were ranked highly in the network, this was based on indirect evidence, and head-to-head trials versus other biologics should be considered. Finally, conclusions relating to infliximab 10mg/kg for induction of remission were based on a single small study.[9] This may, therefore, be underpowered to detect significant differences, although there are also data to support this approach from clinical practice.[65]

These results confirm that all available drugs, other than adalimumab 80/40mg and certolizumab 400mg were more efficacious than placebo for induction of remission of moderate to severe luminal CD between 4 and 16 weeks, and all drugs other than infliximab 10mg/kg and certolizumab 400mg were superior to placebo in terms of clinical response. For maintenance of remission, all drugs other than infliximab 120-240mg 2-weekly, risankizumab 360mg 8-weekly, and ustekinumab 90mg 12-weekly were superior to placebo.

All drugs were safe and well-tolerated. Nevertheless, blanket application of the findings of this meta-analysis should be avoided. Selection of treatment should be informed by these results together with patient choice, which may be influenced by other considerations, including route of administration and convenience, as well as likelihood of adherence, and costs to the health service. In some healthcare systems, the substantial reduction in costs seen with biosimilars will over-ride the possible superior efficacy of some of these newer, but more expensive, drugs. Where anti-TNF- α drugs are used preferentially, our results suggest that higher doses of adalimumab are more likely to induce remission successfully, and that weekly scheduling of adalimumab or a 10mg/kg dose of infliximab are more likely to maintain remission. However, these are suggestions based on our results, and do not consider the results of proactive therapeutic drug monitoring, which are likely to guide decision-making in clinical practice.

This systematic review and network meta-analysis synthesises evidence from a large number of patients included in multiple induction and maintenance of remission trials, with similar patient numbers assigned to each of the active drugs of interest, and confidence in the results from of all direct and indirect comparisons across the network for achievement of clinical remission were rated as either high or moderate. Although the results can be used to help select treatments for luminal CD, more head-to-head RCTs will better inform future network meta-analyses and, ultimately, clinical practice.

ACKNOWLEDGEMENTS

None.

CONTRIBUTOR AND GUARANTOR INFORMATION

Guarantor: ACF is guarantor. He accepts full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Specific author contributions: Study concept and design: BB, DJG, CJB and ACF conceived and drafted the study. BB, CJB, and ACF analysed and interpreted the data. BB and ACF drafted the manuscript. All authors have approved the final draft of the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

COPYRIGHT/LICENSE FOR PUBLICATION

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, a worldwide licence to the Publishers and its licensees in perpetuity, in all forms, formats and media (whether known now or created in the future), to i) publish, reproduce, distribute, display and store the Contribution, ii) translate the Contribution into other languages, create adaptations, reprints, include within collections and create summaries, extracts and/or, abstracts of the Contribution, iii) create any other derivative work(s) based on the Contribution, iv) to exploit all subsidiary rights in the Contribution, v) the inclusion of

electronic links from the Contribution to third party material where-ever it may be located; and, vi) licence any third party to do any or all of the above.

COMPETING INTERESTS DECLARATION

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

TRANSPARENCY STATEMENT

The lead author (ACF, the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

ROLE OF THE FUNDING SOURCE

None.

PATIENT AND PUBLIC INVOLVEMENT STATEMENT

We did not involve patients or the public in this work. We will disseminate our findings in lay terms via the national charity for people living with digestive diseases, “Guts UK”.

DATA SHARING

No additional data available.

REFERENCES

- 1 Torres J, Mehandru S, Colombel JF, Peyrin-Biroulet L. Crohn's disease. *Lancet* 2017;**389**:1741-55.
- 2 Jones GR, Lyons M, Plevris N, Jenkinson PW, Bisset C, Burgess C, *et al.* IBD prevalence in Lothian, Scotland, derived by capture-recapture methodology. *Gut* 2019;**68**:1953-60.
- 3 Kaplan GG. The global burden of IBD: From 2015 to 2025. *Nat Rev Gastroenterol Hepatol* 2015;**12**:720-7.
- 4 Cosnes J, Cattan S, Blain A, Beaugerie L, Carbonnel F, Parc R, *et al.* Long-term evolution of disease behavior of Crohn's disease. *Inflamm Bowel Dis* 2002;**8**:244-50.
- 5 Peyrin-Biroulet L, Loftus EV, Jr., Colombel JF, Sandborn WJ. The natural history of adult Crohn's disease in population-based cohorts. *Am J Gastroenterol* 2010;**105**:289-97.
- 6 Barberio B, Segal JP, Quraishi MN, Black CJ, Savarino EV, Ford AC. Efficacy of oral, topical, or combined oral and topical 5-aminosalicylates, in ulcerative colitis: Systematic review and network meta-analysis. *J Crohns Colitis* 2021;**15**:1184-96.
- 7 Ford AC, Kane SV, Khan KJ, Achkar JP, Talley NJ, Marshall JK, *et al.* Efficacy of 5-aminosalicylates in Crohn's disease: Systematic review and meta-analysis. *Am J Gastroenterol* 2011;**106**:617-29.

- 8 Khan KJ, Dubinsky MC, Ford AC, Ullman TA, Talley NJ, Moayyedi P. Efficacy of immunosuppressive therapy for inflammatory bowel disease: A systematic review and meta-analysis. *Am J Gastroenterol* 2011;**106**:630-42.
- 9 Targan SR, Hanauer SB, van Deventer SJH, Mayer L, Present DH, Braakman T, *et al.* A short-term study of chimeric monoclonal antibody cA2 to tumour necrosis factor à for Crohn's disease. *N Engl J Med* 1997;**337**:1029-35.
- 10 Rutgeerts P, D'Haens G, Targan S, Vasiliasuskas E, Hanauer SB, Present DH, *et al.* Efficacy and safety of retreatment with anti-tumor necrosis factor antibody (infliximab) to maintain remission in Crohn's disease. *Gastroenterology* 1999;**117**:761-9.
- 11 Present DH, Rutgeerts P, Targan S, Hanauer SB, Mayer L, van Hogezaand RA, *et al.* Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med* 1999;**340**:1398-405.
- 12 Sands BE, Anderson FH, Bernstein CN, Chey WY, Feagan BG, Fedorak RN, *et al.* Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med* 2004;**350**:876-85.
- 13 Burr NE, Gracie DJ, Black CJ, Ford AC. Efficacy of biological therapies and small molecules in moderate to severe ulcerative colitis: Systematic review and network meta-analysis. *Gut* 2021;**doi: 10.1136/gutjnl-2021-326390**.
- 14 Singh S, Murad MH, Fumery M, Sedano R, Jairath V, Panaccione R, *et al.* Comparative efficacy and safety of biologic therapies for moderate-to-severe Crohn's disease:

A systematic review and network meta-analysis. *Lancet Gastroenterol Hepatol* 2021;**6**:1002-14.

15 Singh S, Fumery M, Sandborn WJ, Murad MH. Systematic review and network meta-analysis: First- and second-line biologic therapies for moderate-severe Crohn's disease. *Aliment Pharmacol Ther* 2018;**48**:394-409.

16 D'Haens G, Panaccione R, Baert F, Bossuyt P, Colombel J-F, Danese S, *et al.* Risankizumab as induction therapy for Crohn's disease: Results from the phase 3 ADVANCE and MOTIVATE induction trials. *Lancet* 2022;**399**:2015-30.

17 Colombel JF, Panes J, Lacerda AP, Peyrin-Biroulet L, D'Haens GR, Panaccione R, *et al.* Efficacy and safety of upadacitinib induction therapy in patients with moderately to severely active Crohn's disease who failed prior biologics: Results from a randomized phase-3 U-EXCEED study. *Gastroenterology* 2022;**162**:867f.

18 Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions: Version 5.1.0 [updated March 2011]. <http://handbook-5-1.cochrane.org/> 2011.

19 Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, *et al.* The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: Checklist and explanations. *Ann Intern Med* 2015;**162**:777-84.

20 Salanti G, Higgins JP, Ades AE, Ioannidis JP. Evaluation of networks of randomized trials. *Stat Methods Med Res* 2008;**17**:279-301.

- 21 Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: Many names, many benefits, many concerns for the next generation evidence synthesis tool. *Res Synth Methods* 2012;**3**:80-97.
- 22 Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: An overview and tutorial. *J Clin Epidemiol* 2011;**64**:163-71.
- 23 Chaimani A, Higgins JP, Mavridis D, Spyridonos P, Salanti G. Graphical tools for network meta-analysis in STATA. *PLoS One* 2013;**8**:e76654.
- 24 Higgins JP, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: Concepts and models for multi-arm studies. *Res Synth Methods* 2012;**3**:98-110.
- 25 Krahn U, Binder H, König J. A graphical tool for locating inconsistency in network meta-analyses. *BMC Med Res Methodol* 2013;**13**:35.
- 26 Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**:557-60.
- 27 Rucker G, Schwarzer G, Carpenter JR, Schumacher M. Undue reliance on I^2 in assessing heterogeneity may mislead. *BMC Med Res Methodol* 2008;**8**:79.
- 28 da Costa BR, Juni P. Systematic reviews and meta-analyses of randomized trials: Principles and pitfalls. *Eur Heart J* 2014;**35**:3336-45.

- 29 Rucker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. *BMC Med Res Methodol* 2015;**15**:58.
- 30 Morton SC, Murad MH, O'Connor E, Lee CS, Booth M, Vandermeer BW, *et al.* AHRQ methods for effective health care. Quantitative synthesis-an update. *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*. Rockville (MD): Agency for Healthcare Research and Quality (US), 2018.
- 31 Nikolakopoulou A, Higgins JPT, Papakonstantinou T, Chaimani A, Del Giovane C, Egger M, *et al.* CINeMA: An approach for assessing confidence in the results of a network meta-analysis. *PLoS Med* 2020;**17**:e1003082.
- 32 Papakonstantinou T, Nikolakopoulou A, Higgins JPT, Egger M, Salanti G. CINeMA: Software for semiautomated assessment of the confidence in the results of network meta-analysis. *Campbell Systematic Reviews* 2020;**16**:e1080.
- 33 Chiocchia V, Nikolakopoulou A, Higgins JPT, Page MJ, Papakonstantinou T, Cipriani A, *et al.* ROB-MEN: A tool to assess risk of bias due to missing evidence in network meta-analysis. *BMC Med* 2021;**19**:304.
- 34 Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, *et al.* Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010;**362**:1383-95.

- 35 Hanauer SB, Sandborn WJ, Rutgeerts P, Fedorak RN, Lukas M, MacIntosh D, *et al.* Human anti-tumour necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: The CLASSIC-I trial. *Gastroenterology* 2006;**130**:323-33.
- 36 Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Colombel JF, Panaccione R, *et al.* Adalimumab induction therapy for Crohn disease previously treated with infliximab: A randomized trial. *Ann Intern Med* 2007;**146**:829-38.
- 37 Wu KC, Ran ZH, Gao X, Chen M, Zhong J, Sheng JQ, *et al.* Adalimumab induction and maintenance therapy achieve clinical remission and response in Chinese patients with Crohn's disease. *Intest Res* 2016;**14**:152-63.
- 38 Chen B, Gao X, Zhong J, Ren J, Zhu X, Liu Z, *et al.* Efficacy and safety of adalimumab in Chinese patients with moderately to severely active Crohn's disease: Results from a randomized trial. *Ther Adv Gastroenterol* 2020;**13**:1756284820938960.
- 39 D'Haens GR, Sandborn WJ, Loftus EV, Jr., Hanauer SB, Schreiber S, Peyrin-Biroulet L, *et al.* Higher vs standard adalimumab induction dosing regimens and two maintenance strategies: Randomized SERENE CD trial results. *Gastroenterology* 2022;**162**:1876-90.
- 40 Schreiber S, Rutgeerts P, Fedorak RN, Khaliq-Kareemi M, Kamm MA, Boivin M, *et al.* A randomized, placebo-controlled trial of certolizumab pegol (CDP870) for treatment of Crohn's disease. *Gastroenterology* 2005;**129**:807-18.
- 41 Sandborn WJ, Feagan BG, Stoinov S, Honiball PJ, Rutgeerts P, Mason D, *et al.* Certolizumab pegol for the treatment of Crohn's disease. *N Engl J Med* 2007;**357**:228-38.

42 Sandborn WJ, Schreiber S, Feagan BG, Rutgeerts P, Younes ZH, Bloomfield R, *et al.* Certolizumab pegol for active Crohn's disease: A placebo-controlled, randomized trial. *Clin Gastroenterol Hepatol* 2011;**9**:670-8.

43 Sands BE, Feagan BG, Rutgeerts P, Colombel JF, Sandborn WJ, Sy R, *et al.* Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment failed. *Gastroenterology* 2014;**147**:618-27.

44 Sandborn WJ, D'Haens GR, Reinisch W, Panés J, Chan D, Gonzalez S, *et al.* Guselkumab for the treatment of Crohn's disease: Induction results from the phase 2 GALAXI-1 study. *Gastroenterology* 2022;**162**:1650-64.

45 Feagan BG, Sandborn WJ, D'Haens G, Panés J, Kaser A, Ferrante M, *et al.* Induction therapy with the selective interleukin-23 inhibitor risankizumab in patients with moderate-to-severe Crohn's disease: A randomised, double-blind, placebo-controlled phase 2 study. *Lancet* 2017;**389**:1699-709.

46 Second phase 3 induction study confirms upadacitinib (RINVOQ®) improved Clinical and endoscopic outcomes in patients with Crohn's disease.
<https://news.abbvie.com/news/press-releases/news-type/rd-news/second-phase-3-induction-study-confirms-upadacitinib-rinvoq-improved-clinical-and-endoscopic-outcomes-in-patients-with-crohns-disease.htm> Accessed 27th May 2022.

47 Sands BE, Irving PM, Hoops T, Izanec JL, Gao L-L, Gasink C, *et al.* Ustekinumab versus adalimumab for induction and maintenance therapy in biologic-naive patients with

moderately to severely active Crohn's disease: A multicentre, randomised, double-blind, parallel-group, phase 3b trial. *Lancet* 2022;**399**:2200-11.

48 Sandborn WJ, Feagan BG, Rutgeerts P, Hanauer S, Colombel JF, Sands BE, *et al.* Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2013;**369**:711-21.

49 Sandborn WJ, Gasink C, Gao LL, Blank MA, Johanss J, Guzzo C, *et al.* Ustekinumab induction and maintenance therapy in refractory Crohn's disease. *N Engl J Med* 2012;**367**:1519-28.

50 Watanabe K, Motoya S, Ogata H, Kanai T, Matsui T, Suzuki Y, *et al.* Effects of vedolizumab in Japanese patients with Crohn's disease: A prospective, multicenter, randomized, placebo-controlled Phase 3 trial with exploratory analyses. *J Gastroenterol* 2020;**55**:291-306.

51 Watanabe M, Hibi T, Lomax KG, Paulson SK, Chao J, Alam MS, *et al.* Adalimumab for the induction and maintenance of clinical remission in Japanese patients with Crohn's disease. *J Crohns Colitis* 2012;**6**:160-73.

52 Feagan BG, Sandborn WJ, Gasink C, Jacobstein D, Lang Y, Friedman JR, *et al.* Ustekinumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2016;**375**:1946-60.

- 53 Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, *et al.* Maintenance infliximab for Crohn's disease: The ACCENT I randomised trial. *Lancet* 2002;**359**:1541-9.
- 54 Schreiber S, Ben-Horin S, Leszczyszyn J, Dudkowiak R, Lahat A, Gawdis-Wojnarska B, *et al.* Randomized controlled trial: Subcutaneous vs intravenous infliximab CT-P13 maintenance in inflammatory bowel disease. *Gastroenterology* 2021;**160**:2340-53.
- 55 Colombel JF, Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Panaccione R, *et al.* Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: The CHARM trial. *Gastroenterology* 2007;**132**:52-65.
- 56 Sandborn WJ, Hanauer SB, Rutgeerts P, Fedorak RN, Lukas M, MacIntosh DG, *et al.* Adalimumab for maintenance treatment of Crohn's disease: Results of the CLASSIC II trial. *Gut* 2007;**56**:1232-9.
- 57 Rutgeerts P, Van Assche G, Sandborn WJ, Wolf DC, Geboes K, Colombel JF, *et al.* Adalimumab induces and maintains mucosal healing in patients with Crohn's disease: Data from the EXTEND trial. *Gastroenterology* 2012;**142**:1102-11.e2.
- 58 Schreiber S, Khaliq-Kareemi M, Lawrance IC, Ostergaard Thomsen O, Hanauer SB, McColm J, *et al.* Maintenance therapy with certolizumab pegol for Crohn's disease. *N Engl J Med* 2007;**357**:239-50.
- 59 Vermeire S, D'Haens G, Baert F, Danese S, Kobayashi T, Loftus EV, *et al.* Efficacy and safety of subcutaneous vedolizumab in patients with moderately to severely active

Crohn's disease: Results from the VISIBLE 2 randomised trial. *J Crohns Colitis* 2022;**16**:27-38.

60 Ferrante M, Panaccione R, Baert F, Bossuyt P, Colombel J-F, Danese S, *et al.* Risankizumab as maintenance therapy for moderately to severely active Crohn's disease: Results from the multicentre, randomised, double-blind, placebo-controlled, withdrawal phase 3 FORTIFY maintenance trial. *Lancet* 2022;**399**:2031-46.

61 Upadacitinib (RINVOQ®) achieved clinical remission and endoscopic response at one year in phase 3 maintenance study in patients with Crohn's disease. <https://www.benzinga.com/pressreleases/22/05/n27134213/upadacitinib-rinvoq-achieved-clinical-remission-and-endoscopic-response-at-one-year-in-phase-3-mai> Accessed 27th May 2022.

62 Roche abandons Crohn's program following mixed topline verdict. <https://www.biospace.com/article/roche-abandons-crohn-s-program-and-others-while-projecting-stable-revenues-for-2022/> Accessed 4th June 2022.

63 Yzet C, Brazier F, Sebbagh V, Vanelslander P, Dejour V, David B, *et al.* Complete endoscopic healing is associated with lower disability than partial endoscopic healing in Crohn's disease: A prospective multicenter study. *Clin Res Hepatol Gastroenterol* 2022;**46**:101887.

64 Yzet C, Diouf M, Le Mouel JP, Brazier F, Turpin J, Loreau J, *et al.* Complete endoscopic healing associated with better outcomes than partial endoscopic healing in patients with Crohn's disease. *Clin Gastroenterol Hepatol* 2020;**18**:2256-61.

65 Hendler SA, Cohen BL, Colombel JF, Sands BE, Mayer L, Agarwal S. High-dose infliximab therapy in Crohn's disease: Clinical experience, safety, and efficacy. *J Crohns Colitis* 2015;**9**:266-75.

FIGURES**Figure 1. Network Plot for Failure to Achieve Clinical Remission: All Patients with Moderate to Severe Luminal CD.**

Note: Circle (node) size is proportional to the number of study participants assigned to receive each intervention. The line width (connection size) corresponds to the number of studies comparing the individual interventions.

Figure 2a. Forest Plot for Failure to Achieve Clinical Remission: All Patients with Moderate to Severe Luminal CD.

Note: The P-score is the probability of each intervention being ranked as best in the network.

Figure 2b. Forest Plot for Failure to Achieve Clinical Remission: Patients with Moderate to Severe Luminal CD Naïve to Biological Therapies.

Note: The P-score is the probability of each intervention being ranked as best in the network.

Figure 2c. Forest Plot for Failure to Achieve Clinical Remission: Patients with Moderate to Severe Luminal CD Exposed to Biological Therapies Previously.

Note: The P-score is the probability of each intervention being ranked as best in the network.

Figure 3a. Forest Plot for Failure to Achieve Clinical Response: All Patients with Moderate to Severe Luminal CD.

Note: The P-score is the probability of each intervention being ranked as best in the network.

Figure 3b. Forest Plot for Failure to Achieve Clinical Response: Patients with Moderate to Severe Luminal CD Naïve to Biological Therapies.

Note: The P-score is the probability of each intervention being ranked as best in the network.

Figure 3c. Forest Plot for Failure to Achieve Clinical Response: Patients with Moderate to Severe Luminal CD Exposed to Biological Therapies Previously.

Note: The P-score is the probability of each intervention being ranked as best in the network.

Figure 4a. Forest Plot for Failure to Maintain Clinical Remission: All Re-randomised Patients with Luminal CD.

Note: The P-score is the probability of each intervention being ranked as best in the network.

Figure 4b. Forest Plot for Failure to Maintain Clinical Remission: Re-randomised Patients with Luminal CD Naïve to Biological Therapies.

Note: The P-score is the probability of each intervention being ranked as best in the network.

Figure 4c. Forest Plot for Failure to Maintain Clinical Remission: Re-randomised Patients with Luminal CD Exposed to Biological Therapies Previously.

Note: The P-score is the probability of each intervention being ranked as best in the network.