

Biologic drugs for induction and maintenance of remission in Crohn's disease: a network meta-analysis

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Abstract

Rationale

A large proportion of CD patients fail to reach and maintain remission using conventional therapies. Biologic therapies with different mechanisms have been advanced rapidly over the last decades. Comparative data for efficacy and safety are needed in order to clarify the relative position of the biologic agents and guide decision-making.

Objectives

To assess the effects of biologic and advanced treatments for induction and maintenance of remission in Crohn's Disease.

A secondary objective was to rank the included interventions.

Search methods

In June 2025 we searched CENTRAL, Embase, MEDLINE, ClinicalTrials.gov, and WHO ICTRP.

Eligibility criteria

RCTs comparing biologics with any other active comparator, placebo or no treatment for induction or maintenance of remission in adults with CD were included. Non-randomised trials or parts of trials, such as non-randomised induction or maintenance phases, long-term follow-ups, or non-randomised control groups, were excluded.

Outcomes

Clinical remission/relapse; clinical response/loss of response; endoscopic remission/relapse; withdrawals due to; serious; and total adverse events.

Risk of bias

Pairs of review authors independently assessed risk of bias in included studies using RoB1. Disagreements were resolved by a third author.

Synthesis methods

Pairs of review authors independently selected studies and conducted data extraction. Disagreements were resolved by a third author. We expressed outcomes as risk ratios with 95% confidence intervals. We conducted network meta-analyses for a network of induction studies and a network of maintenance studies. We assessed the certainty of the evidence using GRADE.

Included studies

94 RCTs of which 66 were on induction (n=20653) and 22 on maintenance (n=6823).

Synthesis of results

Induction

There is high certainty evidence that ustekinumab (RR 2.01, 95% CI 1.67 to 2.43, NNTB=6, small effect size) is more effective and moderate certainty that adalimumab combined with purine analogues (RR 2.6, 95% CI 1.71 to 3.96, NNTB=3, moderate effect size), guselkumab (RR 2.49, 95% CI 1.95 to 3.18, NNTB=4, moderate effect size), adalimumab (RR 2.36, 95% CI 1.75 to 3.18, NNTB=4, moderate effect size), upadacitinib (RR 1.76, 95% CI 1.34 to 2.3, NNTB=7, small effect size), vedolizumab (RR 1.57, 95% CI 1.15 to 2.13, NNTB= 10, trivial effect size), and natalizumab (RR 1.37, 95% CI 1.08 to 1.73, NNTB= 15, trivial effect size) are probably more effective than placebo for clinical remission. There is low certainty that risankizumab (RR 2.26, 95% CI 1.8 to 2.84, moderate effect), BI695501 (RR 2.09, 95% CI 1.31 to 3.33, small effect), a combination of infliximab with purine analogues (RR 2.04, 95% CI 1.14 to 3.64, small effect) and filgotinib (RR 1.55, 95% CI 1.18 to 2.04, trivial effect) may be more effective in inducing clinical remission.

There is moderate certainty that vedolizumab (RR 0.71 95% CI 0.41 to 1.23), ustekinumab (RR 0.72 95% CI 0.52 to 0.99), and upadacitinib (RR 0.8 95% CI 0.46 to 1.39) probably lead to a similar number of withdrawals due to adverse events. There is low certainty that risankizumab (RR 0.36 95% CI 0.22 to 0.59, small effect size) may lead to less withdrawals due to adverse events and low certainty that humicade (RR 0.81 95% CI 0.39 to 1.68), natalizumab (RR 0.79, 95% CI 0.47 to 1.33), apilimod mesylate (RR 0.84 95% CI 0.36 to 1.95), certolizumab (RR 0.98, 95% CI 0.65 to 1.49), filgotinib (RR 1.06 95% CI 0.64 to 1.78) and tesnatilimab (RR 1.51 95% CI 0.82 to 2.8) may lead to a similar number of withdrawals due to adverse events.

Humicade, combination of natalizumab, infliximab with purine analogues, CTP13 with purine analogues, infliximab, mirikizumab, etrolizumab, certolizumab, tesnatilimab, onercept, andecaliximab, and etanercept were of very low certainty and no conclusions can be drawn.

Maintenance

There is moderate certainty evidence that adalimumab (RR 0.69, 95% CI 0.58 to 0.82, NNTB=2, moderate effect size) is probably more effective than placebo in preventing clinical relapse. There is low certainty that CTP13 (RR 0.55, 95% CI 0.43 to 0.71, large effect size), infliximab (RR 0.68, 95% CI 0.57 to 0.81, moderate effect size) and upadacitinib (RR 0.72, 95% CI 0.56 to 0.94, small effect size) are maybe more effective than placebo in preventing clinical relapse.

There is moderate certainty that vedolizumab (RR 0.84, 95% CI 0.63 to 1.11) probably leads to a similar number of withdrawals due to adverse events. There is low certainty that tofacitinib (RR 0.78, 95% CI 0.47 to 1.31), ustekinumab (RR 0.74, 95% CI 0.4 to 1.38), etrolizumab (RR 1.42, 95% CI 0.73 to 2.77, and upadacitinib (RR 1.51, 95% CI 0.73 to 3.11) may be no different to placebo in withdrawals due to adverse events during maintenance.

Certolizumab, natalizumab, filgotinib, risankizumab, infliximab combined with purine analogues, vedolizumab combined with purine analogues were of very low certainty and no conclusions can be drawn about them.

Certainty of the evidence ranged between high and very low with the main limitations of the evidence being imprecision and risk of bias.

Authors' conclusions

The review has supported indirect evidence generation, but head-to-head comparative trials for key interventional subclasses or specific agents may be needed, as guided by key stakeholders. For example the use of biosimilar version of medications out of patent.

The role of concomitant purine analogues has been a key confounding factor and future studies may not only want to investigate specifically the role of combinations, but also consider stratifying populations or purposefully excluding patients based on this key class of therapy to avoid such heterogeneity.

Given the majority of evidence focusses on the outcomes of clinical remission and relapse, future studies may want to further consider other outcomes of clear interest to clinicians and patients, particularly endoscopic remission.

Finally, long-term safety data is limited throughout the networks. Whilst future studies with longer follow-ups could support increased data, it may be that study designs outside of randomised trials are employed for such outcomes.

Funding

Registration

A protocol for this review was published in 2017: doi.org/10.1002/14651858.CD012751.

Plain language summary

Do biologic and advanced treatments help manage Crohn's Disease?

Key messages

For making symptoms go away, we are most certain that ustekinumab works by leading to a small margin of cases with no symptoms, when compared to placebo (a fake treatment that looks real). Adalimumab and its combination with immune system drugs, guselkumab and upadacitinib probably work with a moderate and small margin respectively, while vedolizumab, and natalizumab probably work but only by a trivial margin.

We are uncertain whether other drugs work or not, compared to placebo.

For stopping symptoms coming back longer term, adalimumab probably works by a moderate margin.

During the short term upadacitinib, ustekinumab, and vedolizumab had the most certain evidence for being similar to placebo in terms of safety.

No conclusions can be drawn on long term safety based on the existing evidence.

What is Crohn's Disease?

Crohn's disease is a chronic (life-long) inflammatory disease that can affect any part of the gut. Common symptoms include bloody poo, diarrhoea, stomach ache, fever, weight loss, fatigue, and others. When someone is experiencing symptoms of Crohn's, they are said to have 'active' disease, and when their symptoms are under control that they are 'in remission'. We don't know what exactly causes Crohn's, but it could be related to a combination of the genes, immune system malfunction, "bad" gut bacteria, and environmental reasons. There is no known cure, but the symptoms are usually managed with drugs, such as steroids, immune system medications, and if necessary surgery. At the turn of the century, a new category of drugs called biologics or advanced treatments, became available and started being widely used for the treatment of Crohn's. These are innovative treatments that target causes of the disease more specifically than the older treatments and are thought to be better and safer.

What did we want to find out?

We wanted to find out whether all the biologics or advanced treatments that are being used or have been tested for the treatment of Crohn's can treat Crohn's, how safe they are, and how they rank compared to each other. The things we looked for were whether a drug can make symptoms go away, improve symptoms, make the gut look healed during a scope test and how safe these drugs are, in the short and long term.

What did we do?

We searched for randomised controlled trials (studies where participants are randomly assigned to one of two or more treatment groups, and can give us the highest standard of evidence) comparing biologics or advanced treatments with any other medical treatment for people with Crohn's Disease. We only included studies with adult patients. We had no restrictions in terms of sex, disease duration or previous medications used. To analyse our data we used a type of analysis called network meta-analysis which allows for head-to-head analysis of each treatment compared to placebo, but also between each other.

What did we find?

We included 94 studies with 27746 participants.

For making symptoms go away, we are most certain that ustekinumab works, leading to a small margin of cases with no symptoms, when compared to placebo. Adalimumab and its combination with immune system drugs, guselkumab and upadacitinib probably work with a moderate and small margin respectively, while vedolizumab, and natalizumab probably work but only by a trivial margin. Risankizumab, BI695501 (a drug that resembles adalimumab), a combination of infliximab with immune system drugs and filgotinib may also work but we are less certain about them.

We are uncertain whether other drugs work or not, compared to placebo.

For stopping symptoms coming back longer term, adalimumab probably works by a moderate margin.

During the short term upadacitinib, ustekinumab, and vedolizumab had the most certain evidence for being similar to placebo in terms of safety. Other drugs like risankizumab, certolizumab and filgotinib, could be similar to placebo too but we're less certain about them.

No conclusions can be drawn on long term safety based on the existing evidence.

What are the limitations of the evidence?

The studies included in this analysis had participants with very different characteristics between them, such as mixes of people who have or have not used biologics or advanced treatments before, people with more or less serious disease, and people using or not using other treatments at the same time. When these participant characteristics are not similar throughout they can lead to findings that are further away from the true results.

The data is mainly around clinical symptoms, and data from scope tests or microscope examination was limited. There were also some issues with the way the included studies were carried out and the quality of the methods they used.

How up-to-date is this review?

This review is up-to-date to June 2025.

Summary of findings

Summary of findings 1

Clinical remission - Biologics for induction in Crohn's disease

Clinical remission (59 studies, n=18765 participants)						
Patient or population: adult people with active Crohn's disease Settings: hospital setting Intervention: biologics/advanced therapies Comparison: placebo (47 studies, n=5089)						
Intervention vs placebo (in order of GRADE certainty)	Network evidence		Anticipated absolute effects for network estimate			Notes
	RR (95% CI)	Certainty	Risk with Placebo ^a	Risk with Biologic ^b (95% CI)	Absolute risk difference with Biologic ^c (95% CI)	
Ustekinumab (9 studies, n=1912)	2.01 (1.67 to 2.43)	High ⊕⊕⊕ ⊕	179 per 1,000	360 per 1,000 (299 to 435)	18.2% more (12.1% more to 25.7% more)	It's better than placebo by a small size effect (ranging from small to moderate)
Adalimumab and purine analogues (3 studies, n=353)	2.6 (1.71 to 3.96)	Moderate ^d ⊕⊕⊕ ⊖	179 per 1,000	465 per 1,000 (306 to 709)	28.9% more (12.8% more to 53.3% more)	It's probably better than placebo by a moderate size effect (ranging from small to large)
Guselkumab (4 studies, n=1045)	2.49 (1.95 to 3.18)	Moderate ^d ⊕⊕⊕ ⊖	179 per 1,000	446 per 1,000 (350 to 569)	26.9% more (17.2% more to 39.2% more)	It's probably better than placebo by a moderate size effect (ranging from small to large)
Adalimumab (5 studies, n=646)	2.36 (1.75 to 3.18)	Moderate ^d ⊕⊕⊕ ⊖	179 per 1,000	422 per 1,000 (313 to 569)	24.4% more (13.5% more to 39.2% more)	It's probably better than placebo by a moderate size effect (ranging from small to large)
Upadacitinib (3 studies, n=857)	1.76 (1.34 to 2.3)	Moderate ^e ⊕⊕⊕ ⊖	179 per 1,000	315 per 1,000 (240 to 412)	13.6% more (6.1% more to 23.5% more)	It's probably better than placebo by a small size effect (ranging from trivial to moderate)
Vedolizumab (5 studies, n=779)	1.57 (1.15 to 2.13)	Moderate ^e ⊕⊕⊕ ⊖	179 per 1,000	281 per 1,000 (206 to 381)	10.2% more (2.7% more to 20.4% more)	It's probably better than placebo by a trivial size effect (ranging from trivial to moderate)
Natalizumab (4 studies, n=1186)	1.37 (1.08 to 1.73)	Moderate ^e ⊕⊕⊕ ⊖	179 per 1,000	245 per 1,000 (193 to 310)	6.6% more (1.4% more to 13.2% more)	It's probably better than placebo by a trivial size effect (ranging from trivial to small)
Risankizumab (4 studies, n=1267)	2.26 (1.8 to 2.84)	Low ^f ⊕⊕⊖ ⊖	179 per 1,000	405 per 1,000 (322 to 508)	22.6% more (14.3% more to 33.1% more)	It's maybe better than placebo by a moderate size effect (ranging from small to large)
BI695501 (Adalimumab biosimilar) (1 study, n=72)	2.09 (1.31 to 3.33)	Low ^g	179 per 1,000	374 per 1,000 (235 to 596)	19.7% more (5.6% more to 42% more)	It's maybe better than placebo by a small size effect (ranging from trivial to large)

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Infliximab with purine analogues (6 studies, n=437)	2.04 (1.14 to 3.64)	Low ^g ⊕⊕⊕ ⊖	179 per 1,000	365 per 1,000 (204 to 651)	18.6% more (2.5% more to 47.6% more)	It's maybe better than placebo by a small size effect (ranging from trivial to large)
Filgotinib (3studies, n=1032)	1.55 (1.18 to 2.04)	Low ^g ⊕⊕⊕ ⊖	179 per 1,000	277 per 1,000 (211 to 365)	9.9% more (3.3% more to 18.7% more)	It's maybe better than placebo by a trivial size effect (ranging from trivial to small)
Tofacitinib (2 studies, n=293)	1.18 (0.81 to 1.72)	Low ^h ⊕⊕⊕ ⊖	179 per 1,000	211 per 1,000 (145 to 308)	3.3% more (3.3% less to 12.9% more)	It may be the same as placebo with a size effect that can range from trivially less than placebo to small effect more than placebo
Apilimod Mesylate (1 study, n=147)	0.67 (0.34 to 1.34)	Low ^h ⊕⊕⊕ ⊖	179 per 1,000	120 per 1,000 (61 to 240)	5.9% less (11.9% less to 6.2% more)	It may be the same as placebo with a size effect that can range from a small effect less than placebo to a trivial effect more than placebo
Humicade (1 study, n=111)	3.14 (0.71 to 13.9)	Very low ⁱ ⊕⊕⊕ ⊖	179 per 1,000	562 per 1,000 (127 to 1000)	38.4% more (5.3% less to 100% more)	The evidence is very uncertain
Natalizumab with Infliximab and purine analogues (1 study, n=52)	2.51 (0.98 to 6.42)	Very low ⁱ ⊕⊕⊕ ⊖	179 per 1,000	449 per 1,000 (175 to 1,000)	27.2% more (0.3% less to 97.6% more)	The evidence is very uncertain
CTP13 (Infliximab biosimilar) and purine analogues (1 study, n=111)	1.92 (0.94 to 3.91)	Very low ⁱ ⊕⊕⊕ ⊖	179 per 1,000	344 per 1,000 (168 to 700)	16.5% more (1.1% less to 52.3% more)	The evidence is very uncertain
Infliximab (4 studies, n=323)	1.77 (1.01 to 3.1)	Very low ^j ⊕⊕⊕ ⊖	179 per 1,000	317 per 1,000 (181 to 555)	13.9% more (0.2% more to 37.7% more)	The evidence is very uncertain
Mirikizumab (2 studies, n=758)	1.65 (1.16 to 2.34)	Very low ^k ⊕⊕⊕ ⊖	179 per 1,000	295 per 1,000 (208 to 419)	11.6% more (2.9% more to 24.1% more)	The evidence is very uncertain
Etrolizumab (2 studies, n=529)	1.3 (0.87 to 1.93)	Very low ^l ⊕⊕⊕ ⊖	179 per 1,000	232 per 1,000 (156 to 345)	5.3% more (2.3% less to 16.7% more)	The evidence is very uncertain
Certolizumab (3 studies, n=623)	1.17 (0.88 to 1.56)	Very low ⁱ ⊕⊕⊕ ⊖	179 per 1,000	209 per 1,000 (157 to 279)	3.1% more (2.2% less to 10.1% more)	The evidence is very uncertain
Tesnatilimab (2 studies, n=221)	1.17 (0.76 to 1.79)	Very low ^m ⊕⊕⊕ ⊖	179 per 1,000	210 per 1,000 (136 to 320)	3.1% more (4.2% less to 14.3% more)	The evidence is very uncertain

Onercept (1 study, n=169)	1 (0.5 to 1.99)	Very low ⊕⊖⊖ ⊖	179 per 1,000	179 per 1,000 (89 to 356)	0% (9% less to 17.9% more)	The evidence is very uncertain
Andecaliximab (1 study, n=159)	0.76 (0.33 to 1.77)	Very low ⊕⊖⊖ ⊖	179 per 1,000	136 per 1,000 (59 to 317)	4.3% less (12.1% less to 13.8% more)	The evidence is very uncertain
Etanercept (1 study, n=23)	0.43 (0.09 to 2.18)	Very low ⊕⊖⊖ ⊖	179 per 1,000	77 per 1,000 (16 to 390)	10.2% less (16.4% less to 21.2% more)	The evidence is very uncertain

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

CI: confidence interval; RR: risk ratio

^aThe risk with placebo has been calculated based on the cumulative placebo rates of all studies with a placebo arm

^bThe risk with treatment has been calculated by multiplying the risk with control with the RR(95% CI). If the calculation results in more than 1000 per 1000 people the number has been capped to 1000. Numbers have been rounded up to the closest whole number.

^cThe % risk difference has been calculated by subtracting the risk with control from the risk with treatment(95% CI) and dividing by 10. If the calculation results in more than 100% the number has been capped to 100%. Numbers have been rounded up to the closest whole number.

^dDowngraded once due to risk of bias

^eDowngraded once due to imprecision

^fDowngraded once due to risk of bias and once due to incoherence

^gDowngraded once due to risk of bias and once due to imprecision

^hDowngraded twice due to serious imprecision

ⁱDowngraded once due to risk of bias and twice due to serious imprecision

^jDowngraded once due to risk of bias, once due to imprecision and once due to incoherence

^kDowngraded once due to risk of bias, once due to imprecision and once due to inconsistency

^lDowngraded once due to inconsistency and twice due to serious imprecision

^mDowngraded once due to inconsistency and twice due to serious imprecision

Summary of findings 2

Withdrawals due to adverse events - Biologics for induction in Crohn's disease

Withdrawals due to adverse events, (59 studies, n=19594 participants)			
Patient or population: adult people with active Crohn's disease			
Settings: hospital setting			
Intervention: biologics/advanced therapies			
Comparison: placebo (46 studies, n=5097)			
	Network evidence	Anticipated absolute effects for network estimate	Notes

Comparisons (in order of GRADE certainty)	RR (95% CI)	Certainty	Risk with Placebo ^a	Risk with Biologic ^b (95% CI)	Absolute risk difference with Biologic ^c (95% CI)	
Vedolizumab (5 studies, n=779)	0.71 (0.41 to 1.23)	Moderate ^e ⊕⊕⊕ ⊖	142 per 1,000	101 per 1,000 (58 to 175)	4.2% less (8.5% less to 3.3% more)	It probably leads to similar withdrawal events compared to placebo (ranging from small effect size less to trivial more)
Ustekinumab (11 studies, n=2490)	0.72 (0.52 to 0.99)	Moderate ^d ⊕⊕⊕ ⊖	142 per 1,000	102 per 1,000 (74 to 141)	4% less (6.8% less to 0.2% less)	It probably leads to less withdrawal events by a trivial effect size compared to placebo
Upadacitinib (3 studies, n=857)	0.8 (0.46 to 1.39)	Moderate ^e ⊕⊕⊕ ⊖	142 per 1,000	114 per 1,000 (65 to 197)	2.9% less (7.1% less to 5.5% more)	It probably leads to similar withdrawal events compared to placebo (ranging from small effect size less to trivial more)
Risankizumab (4 studies, n=1267)	0.36 (0.22 to 0.59)	Low ^f ⊕⊕⊕ ⊖	142 per 1,000	51 per 1,000 (31 to 84)	9.2% less (11.2% less to 5.9% less)	It maybe leads to less withdrawal events by a small effect size compared to placebo (ranging from a small effect less to trivial less)
Humicade (1 study, n=111)	0.81 (0.39 to 1.68)	Low ^f ⊕⊕⊕ ⊖	142 per 1,000	115 per 1,000 (55 to 239)	2.7% less (8.7% less to 9.7% more)	It maybe leads to similar withdrawal events compared to placebo (ranging from small effect size less to small more)
Natalizumab (4 studies, n=1186)	0.79 (0.47 to 1.33)	Low ^f ⊕⊕⊕ ⊖	142 per 1,000	112 per 1,000 (66 to 189)	3% less (7.6% less to 4.7% more)	It maybe leads to similar withdrawal events compared to placebo (ranging from small effect size less to trivial more)
Apilimod Mesylate (1 study, n=147)	0.84 (0.36 to 1.95)	Low ^g ⊕⊕⊕ ⊖	142 per 1,000	119 per 1,000 (51 to 277)	2.3% less (9.2% less to 13.6% more)	It maybe leads to similar withdrawal events compared to placebo (ranging from small effect size less to small more)
Certolizumab (4 studies, n=842)	0.98 (0.65 to 1.49)	Low ^h ⊕⊕⊕ ⊖	142 per 1,000	139 per 1,000 (92 to 212)	0.3% less (5% less to 7% more)	It maybe leads to similar withdrawal events compared to placebo
Filgotinib (n=3 studies, n=1049)	1.06 (0.64 to 1.78)	Low ^f ⊕⊕⊕ ⊖	142 per 1,000	277 per 1,000 (211 to 365)	0.9% more (5.2% less to 11.1% more)	It maybe leads to similar withdrawal events compared to placebo (ranging from trivial effect size less to small more)
Tesnatilimab (2 studies, n=221)	1.51 (0.82 to 2.8)	Low ⁱ ⊕⊕⊕ ⊖	142 per 1,000	214 per 1,000 (116 to 398)	7.3% more (2.6% less to 25.7% more)	It maybe leads to similar withdrawal events compared to placebo (ranging from trivial effect size less to large more)
Mirikizumab (2 studies, n=706)	0.39 (0.15 to 1.03)	Very low ^j ⊕⊖⊖ ⊖	142 per 1,000	55 per 1,000 (21 to 146)	8.7% less (12.2% less to 0.4% more)	The evidence is very uncertain
Tofacitinib (2 studies, n=293)	0.53 (0.26 to 1.08)	Very low ^k ⊕⊖⊖ ⊖	142 per 1,000	75 per 1,000 (37 to 153)	6.7% less (10.6% less to 1.1% more)	The evidence is very uncertain
Onercept (1 study, n=169)	0.52 (0.12 to 2.3)	Very low ^k ⊕⊖⊖ ⊖	142 per 1,000	74 per 1,000 (17 to 327)	6.8% less (12.6% less to 18.5% more)	The evidence is very uncertain

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Adalimumab (5 studies, n=646)	0.88 (0.42 to 1.88)	Very low ⊕ ^l ⊕⊕⊕ ⊖	142 per 1,000	125 per 1,000 (60 to 267)	1.7% less (8.4% less to 12.6% more)	The evidence is very uncertain
Etrolizumab (2 studies, n=529)	0.87 (0.41 to 1.85)	Very low ⊕ ^l ⊕⊕⊕ ⊖	142 per 1,000	124 per 1,000 (58 to 262)	1.9% less (8.4% less to 12.2% more)	The evidence is very uncertain
BI695501 (Adalimumab biosimilar) (1 study, n=72)	0.86 (0.26 to 2.86)	Very low ⊕ ^k ⊕⊕⊕ ⊖	142 per 1,000	122 per 1,000 (37 to 406)	2% less (10.6% less to 26.6% more)	The evidence is very uncertain
Guselkumab (3 studies, n=1031)	0.85 (0.52 to 1.4)	Very low ⊕ ^m ⊕⊕⊕ ⊖	142 per 1,000	121 per 1,000 (74 to 199)	2.1% less (6.8% less to 5.7% more)	The evidence is very uncertain
Adalimumab and purine analogues (3 studies, n=353)	1 (0.33 to 3.01)	Very low ⊕ ^k ⊕⊕⊕ ⊖	142 per 1,000	142 per 1,000 (47 to 427)	0% (9.6% less to 28.7% more)	The evidence is very uncertain
CTP13 (Infliximab biosimilar) and purine analogues (1 study, n=111)	1.06 (0.17 to 6.48)	Very low ⊕ ^k ⊕⊕⊕ ⊖	142 per 1,000	151 per 1,000 (24 to 920)	0.9% more (11.8% less to 78.4% more)	The evidence is very uncertain
Natalizumab with Infliximab and purine analogues (1 study, n=52)	1.22 (0.16 to 9.49)	Very low ⊕ ^k ⊕⊕⊕ ⊖	142 per 1,000	173 per 1,000 (23 to 1,000)	3.1% more (12.1% more to 100% more)	The evidence is very uncertain
Duvakitug (1 study, n=92)	1.16 (0.54 to 2.51)	Very low ⊕ ^k ⊕⊕⊕ ⊖	142 per 1,000	164 per 1,000 (77 to 356)	2.3% more (6.6% less to 21.6% more)	The evidence is very uncertain
Infliximab (3 studies, n=240)	1.25 (0.27 to 5.8)	Very low ⊕ ^k ⊕⊕⊕ ⊖	142 per 1,000	177 per 1,000 (38 to 824)	3.5% more (10.5% less to 68.6% more)	The evidence is very uncertain
Infliximab with purine analogues (6 studies, n=437)	1.34 (0.28 to 6.41)	Very low ⊕ ^k ⊕⊕⊕ ⊖	142 per 1,000	190 per 1,000 (38 to 910)	4.9% more (10.3% less to 77.4% more)	The evidence is very uncertain
Etanercept (1 study, n=23)	1.35 (0.55 to 3.34)	Very low ⊕ ^k ⊕⊕⊕ ⊖	142 per 1,000	192 per 1,000 (78 to 474)	5% more (6.5% less to 33.4% more)	The evidence is very uncertain
Andecaliximab (1 study, n=159)						The evidence is very uncertain

	2.11 (0.25 to 17.52)	Very low ^k ⊕⊖⊖ ⊖	142 per 1,000	300 per 1,000 (35 to 1000)	15.9% more (10.7% less to 100% more)
GRADE Working Group grades of evidence High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect. CI: confidence interval; RR: risk ratio					
^a The risk with placebo has been calculated based on the cumulative placebo rates of all studies with a placebo arm ^b The risk with treatment has been calculated by multiplying the risk with control with the RR(95% CI). If the calculation results in more than 1000 per 1000 people the number has been capped to 1000. Numbers have been rounded up to the closest whole number. ^c The % risk difference has been calculated by subtracting the risk with control from the risk with treatment(95% CI) and dividing by 10. If the calculation results in more than 100% the number has been capped to 100%. Numbers have been rounded up to the closest whole number. ^d Downgraded once due to incoherence ^e Downgraded once due to imprecision ^f Downgraded once due to risk of bias and once due to imprecision ^g Downgraded twice due to serious imprecision ^h Downgraded once due to risk of bias and once due to inconsistency ⁱ Downgraded twice due to serious imprecision ^j Downgraded once due to risk of bias, once due to imprecision and once due to incoherence ^k Downgraded once due to risk of bias and twice due to serious imprecision ^l Downgraded once due to inconsistency and twice due to serious imprecision ^m Downgraded twice due to serious inconsistency and once due to risk of bias					

Summary of findings 3

Clinical relapse - Biologics for maintenance in Crohn's disease

Clinical relapse (23 studies, n=6543 participants)						
Patient or population: adult people with inactive Crohn's disease or with response to biologic treatment						
Settings: hospital setting						
Intervention: biologics and advanced therapies						
Comparison: placebo (19 studies, n=2151)						
Comparisons (in order of GRADE certainty)	Network evidence		Anticipated absolute effects for network estimate			Notes
	RR (95% CI)	Certainty	Risk with Placebo ^a	Risk with Biologic ^b	Absolute risk difference with Biologic ^c (95% CI)	
Adalimumab (4 studies, n=455)	0.69 (0.58 to 0.82)	Moderate ^d ⊕⊕⊕ ⊖	714 per 1,000	492 per 1,000 (414 to 585)	22.3% less (30.1% less to 13.1% less)	It's probably better than placebo by a moderate size effect (ranging from small to moderate)
CTP13 (3 studies, n=359)	0.55 (0.43 to 0.71)	Low ^e	714 per 1,000	392 per 1,000 (307 to 507)	32.2% less (40.9% less to 21% less)	It's maybe better than placebo by a large size effect (ranging from moderate to large)

Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

CI: confidence interval; RR: risk ratio

^aThe risk with placebo has been calculated based on the cumulative placebo rates of all studies with a placebo arm

^bThe risk with treatment has been calculated by multiplying the risk with control with the RR(95% CI). If the calculation results in more than 1000 per 1000 people the number has been capped to 1000. Numbers have been rounded up to the closest whole number.

^cThe % risk difference has been calculated by subtracting the risk with control from the risk with treatment(95% CI) and dividing by 10. If the calculation results in more than 100% the number has been capped to 100%. Numbers have been rounded up to the closest whole number.

^dDowngraded once due to risk of bias

^eDowngraded once due to risk of bias and once due to incoherence

^fDowngraded twice due to very serious imprecision

^gDowngraded once due to risk of bias and twice due to very serious imprecision

^hDowngraded once due to inconsistency and twice due to very serious imprecision

Summary of findings 4

Withdrawals due to adverse events - Biologics for maintenance in Crohn's disease

Withdrawals due to adverse events (21 studies, n=6149 participants)						
Patient or population: adult people with inactive Crohn's disease or with response to biologic treatment Settings: hospital setting Intervention: biologics and advanced therapies Comparison: placebo (17 studies, n=1912)						
Comparisons (in order of GRADE certainty)	Network evidence		Anticipated absolute effects for network estimate			Notes
	RR (95% CI)	Certainty	Risk with Placebo ^a	Risk with Biologic ^b	Absolute risk difference with Biologic ^c (95% CI)	
Vedolizumab (3 studies, n=595)	0.84 (0.63 to 1.11)	Moderate ^d ⊕⊕⊕⊖	221 per 1,000	186 per 1,000 (139 to 245)	4% less (9.1% less to 2.8% more)	It is probably the same as placebo with a size effect that can range from a small effect size less than placebo to a trivial effect more than placebo
Tofacitinib (1 study, n=121)	0.78 (0.47 to 1.31)	Low ^e ⊕⊕⊖⊖	221 per 1,000	393 per 1,000 (104 to 289)	5.3% less (13% less to 7.5% more)	It may be the same as placebo with a size effect that can range from a small effect size less than placebo to a small effect more than placebo
Ustekinumab (2 studies, n=336)	0.74 (0.40 to 1.38)	Low ^e ⊕⊕⊖⊖	221 per 1,000	163 per 1,000 (88 to 305)	6.3% less (14.6% less to 9.2% more)	It may be the same as placebo with a size effect that can range from a moderate effect size less than placebo to a small effect more than placebo
Etrolizumab (1 study, n=217)	1.42 (0.73 to 2.77)	Low ^e ⊕⊕⊖⊖	221 per 1,000	314 per 1,000 (161 to 612)	10.3% more (6.6% less to 43.3% more)	It may be the same as placebo with a size effect that can range from a trivial effect size less than placebo to a large effect more than placebo
Upadacitinib (1 study, n=337)	1.51 (0.73 to 3.11)	Low ^e ⊕⊕⊖⊖	221 per 1,000	334 per 1,000 (161 to 687)	12.5% more (6.6% less to 51.8% more)	It may be the same as placebo with a size effect that can range from a trivial effect size less than placebo to a large effect more than placebo
Natalizumab (1 study, n=214)	0.48 (0.28 to 0.82)	Very low ^f ⊕⊖⊖⊖	221 per 1,000	106 per 1,000 (62 to 181)	12.9% less (17.7% less to 4.5% less)	The evidence is very uncertain
Infliximab (6 studies, n=369)	0.54 (0.29 to 0.99)	Very low ^f ⊕⊖⊖⊖	221 per 1,000	119 per 1,000 (64 to 219)	11.3% less (17.3% less to 0.2% less)	The evidence is very uncertain

Certolizumab (1 study, n=216)	0.58 (0.38 to 0.90)	Very low ^a	221 per 1,000	128 per 1,000 (84 to 199)	10.2% less (15.3% less to 2.3% less)	The evidence is very uncertain
Adalimumab (4 studies, n=162)	0.84 (0.54 to 1.30)	Very low ^a	221 per 1,000	186 per 1,000 (119 to 287)	3.9% less (11.2% less to 7.4% more)	The evidence is very uncertain
Risankizumab (1 study, n=358)	0.87 (0.38 to 2.03)	Very low ^a	221 per 1,000	192 per 1,000 (84 to 449)	3.1% less (15.3% less to 25.3% more)	The evidence is very uncertain
CTP13 (2 studies, n=146)	0.72 (0.21 to 2.45)	Very low ^a	221 per 1,000	159 per 1,000 (46 to 541)	6.8% less (19.3% less to 35.6% more)	The evidence is very uncertain
Infliximab with purine analogues (1 study, n=71)	0.92 (0.31 to 2.68)	Very low ^a	221 per 1,000	203 per 1,000 (69 to 592)	2.1% less (16.8% less to 41.1% more)	The evidence is very uncertain
Filgotinib (1 study, n=217)	2.58 (1.09 to 6.10)	Very low ^a	221 per 1,000	570 per 1,000 (241 to 1000)	38.7% more (2.2% more to 100% more)	The evidence is very uncertain

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

CI: confidence interval; RR: risk ratio

^aThe risk with placebo has been calculated based on the cumulative placebo rates of all studies with a placebo arm

^bThe risk with treatment has been calculated by multiplying the risk with control with the RR(95% CI). If the calculation results in more than 1000 per 1000 people the number has been capped to 1000. Numbers have been rounded up to the closest whole number.

^cThe % risk difference has been calculated by subtracting the risk with control from the risk with treatment(95% CI) and dividing by 10. If the calculation results in more than 100% the number has been capped to 100%. Numbers have been rounded up to the closest whole number.

^dDowngraded once due to imprecision

^eDowngraded twice due to serious imprecision

^fDowngraded once due to risk of bias and twice due to serious imprecision

Background

Description of the condition

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD), characterised by transmural inflammation of the gastrointestinal tract. Its pathophysiology is thought to involve a complex interplay between genetic susceptibility, immune and environmental factors [1]. Worldwide, the incidence of CD is increasing, with the highest incidence in westernised nations and even within these nations the incidence continues to increase [2; 3]

Symptoms depend on the area of bowel involved but often include diarrhoea, abdominal pain, gastrointestinal bleeding and weight loss. Complications may further arise with the development of stricturing or fistulising disease and surgery is a relatively common occurrence for patients.

The most common therapeutic approach until recently was corticosteroids followed by an immunomodulator such as thiopurines (azathioprine, 6-mercaptopurine) which are a subset of purine analogues which act as anti-metabolites, methotrexate, or a TNF inhibitor (infliximab, adalimumab, certolizumab). However, this approach results in up to 55-60% of patients failing to achieve remission at one year following diagnosis [4; 5].

Despite the advent of TNF inhibitors, many patients have either primary non-response or secondary loss of response and as such, new therapies with different mechanisms have been advanced rapidly over the last decade.

Description of the intervention and how it might work

Biologic medications (monoclonal antibodies such as infliximab) and small molecules, such as JAK inhibitors and S1P modulators have revolutionised the treatment of IBD, by targeting specific parts of the immune system. There are currently three tumour necrosis factor-alpha (TNF- α) antagonists approved for the treatment of CD: infliximab, adalimumab and certolizumab pegol. In the last few years, numerous new biologic drug classes have become actively available for treatment of Crohn's disease, with many more in various stages of approval.

Natalizumab and vedolizumab are humanised monoclonal antibodies against the human α 4 (α 4) integrin subunit and the α 4 β 7 (α 4 β 7) integrin on leukocytes, respectively.

Ustekinumab, a fully human monoclonal antibody against the p40 subunit that is shared by interleukin-12 and interleukin-23, is currently available for the treatment of CD. Guselkumab and risankizumab are IL23 binding antibodies that block the activation pro-inflammatory cytokines. Janus Kinase inhibitors such as tofacitinib and filgotinib are small molecules that are orally administered.

Several other integrin and specific IL23 antagonists are under investigation for CD, with some in late-stage clinical development [6].

TNF- α antagonists are monoclonal antibodies directed towards TNF- α . Although TNF- α antagonists have been the benchmark biologic therapies for more than a decade, the exact mechanism of action is still incompletely understood [7]. These drugs specifically and avidly bind to TNF- α , a cytokine with pleiotropic functions that is relevant to the pathogenesis of IBD. However, a decrease in the concentration of inflammatory markers such as serum C-reactive protein (CRP) concentration following treatment with a TNF- α antagonist is not consistently associated with improvement in endoscopic disease activity. Although direct comparisons are lacking, available data suggest that not all TNF- α antagonists are equally effective in IBD. Specifically, soluble (decoy) TNF- α receptors such as etanercept and oncept seem to be ineffective ([8]; Rutgeerts 2006 [9]).

In addition, TNF- α antagonists that lack the Fc region (such as certolizumab pegol) or have an Fc region with strongly reduced affinity towards the Fc receptor, (such as CDP571) demonstrate disappointing results in terms of mucosal healing in CD patients [10]. Collectively, these observations suggest that additional factors beyond the simple neutralisation of soluble TNF- α are relevant to the mechanism of action of this class of drug. In particular, TNF- α antagonists appear to induce lamina propria T-cell apoptosis and potentiation of M2-type wound-healing macrophages, both of which are dependent on the presence of a functional Fc region and binding of membrane-bound TNF- α [7].

Integrin antagonists block the recruitment of lymphocytes from the circulation to the gut by preventing the interaction between the integrins on these cells with endothelial adhesion molecules on intestinal microvascular endothelial cells [11]. Natalizumab blocks the interaction between α 4-expressing lymphocytes and the endothelial adhesion molecules VCAM-1 and MAdCAM-1, whereas vedolizumab only blocks the interaction between α 4 β 7-expressing lymphocytes and MAdCAM-1. Unlike VCAM-1, MAdCAM-1 is exclusively expressed by intestinal microvascular endothelial cells, resulting in the gut-selective action of vedolizumab but not of natalizumab [11]. A drug exposure-response relationship is seen for vedolizumab despite maximal saturation of the target α 4 β 7 at the lowest concentrations, suggesting that other, yet unidentified, mechanisms of actions are involved [12, 13].

Ustekinumab is a fully human monoclonal antibody directed towards p40, a shared subunit of interleukin-12 and interleukin-23 that are involved in T helper 1 and T helper 17 cell responses, respectively [14].

Large phase III trials have demonstrated the efficacy of all three drug classes as induction and maintenance agents in CD, which has led to the market authorisation of these drugs [14, 15].

A major innovation has been the development of small molecules that can be delivered orally as biological therapy. Janus Kinase inhibitors act by competitively blocking the adenosine triphosphate-binding site in the JH1 domain through non-covalent interactions [16]. Sphingosine-1-phosphate works mainly through S1PR1 receptor binding [17].

Conventional therapy can be combined with biologics, known as combination therapy, with increasing numbers of patients using it.

Why it is important to do this review

Recent Cochrane meta-analyses have investigated the role of individual biologics in induction and maintenance of CD [18, 19, 20, 21, 22, 23, 24]. However, comparative efficacy data are needed in order to clarify the relative position of the increasingly complex portfolio of biologic agents and to guide decision-making regarding CD therapeutic algorithms. Specifically, clarity is needed as to whether agents should be positioned as first line therapies to patients who are anti-TNF- α naive [14, 25, 26], or be used as second-line if patients are refractory to the more established biological classes.

These data are best achieved by head-to-head trials. However, such trials take time and will likely compare only two biologic drugs within a specific population, if these trials are conducted at all.

Thus far, there are limited active head-to-head trials comparing biologic treatments for CD. An alternative strategy for obtaining comparative data is to conduct a network meta-analysis in which multiple treatments are compared using both direct comparisons of interventions within randomised controlled trials (RCTs) and indirect comparisons across trials based on a common comparator (i.e. placebo). In other words, if compound A is compared with compound B in one trial, and the same compound B is compared with compound C in another trial, indirect information can be obtained from compound A versus compound C under the assumption of transitivity.

Objectives

To assess the effects of biologic and advanced treatments for induction and maintenance of remission in Crohn's Disease.

A secondary objective was to rank the included interventions.

Methods

The protocol for this review [27] was published by a different author team. We have updated the methods section to match current Cochrane methodology.

Compared to the original protocol, in this review we have included any dosages of any biologic and advanced treatment, irrespective of whether they have received approval by regulatory authorities.

We have considered studies with more than 50% of participants with concomitant purine analogue use as combination studies ([Types of interventions](#)). Purine analogues are an active treatment commonly used for the treatment of Crohn's and their combination with biologics and advanced agents is likely to have different efficacy and safety profiles to monotherapy.

We have removed histologic outcomes and endoscopic response as outcomes, as we did not consider them to be critical. We have amended the pre-planned subgroup analyses, specifically those around dosages and administration route, exposure to immunosuppressives and biological naivety, and deemed those around disease location and clinical and objective measures to determine patient eligibility to not be achievable with the currently available data. The subgroup analysis on disease activity has now been listed as a sensitivity analysis, the sensitivity analysis on 'relevant loss to follow-up' has been removed because attrition is taken into account in the risk of bias assessment, and the one on 'sample size of less than 50% participants' has been replaced with comparison-adjusted funnel plots assessments. We have also updated the network meta-analysis and GRADE assessment methodology according to the latest standards.

We followed the Methodological Expectations of Cochrane Intervention Reviews (MECIR) when conducting the review and PRISMA 2020 for the reporting.

Criteria for considering studies for this review

Types of studies

RCTs (phase 2b or above) comparing biologics or advanced therapies with any other active comparator, placebo or no treatment for induction or maintenance of remission in CD. Studies comparing different regimens of the same biologic were excluded.

Cluster RCTs and the pre-crossover phases of cross-over RCTs were considered for inclusion.

All relevant RCTs published as full-text, abstracts, press releases, or as results posted in a trial register, were considered for inclusion. It would be more informative to include all relevant trials regardless of the availability of

data. Authors could then discuss potential selective outcome reporting of these trials within the results of the review.

Non-randomised or quasi-randomised (such as sequential allocation, allocation by birthdate or medical record number) trials or parts of trials, such as non-randomised induction or maintenance phases, long-term follow-ups, or non-randomised control groups, were excluded.

Types of participants

Trials on adult participants (> 18 years of age) with CD as diagnosed by conventional clinical, radiological or endoscopic criteria were considered for inclusion.

There were no limits on follow-up time, language, setting, gender, disease activity, disease duration, disease location, or any other factors.

Participants with active CD, as defined by the included studies, were included in the network for induction of remission. Participants with inactive CD, or with response to biologics at the beginning of the RCT, as defined by the included studies, were included in the network for maintenance of remission.

Studies with only a subset of eligible participants were included and sensitivity analyses were planned around them.

Types of interventions

All biologic and advanced therapies were considered for inclusion, including, TNF- α inhibitors, anti-integrins, IL23/IL12 antagonists, JAK inhibitors, S1P receptor modulators, and biosimilars. All types of administration routes were considered for inclusion.

All tested dose regimens were considered.

After discussion with the editorial group and the Cochrane methods unit, it was decided that a threshold would be set for populations with mixed exposure to purine analogues. Thus, for studies where more than 50% of participants were receiving concomitant purine analogues, we considered the purine analogues as part of the intervention. I.e. if a comparison was defined by the authors as 'biologic against placebo', however, more than 50% of the participants were on purine analogues during the trial, for our analysis the comparison would be 'biologic and purine analogues against purine analogues'.

Purine analogues and corticosteroids as standalone treatments were ineligible for this review, as they are not biologic treatments. Our search strategy was not designed to comprehensively include all RCTs for these treatments on this review's topic. However, trials comparing them to biologics were eligible and included in the analyses. As the evidence for these treatments in this review is incomplete because trials of purine analogues or corticosteroids versus placebo or other non-biologic interventions were ineligible, we have not assessed or discussed the results we generated for them.

The above criteria for studies, participants, and interventions mean that potential effect modifiers will be evenly distributed among the included studies, ensuring the transitivity assumption will not be violated.

Outcome measures

Only dichotomous outcome data were considered for inclusion, as continuous outcomes were expected to be scarcely reported and less clinically relevant for the context of this review.

Critical outcomes

The primary outcome for induction of remission studies (I.a) was the proportion of patients who entered clinical remission, as defined by the original study (e.g. a Crohn's Disease Activity Index score < 150).

The primary outcome for maintenance of remission studies (M.a) was the proportion of patients who relapsed (failed to maintain clinical remission), as defined in the original study.

If the outcomes were reported at more than one timepoints, we used the one defined as primary by the original studies.

Important outcomes

For the induction studies, the secondary outcome measures were the proportion of patients with:

1. Clinical response, as defined by the original study (using the strictest definition for analysis if more than one available) (I.b)
2. Endoscopic remission, as defined by the original study (I.c)
3. Withdrawals due to adverse events (I.d)
4. Serious adverse events (I.e), and
5. Total adverse events (I.f)

For the maintenance studies, the secondary outcome measures were the proportion of patients with:

1. Clinical loss of response, as defined by the original study (using the strictest definition if more than one available) (M.b)
2. Endoscopic relapse, as defined by the original study (M.c)
3. Withdrawals due to adverse events (M.d)
4. Serious adverse events (M.e), and
5. Total adverse events (M.f)

Search methods for identification of studies

Electronic searches

In June 2025 an Information Specialist searched the following sources:

- Cochrane Central Register of Controlled Trials (CENTRAL) via Cochrane Library (June 2025)
- Embase via Ovid SP (1974 - 2025)
- MEDLINE via Ovid SP (1946 - 2025)
- ClinicalTrials.gov
- World Health Organisation International Clinical Trials Registry Platform (WHO ICTRP)

We followed the latest guidelines from the Cochrane Handbook for Systematic Reviews of Interventions in designing and running the searches [28]. We also used the Cochrane highly sensitive search strategy for identifying randomised trials in MEDLINE (sensitivity-maximising version, 2008 revision, Ovid format) and Cochrane's RCT search filter for Embase [29] for identifying the randomised controlled trials. The MEDLINE search strategy was adapted and translated into the syntax of other sources. We did not apply any date, language, document type, or publication status limitations to this search [30]. The search strategies for all sources are listed in [Supplementary material 1](#).

Searching other resources

Manual searches of reference lists from included studies and potentially relevant publications were performed to ensure that studies that may have been missed by the computer-assisted search were identified.

We also performed hand searches of the conference proceedings of major gastroenterology meetings (e.g. Digestive Disease Week; the annual meeting of the European Crohn's and Colitis Organisation; and United European Gastroenterology Week) from the last five years.

To identify potentially problematic studies we considered any post-publication amendments including expressions of concern, errata, corrigenda and retractions on included or eligible studies. Retracted studies would be excluded, while errata and corrigenda would be considered when extracting data and for our risk of bias assessments. Expressions of concern would be discussed on a case by case basis between authors and our decisions on whether to include them or not would be captured in the review.

Data collection and analysis

Selection of studies

Based on the inclusion criteria above, eligibility of titles and abstracts identified by the search were screened by at least two authors independently. Disagreements were resolved by discussion and consensus. A third author (MG) resolved cases in which consensus was not reached. Full-text screening followed the same method.

Data extraction and management

Pairs of reviewers independently extracted data on outcome data and effect modifiers. Any disagreements were resolved by discussion with a third author. A piloted data extraction form was used. The following data were extracted from the included studies:

- 1) General information (study design, study arms, single or multi-centre, countries, study dates, setting);
- 2) Participant characteristics (disease activity at inclusion; number and percentage of TNF- α naive vs TNF- α experienced patients; disease duration and location; luminal or fistulating disease, age, sex, smoking status)
- 3) Primary and secondary outcomes data
- 4) Sources of funding and conflicts of interest of study authors

We entered data into [31] and we attempted to contact the authors or sponsors of the studies for unclear or missing data.

Risk of bias assessment in included studies

The methodological quality of each included study was independently assessed by pairs of authors using the Cochrane risk of bias tool 1 [32]. Factors assessed were:

- 1) Random sequence generation;
- 2) Allocation concealment;
- 3) Blinding of participants, outcome assessors and investigators;
- 4) Incomplete outcome data;
- 5) Selective outcome reporting; and
- 6) Other potential sources of bias.

The studies were judged to be of low, high or unclear risk bias based on these factors. We assessed the likely magnitude and direction of the bias and whether we considered it likely to impact on the results of our analysis. Any disagreements regarding risk of bias assessment between the pairs of authors were resolved through discussion until consensus was reached. If consensus could not be reached, a third author (MG) was consulted to resolve the disagreement. We attempted to contact the authors or sponsors of the studies for unclear or missing information regarding any unclear risk of bias judgements.

Measures of treatment effect

The treatment effects were summarised as risk ratio (RR) estimates and associated two-sided 95% confidence intervals (CI). We also calculated absolute risk difference percentages (RD%) and number needed to treat (NNT), which is the number of patients you need to treat to prevent one additional bad outcome. NNT was only calculated for treatments with high and moderate certainty of results for our primary outcomes.

Unit of analysis issues

The participant was the unit of the analysis. Correlated effect estimates arising from multiple-arm studies were accounted for by using network meta-analysis methodology, and there was no need for splitting the placebo group evenly in order to avoid a unit of analysis error [33]. In multi-arm studies where different dosages of the same drug were compared, the different dosage arms were combined for the purposes of our analysis.

Where outcomes were reported at several time points, analyses were undertaken for the time-point defined as primary by the original trial. If that was not defined, then the single time point that was consistently reported by the trials was used.

To avoid carry-over effects we only included the first part of the study (i.e. before cross-over) for any included cross-over studies.

No cluster RCTs were eligible for inclusion. If cluster-randomised trials are identified in future updates, these will be included and, if unit of analysis issues are identified (e.g. randomisation and analysis at different units), the sample sizes or standard errors will be adjusted appropriately [34]

Dealing with missing data

We based our analysis on the data made available by the authors. We contacted authors or sponsors for missing data, data that was not reported in sufficient detail, or was unclear.

For all outcomes, we performed analyses, on a modified intention-to-treat basis, that is, we attempted to include all participants randomised to each group in the analyses, and we analysed all participants in the group to which they were allocated, regardless of whether they received the allocated intervention or not.

For safety outcomes, patients with missing or unclear withdrawal data were considered as withdrawals due to adverse events. The denominators used for this outcome were as reported by the authors. For serious and total adverse events we used the numbers of participants with events, as reported by the authors. Outcome data reported for mixes of randomised and non-randomised participants was discarded and not used for analysis.

In maintenance trials, relapse and loss of response rates were rarely reported directly, while remission and response were reported more often. We accounted for that by inverting the reported remission and response rates to infer relapse and loss of response, for the studies where this was the case. Withdrawals have been added to the inverted rates, as all withdrawals have been counted as treatment failures.

Reporting bias assessment

To assess the presence of small-study effects in the network meta-analysis, we used comparison adjusted funnel plots for active treatments versus placebo and used Egger's test for asymmetry[35]. We assumed that small studies may show that the active treatments are more effective than placebo. This accounts for the fact that each set of studies estimates a different summary effect [36]. Publication bias was investigated via visual inspection of funnel plots for each pairwise analysis if there were at least ten studies [37].

Synthesis methods

Pairwise meta-analysis

Direct comparisons of treatment effects

We combined data for meta-analysis from individual studies when the interventions, patient groups, and outcomes were similar, as deemed by review author consensus. We used a random-effects model to pool data [38]. We used RevMan Web for the analyses [31].

Network meta-analysis

Direct, indirect and network comparisons

The direct pairwise comparisons were used to perform the network meta-analysis. Through the NMA direct effect estimates (direct evidence) can be also obtained (adjusted for multi-arm studies). In such cases, effect estimates derived from pairwise meta-analysis may slightly differ from the corresponding direct estimates derived from NMA- this is due to multi-arm studies included as the NMA model used makes adjustments for multi-arm studies.

We initially generated and assessed the network diagrams to determine if a network meta-analysis was feasible. A network diagram represents graphically the connections of the interventions included in the network. Nodes are represented by a point. The lines connecting the points are the connections between the interventions and referred to as edges. Two points connected via a single edge represent a direct comparison, while points connected via more than one edge represent indirect comparisons. A minimum of 10 connected studies was required to perform the network meta-analysis. In case of disconnected networks the largest network would be analysed. If the network did not consist of at least 10 studies the analysis was not performed.

Then we performed the network meta-analysis on all outcomes within a frequentist framework using multivariate meta-analysis. We used the R statistical package [39] and the netmeta library [40].

Relative treatment ranking

We estimated the cumulative probabilities for each biologic being at each possible rank and obtained a treatment hierarchy using the surface under the cumulative ranking curve (SUCRA) based on 100 simulations; the larger the SUCRA the higher its rank among all available agents [41]. The probabilities to rank the treatments are estimated under a Bayesian model with flat priors, assuming that the posterior distribution of the parameter estimates is approximated by a normal distribution with mean and variance equal to the frequentist estimates and variance-covariance matrix. Rankings are constructed drawing 100 samples from their approximate posterior density. For each draw, the linear predictor is evaluated for each trial, and the largest linear predictor is noted [40].

Investigation of heterogeneity and subgroup analysis

Clinical and methodological heterogeneity

To evaluate the presence of clinical heterogeneity, we examined trial and trial population characteristics across all eligible trials that compared each pair of interventions. We assessed the presence of clinical heterogeneity within each direct comparison by comparing these characteristics.

Assessment of statistical heterogeneity

We assessed statistically the presence of heterogeneity within each direct comparison using the I^2 statistic and its 95% CI [34]. We based the assessment of statistical heterogeneity on the magnitude of the heterogeneity variance parameter (τ^2). The heterogeneity estimator was DerSimonian-Laird (DL) both for network and pairwise meta-analyses.

I^2 quantifies heterogeneity and reflects the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). We interpreted I^2 values as follows, as described in the *Cochrane Handbook for Systematic Reviews of Interventions*:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Assessment of transitivity across treatment comparisons

The assumption of transitivity refers to the notion that all studies included in a network are similar in all important aspects other than the interventions compared [42]. These important aspects can also be referred to as potential effect modifiers since if they are not evenly distributed between studies have the potential of modifying the true effect estimates. The potential effect modifiers we considered were setting, age, sex, disease location, disease duration, disease phenotype, disease activity, concomitant steroid use.

We assessed the assumption of transitivity by comparing the distribution of potential effect modifiers listed above across the different pairwise comparisons. In this context we expect that the transitivity assumption will hold assuming the common treatment used to compare different biologic drugs indirectly is similar when it appears in different trials, and all pairwise comparisons do not differ with respect to the distribution of effect modifiers.

We evaluated the assumption of intransitivity epidemiologically by comparing the clinical and methodological characteristics of sets of studies from the various treatment comparisons.

Assessment of statistical inconsistency/incoherence at the network level

Consistency (or coherence) is the statistical manifestation of transitivity. Intransitivity may result in differences between direct and indirect evidence. We assumed a common estimate for the heterogeneity variance across the different comparisons. We used global and local approaches to evaluate the statistical agreement between the various sources of evidence in a network of interventions (coherence). To evaluate the presence of inconsistency locally we used the loop-specific SIDE approach[43]. This method evaluates the consistency assumption in each closed loop of the network separately as the difference between direct and indirect estimates for a specific comparison in the loop (inconsistency factor). Then, the magnitude of the inconsistency factors and their 95% CIs can be used to infer the presence of inconsistency in each loop. To check the assumption of coherence in the entire network we used the 'design-by-treatment' model as described by [33]. This method accounts for different sources of inconsistency that can occur when studies with different designs, among different sets of interventions, give different results as well as disagreement between direct and indirect evidence. Using this approach we inferred the presence of inconsistency from any source in the entire network based on a Chi² test. All analyses were run with R statistical package [39] and the netmeta library [40].

Subgroup analyses

Our pre-planned NMA subgroup analyses were on:

- 1) Patients who were biologically naive or not (whether they had been exposed to a biologic prior to randomisation; if mixed, the threshold of 50% exposure was set to define if a group was classified as naive or exposed)
- 2) Patients who were biologically naive or not (any study with populations with mixed exposure was removed)
- 3) We had originally planned a subgroup analysis on different dosages (not considering dosages used in phase 2a studies; dosages only considered if licenced for patient use). However, as most of the biologics included in the review have not been licenced yet, we did not think it would be clinically appropriate to perform an analysis whereby only the non-licenced dosages of the licenced drugs would be removed.

The assessment of the subgroup analyses was based on visual inspection for overlap between the estimates and confidence intervals for the interventions that had evidence for all subgroups. As the evidence used for the subgroup analyses could only come from the included studies that reported the required data, the interventions lacking data were not represented or connected within each subgroup, and therefore these interventions are not presented.

Equity-related assessment

No equity-related assessment was planned for this review.

Sensitivity analysis

We planned to perform the following NMA sensitivity analyses to examine the impact of the following variables on the pooled effect estimate:

- 1) Random-effects versus fixed-effect modelling;
- 2) Only studies with low risk of bias (removing studies with more than two unclear fields or any high risk of bias fields)
- 3) Removal of studies where the population is mixed regarding the use of immunosuppressives (purine analogues) (>20%)
- 4) In the context of maintenance studies, addition of studies with mixed populations of patients in a state of both clinical remission and clinical response at baseline randomisation
- 5) Removal of studies with patients with more severe forms of disease, such as fistulating disease
- 6) Removal of non-peer-reviewed full-text publications (e.g abstracts, press releases, etc.)

Certainty of the evidence assessment

The summary of findings tables (SoF) present evidence comparing all methods with a reference comparator (placebo). Each table describes key features of the evidence relating to a single outcome. We have presented SoF tables for each primary outcome (clinical remission for induction, and clinical relapse for maintenance) and the safety outcome of 'withdrawals due to adverse events' in accordance with the GRADE approach. Our primary outcomes are presented in the abstract and plain language summary. These outcomes were 'prioritised' for presentation in the summary versions of the review because they are the most clinically important outcomes for decision makers.

We assessed the certainty of the evidence using the GRADE approach as outlined in the GRADE handbook in order to assess the certainty of the body of evidence relating to each outcome for all comparisons [44].

In order to create summary of findings tables, we used [45] to import data from Review Manager 5 [31]. We used the GRADE working group's approach for rating the certainty of the network meta-analysis effect estimates for all the comparisons and all outcomes [46, 47]. We appraised the certainty of the direct, indirect, and network evidence sequentially.

First, we assessed the certainty of the direct evidence (where available) for a given outcome, and rated the evidence using the standard GRADE approach based on consideration of: trial design limitations (risk of bias); inconsistency; imprecision; indirectness and publication bias [48]. In this approach, the direct estimates are rated

for risk of bias, inconsistency, indirectness and publication bias; followed by the indirect estimates are rated based on the lowest ratings of the direct comparisons forming the most dominant loop and intransitivity; and finally the network estimates are rated based on imprecision, incoherence, and the rating of the direct or indirect estimate that contributes the most.

Then we rated the certainty of the indirect evidence for the same given outcomes, based on the lower of the certainty ratings of the two direct arms forming the dominant 'first-order' loop in the network diagram for this outcome.

Finally, we determined the certainty of network evidence based on:

- The higher certainty rating of the direct and indirect evidence;
- Whether the relevant network exhibited 'transitivity', that is, whether all the comparisons contributing data to the estimate were directly consistent with the PICO question;
- Consideration of coherence between direct and indirect effect estimates (visual inspection of how much the direct and indirect evidence estimates agree and their confidence intervals overlap, and the statistical tests described earlier). We considered whether both the direct and indirect estimates contribute importantly to the network estimate, and whether incoherence was associated with intransitivity, imprecision and indirectness [49];
- And precision of the network effect estimate. Imprecision judgements were based on the following thresholds of risk difference[50]:
 - Clinical remission/relapse: <10%: trivial difference; 10-20%: small difference; 20%-31%: moderate difference; >31% large difference
 - Clinical response/loss of response: <13%: trivial difference; 13%-24%: small difference; 24%-35%: moderate difference; >35% large difference
 - Endoscopic remission/relapse: <9%: trivial difference; 9%-17%: small difference; 17%-28%: moderate difference; >28% large difference
 - Withdrawals due to adverse events: <7%: trivial difference; 7%-14%: small difference; 14%-23%: moderate difference; >23% large difference
 - Serious adverse events: <6%: trivial difference; 6%-10%: small difference; 10%-17%: moderate difference; >17% large difference
 - Total adverse events: <8.5%: trivial difference; 8.5%-15.5%: small difference; 15.5%-24%: moderate difference; >24% large difference

At each of these stages, two review authors (MG, VS) independently appraised the certainty ratings for the direct, indirect and network evidence. We resolved disagreements between authors through discussion and consultation. We rated the certainty of network evidence for each outcome as 'high', 'moderate', 'low' or 'very low' in accordance with the GRADE approach.

- High certainty: we are very confident that the true effect lies close to that of the effect.
- Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
- Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Consumer involvement

Consumers were not involved in this review due to limited resource.

Results

Description of studies

Results of the search

Our search , conducted up to June 2025, identified 24290 records. After removing duplicates, 22424 records underwent title and abstract screening to assess eligibility, of which 21691 were excluded. The remaining 733 records, which comprised 154 studies, underwent full-text review, of which 21 studies were excluded with reasons. The remaining records comprised a total of included 94 RCTs.

A total of 66 RCTs (n=20653) were included for induction of remission (Allez 2023 (TRIDENT- Part 1) [51, 52, 53]; Allez 2023 (TRIDENT- Part 2) [54]; Chen 2020 [55, 56, 57]; Colombel 2007 (CHARM) - Induction (non-responders) [58, 59, 60]; Colombel 2010 (SONIC) [61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71]; D'Haens 1999 (refractory CD)

[72, 73, 74]; D'Haens 2008 [75]; D'Haens 2022 (ADVANCE) [76, 77, 78]; D'Haens 2022 (SERENE - Induction) [79, 80, 81]; Duan 2013 [82]; Feagan 2008c [83, 84]; Feagan 2015a (UNITI-1) [85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108]; Feagan 2015b(UNITI-2) [109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132]; Feagan 2017 [133, 134, 135]; Ghosh 2003 [136, 137, 138, 139]; Gordon 2001 [140, 141, 142, 143]; Hanauer 2002 (ACCENT I) - Induction (non-response) [144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161]; Hanauer 2006 (CLASSIC I) [162, 163, 164]; Hanauer 2021 (VOLTAIRE-CD) [165, 166, 167, 168, 169, 170]; Lemann 2006 [171]; Loftus 2023 (U-EXCEED) [172]; Panaccione 2022 (MOTIVATE) [173, 174, 175]; Panes 2017 Induction [176, 177]; Present 1999 [178, 179, 180]; Sandborn 2001a [181]; Sandborn 2001b [182]; Sandborn 2005a (ENACT 1) [183, 184, 185, 186, 187, 188, 189, 190, 191]; Sandborn 2007a [192, 193, 194]; Sandborn 2007c (PRECISE 1) [195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205]; Sandborn 2008 (Population 1) [206, 207, 208, 209, 210]; Sandborn 2008 (Population 2) [211]; Sandborn 2011 [212, 213, 214, 215]; Sandborn 2012 (CERTIFI) - Induction [216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226]; Sandborn 2012 (CERTIFI) - Induction (non-response) [227]; Sandborn 2014 [228]; Sandborn 2023 - BERGAMOT (cohort 1) [229, 230, 231, 232]; Sandborn 2023 - BERGAMOT (cohort 3) [233]; Sandborn 2020d (CELEST) - Induction [234, 235]; Sandborn 2022 - GALAXI 1 [236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252]; Sands 2004 (ACCENT II) Induction (Non-responders) [253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263]; Sands 2007 [264, 265]; Sands 2010 [266]; Sands 2014 (GEMINI III) [267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278]; Sands 2022 (SEAVUE) [279, 280, 281, 282, 283, 284, 285]; Sands 2022 (SERENITY) [286]; Schreiber 2005 [287, 288, 289, 290]; Schreiber 2018a [291, 292]; Schwartz 2021 - ENTERPRISE [293, 294, 295]; Targan 1997 [296, 297, 298, 299]; Targan 2007 (ENCORE) [300, 301, 302, 303, 304, 305, 306, 307, 308]; Loftus 2023 (U-EXCEL) [309, 310, 311]; Vermeire 2017 FITZROY - induction [312]; Vermeire 2017 FITZROY - induction non-responders [313]; Watanabe 2012 - Induction [314, 315]; Watanabe 2020 - Induction [316, 317, 318]; Winter 2004 [319]; Ye 2019 [320, 321, 322, 323, 324, 325, 326]; Chen 2025 [327, 328]; Peyrin-Biroulet 2024 - SEQUENCE [329, 330, 331, 332]; Ferrante 2024 (VIVID-1) [333, 334]; Hart 2025 (GRAVITI) [335, 336]; Jairath 2025 (RELIEVE UCCD) [337]; Panaccione 2024 (GALAXI-2) [338, 339]; Panaccione 2024 (GALAXI-3) [340, 341]; Vermeire 2025 - DIVERSITY A [342, 343]; Vermeire 2025 - DIVERSITY B [344, 345]; Matsumoto 2016 (DIAMOND) [346, 347].

A total of 28 RCTs (n=6823) on maintenance of remission were included (Buhl 2022 (STOP-IT) [348, 349, 350, 351, 352]; Colombel 2007 (CHARM) - Maintenance (responders) [353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384]; D'Haens 2022 (SERENE - Maintenance) [385, 386]; Feagan 2015c (IM-UNITI) [387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417]; Ferrante 2022 - FORTIFY [418, 419, 420]; Hanauer 2002 (ACCENT I) - Maintenance (Responders) [421]; Jorgensen 2017 (NORSWITCH) [422, 423, 424, 425, 426]; Louis 2023 - SPARE [427, 428, 429, 430]; Panes 2017 Maintenance [431]; Rutgeerts 1999 [432]; Rutgeerts 2012 (EXTEND) [433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459]; Sandborn 2005a (ENACT 2) [460, 461, 462, 463, 464, 465, 466]; Sandborn 2007b (CLASSIC II) [467, 468, 469, 470]; Sandborn 2010b (WELCOME) [471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481]; Sandborn 2012 (CERTIFI) - Maintenance [482]; Sandborn 2013 (GEMINI II) - Maintenance [483, 484]; Sandborn 2020d (CELEST) - Maintenance [485]; Sands 2004 (ACCENT II) Maintenance (Responders) [486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497]; Schreiber 2007 (PRECISE 2) [498, 499, 500, 501, 502, 503, 504, 505, 506, 507, 508, 509, 510, 511, 512, 513, 514, 515, 516]; Schreiber 2021 [517, 518, 519, 520]; VanAssche 2012 (SWITCH) [521, 522, 523]; Vermeire 2017 FITZROY - maintenance responders [524]; Vermeire 2021 (VISIBLE 2) [525, 526, 527, 528, 529, 530, 531, 532, 533]; Volkers 2017 - SIMILAR [534, 535, 536]; Watanabe 2012 - Maintenance [537, 538]; Watanabe 2020 - Maintenance [539]; Vermeire 2025 - DIVERSITY (maintenance) [540, 541]; Young 2024 - iBaSS [542, 543]).

There were 15 records of ongoing studies (Supplementary material 5) (ACTRN12621001498886 [544]; ACTRN12622001458729 (DISCUS-IBD) [545]; Chaparro 2019 (GETECCU EXIT) [546, 547, 548]; ChiCTR2200060604 [549]; CTRI/2020/12/029571 [550, 551]; EUCTR2017-001226-18 [552]; EUCTR2018-004614-18 [553]; EUCTR2020-004527-16 (InCharge) [554]; EUCTR2021-002869-18 (AIM-CD) [555]; Jonkers 2021 - CoCros [556]; JRCT2031200406 - DUET [557]; KCT0007470 - CHAMELEON [558]; NCT03759288 - INTREPID [559]; NCT05837897 [560]; NCT06227910 (VICTRIVIA) [561, 562]); and 24 records of studies awaiting classification (Supplementary material 4) (Baima 2016 [563]; EUCTR2005-004104-37 [564]; EUCTR2007-001913-41 [565]; EUCTR2007-003239-21 [566]; EUCTR2008-001131-35 (AZORIX) [567, 568]; EUCTR2008-004926-18 (CHAMP) [569]; EUCTR2012-001723-12 [570]; EUCTR2020-002701-26 [571]; Huang 2012 [572]; JPRN-UMIN000005689 [573]; JPRN-UMIN000010524 (OASIS) [574]; NCT00349752 (COSPAR1) [575, 576, 577]; NCT00796250 [578]; NCT01674413 (CADHUM) [579]; NCT01696942 [580]; NCT02771457 [581]; NCT03221166 [582]; NCT03370601 (STAMP) [583]; NCT03393247 [584]; NCT04131322 (ADA-SWITCH) [585]; NCT04655807 [586]; NCT05057273 [587]; Rogler 2014 [588]; Wu 2016 [589, 590]).

The results of the search are presented in the study flow diagram (Figure 1).

Included studies

A summary of key characteristics and intervention details for the included inductions studies is shown in Table 1 and Table 2, and for the maintenance studies on Table 3 and Table 4. The included studies characteristics tables are in Supplementary material 2.

[Supplementary material 8](#) shows the approved dose and route of administration of the treatments that have been approved so far.

Study design

All studies but Duan 2013 and VanAssche 2012 (SWITCH) were multi-centre RCTs.

Forty-one RCTs were published in papers describing studies where more than one RCT was carried out, such as studies with randomised induction phases followed by randomised maintenance phases of responders, and randomised follow-up phases of non-responders (which we classified under induction) (Allez 2023 (TRIDENT- Part 1); Allez 2023 (TRIDENT- Part 2); Colombel 2007 (CHARM) - Maintenance (responders); D'Haens 2022 (SERENE - Maintenance); Feagan 2015a (UNITI-1); Feagan 2015b(UNITI-2); Feagan 2015c (IM-UNITI); Hanauer 2002 (ACCENT I) - Induction (non-response); Hanauer 2002 (ACCENT I) - Maintenance (Responders); Loftus 2023 (U-ENDURE) [591]; Loftus 2023 (U-EXCEED); Loftus 2023 (U-EXCEL) Panes 2017 Induction; Panes 2017 Maintenance; Sandborn 2005a (ENACT 1); Sandborn 2005a (ENACT 2); Sandborn 2008 (Population 1); Sandborn 2012 (CERTIFI) - Induction; Sandborn 2012 (CERTIFI) - Induction (non-response); Sandborn 2012 (CERTIFI) - Maintenance; Sandborn 2013 (GEMINI II) - Induction [592, 593, 594, 595, 596, 597, 598, 599, 600, 601, 602, 603, 604, 605, 606, 607, 608, 609, 610, 611, 612, 613, 614, 615, 616, 617, 618, 619, 620, 621, 622, 623, 624, 625, 626, 627, 628, 629, 630, 631, 632, 633, 634, 635, 636, 637, 638, 639, 640, 641, 642, 643, 644]; Sandborn 2013 (GEMINI II) - Maintenance; Sandborn 2020d (CELEST) - Induction; Sandborn 2020d (CELEST) - Maintenance; Sandborn 2023 - BERGAMOT (cohort 1); Sandborn 2023 - BERGAMOT (cohort 3); Sandborn 2023 - BERGAMOT Maintenance [645] Sands 2004 (ACCENT II) Induction (Non-responders); Sands 2004 (ACCENT II) Maintenance (Responders); Vermeire 2017 FITZROY - induction; Vermeire 2017 FITZROY - induction non-responders; Vermeire 2017 FITZROY - maintenance responders; Watanabe 2012 - Induction; Watanabe 2012 - Maintenance; Watanabe 2020 - Induction; Watanabe 2020 - Maintenance; Panaccione 2024 (GALAXI-2); Panaccione 2024 (GALAXI-3); Vermeire 2025 - DIVERSITY (maintenance); Vermeire 2025 - DIVERSITY A; Vermeire 2025 - DIVERSITY B).

Induction studies

Of the induction studies, 27 were two-armed (Allez 2023 (TRIDENT- Part 1); Chen 2020; Lemann 2006; Loftus 2023 (U-ENDURE); Loftus 2023 (U-EXCEED); Sandborn 2023 - BERGAMOT (cohort 3); Sands 2022 (SERENITY) Allez 2023 (TRIDENT- Part 1); Sandborn 2001b; Sandborn 2005a (ENACT 1); Sandborn 2007a; Sandborn 2007c (PRECISE 1); Sandborn 2008 (Population 1); Sandborn 2012 (CERTIFI) - Induction; Sandborn 2013 (GEMINI II) - Induction; Sands 2004 (ACCENT II) Induction (Non-responders); Sands 2007; Sands 2014 (GEMINI III); Sands 2022 (SEAVUE); Targan 2007 (ENCORE); Loftus 2023 (U-EXCEL); Vermeire 2017 FITZROY - induction; Watanabe 2020 - Induction; Ye 2019; Chen 2025; Peyrin-Biroulet 2024 - SEQUENCE; Matsumoto 2016 (DIAMOND)); 20 three-armed (Colombel 2007 (CHARM) - Induction (non-responders); Colombel 2010 (SONIC); D'Haens 2022 (ADVANCE); Duan 2013; Feagan 2008c; Feagan 2015a (UNITI-1); Feagan 2015b(UNITI-2); Feagan 2017; Hanauer 2002 (ACCENT I) - Induction (non-response); Panaccione 2022 (MOTIVATE); Present 1999; Sandborn 2023 - BERGAMOT (cohort 1); Sands 2010; Vermeire 2017 FITZROY - induction non-responders; Watanabe 2012 - Induction; Ferrante 2024 (VIVID-1); Hart 2025 (GRAVITI); Jairath 2025 (RELIEVE UCCD); Vermeire 2025 - DIVERSITY A; Vermeire 2025 - DIVERSITY B.); 12 were four-armed (D'Haens 1999 (refractory CD); Ghosh 2003; Hanauer 2006 (CLASSIC I); Panes 2017 Induction; Sandborn 2008 (Population 1); Sandborn 2012 (CERTIFI) - Induction; Sandborn 2014; Schreiber 2005; Schwartz 2021 - ENTERPRISE; Targan 1997; Panaccione 2024 (GALAXI-2); Panaccione 2024 (GALAXI-3)); 3 were five-armed (Allez 2023 (TRIDENT- Part 2) Sandborn 2022 - GALAXI 1; Winter 2004); and 2 were six-armed (Sandborn 2001a; Sandborn 2020d (CELEST) - Induction).

Five studies had more than 50% of their participants receiving concomitant purine analogues during the trial, without considering them part of their interventions. We considered them as part of their interventions for the purposes of our review (Chen 2020; Sandborn 2007a; Sands 2004 (ACCENT II) Induction (Non-responders); Sands 2007; Ye 2019).

Seventeen studies were on participants naive to biologics (Chen 2020; Colombel 2010 (SONIC); D'Haens 1999 (refractory CD); D'Haens 2008; Feagan 2008c; Ghosh 2003; Gordon 2001; Hanauer 2002 (ACCENT I) - Induction (non-response); Hanauer 2006 (CLASSIC I); Lemann 2006; Present 1999; Sandborn 2001a; Sandborn 2011; Sands 2004 (ACCENT II) Induction (Non-responders); Sands 2022 (SEAVUE); Targan 1997; Ye 2019) and twenty-two studies on participants not naive to biologics (Allez 2023 (TRIDENT- Part 1); Allez 2023 (TRIDENT- Part 2); D'Haens 2022 (ADVANCE); Feagan 2015a (UNITI-1); Feagan 2017; Sandborn 2007a; Sandborn 2012 (CERTIFI) - Induction; Sandborn 2012 (CERTIFI) - Induction (non-response); Sandborn 2020d (CELEST) - Induction; Sands 2007; Sands 2014 (GEMINI III); Schreiber 2018a; Loftus 2023 (U-EXCEL); Chen 2025; Peyrin-Biroulet 2024 - SEQUENCE; Ferrante 2024 (VIVID-1); Hart 2025 (GRAVITI); Jairath 2025 (RELIEVE UCCD); Panaccione 2024 (GALAXI-2); Panaccione 2024 (GALAXI-3); Vermeire 2025 - DIVERSITY A; Vermeire 2025 - DIVERSITY B). One study was unclear on this (Duan 2013) and the rest were on mixed population of naive and not naive patients.

One study (Present 1999) was exclusively on fistulating disease.

All studies took place in hospital settings. The median age and SD in the included studies was 37.3(12.95), but age at diagnosis was not reported. 47.3% were male and 52.7% female. In 41% of patients disease location was colonic, 38.6% ileocolonic, and 20.6% ileal. Median disease duration was 8.4 years, with some studies including disease duration of up to 20 years. Disease phenotype was not well reported. Disease activity was moderate to severe in all studies, with only two studies also including people with mild disease (Gordon 2001; Present 1999). All

studies that reported baseline clinical disease activity reported it on the CDAI scale, and some also reported it in IBDQ scores. Median CDAI was 300(150-350) and IBDQ 124(100-160). Endoscopic baseline activity was only reported in about 40% of studies. SES-CD scores ranged between 9-16 and CDEIS 8-15. Only one study (Feagan 2008c) required systemic steroids to be excluded. In the rest of the studies that reported steroids use about 40% of participants were receiving steroids at baseline and were allowed to keep using them at stable or tapering dosages, but reporting varied. Details on interventions, length of treatment and outcome definitions can be found in [Synthesis of results](#) and details per study in [Table 1](#) and [Table 2](#).

Based on the available data and distributions, effect modifiers were similarly distributed or assessed between the included studies to support the assumption of transitivity.

Maintenance studies

Twenty maintenance studies were two-armed (Buhl 2022 (STOP-IT); Colombel 2007 (CHARM) - Maintenance (responders); Feagan 2015c (IM-UNITI); Hanauer 2002 (ACCENT I) - Maintenance (Responders); Jorgensen 2017 (NORSWITCH); Panes 2017 Maintenance; Rutgeerts 1999; Rutgeerts 2012 (EXTEND); Sandborn 2005a (ENACT 2); Sandborn 2007b (CLASSIC II); Sandborn 2012 (CERTIFI) - Maintenance; Sandborn 2013 (GEMINI II) - Maintenance; Sands 2004 (ACCENT II) Maintenance (Responders); Schreiber 2007 (PRECISE 2); VanAssche 2012 (SWITCH); Vermeire 2021 (VISIBLE 2); Volkers 2017 - SIMILAR; Watanabe 2012 - Maintenance; Watanabe 2020 - Maintenance; Young 2024 - iBaSS); 2 studies were three-armed (Ferrante 2022 - FORTIFY; Louis 2023 - SPARE; Vermeire 2025 - DIVERSITY (maintenance)) and 1 was four-armed (Vermeire 2017 FITZROY - maintenance responders).

One study had more than 50% of their participants receiving concomitant purine analogues during the trial, without considering them part of their interventions. We considered them as part of their interventions for the purposes of our review (Sandborn 2013 (GEMINI II) - Maintenance).

Two studies were exclusively on participants on remission at randomisation point (Buhl 2022 (STOP-IT); Sandborn 2007b (CLASSIC II)). All other maintenance studies were on mixed populations of people on remission and response to a biologic, or only on people who have responded. Mean or median at disease activity at baseline could not be meaningfully established as many studies reported activity before remission or response to treatment was reached (induction phases). Five studies reported endoscopic activity, four in the SES-CD (Buhl 2022 (STOP-IT); Ferrante 2022 - FORTIFY; Rutgeerts 2012 (EXTEND); Sandborn 2023 - BERGAMOT Maintenance, mean range: 0-13.2) and one in the CDEIS (Lemann 2006, range: 2.8-3.5).

No studies were on participants naive to biologics.

One study had not been published as full papers by the time this review was conducted (Volkers 2017 - SIMILAR).

One study (Sands 2004 (ACCENT II) Maintenance (Responders)) was exclusively on fistulating disease.

All studies took place in hospital settings. Median age ranged between 30-42, but age at diagnosis was not reported. 48% were male and 52% female. In 24% of patients disease location was colonic, 38% ileocolonic, and 30% ileal. Median disease duration was 7.5 years, with some studies including disease duration of up to 15 years. Disease phenotype was not well reported. Two studies (Buhl 2022 (STOP-IT); Louis 2023 - SPARE) required steroids to be excluded. In the rest of the studies that reported steroid use about 45-55% of participants were receiving steroids at baseline and were allowed to keep using them at stable or tapering dosages, but reporting varied. Details on interventions, length of treatment and outcome definitions can be found in [Synthesis of results](#) and details per study in [Table 3](#) and [Table 4](#).

Based on the available data and distributions, effect modifiers were similarly distributed or assessed between the included studies to support the assumption of transitivity.

Funding

Three studies (Buhl 2022 (STOP-IT); Jorgensen 2017 (NORSWITCH) were publicly funded or did not receive financial support (Matsumoto 2016 (DIAMOND)). Two had unclear funding (Duan 2013; Volkers 2017 - SIMILAR).

The rest of the studies were fully or partly funded by pharmaceutical companies. Twelve studies were funded by AbbVie (Chen 2020; D'Haens 2022 (ADVANCE); D'Haens 2022 (SERENE - Induction); D'Haens 2022 (SERENE - Maintenance); Feagan 2017; Ferrante 2022 - FORTIFY; Panaccione 2022 (MOTIVATE); Sandborn 2020d (CELEST) - Induction; Sandborn 2020d (CELEST) - Maintenance; Loftus 2023 (U-EXCEL); Wu 2016; Peyrin-Biroulet 2024 - SEQUENCE). Nine studies were funded by Abbott (Colombel 2007 (CHARM) - Induction (non-responders); Colombel 2007 (CHARM) - Maintenance (responders); Hanauer 2006 (CLASSIC I); Rutgeerts 2012 (EXTEND); Sandborn 2007a; Sandborn 2007b (CLASSIC II); VanAssche 2012 (SWITCH); Watanabe 2012 - Induction; Watanabe 2012 - Maintenance). Twelve studies were funded by Centocor (Colombel 2010 (SONIC); D'Haens 1999 (refractory CD); D'Haens 2008; Hanauer 2002 (ACCENT I) - Induction (non-response); Hanauer 2002 (ACCENT I) - Maintenance (Responders); Present 1999; Rutgeerts 1999; Sandborn 2008 (Population 1); Sandborn 2008 (Population 2); Sands 2004 (ACCENT II) Induction (Non-responders); Sands 2004 (ACCENT II) Maintenance (Responders); Targan 1997). Thirteen studies were funded by Janssen/Johnson & Johnson (Allez 2023 (TRIDENT- Part 1); Allez 2023 (TRIDENT- Part 2); Feagan 2015a (UNITI-1); Feagan 2015b (UNITI-2); Feagan 2015c (IM-UNITI); Allez 2023 (TRIDENT- Part 1); Sandborn 2012 (CERTIFI) - Induction; Sandborn 2012 (CERTIFI) - Induction (non-response); Sandborn 2012 (CERTIFI) - Maintenance; Sandborn 2022 - GALAXI 1; Sands 2022 (SEAVUE); Hart 2025 (GRAVITI); Panaccione 2024 (GALAXI-2); Panaccione 2024 (GALAXI-3)). Three studies were funded by Millennium (Feagan 2008c; Sandborn 2013 (GEMINI II) - Induction; Sandborn 2013 (GEMINI II) - Maintenance). Six studies were funded by Takeda (Sands 2014 (GEMINI III); Schwartz 2021 -

ENTERPRISE; Vermeire 2021 (VISIBLE 2); Watanabe 2020 - Induction; Watanabe 2020 - Maintenance; Chen 2025). Six studies were funded by Elan (Ghosh 2003; Gordon 2001; Sandborn 2005a (ENACT 1); Sandborn 2005a (ENACT 2); Sandborn 2007a; Targan 2007 (ENCORE)). One study was funded by Boehringer Ingelheim (Hanauer 2021 (VOLTAIRE-CD)). Two studies were funded by the GETAID group (Lemann 2006; Louis 2023 - SPARE). Three studies were funded by Pfizer (Panes 2017 Induction; Panes 2017 Maintenance; Sandborn 2014). Three studies were funded by Celltech (Sandborn 2001a; Schreiber 2005; Winter 2004). Four studies were funded by UCB (Sandborn 2007c (PRECISE 1); Sandborn 2010b (WELCOME); Sandborn 2011; Schreiber 2007 (PRECISE 2)). One study was funded by Immunex (Sandborn 2001b). One study was funded by Synta (Sands 2010). One study was funded by Gilead (Schreiber 2018a), three studies were funded by Galapagos (Vermeire 2017 FITZROY - induction; Vermeire 2017 FITZROY - induction non-responders; Vermeire 2017 FITZROY - maintenance responders), and three by both (Vermeire 2025 - DIVERSITY (maintenance); Vermeire 2025 - DIVERSITY A; Vermeire 2025 - DIVERSITY B). Two studies were funded by Celltrion (Schreiber 2021; Ye 2019). One study was funded by Hoffmann-La Roche (Sandborn 2023 - BERGAMOT (cohort 1)), one study by Eli Lilly (Ferrante 2024 (VIVID-1)), one by Teva/Sanofi (Jairath 2025 (RELIEVE UCCD)), and one by Biogen (Young 2024 - iBaSS).

Conflicts of interest

No studies declared all their authors to be conflict free. All of them either had conflicted authors or did not clearly report conflicts.

The majority of authors were contacted for clarifications on their methods and data when the published information was unclear. Authors were not contacted when we had no questions for them. Responses varied between some authors not responding at all and others answering our questions, redirecting us to others or not being able to answer.

A data package can be accessed in [Supplementary material 7](#).

Excluded studies

The reasons for exclusion for seventeen example excluded studies are presented in [Excluded studies](#).

The main reasons for exclusion were non-RCT designs, and wrong interventions such as comparisons of pharmacokinetics, trough levels, or treatments strategies, and all included patients receiving the same biologic, therefore not being able to use it as a node in the NMA.

The included studies characteristics tables are in [Supplementary material 3](#).

Risk of bias in included studies

The risk of bias of included studies is summarised and presented graphically in [Figure 2](#) and [Figure 3](#). We've contacted authors and/or study sponsors for clarifications on unclear judgements.

77/94 were judged at low risk of bias for random sequence generation and the remaining 17 were judged at unclear risk. 74/94 were judged at low risk of bias for allocation concealment and the remaining 20 were judged at unclear risk.

6/94 studies were judged at high risk of bias for blinding of participants/personnel and 86/94 at low risk. Two studies were judged as unclear risk. 4/94 were judged at high risk of bias for blinding of outcome assessment and 61/94 at low risk of bias. 29/94 studies were judged as unclear risk.

One study was judged as high risk of bias for attrition bias and 73/94 at low risk of bias. 20 studies were judged at unclear risk.

Four studies were judged as high risk of bias for selective reporting and 58/94 at low risk. 32 studies were judged at unclear risk.

83/94 studies were judged as low risk of bias for other bias and 11/94 studies at unclear risk.

Synthesis of results

All analyses presented in [Supplementary material 6](#) relate to the pairwise evidence and we used them to grade the evidence, as described in our methods. The following section presents the results as reported in all of the figures.

The figures present the results as network diagrams, forest plots with direct, indirect and network (combining direct and indirect) effect estimates, and SUCRA rankings, and GORDON plots which combine numerical results, statistical ranking and GRADE certainty, for all the outcomes with available data.

The figures present the results for all biologics included in the review in comparison to placebo.

The treatments are ordered by GRADE certainty and whether the results showed difference with placebo or not (crossed the line of no effect). Within GRADE certainty treatments are ordered by their SUCRA rankings. However, SUCRA rankings are only mentioned if a treatment showed difference from placebo with high, moderate, or low GRADE certainty.

Results are based on random-effects model analyses.

Biologic drugs for induction of remission in Crohn's Disease

The extraction data for the induction studies can be found in [Table 5](#). Outcome measurements ranged from 2 weeks to 26 weeks.

Primary outcome: Clinical Remission

The results for this outcome are presented in [Summary of findings table 1](#), with placebo as the reference treatment. A GORDON plot of the network estimates ordered by GRADE certainty and SUCRA ranking for the treatments not crossing the line of no effect with high, moderate, and low certainty, can be seen in [Figure 4](#). A comparison-adjusted funnel plot, network plot, direct, indirect and network estimates plot, forest plot of all treatments compared to placebo, and SUCRA rankings for this outcome can be seen in [Figure 5](#); [Figure 6](#); [Figure 7](#); [Figure 8](#); [Figure 9](#). The comparison-adjusted funnel plot did not reveal large imbalances.

All studies included in the analysis defined remission as a CDAI score of more than 150 except Present 1999 who defined 'complete response' of as the absence of any draining fistulas at two consecutive visits, and Sandborn 2020d (CELEST) - Induction who defined it as daily Stool Frequency of ≤ 1.5 and AP score of ≤ 1.0 , with neither worse than the baseline value.

A total of 27 treatments were included in this network from a total of 59 studies (n=18765 participants), and 67 pairwise comparisons were carried out.

Direct comparisons to placebo included two studies on infliximab (n=202), two on mirikizumab (n=758), one on humicade (n=169), four on guselkumab (n=1045), three on risankizumab (n=1551), two on adalimumab (n=388), seven on ustekinumab (n=2454), three on filgotinib (n=1032), three on upadacitinib (n=1241), five on vedolizumab (n=1341), four on natalizumab (n=1692), two on etrolizumab (n=685), three on certolizumab (n=1193), two on tofacitinib (n=419), two on tesnatilimab (n=341), one on oncept (n=207), one on andecaliximab (n=187), one on etanercept (n=43), and one on apilimod mesylate (n=220).

There is high certainty evidence that ustekinumab (RR 2.01, 95% CI 1.67 to 2.43, SUCRA = 0.71, NNT=6, small effect size) is more effective in inducing clinical remission in Crohn's Disease compared to placebo.

There is moderate certainty evidence that adalimumab combined with purine analogues (RR 2.6, 95% CI 1.71 to 3.96, SUCRA = 0.87, NNT=3, moderate effect size), guselkumab (RR 2.49, 95% CI 1.95 to 3.18, SUCRA = 0.86, NNT=4, moderate effect size), adalimumab (RR 2.36, 95% CI 1.75 to 3.18, SUCRA=0.83, NNT=4, moderate effect size), upadacitinib (RR 1.76, 95% CI 1.34 to 2.3, SUCRA = 0.63, NNT=7, small effect size), vedolizumab (RR 1.57, 95% CI 1.15 to 2.13, SUCRA = 0.51, NNT= 10, trivial effect size), and natalizumab (RR 1.37, 95% CI 1.08 to 1.73, SUCRA = 0.41, NNT= 15, trivial effect size) are probably more effective in inducing clinical remission in Crohn's Disease compared to placebo.

There is low certainty evidence that risankizumab (RR 2.26, 95% CI 1.8 to 2.84, SUCRA = 0.82, moderate effect), BI695501 (RR 2.09, 95% CI 1.31 to 3.33, SUCRA = 0.74, small effect), a combination of infliximab with purine analogues (RR 2.04, 95% CI 1.14 to 3.64, SUCRA = 0.71, small effect) and filgotinib (RR 1.55, 95% CI 1.18 to 2.04, SUCRA = 0.5, trivial effect) may be more effective in inducing clinical remission in Crohn's Disease compared to placebo.

There is low certainty evidence that tofacitinib (RR 1.18, 95% CI 0.81 to 1.72) and apilimod mesylate (RR 0.67, 95% CI 0.34 to 1.34) may be equally effective to placebo in inducing clinical remission in Crohn's Disease.

The evidence for all other treatments was of very low certainty and no conclusions can be drawn.

The τ^2 for this outcome was 0.0025 and the I^2 4.3% (total $Q=50.07$, $p\text{-value}=0.0742$). The χ^2 test results and $p\text{-values}$ for assessing inconsistency within study designs was not statistically significant ($Q=24.28$, $p\text{-value}=0.71$). Between study designs ($Q=25.78$, $p\text{-value}=0.0011$), the designs between tensatilimab and ustekinumab ($Q=19.62$, $p\text{-value}=0.0032$), tesnatilimab and placebo ($Q=22.74$, $p\text{-value}=0.0019$, adalimumab and ustekinumab ($Q=22.91$, $p\text{-value}=0.0018$), ustekinumab and placebo ($Q=25.17$, $p\text{-value}=0.0007$), guselkumab and placebo ($Q=25.56$, $p\text{-value}=0.0006$), infliximab with purine analogues and purine analogues ($Q=25.72$, $p\text{-value}=0.0006$), and adalimumab and placebo ($Q=25.77$, $p\text{-value}=0.0006$) were statistically significant.

Subgroup analyses

The forest plots for the subgroup analysis for studies with more and less than 50% of participants naive to biologics for induction of clinical remission can be seen in [Figure 10](#). For the treatments that could be compared (adalimumab, tofacitinib, ustekinumab, vedolizumab) no major differences were observed upon visual inspection of the plots.

The forest plots for the subgroup analysis for studies with participants exclusively naive or not to biologics for induction of clinical remission can be seen in [Figure 11](#). For the treatments that could be compared (ustekinumab, vedolizumab) no major differences were observed upon visual inspection of the plots.

Sensitivity analyses

The sensitivity analysis using a fixed effect model revealed no differences to the random effects model analysis ([Figure 12](#)).

The forest plots for the sensitivity analysis for risk of bias can be seen in [Figure 13](#). Differences were observed for infliximab and the combinations of infliximab, CTP13 and adalimumab with purine analogues compared to the main analysis, however, due to the higher degree of imprecision in the sensitivity network no clear comments can be made.

The forest plots for the sensitivity analysis for studies with less or more than 20% of participants on concomitant purine analogues can be seen in [Figure 14](#). No major differences to the main analysis were observed.

The sensitivity analysis excluding studies exclusively on severe forms of Crohn's (fistulating disease) and the sensitivity analysis excluding studies not published as full papers could not be performed as no networks could be formed (1 fistulating study and 2 studies not published in full).

Secondary outcomes

Clinical response

A GORDON plot, comparison-adjusted funnel plot, network plot, direct, indirect and network estimates plot, forest plot of all treatments compared to placebo, and SUCRA rankings can be seen in [Figure 15](#); [Figure 16](#); [Figure 17](#); [Figure 18](#); [Figure 19](#); [Figure 20](#). The comparison-adjusted funnel plot did not reveal large imbalances visually for the individual interventions, but the Egger test was statistically significant indicating the presence of publication bias in the network.

All studies included in the analysis defined response as a reduction of 70 or 100 points in the CDAI scale, except Present 1999 who defined it as a reduction of 50 percent or more from baseline in the number of draining fistulas observed at two or more consecutive study visits, Sands 2004 (ACCENT II) Induction (Non-responders) who defined loss of response as the recrudescence of draining fistulas, the need for a change in medication for Crohn's disease or the need for additional therapy for persistent or worsening luminal disease activity, the need for a surgical procedure for Crohn's disease, or the discontinuation of the study medication owing to a perceived lack of efficacy, and Schreiber 2018a who defined it as liquid or very soft stool frequency and abdominal pain composite score ≤ 8 at week 8.

A total of 24 treatments were included in this network from a total of 51 studies (n=16702 participants), and 59 pairwise comparisons were carried out.

Direct comparisons to placebo included two studies on infliximab (n=202), two on mirikizumab (n=758), one on humicade (n=169) two on guselkumab (n=457), three on risankizumab (n=1551), two on adalimumab (n=388), seven on ustekinumab (n=2454), three on filgotinib (n=1074), three on upadacitinib (n=1241), five on vedolizumab (n=1341), three on natalizumab (n=1662), four on certolizumab (n=1485), two on tofacitinib (n=419), two on tesnatilimab (n=341), one on oncept (n=207), one on andecaliximab (n=187), one on etanercept (n=43), and one on apilimod mesylate (n=220).

We did not judge any treatments at high GRADE certainty for this outcome.

There is moderate certainty evidence that BI695501 (RR 2.47, 95%CI 1.47 to 4.15, SUCRA=0.88, large effect size), risankizumab (RR 2.08, 95% CI 1.61 to 2.67, SUCRA = 0.79, moderate effect size), and ustekinumab (RR 1.86, 95% CI 1.56 to 2.23, SUCRA = 0.7, moderate effect size) are probably more effective in inducing clinical response in Crohn's Disease compared to placebo.

There is low certainty evidence that adalimumab (RR 2.21, 95%CI 1.52 to 3.21, SUCRA=0.8, large effect size), a combination of adalimumab and purine analogues (RR 2.07, 95% CI 1.32 to 3.25, SUCRA = 0.79, moderate effect size), guselkumab (RR 2.06, 95%CI 1.56 to 2.73, SUCRA=0.78, moderate effect size), a combination of infliximab with purine analogues (RR 2.04, 95% CI 1.21 to 3.43, SUCRA = 0.75, moderate effect size), a combination of CTP13 (infliximab biosimilar) and purine analogues (RR 2.09, 95% CI 1.1 to 3.97, SUCRA =0.75, moderate effect size), infliximab (RR 1.97, 95% CI 1.26 to 3.1, SUCRA = 0.74, moderate effect size), upadacitinib (RR 1.74, 95% CI 1.32 to 2.28, SUCRA = 0.62, small effect size), mirikizumab (RR 1.49, 95% CI 1.11 to 2.01, SUCRA = 0.49, moderate effect), natalizumab (RR 1.41, 95% CI 1.12 to 1.77, SUCRA = 0.41, trivial effect size), and vedolizumab (RR 1.36, 95% CI 1.08 to 1.72, SUCRA = 0.39, trivial effect size) may be more effective in inducing clinical response in Crohn's Disease compared to placebo.

There is low certainty evidence that tesnatilimab (RR 1.23, 95% CI 0.86 to 1.77) and apilimod mesylate (RR 0.59, 95% CI 0.33 to 1.05) may be equally effective to placebo in inducing clinical response in Crohn's Disease.

The evidence for all other treatments was of very low certainty and no conclusions can be drawn.

The tau² for this outcome was 0.0255 and the I² 44.8% (total Q=57.97, p-value=0.0033). The Chi² test results and p-values for assessing inconsistency within study designs were not statistically significant (Q=37.24, p-value=0.0711). Between study designs (Q=20.73, p-value=0.0021), the designs between tesnatilimab and ustekinumab (Q=13.6, p-value=0.0087), tesnatilimab and placebo (Q=17.75, p-value=0.0033, guselkumab and placebo (Q=19.73, p-value=0.0014), infliximab with purine analogues and purine analogues (Q=20.35, p-value=0.0011), and guselkumab, placebo and ustekinumab (Q=16.63, p-value=0.0023) were statistically significant.

Endoscopic remission

A GORDON plot, comparison-adjusted funnel plot, network plot, direct, indirect and network estimates plot, forest plot of all treatments compared to placebo, and SUCRA rankings can be seen in [Figure 21](#); [Figure 22](#); [Figure 23](#); [Figure 24](#); [Figure 25](#); [Figure 26](#). The comparison-adjusted funnel plot did not reveal large imbalances.

A total of 11 treatments were included in this network from a total of 20 studies (n=7543 participants), and 22 pairwise comparisons were carried out.

Direct comparisons to placebo included two studies on mirikizumab (n=822), two on guselkumab (n=459), three on risankizumab (n=1551), one on adalimumab (n=129), one on ustekinumab (n=141), three on filgotinib (n=601), three to upadacitinib (n=1241), two on tesnatilimab (n=341), and one on etrolizumab (n=385).

We did not judge any treatments at high GRADE certainty for this outcome.

There is moderate certainty evidence that upadacitinib (RR 5.1, 95% CI 2.74 to 9.49, SUCRA = 0.95, large effect size), and risankizumab (RR 3.48, 95% CI 2.18 to 5.58, SUCRA = 0.86, NNT = 6, moderate effect size) are probably more effective in inducing endoscopic remission in Crohn's Disease compared to placebo.

There is low certainty evidence that mirikizumab (RR 3.28, 95% CI 1.44 to 7.48, SUCRA = 0.83, small effect size) may be more effective in inducing endoscopic remission in Crohn's Disease compared to placebo.

There is low certainty evidence that etrolizumab (RR 1.56, 95% CI 0.63 to 3.86), guselkumab (RR 1.69, 95% CI 0.97 to 2.95), filgotinib (RR 1.13, 95% CI 0.62 to 2.04), and tesnatilimab (RR 0.83, 95% CI 0.36 to 1.92) may be equally effective to placebo in inducing endoscopic remission in Crohn's Disease.

The evidence for all other treatments was of very low certainty and no conclusions can be drawn.

The τ^2 for this outcome was 0.0762 and the I^2 33.4% (total $Q=16.52$, $p\text{-value}=0.1229$). The χ^2 test results and p -values for assessing inconsistency within study designs was not statistically significant ($Q=15.27$, $p\text{-value}=0.0541$), but the design within tesnatilimab and placebo was statistically significant ($Q=5.64$, $p\text{-value}=0.0176$). Between study designs ($Q=1.25$, $p\text{-value}=0.7407$) the results were not statistically significant.

Withdrawal due to adverse events

A GORDON plot, comparison-adjusted funnel plot, network plot, direct, indirect and network estimates plot, forest plot of all treatments compared to placebo, and SUCRA rankings can be seen in [Figure 27](#); [Figure 28](#); [Figure 29](#); [Figure 30](#); [Figure 31](#); [Figure 32](#). The comparison-adjusted funnel plot did not reveal large imbalances.

A total of 28 treatments were included in this network from a total of 59 studies (n=19594 participants), and 71 pairwise comparisons were carried out.

Direct comparisons to placebo included one study on infliximab (n=94), two on mirikizumab (n=770), one on humicade(n=169), three on guselkumab (n=1041), three on risankizumab (n=1551), two on adalimumab (n=388), nine on ustekinumab (n=3032), three on filgotinib (n=1071), three on upadacitinib (n=1241), five on vedolizumab (n=1341), four on natalizumab (n=1692), two on etrolizumab (n=685), four on certolizumab (n=1485), two on tofacitinib (n=419), two on tesnatilimab (n=341), one on onercept (n=207), one on andecaliximab (n=187), one on etanercept (n=43), one on apilimod mesylate (n=220), and one on duvakitug (n=92).

We did not judge any treatments at high GRADE certainty for this outcome.

There is moderate certainty evidence that vedolizumab (RR 0.71 95% CI 0.41 to 1.23), ustekinumab (RR 0.72 95% CI 0.52 to 0.99), and upadacitinib (RR 0.8 95% CI 0.46 to 1.39) probably lead to a similar number of withdrawals due to adverse events during induction compared to placebo.

There is low certainty evidence that risankizumab (RR 0.36 95% CI 0.22 to 0.59, small effect size) may lead to less withdrawals due to adverse events compared to placebo.

There is low certainty evidence that humicade (RR 0.81 95% CI 0.39 to 1.68), natalizumab (RR 0.79, 95% CI 0.47 to 1.33), apilimod mesylate (RR 0.84 95% CI 0.36 to 1.95), certolizumab (RR 0.98, 95% CI 0.65 to 1.49), filgotinib (RR 1.06 95% CI 0.64 to 1.78) and tesnatilimab (RR 1.51 95% CI 0.82 to 2.8) may lead to a similar number of withdrawals due to adverse events during induction compared to placebo.

The evidence for all other treatments was of very low certainty and no conclusions can be drawn.

The τ^2 for this outcome was 0.123 and the I^2 50.4% (total $Q=76.58$, $p\text{-value}=0.0002$). The χ^2 test results and p -values for assessing inconsistency within study designs ($Q=58.41$, $p\text{-value}=0.0006$), showed the designs within guselkumab, placebo and ustekinumab ($Q=24.25$, $p\text{-value}<0.0001$), and certolizumab and placebo ($Q=7.99$, $p\text{-value}=0.0461$) to be statistically significant. Between study designs ($Q=18.17$, $p\text{-value}=0.0522$), the designs between purine analogues and infliximab with purine analogues ($Q=17.37$, $p\text{-value}=0.0433$), risankizumab and ustekinumab ($Q=17.38$, $p\text{-value}=0.0432$), placebo and risankizumab ($Q=17.38$, $p\text{-value}=0.0432$), placebo and tesnatilimab ($Q=17.71$, $p\text{-value}=0.0387$), mirikizumab and placebo ($Q=17.94$, $p\text{-value}=0.0359$), adalimumab, purine analogues, and adalimumab with purine analogues ($Q=17.95$, $p\text{-value}=0.0358$), infliximab and placebo ($Q=17.95$, $p\text{-value}=0.0358$), placebo and ustekinumab ($Q=18.02$, $p\text{-value}=0.035$), mirikizumab, placebo and ustekinumab ($Q=16.6$, $p\text{-value}=0.0345$), purine analogues, infliximab, and infliximab with purine analogues ($Q=17.16$, $p\text{-value}=0.0285$), and placebo, tesnatilimab and ustekinumab ($Q=17.63$, $p\text{-value}=0.0242$) were statistically significant.

Serious adverse events

A GORDON plot, comparison-adjusted funnel plot, network plot, direct, indirect and network estimates plot, forest plot of all treatments compared to placebo, and SUCRA rankings can be seen in [Figure 33](#); [Figure 34](#); [Figure 35](#); [Figure 36](#); [Figure 37](#); [Figure 38](#). The comparison-adjusted funnel plot did not reveal large imbalances.

A total of 26 treatments were included in this network from a total of 52 studies (n=17789 participants), and 60 pairwise comparisons were carried out.

Direct comparisons to placebo included one study on infliximab (n=94), two on mirikizumab (n=821), two on guselkumab (n=457), three on risankizumab (n=1551), two on adalimumab (n=388), eight on ustekinumab (n=2763), three on filgotinib (n=1071), three on upadacitinib (n=1241), five on vedolizumab (n=1341), three on natalizumab (n=1662), one on etrolizumab (n=385), four on certolizumab (n=1485), two on tofacitinib (n=419), two on tesnatilimab (n=341), one on onercept (n=207), one on andecaliximab (n=187), one on etanercept (n=43), and one on apilimod mesylate (n=220).

There is high certainty evidence that ustekinumab (RR 0.77, 95% CI 0.61 to 0.98), vedolizumab (RR 0.91 95% CI 0.71 to 1.18) and upadacitinib (RR 1.05 9% CI 0.7 to 1.59) lead to a similar number of serious adverse events during induction compared to placebo.

There is moderate certainty evidence that apilimod mesylate (RR 0.62 95% CI 0.26 to 1.51), guselkumab (RR 0.7, 95% CI 0.42 to 1.17), etrolizumab (RR 0.84, 95% CI 0.38 to 1.85), tofacitinib (RR 0.95, 95% CI 0.54 to 1.65), adalimumab (RR 0.88 95% CI 0.54 to 1.42), and filgotinib (RR 1.13, 95% CI 0.82 to 1.54) are probably no different to placebo for serious adverse events.

There is low certainty evidence that that etanercept (RR 0.35, 95% CI 0.08 to 1.6), risankizumab (RR 0.48, 95% CI 0.34 to 0.68), mirikizumab (RR 0.63, 95% CI 0.46 to 0.88), natalizumab (RR 0.81, 95% CI 0.54 to 1.19), and certolizumab (RR 1.41, 95% CI 0.97 to 2.06) may lead to a similar number of serious adverse events during induction compared to placebo.

The evidence for all other treatments was of very low certainty and no conclusions can be drawn.

The tau² for this outcome was 0 and the I² 0% (total Q=20.98, p-value=0.89). The Chi² test results and p-values for assessing inconsistency within study designs (Q=13.72, p-value=0.91) were not statistically significant. Between study designs (Q=7.26, p-value=0.51) there were no statistically significant results.

Total adverse events

A GORDON plot, comparison-adjusted funnel plot, network plot, direct, indirect and network estimates plot, forest plot of all treatments compared to placebo, and SUCRA rankings can be seen in [Figure 39](#); [Figure 40](#); [Figure 41](#); [Figure 42](#); [Figure 43](#); [Figure 44](#). The comparison-adjusted funnel plot did not reveal large imbalances.

A total of 26 treatments were included in this network from a total of 53 studies (n=17897 participants), and 61 pairwise comparisons were carried out.

Direct comparisons to placebo included one study on infliximab (n=94), one on mirikizumab (n=191), three on guselkumab (n=1052), three on risankizumab (n=1551), two on adalimumab (n=388), eight on ustekinumab (n=2754), three on filgotinib (n=1071), three on upadacitinib (n=1241), five on vedolizumab (n=1341), three on natalizumab (n=1662), one on etrolizumab (n=385), four on certolizumab (n=1485), two on tofacitinib (n=419), two on tesnatilimab (n=341), one on onercept (n=207), one on andecaliximab (n=187), one on etanercept (n=43), one on apilimod mesylate (n=220), and one on duvakitug (n=92).

There is high certainty evidence that ustekinumab (RR 1.03, 95% CI 0.94 to 1.13) leads to a similar number of total adverse events during induction compared to placebo.

There is moderate certainty evidence that adalimumab (RR 1.02, 95% CI 0.86 to 1.2), vedolizumab (RR 1.04, 95% CI 0.92 to 1.19) and upadacitinib (RR 1.07, 95% CI 0.93 to 1.25) are probably no different to placebo for total adverse events.

There is low certainty evidence that mirikizumab (RR 0.91, 95% CI 0.68 to 1.21), apilimod mesylate (RR 0.94, 95% CI 0.74 to 1.21), tofacitinib (RR 0.95, 95% CI 0.76 to 1.19), natalizumab (RR 1.02, 95% CI 0.89 to 1.16), certolizumab (RR 1.05, 95% CI 0.92 to 1.21), and etrolizumab (RR 1.19, 95% CI 0.89 to 1.59) may lead to a similar number of total adverse events during induction compared to placebo.

The evidence for all other treatments was of very low certainty and no conclusions can be drawn.

The tau² for this outcome was 0.01 and the I² 60.9% (total Q=81.76, p-value<0.0001). The Chi² test results and p-values for assessing inconsistency within study designs (Q=53.54, p-value=0.0005) showed the designs within filgotinib and placebo (Q=19.64, p-value<0.0001), guselkumab, placebo and ustekinumab (Q=13.1, p-value=0.0014), and placebo and risankizumab (9.92, p-value=0.007) to be statistically significant. Between study designs (Q=28.22, p-value=0.0004) all the designs were found to have statistically significant results (Q range 13.19-28.22, all p-values< 0.05).

Biologic drugs for maintenance of remission in Crohn's Disease

The extraction data for the maintenance studies can be found in [Table 6](#). Outcome measurements ranged from 26 weeks to 60 weeks.

Primary outcome: Clinical Relapse

The results for this outcome are presented in [Summary of findings table 3](#), with placebo as the reference treatment. A GORDON plot of the network estimates ordered by GRADE certainty and SUCRA ranking for the treatments not crossing the line of no effect with high, moderate, and low certainty, can be seen in [Figure 45](#). A comparison-adjusted funnel plot, network plot, direct, indirect and network estimates plot, forest plot of all treatments compared to placebo, and SUCRA rankings for this outcome can be seen in [Figure 46](#); [Figure 47](#); [Figure 48](#); [Figure 49](#); [Figure 50](#). The comparison-adjusted funnel plot did not reveal large imbalances.

All studies included in the analysis defined remission as CDAI score of less than 150, except Jorgensen 2017 (NORSWITCH) who defined remission as a reduction in the HBI scale of ≤ 4 points and partial Mayo Score ≤ 2 points, and Sands 2004 (ACCENT II) Maintenance (Responders) as a reduction of at least 50 percent from baseline in the number of draining fistulas at consecutive visits four or more weeks apart.

A total of 16 treatments were included in this network from a total of 24 studies (n=6543 participants), and 26 pairwise comparisons were carried out.

Direct comparisons to placebo included one study on CT-P13 (n=325), three on infliximab (n=603), four on adalimumab (n=731), one on certolizumab (n=428), one on upadacitinib (n=502), two on vedolizumab (n=434), two on ustekinumab (n=542), one on natalizumab (n=428), one on tofacitinib (n=180), one on etrolizumab (n=434), one on risankizumab (n=542), and one on filgotinib (n=329).

We did not judge any treatments at high GRADE certainty for this outcome.

There is moderate certainty evidence that adalimumab (RR 0.69, 95% CI 0.58 to 0.82, SUCRA = 0.76, NNT=2, moderate effect size) is probably more effective than placebo in preventing clinical relapse in Crohn's Disease.

There is low certainty evidence that CTP13 (RR 0.55, 95% CI 0.43 to 0.71, SUCRA=0.95, large effect size), infliximab (RR 0.68, 95% CI 0.57 to 0.81, SUCRA=0.8, moderate effect size) and upadacitinib (RR 0.72, 95% CI 0.56 to 0.94, SUCRA = 0.71, small effect size) are maybe more effective than placebo in preventing clinical relapse in Crohn's Disease.

There is low certainty evidence that there may be no difference between vedolizumab (RR 0.78, 95% CI 0.6 to 1.01), ustekinumab (RR 0.83, 95% CI 0.67 to 1.03), etrolizumab (RR 0.89, 95% CI 0.67 to 1.17), tofacitinib (RR 0.9, 95% CI 0.67 to 1.21) and placebo in preventing clinical relapse in Crohn's Disease.

The evidence for all other treatments was of very low certainty and no conclusions can be drawn.

The τ^2 for this outcome was 0.01 and the I^2 47% (total Q=18.88, p-value=0.0418). The χ^2 test results and p-values for assessing inconsistency within study designs (Q=9.02, p-value=0.3402) showed no statistically significant differences. Between study designs (Q=9.86, p-value=0.0072) the designs between CTP13, infliximab and placebo (Q=4.46, p-value=0.0346), and purine analogues and infliximab with purine analogues (Q=5.39, p-value=0.0202) were statistically significant.

Subgroup analyses

The subgroup analyses on biologic naivety could not be conducted as there were no maintenance RCTs on biologically naive patients.

Sensitivity analyses

The sensitivity analysis using a fixed effect model revealed no differences to the random effects model analysis (Figure 51).

The rest of the sensitivity analyses could not be conducted as there were not enough studies to form networks for comparison based on the sensitivity analyses plans. Six studies were judged to be at higher risk of bias (Ferrante 2022 - FORTIFY; Louis 2023 - SPARE; Röder 2021 [646]; Schreiber 2007 (PRECISE 2); Vermeire 2025 - DIVERSITY (maintenance); Watanabe 2012 - Maintenance). Three studies had less than 20% of participants using concomitant immunosuppressants (Loftus 2023 (U-ENDURE); Panes 2017 Maintenance; Röder 2021). Two studies had all participants in clinical remission at baseline (Buhl 2022 (STOP-IT); Sandborn 2007b (CLASSIC II)). One study was on a fistulating population (Sands 2004 (ACCENT II) Maintenance (Responders)). One study was not fully published a peer review publication (Röder 2021).

Secondary outcomes

Clinical loss to response

A GORDON plot, comparison-adjusted funnel plot, network plot, direct, indirect and network estimates plot, forest plot of all treatments compared to placebo, and SUCRA rankings can be seen in Figure 52; Figure 53; Figure 54; Figure 55; Figure 56; Figure 57. The comparison-adjusted funnel plot did not reveal large imbalances.

All studies included in the analysis defined response as a reduction of 70 or 100 points in the CDAI scale, except Jorgensen 2017 (NORSWITCH), who defined disease worsening as a reduction in the HBI scale and Sands 2004 (ACCENT II) Maintenance (Responders) who defined loss of response as the recrudescence of draining fistulas, the need for a change in medication for Crohn's disease or the need for additional therapy for persistent or worsening luminal disease activity, the need for a surgical procedure for Crohn's disease, or the discontinuation of the study medication owing to a perceived lack of efficacy.

A total of 11 treatments were included in this network from a total of 15 studies (n=4268 participants), and 17 pairwise comparisons were carried out.

Direct comparisons to placebo included one study on CT-P13 (n=325), two on infliximab (n=268), three on adalimumab (n=627), one on certolizumab (n=428), one on upadacitinib (n=502), two on vedolizumab (n=434), two on ustekinumab (n=542), one on natalizumab (n=428), one on tofacitinib (n=180), and one on filgotinib (n=329).

There is high certainty evidence that upadacitinib (RR 0.64, 95% CI 0.57 to 0.72, SUCRA = 0.69, moderate effect size) is effective in preventing loss of response compared to placebo.

There is moderate certainty evidence that CTP13 (RR 0.46, 95% CI 0.38 to 0.57, SUCRA = 0.98, large effect size), natalizumab (RR 0.54, 95% CI 0.43 to 0.68, SUCRA= 0.86, moderate effect size), certolizumab (RR 0.57, 95% CI 0.47 to 0.7, SUCRA = 0.81, moderate effect), adalimumab (RR 0.68, 95%CI 0.61 to 0.75, SUCRA = 0.58, small effect) and ustekinumab (RR 0.73, 95% CI 0.61 to 0.86, SUCRA = 0.44, small effect) are probably more effective than placebo in preventing loss of clinical response in Crohn's Disease.

There is low certainty evidence that infliximab (RR 0.71, 95% CI 0.6 to 0.83, SUCRA=0.5, small effect) and vedolizumab (RR 0.82, 95% CI 0.68 to 0.99, SUCRA = 0.28, trivial effect) are maybe more effective than placebo in preventing loss of clinical response in Crohn's Disease.

There is low certainty evidence that there may be no difference between tofacitinib (RR 0.9, 95% CI 0.74 to 1.09), filgotinib (RR 0.92, 95% CI 0.79 to 1.08) and placebo in preventing loss of clinical response in Crohn's Disease.

The evidence for all other treatments was of very low certainty and no conclusions can be drawn.

The tau² for this outcome was 0 and the I² 0% (total Q=5.79, p-value=0.56). The Chi² test results and p-values for assessing inconsistency within study designs (Q=4.75, p-value=0.44) showed no statistically significant differences. Between study designs (Q=1.04, p-value=0.59) there were no statistically significant differences.

Endoscopic relapse

There was not enough data to conduct a network meta-analysis for this outcome as only six studies reported data (Buhl 2022 (STOP-IT); Colombel 2023 - LIBERTY-CD [647, 648, 649]; Ferrante 2022 - FORTIFY; Loftus 2023 (U-ENDURE); Rutgeerts 2012 (EXTEND); Sandborn 2023 - BERGAMOT Maintenance). The extracted data can be found in Table 6.

Withdrawal due to adverse events

A GORDON plot, comparison-adjusted funnel plot, network plot, direct, indirect and network estimates plot, forest plot of all treatments compared to placebo, and SUCRA rankings can be seen in Figure 58; Figure 59; Figure 60; Figure 61; Figure 62; Figure 63. The comparison-adjusted funnel plot did not reveal large imbalances.

A total of 15 treatments were included in this network from a total of 21 studies (n=6149 participants), and 23 pairwise comparisons were carried out.

Direct comparisons to placebo included one study on CT-P13 (n=325), two on infliximab (n=268), three on adalimumab (n=234), one on certolizumab (n=428), three on vedolizumab (n=895), two on ustekinumab (n=542), one on natalizumab (n=428), one on tofacitinib (n=180), one on etrolizumab (n=434), and one on filgotinib (n=329).

We did not judge any treatments at high GRADE certainty for this outcome.

There is moderate certainty evidence that vedolizumab (RR 0.84, 95% CI 0.63 to 1.11) is probably no different to placebo in withdrawals due to adverse events during maintenance.

There is low certainty evidence that tofacitinib (RR 0.78, 95% CI 0.47 to 1.31), ustekinumab (RR 0.74, 95% CI 0.4 to 1.38), etrolizumab (RR 1.42, 95% CI 0.73 to 2.77, and upadacitinib (RR 1.51, 95% CI 0.73 to 3.11) may be no different to placebo in withdrawals due to adverse events during maintenance.

The evidence for all other treatments was of very low certainty and no conclusions can be drawn.

The tau² for this outcome was 0.351 and the I² 31.8% (total Q=11.74, p-value=0.1633). The Chi² test results and p-values for assessing inconsistency within study designs (Q=7.38, p-value=0.39) showed no statistically significant differences. Between study designs (Q=4.36, p-value=0.0368) there were no local designs that could be assessed.

Serious adverse events

A GORDON plot, comparison-adjusted funnel plot, network plot, direct, indirect and network estimates plot, forest plot of all treatments compared to placebo, and SUCRA rankings can be seen in Figure 64; Figure 65; Figure 66; Figure 67; Figure 68; Figure 69. The comparison-adjusted funnel revealed potential imbalances.

A total of 16 treatments were included in this network from a total of 18 studies (n=6032 participants), and 20 pairwise comparisons were carried out.

Direct comparisons to placebo included one study on CT-P13 (n=325), three on adalimumab (n=234), one on certolizumab (n=428), two on vedolizumab (n=434), one on ustekinumab (n=397), one on natalizumab (n=428), one on tofacitinib (n=180), one on etrolizumab (n=434), one on risankizumab (n=542) one upadacitinib (n=673, and one on filgotinib (n=329).

We did not judge any treatments at high or moderate GRADE certainty for this outcome.

There is low certainty evidence that adalimumab (RR 0.52, 95% CI 0.23 to 1.18), vedolizumab (RR 0.75, 95% CI 0.42 to 1.34), ustekinumab (RR 0.73, 95% CI 0.43 to 1.24), upadacitinib (RR 0.8, 95% CI 0.53 to 1.21), tofacitinib (RR 0.94, 95% CI 0.52 to 1.7), and etrolizumab (RR 1, 95% CI 0.4 to 2.47) may be no different to placebo for serious adverse events during maintenance.

The evidence for all other treatments was of very low certainty and no conclusions can be drawn.

The tau² for this outcome was 0 and the I² 0% (total Q=2.66, p-value=0.6162). The Chi² test results and p-values for assessing inconsistency within study designs (Q=1.19, p-value=0.755) showed no statistically significant

differences. Between study designs ($Q=1.47$, $p\text{-value}=0.2256$) there were no local designs that could be assessed.

Total adverse events

A GORDON plot, comparison-adjusted funnel plot, network plot, direct, indirect and network estimates plot, forest plot of all treatments compared to placebo, and SUCRA rankings can be seen in [Figure 70](#); [Figure 71](#); [Figure 72](#); [Figure 73](#); [Figure 74](#); [Figure 75](#). The comparison-adjusted funnel plot did not reveal large imbalances.

A total of 13 treatments were included in this network from a total of 18 studies ($n=5151$ participants), and 18 pairwise comparisons were carried out.

Direct comparisons to placebo included one study on CT-P13 ($n=325$), one on infliximab ($n=73$), three on adalimumab ($n=234$), one on certolizumab ($n=428$), two on vedolizumab ($n=434$), one on ustekinumab ($n=397$), one on natalizumab ($n=428$), one on tofacitinib ($n=180$), one on etrolizumab ($n=434$), one on risankizumab ($n=542$), one upadacitinib ($n=673$) and one on filgotinib ($n=329$).

We did not judge any treatments at high or moderate GRADE certainty for this outcome.

There is low certainty evidence that risankizumab (RR 0.98, 95% CI 0.69 to 1.38), vedolizumab (RR 0.95, 95% CI 0.71 to 1.27), ustekinumab (RR 0.97, 95% CI 0.69 to 1.36), etrolizumab (RR 0.99, 95% CI 0.71 to 1.39), upadacitinib (RR 1, 95% CI 0.71 to 1.4) and tofacitinib (RR 1.09, 95% CI 0.75 to 1.57) may be no different to placebo for total adverse events during maintenance.

The evidence for all other treatments was of very low certainty and no conclusions can be drawn.

The τ^2 for this outcome was 0.0278 and the I^2 73.6% (total $Q=22.73$, $p\text{-value}=0.0009$). The χ^2 test results and $p\text{-values}$ for assessing inconsistency within study designs ($Q=15.27$, $p\text{-value}=0.0042$) showed the design within adalimumab and placebo ($Q=13.18$, $p\text{-value}=0.0014$) to be statistically significant. Between study designs ($Q=7.47$, $p\text{-value}=0.0239$) the designs between adalimumab and infliximab ($Q=7.39$, $p\text{-value}=0.0066$) and adalimumab and placebo ($Q=7.39$, $p\text{-value}=0.0066$) were statistically significant.

Equity assessment

No equity assessment was planned for this review.

Reporting biases

Assessing publication bias with funnel plots was not possible as no pairwise comparisons included at least ten studies.

Discussion

Summary of main results

Network meta-analysis showed that for our primary outcome for induction therapy, 'clinical remission', ustekinumab (number needed to benefit, NNTB=6) has high certainty for efficacy, while adalimumab with purine analogues (NNTB=3), guselkumab (NNTB=4), adalimumab (NNTB=4) upadacitinib (NNT=7), vedolizumab (NNT=10), and natalizumab (NNT=15) moderate certainty.

Risankizumab, BI695501, and combination of infliximab with purine analogues were high on the rankings with low certainty evidence.

It is of note that subgroup analyses for studies different patient baseline characteristics regarding previous biologic exposure found no major differences in the magnitude or ranking of effects.

Upadacitinib (NNTB = 3), and risankizumab (NNTB = 6) showed efficacy for endoscopic remission with moderate certainty.

Upadacitinib, ustekinumab, and vedolizumab were found to be similar to placebo with moderate and high certainty across all safety outcomes. For other treatments no clear conclusions can be drawn due to low or very low certainty evidence.

Network meta-analysis showed that for our primary outcome for maintenance therapy, 'clinical relapse', adalimumab (NNT=2) was of moderate certainty evidence for efficacy, and CTP13, infliximab, and upadacitinib were of low certainty. Vedolizumab, ustekinumab, tofacitinib, and etrolizumab may be no different to placebo.

In regards to our safety outcomes, vedolizumab showed moderate certainty for no differences to placebo for withdrawals due to adverse events and low certainty for serious and total events. All other treatments were of low or very low certainty for no difference to placebo.

Results were limited by a sparse network.

Limitations of the evidence included in the review

The studies were thoroughly reviewed for quality and bias assessed.

Overall, the risk of bias of studies was of predominately low risk.

There were results of outcomes on GRADE analysis with high or moderate certainty in our network analysis, but imprecision was the main reason for downgrading, while remaining unclarity for risk of bias also played a role in downgrading.

Reporting of adverse events was also sparse during maintenance and long-term and so this was reflected in the GRADE analysis.

The evidence is complete and applicable in a number of ways. Evidence on the full range of biological therapies has been included and this has allowed effect, magnitude and certainty to be considered. The results on sensitivity analysis enhance the reliability of findings and subgroup analysis accounting for the key issue of previous biologic exposure at induction adds to the utility of the findings. The transitivity assumption which underpins the use of our methods appears to be met and there was limited incoherence in our outcomes.

There are a number of ways in which the evidence is lacking. The majority of studies included in this review used the CDAI to recruit patients to studies and assess clinical remission and response at different endpoints, which is considered the standard tool in Crohn's disease research. However, other measures of disease state and in turn endpoints for studies, such as endoscopic measures, were limited in reporting and networks could not be produced.

Moreover, heterogeneity of patients at entry is a factor that we have attempted to transparently present and account for in subgroup and sensitivity analysis, but was still a key area in which the primary evidence and in turn the findings of the review are limited when compared to other contexts of study [650, 651, 652].

The role of concomitant purine analogues is a key issue that must be commented on. Whilst most studies did not explicitly seek to investigate concomitant purine use or compare to purines, many studies included more than 50% of people on such therapy and as such assumptions were made to manage this issue. This may limit the utility of our results.

A limited number of head to head trials have been conducted thus far (Peyrin-Biroulet 2024 - SEQUENCE; Sands 2022 (SEAVUE); Allez 2023 (TRIDENT- Part 2); Sandborn 2022 - GALAXI 1), which have produced outcome results which have been used in our networks. However, our networks remain relatively sparse, with the clear majority of the evidence comparing single agents to placebo.

The reporting of adverse events is another area of concern. It is not uncommon to experience difficulties in reporting related to heterogeneity of thresholds of defining serious or severe events, and as such withdrawals is often the most available measure. For common effects, randomised trial data can be sufficient to consider safety [653], but this is not the case for rarer and possibly more devastating outcomes where long term safety data is not addressed by this synthesis.

For our analyses we have used all dosages compared in the original RCTs, including non-licensed and non-clinically practically used dosages, and data from phase 2b trials that may not have progressed to phase 3. Whilst we do not think this might have affected our efficacy data, it might have potentially affected our safety outcomes and must be considered by those utilising our review.

In this review we have included biologic and advanced treatments irrespective of whether they have received approval by regulatory authorities. This was to capture the complete evidence basis in our networks and because new treatments may share similar medication class properties with their same-class approved treatments.

We have excluded non-randomised, treat-through maintenance designs as per our review inclusion criteria they are not RCTs, ensuring only trials of properly randomised designs have been included.

Studies solely comparing purine analogue or steroid monotherapy to placebo have not been included in this review. They appear in some of our plots because some studies included them in comparison to advanced treatments, and we have included all studies on advanced treatment irrespective of what they were compared to. As purine analogue and steroid monotherapies were not in the scope of the review, no assessments have been made of these treatments and they are not discussed in this review.

Finally, sample size of trials has resulted in issues with precision and limited analyses for maintenance therapy. This is a pervasive issue within the field [654, 655].

Limitations of the review processes

Gaps in information to judge risk of bias was initially pervasive. The review authors chose to contact the study authors for clarification or additional information, with many authors responding. The use of such unpublished data can also be seen as a source of bias.

We are aware of the possibility of industry funding for the validity of the results. Funding from manufacturing companies or any conflicts of interests from both primary studies and the review team have been reported, but are almost universal within the field and so must be considered as a constant and overarching potential source of bias.

The methodological approaches and assumption in the review have been transparently reported, discussed and the impact of such assumptions tested on sensitivity analysis. However, of particular note is the handling of concomitant purine analogues. This was an unexpectedly pervasive issue within the evidence. The approach used represents consensus of the team, editorial and methods support from Cochrane and clinical advice from experts in the field. But this must be considered a key potential source of bias.

Agreements and disagreements with other studies or reviews

The results broadly support current international guidelines in UK [656], Europe [657] and North America [658] in the role of established therapies. For novel therapies, these are not discussed in any of these guidelines and as such the evidence in this review may support them in updates. None of these guidelines employed network meta-analysis data and so this is not reflected in their guidance. Most of these guidelines propose a role for combination of purine and biologic. However, within the network purine combinations were of low or very low certainty for efficacy and safety. The newest British Society of Gastroenterology guidelines on IBD, have used network meta-analyses for their formulation and have arrived to their recommendations using the GRADE evidence to decision framework based on evidence similar to this review's results [659]. It's worth noting that the results of any network meta-analysis should not be interpreted as a clinical guideline on their own. Any evidence needs the clinical interpretation of a guideline development group which needs to carefully consider all aspects that need to be considered when making recommendations.

Our results agree with the most recent Cochrane pairwise meta-analyses on the individual agents for which they have been conducted in terms of the similarity in effect estimations and GRADE certainty assessments [18, 19, 20, 21, 22, 23, 24]

Broadly, our results agree with recent NMAs on the subject, even though one key difference is that these tend to rely on statistical rankings and omit assessments of certainty of the evidence. Our review relies primarily on GRADE assessments, which in combination with our pre-defined thresholds for magnitude size has allowed us to make more transparent and nuanced conclusions [660][661]

Authors' conclusions

Implications for practice

For patients with active Crohn's disease for induction of clinical remission, we found the following results from our network meta-analysis:

- The most effective interventions when compared to placebo were ustekinumab (number needed to benefit, NNTB=6), adalimumab with purine analogues (NNTB=3), adalimumab (NNTB=4), guselkumab (NNTB=4), upadacitinib (NNTB=7), vedolizumab (NNTB=10), and natalizumab (NNTB=15) all effective with moderate and high certainty evidence.
- Risankizumab, infliximab with purine analogues, infliximab, filgotinib, and BI695501 (adalimumab biosimilar) had low certainty for efficacy
- Tofacitinib and apilimod mesylate may be of no difference to placebo.
- Upadacitinib, ustekinumab, and vedolizumab were found to be similar to placebo with moderate and high certainty across all safety outcomes.

For patients with Crohn's disease in remission for maintenance therapy, we found the following results for prevention of clinical relapse from our network meta-analysis:

- Adalimumab (number needed to treat, NNT=2) was of moderate certainty evidence for efficacy. CTP13, infliximab, and upadacitinib were of low certainty.
- Vedolizumab, ustekinumab, tofacitinib, and etrolizumab may be no different to placebo
- All treatments were mostly of low and very low certainty regarding safety outcomes.

Results were limited by a sparse network.

Implications for research

This Network meta-analysis has supported indirect evidence generation, but head-to-head comparative trials for key interventional subclasses or specific agents may be needed, as guided by key stakeholders. One example would be the use of biosimilar version of medications out of patent.

The role of concomitant purine analogues has been a key confounding factor and future studies may not only want to investigate specifically the role of combinations, but also consider stratifying populations or purposefully excluding patients based on this key class of therapy to avoid such heterogeneity.

Given the majority of evidence focusses on the outcomes of clinical remission and relapse, future studies may want to further consider other outcomes of clear interest to clinicians and patients, particularly endoscopic remission.

Finally, safety data is limited especially during maintenance and the long term. Whilst future studies with longer follow-ups could support increased data, it may be that study designs outside of randomised trials are employed for such outcomes.

Supplementary materials

[For display in the published PDF only] Supplementary materials are available with the online version of this article: [10.1002/14651858.CD012751](https://doi.org/10.1002/14651858.CD012751).

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Supplementary material 1

[CD012751-SUP-01-searchStrategy.html](#)

Search strategies

Supplementary material 2

[CD012751-SUP-02-characteristicsOfIncludedStudies.html](#)

Characteristics of included studies

Supplementary material 3

[CD012751-SUP-03-characteristicsOfExcludedStudies.html](#)

Characteristics of excluded studies

Supplementary material 4

[CD012751-SUP-04-characteristicsOfAwaitingStudies.html](#)

Characteristics of studies awaiting classification

Supplementary material 5

[CD012751-SUP-05-characteristicsOfOngoingStudies.html](#)

Characteristics of ongoing studies

Supplementary material 6

[CD012751-SUP-06-analyses.html](#)

Analyses

Supplementary material 7

[CD012751-SUP-07-dataPackage.zip](#)

Data package

Supplementary material 8

[CD012751-SUP-08-other.html](#)

Appendix 1: Approved dose and route of administration

Additional information

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Contributions of authors

Morris Gordon: secured funding, designed and developed, screened, extracted, resolved conflicts, assessed certainty, contributed to writing and editing, advised on, approved the final version prior to submission, and is a guarantor of the review.

Vassiliki Sinopoulou: screened, extracted, assessed certainty, contributed to writing and editing, did administrative work, advised on, approved the final version prior to submission

Muhammad Ibrahim Khan, Masitara Masitara, Alireza Sherafat, Rose Cherayath: screened, extracted, did administrative work, contributed to writing and editing, approved the final version prior to submission

Assem Elleithy, Fareed Alqusous, Sanjana Phlananthachai: screened, did administrative work, approved the final version prior to submission

Anthony K Akobeng: contributed to validation, and reviewed and approved the final version prior to submission

Gordon William Moran: contributed to supervision, analysis, validation, and reviewed and approved the final version prior to submission

Suzanna C Freeman: provided statistical network meta-analysis guidance

The authors of the protocol of this review (published in 2017) are no longer included on the author byline: Pieter Hindryckx, GY Zou, Brian G Feagan, Sushil K Garg, Jasvinder A Singh, Triana Lobaton, Siddharth Singh, Claire E Parker, Tran M Nguyen, Orli M Silverberg, Reena Khanna and Vipul Jairath. Some of the content retained in this review reflects their contributions.

Declarations of interest

Vassiliki Sinopoulou has nothing to disclose.

Morris Gordon is co-Editor of Cochrane Gut. He was not involved in the editorial process for this review.

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Anthony Akobeng is Coordinating Editor, Cochrane Gut Group. He was not involved in the editorial process for this review. Anthony has published opinions on the treatment of Crohn's disease in a number of peer reviewed medical journals and is a Consultant Clinical Adviser for National Institute for Care and Health Excellence, UK.

Fareed Al Qusous has nothing to disclose.

Rose Cherayath has nothing to disclose.

Assem Elleithy has nothing to disclose.

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Registration and protocol

A protocol for this review has been published in 2017 [27] doi.org/10.1002/14651858.CD012751

Data, code and other materials

As part of the published Cochrane review, the following is made available for download for users of the Cochrane Library (see [Supplementary material 1](#); [Supplementary material 2](#); [Supplementary material 3](#); [Supplementary material 4](#); [Supplementary material 5](#); [Supplementary material 6](#); [Supplementary material 7](#)): full search strategies for each database; full citations of each unique report for all studies (included, ongoing or awaiting classification, or excluded at the full text screen) in the final review; study data, including study information, study arms, and study results or test data; consensus risk of bias assessments; and analysis data, including overall estimates and settings, subgroup estimates, and individual data rows. Appropriate permissions have been obtained for such use. Analyses and data management were conducted within Cochrane's authoring tool, RevMan, using the inbuilt computation methods. The following scripts and artefacts were used to generate analyses outside of RevMan: R statistical package, gordonplots.shinyapps.io/shiny_gordon_plots/. Template data extraction forms from (Covidence, Excel, etc.) are available from the authors on reasonable request.

Notes

A protocol for this review was published in 2017 [27]

History

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Tables

Table 1

Induction studies' characteristics

Study ID	Numbers randomised	Purine analogues use	Biologic naive or not
Chen 2020	IG(ada)-102 CG(placebo)- 103	n(%) Azathioprine: CG-59 (57%), IG-60 (59%) Mercaptopurine CG- 2 (2%) IG- 0 >50%	Naive
Colombel 2007 (CHARM) - Induction (non-responders)	CG(placebo): 91 IG1(AdaEow): 88 IG2(AdaWeekly): 100	n(%) AZA: 88/279 6-MP: 27/279 <50%	Mixed naive and not 152 (54.5%) out of 279 participants were naive at recruitment
Colombel 2010 (SONIC)	CG (AZA only) - 170 IG1 (IFX only) - 169 IG2 (Combination therapy) - 169	Part of the intervention	Naive
D'Haens 1999 (refractory CD)	CG(placebo) 8 IG(ifx5mg) 7 IG(ifx10mg) 7 IG(ifx20mg) 8	Concomitant azathioprine, n CG(placebo) 3/8 IG(ifx5mg) 3/7 IG(ifx10mg) 1/7 IG(ifx20mg) 5/8 <50%	Naive
D'Haens 2008	CG(corticosteroids) - 66 IG(ifx+aza) 67	Part of the intervention	Naive
D'Haens 2022 (ADVANCE)	CG(placebo) 186 IG1(ris600mg) 373 IG2(ris1200mg) 372	Unclear (abstract only)	Not
D'Haens 2022 (SERENITY - Induction)	IG Ada(high) 308 CG Ada(standard) 206	Immunosuppressant use (n, %) IG 78 (25.3) CG 61 (29.6) <50%	Not The study allowed enrollment of patients with secondary loss of response or intolerance to infliximab (up to 25% of the total study population).
Duan 2013	IG(ifx) - 8 IG(aza) - 8 IG(comb) - 8	Part of the intervention	Unclear

Feagan 2008c	CG(placebo): 58 IG1(Ved0.5mg): 62 IG2(Ved2mg): 65	Patients on immunosuppressives were excluded <50%	Naive
Feagan 2015a (UNITI-1)	CG(placebo) 247 IG(ust130mg) 245 IG2(ust6mg/kg) 249	Immunosuppressants including azathioprine, mercaptopurine, and methotrexate, n(%) CG(placebo)= 81 (32.8) IG(ust8wks)= 74 (30.2) IG(ust12wks)= 78 (31.3) <50%	Not History of disease refractory to treatment with TNF antagonist, n(%) CG(placebo) 246 (99.6) IG(ust160mg) 243 (99.2) IG2(ust6mg/kg) 246 (98.8)
Feagan 2015b(UNITI-2)	CG(placebo) 210 IG(ust130mg) 209 IG2(ust6mg/kg) 209	Immunosuppressants including azathioprine, mercaptopurine, and methotrexate, n(%) CG(placebo)= 73 (34.8) IG(ust8wks)= 74 (35.4) IG(ust12wks)= 72 (34.4) <50%	Mixed naive and not No history of TNF antagonist treatment CG(placebo) 131 (62.4) IG(ust160mg) 152 (72.7) IG2(ust6mg/kg) 144 (68.9)
Feagan 2017	CG(placebo) 39 IG(Ris200mg) 41 IG(Ris600mg) 41	Immunosuppressants and corticosteroids, n CG(placebo) 5 (13%) IG(Ris200mg) 3(7%) IG(Ris600mg) 3(7%) Immunosuppressants, n(%) CG(placebo) 8(21%) IG(Ris200mg) 7(17%) IG(Ris600mg) 5(12%) <50%	Not (more than 90% were not naive)
Ghosh 2003	CG(placebo) - 63 IG(nat1x3mg) - 68 IG(nat2x3mg) - 66 IG(nat2x6mg) - 51	Azathioprine or mercaptopurine, (%) CG(placebo) 22(35) IG(nat1x3mg) 26(38) IG(nat2x3mg) 17(26) IG(nat2x6mg) 9(18) <50%	Naive
Gordon 2001	CG(placebo) 12 IG(nat) 18	Azathioprine, n(%) CG 2 (17) IG 6 (33) <50%	Naive
Hanauer 2002 (ACCENT I) - Induction (non-response)	CG(placebo) - 78 IG1(ifx5mg) - 79 IG2(ifx5+10mg) - 81	6-mercaptopurine and azathioprine, n(%) 63 (27%) of all randomised non-responders <50%	Naive
Hanauer 2006 (CLASSIC I)	CG(placebo) 74 IG1(Ada40/20mg) 74 IG2(Ada80/40mg) 75	Azathioprine, n(%) CG 13 (18) IG1 13 (18) IG2 9 (12)	Naive

	IG3(Ada160/80mg) 76	IG3 11 (14) 6-Mercaptopurine, n(%) CG 8 (11) IG1 6 (8) IG2 10 (13) IG3 10 (13) <50%	
Hanauer 2021 (VOLTARE-CD)	CG(ada) :75 IG(BI 695501): 72	Unclear	Naive, except for previous exposure to infliximab CG 7(10%) IG 5(7%)
Lemann 2006	CG(aza) 58 IG(aza+ifx) 57	Part of the intervention	Naive
Allez 2023 (TRIDENT-Part 1)	CG(placebo) 72 IG(Tesnatilimab) 73	Unclear (trial registration results only)	Unclear (trial registration results only)
Panaccione 2022 (MOTIVATE)	CG(placebo) 187 IG1(ris600mg) 191 IG2(ris1200mg) 191	Unclear (abstract only)	Mixed naive and not Failed one or more biologics, n CG 37 IG1 81 IG2 77
Panes 2017 Induction	CG(placebo) 92 IG(tof5mg) 86 IG(tof10mg) 86 IG(tof15mg) 16 (the intervention was discontinued)	Patients receiving azathioprine, 6-mercaptopurine or methotrexate were required to stop these agents at least two weeks before randomisation <50%	Mixed naive and not Prior use of TNFi n(%) CG(placebo) 70 (76.9) IG(tof5mg) 68 (79.1) IG(tof10mg) 66 (76.7) IG(tof15mg) 11 (68.8)
Present 1999	CG(placebo):31 IG1(ifx5mg):31 IG2(ifx10mg):32	Mercaptopurine or azathioprine, n(%) CG 9(29%) IG1 12(39%) IG2 17(53%) <50%	Naive
Sandborn 2001a	CG(placebo 8 weekly): 27 CG (placebo 12 weekly): 31 IG1 (CDP57110mg/kg 8 weekly): 29 IG1 (CDP57110mg/kg 12 weekly): 25 IG2 (CDP57120mg/kg 8 weekly): 28 IG2 (CDP57120mg/kg 12 weekly): 29	Azathioprine or 6-mercaptopurine, n CG(placebo 8 weekly): 9 CG (placebo 12 weekly): 18 IG1 (CDP57110mg/kg 8 weekly): 18 IG1 (CDP57110mg/kg 12 weekly): 13 IG2 (CDP57120mg/kg 8 weekly): 14 IG2 (CDP57120mg/kg 12 weekly): 17 <50%	Naive
Sandborn 2001b	CG(placebo) – 20	Mercaptopurine or azathioprine, n	Mixed naive and not

	IG(etanercept) – 23	CG 7 IG 10 <50%	Prior treatment with infliximab CG 8 IG 12
Sandborn 2005a (ENA CT 1)	CG(placebo) - 181 IG(nat) - 724	Immunosuppressants, n(%) CG 52 (29) IG 247(34) <50%	Mixed naive and not Previous receipt of therapy against TNF-a, n(%) CG 69 (38) IG 291 (40)
Sandborn 2007a	CG(placebo) – 166 IG(ada) – 159	Immunosuppressants, n(%) CG 85 (51) IG 73(46) >50%	Not
Sandborn 2007c (PRECISE 1)	CG(placebo): 329 IG(cert): 333	Immunosuppressants, n(%) CG 66 (20) IG 69(21) <50%	Mixed naive and not Previous ifx therapy, n(%) CG 85 (26) IG 100 (30)
Sandborn 2008 (Population 1)	CG1(placeboSC)– 26 CG2(placeboIV)– 27 IG1(ustSC)– 25 IG2(ustIV)– 26	Immunosuppressants, n(%) CG1 10(39) CG2 19(37) IG1 2(20) IG2 10(39) <50%	Mixed naive and not Patients with prior infliximab use CG1 – 16(32.65%) CG2 – 11(22.45%). IG1 - 14(28.57%). IG2 - 8(16.33%)
Sandborn 2008 (Population 2)	1G1 (ustSC) – 14 IG2 (ustIV)– 13	Immunosuppressants, n(%) IG1 6 (43) IG2 8(62) >50%	Not
Sandborn 2011	CG(placebo) 216 IG(cert) 223	Immunosuppressants, n(%) CG 67(31.2) IG 77 (34.5) <50%	Naive
Sandborn 2012 (CERTIFI) - Induction	CG(placebo)132 IG1(ust1) 131 IG2(ust3) 132 IG3(ust6) 131	Immunomodulatory drug CG 30 (22.7) IG1 33(25.2) IG2 28 (21.2) IG3 35(26.7) <50%	Not
Sandborn 2012 (CERTIFI) - Induction (non-response)	CG(placebo) – 110 IG(ust) – 109	<50% (assumption based on the above, not provided separately for this population)	Not (as above)
Sandborn 2013 (GEMIN I II) - Induction	CG(placebo)=148 IG1(ved)=220	Immunosuppressive agents, n(%) CG 25 (16.9) IG 37 (16.8)	Mixed naive and not Prior TNF antagonist therapy, n(%) CG 72 (48.6)

		<50%	IG 111(50.5)
Sandborn 2014	CG(placebo) - 34 IG1(Tof1) 36 IG2(Tof5) 34 IG3(Tof15) 35	None except for 2 patients in IG3 <50%	Mixed naive and not Anti-TNFα use within the previous 12 months, n CG 1 IG1 4 IG2 1 IG3 4
Sandborn 2023 - BERG AMOT (cohort 1)	CG(placebo) - 59 IG1(etoro105mg) - 120 IG2(etoro210(mg) - 121	Patients were refractory to immunosuppressives but concurrent medications are not reported	73% of patients were TNF-experienced
Sandborn 2020d (CELEST) - Induction	CG(placebo) - 37 IG(Upa3B) - 39 IG(Upa6B) - 37 IG(Upa12B) - 36 IG-(Upa24B) - 36 IG(Upa24Q) - 35	None, patients had to discontinue these drugs <50%	Not (<5% was naive)
Sandborn 2022 - GALAXI 1	CG(placebo) - 70 IG-Gus200 - 73 IG-Gus600 - 73 IG-Gus1200 - 73 IG-UST - 71	Immunomodulatory therapy, n(%) CG 26 (42.6) IG-G200 - 15(24.6) IG-G600 - 18 (28.6) IG-G1200 - 25 (41.0) IG-UST - 26(41.3) <50%	Mixed naive and not Biologic naive, n(%) CG 19 (31.1) IG-G200 - 25 (41.0) IG-G600 - 24(38.1) IG-G1200 - 25 (41.0) IG-UST - 19 (30.2)
Sands 2004 (ACCENT I) I) Induction (Non-responders)	CG(placebo) 44 IG(ifx) 43	Mercaptopurine or azathioprine, n(%) 53/87 (61) >50(%)	Naive
Sands 2007	CG(ifx):27 IG1(ifx+nat):52	Azathioprine, mercaptopurine, or methotrexate, n(%) CG 15 (56) IG1 15 (56) >50(%)	Not
Sands 2010	CG(placebo) 73 IG1(AM50mg) 73 IG2(AM100mg) 74 AM=apilimod mesylate	Azathioprine or mercaptopurine, n(%) CG 1(1) IG1 2(3) IG2 4(5) <50(%)	Mixed naive and not Previous biologic use, n(%) CG 38(52) IG1 47(64) IG2 45(61)
Sands 2014 (GEMINI II) I)	CG(placebo) 207 IG(ved) 209	Immunosuppressive use, n (%) CG 69 (33) IG 69 (33) <50(%)	Not All patients had experienced an inadequate response, loss of response, or intolerance to TNF antagonists, immunosuppressives, or corticosteroids within the past 5 years Results presented separately for naive and not
Sands 2022 (SEAVUE)	CG(ada) - 195	Unclear (abstract only)	Naive

	IG(ust) – 191		
Schreiber 2005	CG(placebo): 73 IG1(cert100mg): 74 IG2(cert200mg): 72 IG3(cert400mg): 73	Immunomodulators, n(%) CG 26 (35.6) IG1 26 (35.1) IG2 29 (40.3) IG3 27 (37.5) <50(%)	Mixed naive and not CG 16 (21.9) IG1 18 (24.3) IG2 17 (23.6) IG3 12 (16.7)
Schreiber 2018a	CG(placebo) = 28 IG1 Ande 150 mg Q2 W= 53 IG2 Ande 150 mg QW = 53 IG3 Ande 300 mg QW = 53	Immunomodulators, n(%) CG 19 (35.8) IG1 17 (32.1) IG2 8 (15.1) IG3 8 (28.6) <50(%)	Not (vast majority) CG 46 (86.8) IG1 45 (84.9) IG2 43 (81.1) IG3 24 (85.7)
Schwartz 2021 - ENTE RPRISE	IG1(ved) 16 IG2(ved+) 18 The study compared vedolizumab regimens	Immunosuppressants, n(%) IG1 4(28.6) IG2 3(21.4) <50(%)	Mixed naive and not "In each regimen, 11 patients (78.6%) had prior anti-TNF therapy at baseline"
Targan 1997	CG(placebo): 25 IG1(ifx5mg): 27 IG2(ifx10mg): 28 IG3(ifx20mg): 28	Mercaptopurine, n(%) CG 4 (16) IG1 4 (15) IG2 4 (14) IG3 4 (14) Azathioprine, n(%) CG 7 (28) IG1 5 (19) IG2 4 (14) IG3 8 (29) <50%	Naive
Targan 2007 (ENCORE)	CG(placebo): 250 IG(nat): 259	Immunosuppressants, n(%) CG 96 (38) IG 97 (37) <50%	Mixed naive and not Prior use of anti-tumor necrosis factor agents, n(%) CG 112 (45) IG 130 (50)
Vermeire 2017 FITZROY - induction	CG(placebo) – 44 IG(fil) – 130	Immunomodulators (eg, thiopurines and methotrexate) must have been discontinued at least 25 days before the first dose of the study drug immunomodulators (eg, thiopurines and methotrexate) must have been discontinued at least 25 days before the first dose of the study drug <50%	Mixed naive and not Previous anti-TNF exposure, n(%) CG 28 (64) IG 73 (56)
Vermeire 2017 FITZROY - induction non-responders	CG(placebo) – 9 IG2(fil200mg) - 25	<50% (as above)	Mixed naive and not (as above, not provided separately)

Watanabe 2012 - Induction	CG(placebo) 23 IG1(ada80/40mg) 34 IG2(ada160/80mg) 33	Immunosuppressants, n(%) CG 8 (34.8) IG1 11 (32.4) IG2 10 (30.3) <50%	Mixed naive and not Previous use of infliximab or biologic at baseline CG 13 (56.5) IG1 20 (58.8) IG2 19 (57.6) Previous exposure to anti-TNF agents other than adalimumab was allowed; primary non-responders to prior anti-TNF therapy were excluded
Watanabe 2020 - Induction	CG(placebo) – 78 IG(ved) – 79	Corticosteroids and immunomodulators, n(%) CG 11 (14.1) IG 9 (11.4) <50%	Mixed naive and not Prior anti-TNFa treatment, n(%) CG 62 (79.5) IG 61 (77.2)
Winter 2004	CG(placebo)= 25 IG1(cert1.25mg)=2 IG2(cert5mg)=25 IG3(cert10mg)=17 IG4(cert20mg)=23	Patients receiving immunosuppressive therapy, n(%) CG 11 (44) IG1 0(0) IG2 11 (44) IG3 9 (53) IG4 10(44) <50%	Mixed naive and not Prior anti-TNFa treatment, n(%) CG 3 (13) IG1 1 (50) IG2 6 (23) IG3 5 (29) IG4 7 (30)
Ye 2019	CG(ifx) 109 IG(CT-P13) 111	Treatment with immunomodulators, n(%) CG 80(73%) IG 84 (76%) >50%	Naive
Loftus 2023 (U-EXCEL)	CG(placebo) 176 IG(upa) 350	Unclear (press release only)	Not

Table 2

Induction studies' intervention details

Study ID	Intervention medications IG	Intervention medications CG	Previous experience of biologic therapy	Medications up to study beginning	Medications that had to be discontinued prior to starting study	Mandatory medications per study protocol	Concomitant Medications during study
Chen 2020	Patients were randomized to double-blind adalimumab 160/80 mg at weeks 0/2 and 40 mg at weeks 4/6 or placebo at weeks 0/2 followed by blinded adalimumab 160/80 mg at weeks 4/6.	Placebo at weeks 0/2 followed by blinded adalimumab 160/80 mg at weeks 4/6.	Patients were naïve to anti-TNF therapy	Corticosteroid use : CG- 32 (31%), IG- 31 (30%) Immunosuppressant use, CG- 65 (63%), IG- 61 (60%) Azathioprine: CG-59 (57%), IG-60 (59%) Mercaptopurine : CG- 2 (2%), IG- 0 Methotrexate: 4 (4%), IG-1 (1%)	NR	NR	Doses of other CD-related medications (e.g., immunosuppressants, aminosalicylates, and CD-related antibiotics) were to remain stable during the study except if treatment-related toxicities were considered moderate to severe in the opinion of the investigator.

Colombes I 2007 (CHARM) - Induction (non-responders)	IG1 (eow): adalimumab 40mg once every other week, subcutaneous IG2 (weekly): adalimumab 40mg weekly, subcutaneous	Placebo (no further details)	Previous TNF-antagonist exposure: n(%) 152 (54.5) out of 279 participants	Concurrent therapies for CD, including stable dosages (for at least 4 weeks before screening) of azathioprine, 6-mercaptopurine, methotrexate, 5-aminosalicylates, sulfasalazine, oral mesalamine, and CD-related antibiotics, were permitted, as were stable dosages (for at least 2 weeks before screening) of prednisone (≤ 30 mg/day or equivalent) or budesonide (≤ 9 mg/day) (patients could not be on both prednisone and budesonide). Patients who had received infliximab or any TNF antagonist other than adalimumab more than 12 weeks before screening could be enrolled provided that they did not exhibit initial nonresponse to the agent (ie, no clinical response to first injection as judged by the investigator). Female patients of childbearing potential were required to use an effective form of birth control.	Patients could not be enrolled if : currently, on parenteral nutrition; had received investigational chemical agents within 30 days or investigational biologic therapy within 3 months before screening; had received antibiotic treatment for non-CD-related infections within 3 weeks before screening; had received treatment with adalimumab or participated in an adalimumab clinical study; had received enema therapy within 2 weeks before screening; had received cyclosporine, mycophenolate mofetil, or tacrolimus within 8 weeks of screening	All patients entered a 2-week screening period before their baseline assessment. At the baseline visit (week 0), all eligible patients received open-label adalimumab 80mg subcutaneously followed by a 40-mg dose at week 2.	From all three groups n(%) out of 279 participants Any corticosteroid: 129; prednisone: 86; budesonide: 39 Any immunosuppressive: 126; Azathioprine: 88; 6-mercaptopurine: 27; methotrexate: 29 5-aminosalicylates: 100
Colombes I 2010 (SONIC)	IG1 - Infliximab (IFX) only group - intravenous infusions of infliximab at 5mg/kg of body weight at wk 0, 2, 6, 14, 22 plus daily oral placebo through wk 30 IG2 - Combination therapy - intravenous infusion of infliximab at 5mg/kg of body weight at wk 0, 2, 6, 14, 22 plus daily oral azathioprine at 2.5mg/kg of body weight through wk 30	CG - Azathioprine only group - daily oral azathioprine at 2.5mg/kg of body weight through wk 30 plus intravenous placebo infusions at wk 0, 2, 6, 14, 22	It was ensured that there was previous use of anti-TNF alpha drugs but no mention of other biologics	Patients who received systemic corticosteroids during main study: Baseline IG1 - IFX only - 40 patients at mean dose of 24.8 ± 16.2 mg/day; Baseline IG2 - 24.9 $\pm$ 12.8 mg/day; Baseline CG - 23.8 $\pm$ 12.6 mg/day	Not reported	Not reported	Systemic corticosteroids could be initiated (for patients not receiving them at baseline) with the dose maintained, increased, or decreased until week 14 (maximum allowed dose, 40 mg per day). Patients who received systemic corticosteroid during the main study: Week 2: CG (AZA) - 48 patients at mean dose of 22.9 ± 12.5 mg/day; IG1 (IFX) - 50 patients at mean dose of 24.8 ± 16.2 mg/day; IG2 (Combo) - 49 patients at mean dose of 22.8 ± 11.9 mg/day Week 6: CG (AZA) - 53 patients at mean dose of 18.6 ± 11.6 mg/day; IG1 (IFX) - 52 patients at mean dose of 17.7 ± 11.0 mg/day; IG2 (Combo) - 51 patients at mean dose of 18.3 ± 11.6 mg/day Week 10: CG (AZA) - 56 patients at mean dose of 16.

							2±11.2 mg/day; IG1 (IFX) - 56 patients at mean dose of 15.7±14.9 mg/day; IG2 (C ombo) - 52 patients at mean dose of 15.0±11.1 mg/day Week 18: CG (AZA) - 59 patients at mean dose of 13.5±10.9 mg/day; IG1 (IFX) - 57 patients at mean dose of 13.2±17.2 mg/day; IG2 (C ombo) - 56 patients at mean dose of 11.6±10.9 mg/day Week 26: CG (AZA) - 60 patients at mean dose of 11.6±10.3 mg/day; IG1 (IFX) - 60 patients at mean dose of 11.0±16.0 mg/day; IG2 (C ombo) 58 patients at mean dose of 9.4±10.1 mg/day
D'Haeens 1999 (refractory CD)	IG-IFX5 Infliximab 5mg/kg. Single 2-hour Intravenous infusion. IG-IFX10 Infliximab 10mg/kg. Single 2-hour Intravenous infusion. IG-IFX20 Infliximab 20mg/kg. Single 2-hour Intravenous infusion.	CG 0.1% Human Serum Albumin identical in appearance to the infliximab solution. Single 2-hour Intravenous infusion (DOSE NOT REPORTED)	NOT REPORTED	Patients were eligible if CD was refractory to: mesalamine for 8 or more weeks (at least 4 weeks' stable dose); corticosteroids up to 40mg prednisone-equivalent per day for 8 or more weeks with stable doses for at least 2 weeks; and mercaptopurine or azathioprine for 6 or more months, with stable doses for at least 8 weeks before screening Concomitant medication – (i) Azathioprine – CG 3/8 (37.50%). IG-IFX5 3/7 (42.86%). IG-IFX10 1/7 (14.29%). IG-IFX20 5/8 (62.50%). (ii) Steroids – CG 5/8 (62.50%). IG-IFX5 4/7 (57.14%). IG-IFX10 3/7 (42.86%). IG-IFX20 4/8 (50.0%)	Patients were excluded if they underwent treatment with cyclosporine, methotrexate, or experimental agents within 3 months before inclusion	NOT REPORTED – No protocol found	Patients were eligible if CD was refractory to: mesalamine for 8 or more weeks (at least 4 weeks' stable dose); corticosteroids up to 40mg prednisone-equivalent per day for 8 or more weeks with stable doses for at least 2 weeks; and mercaptopurine or azathioprine for 6 or more months, with stable doses for at least 8 weeks before screening Concomitant medication – (i) Azathioprine – CG 3/8 (37.50%). IG-IFX5 3/7 (42.86%). IG-IFX10 1/7 (14.29%). IG-IFX20 5/8 (62.50%). (ii) Steroids – CG 5/8 (62.50%). IG-IFX5 4/7 (57.14%). IG-IFX10 3/7 (42.86%). IG-IFX20 4/8 (50.0%)
D'Haeens 2008	Early Combined Immunosuppression - Patients assigned to early combined immunosuppression received three infusions of infliximab in doses of 5 mg/kg bodyweight	Conventional management -Patients received induction treatment with either methylprednisolone or budesonide. For those who responded to these treatments, the dose of corticosteroid was	According to inclusion criteria, eligible patients included those who had not previously received biologic therapy. THEREFORE, CG - N, IG - N.	Mesalazine use - CG 2/64 (3.1%). IG 3/65 (4.6%)	NOT REPORTED	NOT REPORTED - No protocol	NOT REPORTED - may possibly be the same as medication up to study beginning but authors have not mentioned whether mesalazine was continued or discontinued when study began

	light at weeks 0, 2, and 6, in combination with azathioprine in doses of 2–2.5 mg/kg per day from day 0 onwards. If a patient responded to and tolerated both drugs, azathioprine was continued for the duration of the trial. Patients who were intolerant to azathioprine were given subcutaneous methotrexate at an initial dose of 25 mg each week for 12 weeks with the dose reduced to 15 mg per week thereafter	tapered. For methylprednisolone, an initial daily dose of 32 mg was prescribed for 3 weeks, followed by tapering by 4 mg per week to discontinuation. Patients who received budesonide were prescribed 9 mg per day for 8 weeks with tapering to discontinuation by 3 mg per week thereafter. Hence treatment with either drug lasted 10 weeks. If a patient's symptoms worsened during the course of corticosteroid tapering, the dose increased to the initial dose and repeated the induction treatment. If their symptoms continued to worsen despite this manoeuvre, azathioprine was introduced (2–2.5 mg/kg per day). Patients who relapsed after withdrawal of corticosteroids were given a second course of corticosteroids in combination with azathioprine. For patients who failed 4 weeks of corticosteroid treatment, authors increased the methylprednisolone dose to 64 mg per day and added azathioprine. They gave 64 mg methylprednisolone per day for 2 weeks and then tapered this dose by 8 mg per week to a daily dose of 32 mg. Thereafter, methylprednisolone was tapered by 4 mg each week. Any patients who remained symptomatic after 16 w					
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		weeks of azathioprine treatment received an induction course of infliximab (5 mg/kg bodyweight at weeks 0, 2, and 6) and continued antimetabolite treatment. Patients who relapsed despite the use of methotrexate or those who were intolerant to both azathioprine and methotrexate also received infliximab, without antimetabolite treatment. They repeated the infusion on relapse of symptoms in these patients.					
Duan 2013	IG1 - Infliximab 5 mg/kg at Week 0, Week 2, and Week 6 to induce remission followed by Infliximab 5mg/kg every 8 weeks to maintain remission. Route NOT REPORTED. IG2 - the combination treatment group was given azathioprine 2.5 mg/kg qd, and on the 0th and 2nd, Infliximab 5 mg/kg was given for 6 weeks, and then infliximab 5 mg/kg was given every 8 weeks. Route NOT REPORTED	CG: Azathioprine 2.5 mg/kg qd Route NOT REPORTED	NOT REPORTED	NOT REPORTED	NOT REPORTED	No Protocol	NOT REPORTED
Feagan 2008c	IG1: MLN0002 (vedolizumab) 0.5 mg/kg IV at days 1 and 29 IG2: MLN0002 (vedolizumab) 2.0 mg/kg IV at days 1 and 29	CG: placebo IV at days 1 and 29 (AGENT and DOSE NOT REPORTED)	Patients previously treated with biologic therapy for Crohn's disease were ineligible. Therefore, it can be assumed that - previous experience of biologic therapy - CG N. IG1 N. IG2 N.	Mesalamine [%age converted to numbers] CG: 47% -> 27.26 -> 27/58; IG1: 55% -> 34.1 -> 34/62; IG2: 42% -> 27.3 -> 27/65 Months on oral or continuous intravenous steroid therapy [mean(SD)] CG: 3.8(6.72)	Patients requiring cyclosporine or immunosuppressives within 3 months or investigational drugs within 30 days before screening, systemic corticosteroids, heparin, nonsteroidal anti-inflammatory drugs, tube feeding, defined formula diets, or parenteral alimentation, were excluded New treatments for Crohn's disease were not permitted during the study	NOT REPORTED - No protocol	Participants could receive concomitant treatment for Crohn's disease with mesalamine or antibiotics provided they had been maintained on a stable dose for 2 weeks immediately before screening. Mesalamine [%age converted to numbers]

				IG1: 2.6(5.59) IG2: 3.3(6.08)		CG: 47% -> 27.26 -> 27/58; IG1: 55% -> 34.1 -> 34/62; IG2: 42% -> 27.3 -> 27/65 Months on oral or continuous intravenous steroid therapy [mean(SD)] CG: 3.8(6.72) IG1: 2.6(5.59) IG2: 3.3(6.08)	
Feagan 2015a (UNITI-1)	Interventions IG (if more than one, please separate in IG1, IG2, etc.): to receive a single intravenous infusion of 130 mg of ustekinumab, a weight-range-based dose that approximated 6 mg of ustekinumab per kilogram of body weight, or placebo. (The administration of 6 mg of ustekinumab per kilogram meant that patients weighing ≤55 kg received 260 mg, those weighing >55 kg and ≤85 kg received 390 mg, and those weighing >85 kg received 520 mg.)	CG: Placebo (not specified)	History of TNF antagonist treatment failure — no. (%) 1) CG IG1 IG2 Patients who received 1 drug CG 112 (45.3) IG1 124 (50.6) IG2 120 (48.2) received 2 or 3 drugs CG 134 (54.3) IG1 119 (48.6) IG2 126 (50.6)	Medications for Crohn's disease taken at baseline — no. (%) 1) CG IG1 IG2 One or more medications CG 185 (74.9) IG1 178 (72.7) IG2 174 (69.9) Immunosuppressant CG 81 (32.8) IG1 74 (30.2) IG2 78 (31.3) Aminosalicylate CG 54 (21.9) IG1 50 (20.4) IG2 50 (20.1) Glucocorticoid CG 111 (44.9) IG1 121 (49.4) IG2 108 (43.4)	NR	NR	Stable doses of immunosuppressants, mesalamine, antibiotics, or oral glucocorticoids (≤40 mg of prednisone per day or ≤9 mg of budesonide per day) or a combination thereof were permitted.
Feagan 2015b (UNITI-2)	IG (if more than one, please separate in IG1, IG2, etc.): At week 0, patients in both induction trials were randomly assigned, in a 1:1:1 ratio, to receive a single intravenous	CG: Placebo (not specified)	In UNITI-2, 68.6% of patients had not received TNF antagonists (data not shown). NR	Medications for Crohn's disease taken at baseline — no. (%) One or more medications CG 185 (75.2) IG1 161 (77.0) IG2 170 (81.3) Immunosuppressant¶	NR	NR	Stable doses of immunosuppressants, mesalamine, antibiotics, or oral glucocorticoids (≤40 mg of prednisone per day or ≤9 mg of budesonide per day) or a combination thereof were permitted.

	us infusion of 130 mg of ustekinumab, a weight-range-based dose that approximated 6 mg of ustekinumab per kilogram of body weight, or placebo. (The administration of 6 mg of ustekinumab per kilogram meant that patients weighing ≤55 kg received 260 mg, those weighing >55 kg and ≤85 kg received 390 mg, and those weighing >85 kg received 520 mg.)			CG 73 (34.8) IG1 74 (35.4) IG2 72 (34.4) Aminosalicilate CG 89 (42.4) IG1 89 (42.6) IG2 93 (44.5) Glucocorticoid CG 75 (35.7) IG1 80 (38.3) IG2 92 (44.0)			
Feagan 2017	IG-R200: Risankizumab 200mg Intravenous (clear solution) at weeks 0, 4, and 8. IG-R600: Risankizumab 600mg Intravenous (clear solution) at weeks 0, 4, and 8. IG-RP: This is the combination of IG-R200 and IG-R600 (Risankizumab groups). This is not a separate study arm by itself.	Placebo (clear solution) Intravenous at weeks 0, 4, and 8 (Agent and Dose NOT REPORTED)	Previous TNF antagonist use [number of patients/total patients in given group (percentage)] – (i) 1 – CG 12/39 (31%). IG-R200 9/41 (22%). IG-R600 9/41 (22%). IG-RP 18/82 (22%). (ii) 2 – CG 20/39 (51%). IG-R200 23/41 (56%). IG-R600 24/41 (59%). IG-RP 47/82 (57%). (iii) ≥3 – CG 5/39 (13%). IG-R200 7/41 (17%). IG-R600 4/41 (10%). IG-RP 11/82 (13%). (iv) Missing – CG 2/39 (5%). IG-R200 2/41 (5%). IG-R600 4/41 (10%). IG-RP 6/82 (7%) Worst outcome of ≥1 previous TNF antagonists [number of patients/total patients in given group (percentage)] – (i) Inadequate response – CG 10/39 (26%). IG-R200 16/41 (39%). IG-R600 11/41 (27%). IG-RP 27/82 (33%). (ii) Loss of response – CG	Corticosteroids only [number of patients/total patients in given group (percentage)] – CG 6/39 (15%). IG-R200 7/41 (17%). IG-R600 9/41 (22%). IG-RP 16/82 (20%) Corticosteroids AND IM [number of patients/total patients in given group (percentage)] – CG 5/39 (13%). IG-R200 3/41 (7%). IG-R600 3/41 (7%). IG-RP 6/82 (7%) IM only [number of patients/total patients in given group (percentage)] – CG 8/39 (21%). IG-R200 7/41 (17%). IG-R600 5/41 (12%). IG-RP 12/82 (15%)	NOT REPORTED	NOT REPORTED – No protocol	Note – These are the same as Medications up to study beginning Corticosteroids only [number of patients/total patients in given group (percentage)] – CG 6/39 (15%). IG-R200 7/41 (17%). IG-R600 9/41 (22%). IG-RP 16/82 (20%) Corticosteroids AND IM [number of patients/total patients in given group (percentage)] – CG 5/39 (13%). IG-R200 3/41 (7%). IG-R600 3/41 (7%). IG-RP 6/82 (7%) IM only [number of patients/total patients in given group (percentage)] – CG 8/39 (21%). IG-R200 7/41 (17%). IG-R600 5/41 (12%). IG-RP 12/82 (15%)

			21/39 (54%). IG-R200 13/41 (32%). IG-R600 17/41 (41%). IG-RP 30/82 (37%). (iii) Unacceptable adverse events – CG 1/39 (3%). IG-R200 2/41 (5%). IG-R600 5/41 (12%). IG-RP 7/82 (9%). (iv) Other – CG 2/39 (5%). IG-R200 3/41 (7%). IG-R600 1/41 (2%). IG-RP 4/82 (5%). (v) Unknown – CG 1/39 (3%). IG-R200 3/41 (7%). IG-R600 2/41 (5%). IG-RP 5/82 (6%) Data on non-TNF antagonist biologics is NOT REPORTED				
Ghosh 2003	IG1 - One infusion of Natalizumab dose 3mg/kg (Route NOT REPORTED) followed by one infusion of Placebo (Agent NOT REPORTED, Route NOT REPORTED, Dose NOT REPORTED) four weeks later. IG2 - Two infusions of Natalizumab 3mg/kg four weeks apart (Route NOT REPORTED). IG3 - Two infusions of Natalizumab 6mg/kg four weeks apart (Route NOT REPORTED)	CG Dose, regimen, route: Placebo. Two infusions four weeks apart. Agent NOT REPORTED. Route NOT REPORTED. Dose NOT REPORTED	Excluded patients with previous biologic treatment 'criteria for exclusion included prior treatment with any antibody agent'	At baseline patients were receiving (listed as concomitant medications in paper but not made clear whether they were started at baseline or if patients were already on them before study): None for Crohn's disease* - CG 12 (19%). IG1 10 (15%). IG2 9 (14%). IG3 5 (10%) 5-Aminosalicylate compounds - CG 30 (48%). IG1 41 (60%). IG2 41 (62%). IG3 30 (59%) Oral corticosteroids - CG 31 (49%). IG1 31 (46%). IG2 37 (56%). IG3 32 (63%). Azathioprine or mercaptopurine with or without corticosteroids - CG 22 (35%). IG1 26 (38%). IG2 17 (26%). IG3 9 (18%). *The patients were not receiving 5-aminosalicylate compounds, corticosteroids, or immunosuppressants	NOT REPORTED but paper states 'Patients who had received methotrexate, cyclosporine, or any investigational agents within three months before randomization were excluded; patients who were receiving azathioprine or mercaptopurine were required to have been taking a stable dose for at least four months before randomization. Other criteria for exclusion included prior treatment with any antibody agent, current use of oral prednisolone at a dose of more than 25 mg per day or another corticosteroid at an equivalent dose'	NOT REPORTED/No Protocol	None for Crohn's disease* - CG 12 (19%). IG1 10 (15%). IG2 9 (14%). IG3 5 (10%) 5-Aminosalicylate compounds - CG 30 (48%). IG1 41 (60%). IG2 41 (62%). IG3 30 (59%) Oral corticosteroids - CG 31 (49%). IG1 31 (46%). IG2 37 (56%). IG3 32 (63%). Azathioprine or mercaptopurine with or without corticosteroids - CG 22 (35%). IG1 26 (38%). IG2 17 (26%). IG3 9 (18%). *The patients were not receiving 5-aminosalicylate compounds, corticosteroids, or immunosuppressants
Gordon 2001	Natalizumab	Placebo	Previous exposure to infliximab IG :5 (7%) CG :7 (10%)	NR	NR	NR	NR
Hanauer 2002 (ACC)	At week 0, all eligible patients received a 5 mg/kg intravenous infusion of infliximab.	At week 0, all eligible patients received a 5 mg/kg intravenous infusion of infliximab.	'Patients were excluded from the study if they had received previous treatment with i	Patients receiving the following treatments were eligible: 5-aminosalicylates or antibiotics (if the dose	Patients not receiving medical therapy had to have discontinued treatment for at least 4 weeks before screening	NOT REPORTED – No protocol	Note* - SAME AS Medications up to study beginning Patients receiving the following treatments

NT I) - I nduc tion (non- res pon se)	usion of infliximab. IG1: 5 mg/kg infliximab infusions at week 2, 6 and every 8 weeks thereafter until week 46 IG2: 10 mg/kg infliximab infusions at week 2, 6 and every 8 weeks thereafter until week 46	CG: Placebo infusion at week 2, 6 and every 8 weeks thereafter until week 46	infliximab or any other agent targeted at TNF.' THEREFORE, IG – N. CG – N.	remained constant for 4 weeks before the screening visit); corticosteroids (prednisone, prednisolone, or budesonide) at the equivalent of 40 mg per day of prednisone or less (stable dose for 3 weeks); azathioprine and 6-mercaptopurine (stable dose for 8 weeks); or methotrexate (stable dose for 6 weeks) NOT REPORTED per IG/CG so the following data is based on non-responders as a whole. 5-Aminosalicylates – 129/238 (54%) 6-Mercaptopurine and Azathioprine – 63/238 (27%) Methotrexate – 13/238 (6%) Corticosteroids of which (i) Any – 118/238 (50%) (ii) >20mg per day – 32/238 (13%)		were eligible: 5-aminosalicylates or antibiotics (if the dose remained constant for 4 weeks before the screening visit); corticosteroids (prednisone, prednisolone, or budesonide) at the equivalent of 40 mg per day of prednisone or less (stable dose for 3 weeks); azathioprine and 6-mercaptopurine (stable dose for 8 weeks); or methotrexate (stable dose for 6 weeks) NOT REPORTED per IG/CG so the following data is based on non-responders as a whole. 5-Aminosalicylates – 129/238 (54%) 6-Mercaptopurine and Azathioprine – 63/238 (27%) Methotrexate – 13/238 (6%) Corticosteroids of which (i) Any – 118/238 (50%) (ii) >20mg per day – 32/238 (13%)
Hauer 2006 (CLAS SIC I)	IG1=Adalimumab 40 mg/20 mg week 0 and week 2 subcutaneous IG2=Adalimumab 80 mg/40 mg week 0 and week 2 subcutaneous IG3=Adalimumab 160 mg/80 mg subcutaneous week 0 and week 2	CG= Placebo weeks 0 and 2	Patients are naive	Corticosteroid use: CG=25 IG1=17 IG2=32 IG3=24 Immunosuppressive agents: CG=22 IG1=23 IG2=21 IG3=22 Crohn's disease-related antibiotics: CG=5 IG1=10 IG2=7 IG3=4 5-Aminosalicylates: CG=37		

				IG1=37 IG2=40 IG3=39			
Hanauer 2021 (VOLT AIR E-CD)	BI 695501	Adalimumab	Previous exposure to infliximab IG=5 (7%) CG=7 (10%)	NR	NR	NR	NR
Lemann 2006	According to the randomization, patients received at 0, 2, and 6 weeks either a 2-hour infusion of infliximab (Remicade) administered at a dose of 5 mg/kg or an infusion of an identical placebo	Placebo exact name not mentioned. but given at same dosage and interval as infliximab	31 patients on Infliximab and 27 patients on placebo were naive	Steroids. At baseline, all patients were treated with prednisone or prednisolone at a daily dose of 10 mg or more.	Concomitant treatment that has been shown to facilitate steroid withdrawal in steroid-dependent patients such as mesalamine, budesonide, artificial nutrition, or other immunosuppressive drugs were not allowed during the study.	All patients were treated with AZA (2-3 mg/kg per day) or 6-MP (1-1.5 mg/kg per day). Patients previously treated with AZA or 6-MP (failure stratification) continued their treatment at the same dose; in the intensive-stratum patients, AZA (2-2.5 mg/kg per day) was started 1 week after the first infliximab infusion (to differentiate side effects related to infliximab from those related to AZA).	Not reported separately for IG/CG
Present 1999	CG: placebo IG1 : Infliximab 5mg/kg (0,2,6,)		CG Corticosteroids 11 (35) Mercaptopurine or azathioprine 9 (29)	- cyclosporin - steroids ,methotrexate azathioprine ,mercaptopurine and antibiotics IF not already on (and stable)		CG Corticosteroids 11 (35) Mercapto	

	IG2: Infliximab 10mg /kg (0,2,6,)		Aminosalicylates 19 (61) Antibiotics11 (35) IG1 Corticosteroids 12 (39) Mercaptopurine or azathioprine12 (39) Aminosalicylates 17 (55) Antibiotics6 (19) IG2 Corticosteroids 10 (31) Mercaptopurine or azathioprine17 (53) Aminosalicylates 16 (50) Antibiotics11 (34)	these medications, they had to have discontinued therapy at least four weeks before enrollment		purine or a zathioprine9 (29) Aminosalicylates 19 (61) Antibiotics 11 (35) IG1 Corticosteroids 12 (39) Mercaptopurine or a zathioprine12 (39) Aminosalicylates 17 (55) Antibiotics 6 (19) IG2 Corticosteroids 10 (31) Mercaptopurine or a zathioprine17 (53) Aminosalicylates 16 (50) Antibiotics 11 (34)	
Pan es 2 017 Indu ction	IG-T5 – Tofacitinib 5mg twice daily for 8 weeks (ROUTE NOT REPORTED but likely to be ORAL given it is twice daily over a period of 8 weeks). IG-T10 – Tofacitinib 10mg twice daily for 8 weeks (ROUTE NOT REPORTED but likely to be ORAL given it is twice daily over a period of 8 weeks). IG-T15 – Tofacitin	CG – Placebo twice daily for 8 weeks (ROUTE, DOSE, and AGENT NOT REPORTED but ROUTE is likely to be ORAL given it is twice daily over a period of 8 weeks)	Prior use of TNFi – Y CG 70/91 (76.9%). IG-T5 68/86 (79.1%). IG-T10 66/86 (76.7%). IG-T15 11/16 (68.8%) Previous exposure to biologics as a whole (which includes JAK inhibitors) is NOT REPORTED	Concomitant corticosteroids were allowed up to oral prednisone-equivalent 30mg/day or budesonide 9mg/day, provided a stable dose had been taken for at least 2 weeks prior to baseline. Concomitant oral 5-ASA or sulfasalazine (stable dose for at least 4 weeks prior to baseline), chronic treatment for CD with antibiotics (e.g. metronidazole, rifaximin; stable dose for at least 2 weeks prior to baseline), rectally administered formulation of corticosteroids or 5-ASA (stable dose for at least 2 weeks prior to baseline) was also permitted but only data on corticosteroids is provided.	Patients receiving azathioprine, 6-mercaptopurine or methotrexate were required to stop these agents at least two weeks before randomisation Concomitant tumour necrosis factor inhibitor (TNFi) were not allowed, and a wash-out period of at least eight weeks prior to randomisation was required Cyclosporine, mycophenolate or tacrolimus were required to be stopped at least 4 weeks prior to baseline Intravenous Corticosteroids were required to be stopped at least 2 weeks prior to baseline Other investigational or marketed biologics with immunomodulatory properties were required to be stopped at least 3 months prior to baseline Treatment with Natalizumab or any anti-adhesion molecule was to be stopped at least 1 year prior to baseline	N/A – No protocol found	Note - Same as medication up to study beginning Concomitant corticosteroids were allowed up to oral prednisone-equivalent 30mg/day or budesonide 9mg/day, provided a stable dose had been taken for at least 2 weeks prior to baseline. Concomitant oral 5-ASA or sulfasalazine (stable dose for at least 4 weeks prior to baseline), chronic treatment for CD with antibiotics (e.g. metronidazole, rifaximin; stable dose for at least 2 weeks prior to baseline), rectally administered formulation

	ib 15mg twice daily for 8 weeks (ROUTE NOT REPORTED but likely to be ORAL given it is twice daily over a period of 8 weeks)			Use of corticosteroids at study entry – CG 35/91 (38.5%). IG-T5 32/86 (37.2%). IG-T10 28/86 (32.6%). IG-T15 4/16 (25.0%)	Moderate to potent CYP3A inducers were prohibited within 28 days or 5 half-lives, whichever was longer, prior to first dose of study drug Moderate to potent CYP3A inhibitors were prohibited within 7 days or 5 half-lives whichever was longer prior to first dose of study drug	of corticosteroids or 5-ASA (stable dose for at least 2 weeks prior to baseline) was also permitted but only data on corticosteroids is provided. Use of corticosteroids at study entry – CG 35/91 (38.5%). IG-T5 32/86 (37.2%). IG-T10 28/86 (32.6%). IG-T15 4/16 (25.0%)
Sanborn 2001a	IG1: 2-hr IV infusion CDP571 (humicade) 10 mg/kg IG2: 2-hr IV infusion CDP571 20 mg/kg	CG: 2-hr IV infusion Placebo: 5% (wt/vol) dextrose	Patients who had previously received anti-TNF therapies were ineligible	- Patients receiving prednisone or budesonide for at least 4 weeks with a stable prednisone dose of 10 –30mg/day or a budesonide dose of 9 mg for at least 2 weeks were eligible - Patients receiving stable doses of azathioprine (atleast 1.5 mg /kg/day) or 6-mercaptopurine (at least 0.75mg/kg/day) for at least 4 months, or methotrexate (at least 15 mg/week) for at least 3 months were eligible	NR	NR Corticosteroids and/or immunosuppressive: CG (8 weekly)- 18 CG (12 weekly)- 20 IG1 (8 weekly)- 20 IG1 (12 weekly)- 17 IG2 (8 weekly)- 19 IG2 (12 weekly)- 20 Corticosteroids: CG (8 weekly)- 9 CG (12 weekly)- 18 IG1 (8 weekly)- 18 IG1 (12 weekly)- 13 IG2 (8 weekly)- 14 IG2 (12 weekly)- 17 Azathioprine or 6-mercaptopurine: CG (8 weekly)- 10 CG (12 weekly)- 10 IG1 (8 weekly)- 5 IG1 (12 weekly)- 8 IG2 (8 weekly)- 7 IG2 (12 weekly)- 7 Methotrexate: CG (8 weekly)- 2 CG (12 weekly)- 3 IG1 (8 weekly)- 0 IG1 (12 weekly)- 1 IG2 (8 weekly)- 1 IG2 (12 weekly)- 2 5-Aminosalicylates (mesalamine, sulfasalazine, olsal

							azine): CG (8 weekly)- 17 CG (12 weekly)- 16 IG1 (8 weekly)- 17 IG1 (12 weekly)- 13 IG2 (8 weekly)- 17 IG2 (12 weekly)- 12
San d bor n 20 01b	IG – Etanercept 25mg subcutaneous TWICE WEEKLY for 8 weeks, injected by patients. Etanercept was supplied in single dose vials containing a lyophilized powder consisting of 25mg etanercept, 40mg of mannitol, 10mg of sucrose, and 1.2mg of tromethamine. The study drug was reconstituted with 1.0 mL of bacteriostatic water and dispensed in prefilled syringes by an unblinded study pharmacist at each center. Etanercept preparation had a clear and colorless appearance similar to the placebo preparation.	CG – Placebo subcutaneous TWICE WEEKLY for 8 weeks, injected by patients. Preparation was supplied in single dose vials containing a lyophilized powder consisting of 40mg mannitol, 10mg sucrose, and 1.2mg of tromethamine. The study drug was reconstituted with 1.0 mL of bacteriostatic water and dispensed in prefilled syringes by an unblinded study pharmacist at each center. Placebo preparation had a clear and colorless appearance similar to the etanercept preparation.	Prior treatment with infliximab within the last year – CG 7/20 (35.00%). IG 9/23 (39.13%). Prior treatment with infliximab at any time – CG 8/20 (40.00%). IG 12/23 (52.17%) Previous exposure to other biologics or biologics as a whole is NOT REPORTED	Patients receiving prednisone (no upper limit on prednisone dose) or budesonide for at least 4 weeks with a stable dose for at least 2 weeks were eligible. Patients receiving stable doses of azathioprine or 6-mercaptopurine for at least 12 weeks, or methotrexate or mycophenolate mofetil for at least 8 weeks were eligible. Continued treatment with oral or rectal 5-aminosalicylates, rectal corticosteroids, and oral antibiotics was allowed, provided the dose had been stable for at least 2 weeks Corticosteroids – CG 7/20. IG 10/23. Azathioprine or 6-mercaptopurine – CG 7/20. IG 10/23. Methotrexate – CG 1/20. IG 1/20. Antibiotics – CG 5/20. IG 4/23. 5-Aminosalicylates* – CG 9/20. IG 11/23 *5-Aminosalicylates indicates: mesalamine, sulfasalazine, and olsalazine	Patients who had received anti-TNF therapy with infliximab within 12 weeks were ineligible. No patient received other investigational therapies within 28 days preceding randomisation. Patients who had received tacrolimus, cyclosporine, thalidomide, interleukin 10, or interleukin 11 within 4 weeks were not eligible. Nutritional therapy (parenteral nutrition or enteral nutrition with elemental or semi-elemental diet) was discontinued at the screening visit and was not permitted during the trial, with the exception of nocturnal tube feedings for adolescent patients with growth failure and enteral nutrition supplements for adult patients with malnutrition who were receiving a stable regimen for at least 2 weeks and continued that same regimen throughout the 8-week study.	NOT REPORTED – No protocol found	Patients receiving prednisone (no upper limit on prednisone dose) or budesonide for at least 4 weeks with a stable dose for at least 2 weeks were eligible. Patients receiving stable doses of azathioprine or 6-mercaptopurine for at least 12 weeks, or methotrexate or mycophenolate mofetil for at least 8 weeks were eligible. Continued treatment with oral or rectal 5-aminosalicylates, rectal corticosteroids, and oral antibiotics was allowed, provided the dose had been stable for at least 2 weeks Corticosteroids – CG 7/20. IG 10/23. Azathioprine or 6-mercaptopurine – CG 7/20. IG 10/23. Methotrexate – CG 1/20. IG 1/20. Antibiotics – CG 5/20. IG 4/23. 5-Aminosalicylates* – CG 9/20. IG 11/23 *5-Aminosalicylates indicates: mesalamine, sulfasalazine, and olsalazine
San d bor n 20 05a (EN ACT 1)	Natalizumab, 300mg at week 0, 4, and 8, Intravenous	Placebo (exact agent and dosage NOT REPORTED), dose at week 0,4, and 8, Intravenous	IG - Y 291 (40%), Refractory to such therapy 196 (27%) CG - Y 69 (38%), Refractory to such therapy 46 (25%)	NOT REPORTED for either IG or CG. May be possible that these are the same as concomitant medications (i.e. patients may already be on them before study) but it is not explicitly stated. Need to contact authors to confirm	NOT REPORTED	No Protocol	For both IG and CG, concurrent therapies, including stable doses of 5-aminosalicylates, prednisolone (25 mg per day or less) or equivalent, budesonide (6 mg per day or less), azathioprine, mercaptopurine, methotrexate, and antibiotics, were permitted. Corticosteroids - CG 70 (39%) IG 271 (37%). Prednisone - CG 53 (29%) IG 197

						(27%). Budesonide CG 20 (11%) IG 79 (11%) Immunosuppressants - CG 52 (29%) IG 247 (34%). Azathioprine - CG 38 (21%) IG 167 (23%). Mercaptopurine - CG 8 (4%) IG 49 (7%). Methotrexate - CG 6 (3%) IG 31 (4%) Antibiotics (metronidazole, tinidazole, ciprofloxacin, and clarithromycin) - CG 12 (7%) IG 43 (6%) 5-Aminosalicylates (mesalamine, sulfasalazine, and olsalazine) - CG 80 (44%) IG 343 (47%) ≥1 Corticosteroids or immunosuppressants - CG 100 (55%) IG 407 (56%) Corticosteroids and immunosuppressants - CG 22 (12%) IG 111 (15%)
Sanborn 2007a	Subcutaneous Adalimumab 160 mg at week 0 then Subcutaneous Adalimumab 80 mg at week 2	Placebo at week 0 then Placebo at week 2. Dose, Route, and Agent NOT REPORTED	The paper states 'To be included, patients must have been intolerant of infliximab or must have previously responded to infliximab and then lost response.' Therefore, number of patients with previous biologic experience - CG 166 (100%). IG 159 (100%) Previous loss of response to infliximab - CG 87 (52%). IG 77 (48%). Previous intolerance to infliximab - CG 95 (57%). IG 95 (60%). Of which (i) Acute reaction CG 63 (38%). IG 68 (43%). (ii) Delayed reaction CG 52 (31%). IG 43 (27%). (iii) Acute AND Delayed reaction CG 20 (12%). IG 15 (9%). Previous loss of response to infliximab AND previous intolerance to infliximab	NOT REPORTED EXPLICITLY. Paper states 'Concurrent therapies, including stable dosages of 5-aminosalicylates, prednisone (≤40 mg/d), budesonide (≤9 mg/d), azathioprine, 6-mercaptopurine, methotrexate, and antibiotics, were permitted' 'Dosages of all these medications were required to remain stable during the study'. Not stated whether these patients were already on these medications prior to study or were initiated at baseline during study. It is possible that the numbers of patients on each of the medications here is the same as for concomitant medications	Paper states 'We excluded patients who had a primary nonresponse to infliximab as defined by the investigator, received infliximab or another TNF antagonist within the past 8 weeks, previously received adalimumab (Humira, Abbott Laboratories, Abbott Park, Illinois), or participated in an adalimumab clinical trial' 'We excluded patients who changed dosages or discontinued azathioprine, 6-mercaptopurine, or methotrexate treatment within 12 weeks of screening. Similarly, we excluded patients who changed dosages or discontinued 5-aminosalicylates, mesalamine, or sulfasalazine treatment within 4 weeks of screening. Prednisone (≤40 mg/d) and budesonide (≤9 mg/d) dosages must have been stable for 2 weeks or more before screening. Dosages of all these medications were required to remain stable during the study.' 'We also excluded patients who had received antibiotic treatment for infections not related to Crohn disease within 3 weeks of the study' 'We also excluded patients with a history of clinically significant drug or alcohol abuse in the past year'	No Protocol. NOT REPORTED. Steroids* CG 73 (44%) IG 55 (35%). Any immunosuppressive agent CG 85 (51%) IG 73 (46%). 5-Aminosalicylates** CG 60 (36%) IG 45 (28%). *Budesonide, Betamethasone, Cortisone, Cloprednol, Corticosteroids, Dexamethasone, Deflazacort, Fluocortolone, Glucocorticoids, Glucocorticosteroids, Hydrocortisone, Methylprednisolone, Paramethasone, Prednisolone, Prednisone, or, Prednylidene. **Balsalazide, Mesalamine, Olsalazine, or Sulfasalazine.

			mab - CG 21 (13%). IG 19 (12%). Antibodies to infliximab (i) Absent CG 91 (57%) I G 88 (59%). (ii) Indeterminate* CG 8 (6%)** IG 12 (8%). (iii) Present CG 60 (38%)** IG 50 (33%) *Results are indeterminate because of presence of infliximab in 8 Placebo group patients and 12 Adalimumab group patients **One patient in Placebo group had measurable infliximab concentration and antibody to infliximab				
Sanborn 2007c (PR ECI SE 1)	injections of placebo Subcutaneous injections of certolizumab pegol at a dose of 400 mg	Subcutaneous injections of placebo (agent: NR)	Patients who had received any anti-TNF agent within the previous 3 months or who had had a severe hypersensitivity reaction or a lack of response to the first dose of another TNF antagonist were excluded	Glucocorticoids only: CG- 75 (23%) IG- 72 (22%) Immunosuppressive agents only: CG- 66 (20%) IG- 69 (21%) Glucocorticoids combined with immunosuppressive agents: CG- 55 (17%) IG- 57 (17%) Neither glucocorticoids nor immunosuppressive agents: CG- 132 (40%) IG- 133 (40%)	NR	NR	Patients could receive concomitant therapy with stable doses of 5-aminosalicylates, prednisolone or its equivalent (at a dose of 30 mg per day or less), azathioprine, 6-mercaptopurine, methotrexate, or antibiotics
Sanborn 2008 (Population 1)	IG SC-UST – Ustekinumab 90mg Subcutaneous at weeks 0, 1, 2, and 3. IG IV-PBO – Placebo (Agent and Dose NOT REPORTED). Intravenous Placebo at week 0. IG IV-UST – Ustekinumab 4.5mg/kg Intravenous at week 0. Note – Crossover to alternative th	CG SC-PBO Placebo (Agent and Dose NOT REPORTED). Subcutaneous placebo at weeks 0, 1, 2, and 3. Note – crossover to Ustekinumab 90mg Subcutaneous occurred at week 8 from which point we are not considering the data in our NMA	CG SC-PBO - Y 16/26 (62%). IG SC-UST - Y 14/25 (56%). IG IV-PBO - Y 11/27 (41%). IG IV-UST - Y 8/26 (31%) Note - These patients received infliximab more than 16 weeks before randomisation (see medications that had to be stopped prior to study)	Concomitant use of 5-aminosalicylates, antibiotics, prednisolone at a maximum daily dose of 20 mg, azathioprine, 6-mercaptopurine, or methotrexate was permitted. Concomitant medication doses remained constant, except corticosteroids, which could be tapered by 2.5 mg/wk after week 8. The following are reported in baseline characteristics (Table 1 for the whole population and table 2 for patients with previous infliximab exposure). A. Whole population	Patients were excluded from study if recent treatment with any investigational agent or an anti-TNF agent including infliximab within the past 16 weeks. Therefore, these agents needed to have been stopped at least 16 weeks prior to study	NOT REPORTED. No protocol	Note* Same as Medications up to study beginning Concomitant use of 5-aminosalicylates, antibiotics, prednisolone at a maximum daily dose of 20 mg, azathioprine, 6-mercaptopurine, or methotrexate was permitted. Concomitant medication doses remained constant, except corticosteroids, which could be tapered by 2.5 mg/wk after week 8. The following are reported in baseline characteristics (Table 1 for the whole population)

erapy occurred at week 8 from which point we are not considering the data in our NMA

Concomitant medications - CG SC-PBO 21/26 (81%). IG SC-UST 19/25 (76%). IG IV-PBO 19/27 (70%). IG IV-UST 20/26 (77%).

Oral Corticosteroids - CG SC-PBO 8/26 (31%). IG SC-UST 10/25 (40%). IG IV-PBO 8/27 (30%). IG IV-UST 7/26 (27%). Of which (i) **<=20mg/day - CG SC-PBO 7/26 (27%). IG SC-UST 9/25 (36%). IG IV-PBO 6/27 (22%). IG IV-UST 5/26 (19%).** (ii) **>20mg/day - CG SC-PBO 1/26 (4%). IG SC-UST 1/25 (4%). IG IV-PBO 2/27 (7%). IG IV-UST 2/26 (8%).**

Immunosuppressants - CG SC-PBO 10/26 (39%). IG SC-UST 5/25 (20%). IG IV-PBO 10/27 (37%). IG IV-UST 10/26 (39%). Of which (i) **6-Mercaptopurine, Azathioprine - CG SC-PBO 7/26 (27%). IG SC-UST 4/25 (16%). IG IV-PBO 8/27 (30%). IG IV-UST 9/26 (35%).** (ii) **Methotrexate - CG SC-PBO 3/26 (12%). IG SC-UST 1/25 (4%). IG IV-PBO 2/27 (7%). IG IV-UST 1/26 (4%).**

Oral Corticosteroids OR Immunosuppressants - CG SC-PBO 14/26 (54%). IG SC-UST 13/25 (52%). IG IV-PBO 14/27 (52%). IG IV-UST 15/26 (58%).

Oral Corticosteroids AND Immunosuppressants - CG SC-PBO 4/26 (15%). IG SC-UST 2/25 (8%). IG IV-PBO 4/27 (15%). IG IV-UST 2/26 (8%).

Antibiotics - CG SC-PBO 2/26 (8%). IG SC-UST 2/25 (8%). IG IV-PBO 2/27 (7%). IG IV-UST 1/26 (4%).

Aminosalicylates - CG SC-PBO 13/26 (50%). IG SC-UST 9/25 (36%). IG IV-PBO 14/27 (52%). IG IV-UST 10/26 (39%).

B. Patients with previous infliximab use

Concomitant medications - CG SC-PBO 12/16 (75%). IG SC-UST

lation and table 2 for patients with previous infliximab exposure).

A. Whole population

Concomitant medications - CG SC-PBO 21/26 (81%). IG SC-UST 19/25 (76%). IG IV-PBO 19/27 (70%). IG IV-UST 20/26 (77%).

Oral Corticosteroids - CG SC-PBO 8/26 (31%). IG SC-UST 10/25 (40%). IG IV-PBO 8/27 (30%). IG IV-UST 7/26 (27%). Of which (i) **<=20mg/day - CG SC-PBO 7/26 (27%). IG SC-UST 9/25 (36%). IG IV-PBO 6/27 (22%). IG IV-UST 5/26 (19%).** (ii) **>20mg/day - CG SC-PBO 1/26 (4%). IG SC-UST 1/25 (4%). IG IV-PBO 2/27 (7%). IG IV-UST 2/26 (8%).**

Immunosuppressants - CG SC-PBO 10/26 (39%). IG SC-UST 5/25 (20%). IG IV-PBO 10/27 (37%). IG IV-UST 10/26 (39%). Of which (i) **6-Mercaptopurine, Azathioprine - CG SC-PBO 7/26 (27%). IG SC-UST 4/25 (16%). IG IV-PBO 8/27 (30%). IG IV-UST 9/26 (35%).** (ii) **Methotrexate - CG SC-PBO 3/26 (12%). IG SC-UST 1/25 (4%). IG IV-PBO 2/27 (7%). IG IV-UST 1/26 (4%).**

Oral Corticosteroids OR Immunosuppressants - CG SC-PBO 14/26 (54%). IG SC-UST 13/25 (52%). IG IV-PBO 14/27 (52%). IG IV-UST 15/26 (58%).

Oral Corticosteroids AND Immunosuppressants - CG SC-PBO 4/26 (15%). IG SC-UST 2/25 (8%). IG IV-PBO 4/27 (15%). IG IV-UST 2/26 (8%).

Antibiotics - CG SC-PBO 2/26 (8%). IG SC-UST 2/25

				T 10/14 (71%). IG IV-PBO 7/11 (64%). IG IV-UST 6/8 (75%). Oral Corticosteroids - CG SC-PBO 5/16 (31%). IG SC-UST 6/14 (43%). IG IV-PBO 3/11 (27%). IG IV-UST 3/8 (38%). Of which (i) <=20mg/day - CG SC-PBO 4/16 (25%). IG SC-UST 5/14 (36%). IG IV-PBO 3/11 (27%). IG IV-UST 1/8 (13%). (ii) >20mg/day - CG SC-PBO 1/16 (6%). IG SC-UST 1/14 (7%). IG IV-PBO 0/11 (0%). IG IV-UST 2/8 (25%). Immunosuppressants - CG SC-PBO 8/16 (50%). IG SC-UST 3/14 (21%). IG IV-PBO 5/11 (46%). IG IV-UST 4/8 (50%). Of which (i) 6-Mercaptopurine, Azathioprine - CG SC-PBO 5/16 (31%). IG SC-UST 2/14 (14%). IG IV-PBO 3/11 (27%). IG IV-UST 4/8 (50%). (ii) Methotrexate - CG SC-PBO 3/16 (19%). IG SC-UST 1/14 (7%). IG IV-PBO 2/11 (18%). IG IV-UST 0/8 (0%). Oral Corticosteroids OR Immunosuppressants - CG SC-PBO 10/16 (63%). IG SC-UST 9/14 (64%). IG IV-PBO 6/11 (55%). IG IV-UST 5/8 (63%). Oral Corticosteroids AND Immunosuppressants - CG SC-PBO 3/16 (19%). IG SC-UST 0/14 (0%). IG IV-PBO 2/11 (18%). IG IV-UST 2/8 (25%). Antibiotics - CG SC-PBO 1/16 (6%). IG SC-UST 1/14 (7%). IG IV-PBO 2/11 (18%). IG IV-UST 1/8 (13%). Aminosalicylates - CG SC-PBO 6/16 (38%). IG SC-UST 3/14 (21%). IG IV-PBO 3/11 (27%). IG IV-UST 2/8 (25%).	
				(8%). IG IV-PBO 2/27 (7%). IG IV-UST 1/26 (4%). Aminosalicylates - CG SC-PBO 13/26 (50%). IG SC-UST 9/25 (36%). IG IV-PBO 14/27 (52%). IG IV-UST 10/26 (39%). B. Patients with previous infliximab use Concomitant medications - CG SC-PBO 12/16 (75%). IG SC-UST 10/14 (71%). IG IV-PBO 7/11 (64%). IG IV-UST 6/8 (75%). Oral Corticosteroids - CG SC-PBO 5/16 (31%). IG SC-UST 6/14 (43%). IG IV-PBO 3/11 (27%). IG IV-UST 3/8 (38%). Of which (i) <=20mg/day - CG SC-PBO 4/16 (25%). IG SC-UST 5/14 (36%). IG IV-PBO 3/11 (27%). IG IV-UST 1/8 (13%). (ii) >20mg/day - CG SC-PBO 1/16 (6%). IG SC-UST 1/14 (7%). IG IV-PBO 0/11 (0%). IG IV-UST 2/8 (25%). Immunosuppressants - CG SC-PBO 8/16 (50%). IG SC-UST 3/14 (21%). IG IV-PBO 5/11 (46%). IG IV-UST 4/8 (50%). Of which (i) 6-Mercaptopurine, Azathioprine - CG SC-PBO 5/16 (31%). IG SC-UST 2/14 (14%). IG IV-PBO 3/11 (27%). IG IV-UST 4/8 (50%). (ii) Methotrexate - CG SC-PBO 3/16 (19%). IG SC-UST 1/14 (7%). IG IV-PBO 2/11 (18%). IG IV-UST 0/8 (0%). Oral Corticosteroids OR Immunosuppressants - CG SC-PBO 10/16 (63%). IG SC-UST 9/14 (64%). IG IV-PBO 6/11 (55%). IG IV-UST 5/8 (63%). Oral Corticosteroids AND Immunosuppressants - CG SC-PBO 3/16 (19%). IG SC-UST 0/14 (0%). IG IV-PBO 2/11 (18%). IG IV-UST 2/8 (25%).	

							ST 0/14 (0%). IG IV-PBO 2/11 (18%). IG IV-UST 2/8 (25%). Antibiotics - CG SC-PBO 1/16 (6%). IG SC-UST 1/14 (7%). IG IV-PBO 2/11 (18%). IG IV-UST 1/8 (13%). Aminosalicylates - CG SC-PBO 6/16 (38%). IG SC-UST 3/14 (21%). IG IV-PBO 3/11 (27%). IG IV-UST 2/8 (25%).
Sanborn 2008 (Population 2)	IG IV-UST – Ustekinumab Intravenous 4.5mg/kg at week 0	CG SC-UST - Ustekinumab subcutaneous 90mg at weeks 0, 1, 2, and 3	IG IV-UST - Y 13/13 (100%) CG SC-UST - Y 14/14 (100%) Note - These patients received infliximab more than 16 weeks before randomisation (see medications that had to be stopped prior to study)	Concomitant use of 5-aminosalicylates, antibiotics, prednisolone at a maximum daily dose of 20 mg, azathioprine, 6-mercaptopurine, or methotrexate was permitted. Concomitant medication doses remained constant, except corticosteroids, which could be tapered by 2.5 mg/wk after week 8. The following are reported in baseline characteristics (Table 1). Concomitant medications - IG IV-UST 11/13 (85%). CG SC-UST 10/14 (71%) Oral corticosteroids - IG IV-UST 4/13 (31%). CG SC-UST 6/14 (43%). Of which (i) <=20mg per day - IG IV-UST 1/13 (8%). CG SC-UST 4/14 (29%). (ii) >20mg per day - IG IV-UST 3/13 (23%). CG SC-UST 2/14 (14%) Immunosuppressants - IG IV-UST 8/13 (62%). CG SC-UST 6/14 (43%). Of which (i) 6-Mercaptopurine, Azathioprine - IG IV-UST 8/13 (62%). CG SC-UST 4/14 (29%). (ii) Methotrexate - IG IV-UST 0/13 (0%). CG SC-UST 2/14 (14%) Oral corticosteroids OR Immunosuppressants - IG IV-UST 8/13 (62%). CG SC-UST 9/14 (64%) Oral corticosteroids AND Immunosuppressants - IG IV-UST 4/13 (31%). CG SC-UST 3/14 (21%)	Patients were excluded from study if recent treatment with any investigational agent or an anti-TNF agent including infliximab within the past 16 weeks. Therefore, these agents needed to have been stopped at least 16 weeks prior to study	NOT REPORTED. No protocol	Note* - Same as medications up to study beginning Concomitant use of 5-aminosalicylates, antibiotics, prednisolone at a maximum daily dose of 20 mg, azathioprine, 6-mercaptopurine, or methotrexate was permitted. Concomitant medication doses remained constant, except corticosteroids, which could be tapered by 2.5 mg/wk after week 8. The following are reported in baseline characteristics (Table 1). Concomitant medications - IG IV-UST 11/13 (85%). CG SC-UST 10/14 (71%) Oral corticosteroids - IG IV-UST 4/13 (31%). CG SC-UST 6/14 (43%). Of which (i) <=20mg per day - IG IV-UST 1/13 (8%). CG SC-UST 4/14 (29%). (ii) >20mg per day - IG IV-UST 3/13 (23%). CG SC-UST 2/14 (14%) Immunosuppressants - IG IV-UST 8/13 (62%). CG SC-UST 6/14 (43%). Of which (i) 6-Mercaptopurine, Azathioprine - IG IV-UST 8/13 (62%). CG SC-UST 4/14 (29%). (ii) Methotrexate - IG IV-UST 0/13 (0%). CG SC-UST 2/14 (14%) Oral corticosteroids OR Immunosuppressants - IG IV-

				Antibiotics - IG IV-UST 1/13 (8%). CG SC-UST 2/14 (14%) Aminosalicylates - IG IV-UST 5/13 (39%). CG SC-UST 7/14 (50%)			UST 8/13 (62%). CG SC-UST 9/14 (64%) Oral corticosteroids AND Immunosuppressants - IG IV-UST 4/13 (31%). CG SC-UST 3/14 (21%) Antibiotics - IG IV-UST 1/13 (8%). CG SC-UST 2/14 (14%) Aminosalicylates - IG IV-UST 5/13 (39%). CG SC-UST 7/14 (50%)
Sanborn 2011	Certolizumab	Placebo					
Sanborn 2012 (CERTIFI) - Induction	IG-UST1 IV Ustekinumab 1 mg/kg at week 0. IG-UST3 IV Ustekinumab 3 mg/kg at week 0. IG-UST6 IV Ustekinumab 6 mg/kg at week 0.	CG-PBO Placebo IV at week 0. Placebo agent and dose NOT REPORTED	Previous experience of biologics* - CG-PBO 132/132 (100%). IG-UST1 131/131 (100%). IG-UST3 132/132 (100%). IG-UST6 131/131 (100%). Of which (i) 1 drug - CG-PBO 71/132 (53.8%). IG-UST1 64/131 (48.9%). IG-UST3 66/132 (50.0%). IG-UST6 66/131 (50.4%). (ii) 2 or 3 drugs - CG-PBO 60/132 (45.5%). IG-UST1 67/131 (51.1%). IG-UST3 66/132 (50.0%). IG-UST6 64/131 (48.9%) Failure criteria met**. (i) Primary nonresponse - CG-PBO 44/132 (33.3%). IG-UST1 39/131 (29.8%). IG-UST3 41/132 (31.1%). IG-UST6 36/131 (27.5%). (ii) Secondary nonresponse - CG-PBO 91/132 (68.9%). IG-UST1 96/131 (73.3%). IG-UST3 98/132 (74.2%). IG-UST6 95/131 (72.5%). (iii) Unacceptable side effects - CG-PBO 41/132 (31.1%). IG-UST1 48/131 (36.6%). IG-UST3 40/132 (30.3%). IG-UST6 47/131 (35.9%). *Although not stated explicitly the proportion of patients	Patients were permitted to continue receiving stable doses of drugs for the treatment of Crohn's disease, including oral prednisolone (<=40 mg per day) or budesonide (<=9 mg per day), immunomodulators (e.g. azathioprine, mercaptopurine, or methotrexate), mesalamine, and antibiotics, if they had been taking the drugs for at least the prespecified period before study entry of 3 weeks, 4 weeks, 3 weeks, and 3 weeks, respectively. Patients had not received previous therapies targeting interleukin-12 or interleukin-23. Crohn's disease drugs at baseline of which (i) >= 1 medication - CG-PBO 101/132 (76.5%). IG-UST1 91/131 (69.5%). IG-UST3 96/132 (72.7%). IG-UST6 92/131 (70.2%). (ii) Immunomodulatory drug* - CG-PBO 30/132 (22.7%). IG-UST1 33/131 (25.2%). IG-UST3 28/132 (21.2%). IG-UST6 35/131 (26.7%). (iii) Aminosalicylate drug - CG-PBO 24/132 (18.2%). IG-UST1 20/131 (15.3%). IG-UST3 22/132 (16.7%). IG-UST6 25/131 (19.1%). (iv) Glucocorticoid**- CG-PBO 73/132 (55.3%). IG-UST1 59/131 (45.0%). IG-UST3 71/132 (53.8%). IG-UST6 59/131 (45.0%). (ivA) Baseline Corticosteroid	IV Glucocorticoids were not permitted at least 3 weeks before study entry TNF antagonists were not permitted at least 8 weeks before study entry Natalizumab was not permitted for at least 12 months before study entry	N/A - No protocol Patients were permitted to continue receiving stable doses of drugs for the treatment of Crohn's disease, including oral prednisolone (<=40 mg per day) or budesonide (<=9 mg per day), immunomodulators (e.g. azathioprine, mercaptopurine, or methotrexate), mesalamine, and antibiotics, if they had been taking the drugs for at least the prespecified period before study entry of 3 weeks, 4 weeks, 3 weeks, and 3 weeks, respectively. Patients had not received previous therapies targeting interleukin-12 or interleukin-23. Crohn's disease drugs at baseline of which (i) >= 1 medication - CG-PBO 101/132 (76.5%). IG-UST1 91/131 (69.5%). IG-UST3 96/132 (72.7%). IG-UST6 92/131 (70.2%). (ii) Immunomodulatory drug* - CG-PBO 30/132 (22.7%). IG-UST1 33/131 (25.2%). IG-UST3 28/132 (21.2%). IG-UST6 35/131 (26.7%). (iii) Aminosalicylate drug - CG-PBO 24/132 (18.2%). IG-UST1 20/131 (15.3%). IG-UST3 22/132 (16.7%). IG-UST6 25/131 (19.1%).	

	ients with previous experience, it can be safely assumed to be 100% for all groups as it is a study looking at efficacy of UST in CD refractory to TNF treatment. It is stated in the main paper 'In this 36-week, randomized, double-blind, placebo-controlled phase 2b trial of ustekinumab (comprising 8-week induction and 28-week maintenance phases), we evaluated patients with moderate-to-severe Crohn's disease that was resistant to TNF antagonists.' **These failure criteria seem to relate to all drugs (i.e.both TNF antagonists and also other drugs such as Corticosteroids) combined. Separate data for TNF antagonists have not been reported. Patients may have reported more than one reason for treatment failure. Primary nonresponse refers to absence of an initial response. Secondary nonresponse refers to an initial response that was not maintained	eroid dose, no., mg/day – CG-PBO 60, 20.0. IG-UST1 51, 15.0. IG-UST3 62, 20.0. IG-UST6 50, 20.0. (ivB) Baseline Budesonide dose, no., mg/day – CG-PBO 13, 9.0. IG-UST1 9, 9.0. IG-UST3 9, 9.0. IG-UST6 10, 9.0. (v) Antibiotics – CG-PBO 7/132 (5.3%). IG-UST1 12/131 (9.2%). IG-UST3 11/132 (8.3%). IG-UST6 12/131 (9.2%) Previous treatment failure of any immunomodulatory drug* – CG-PBO 113/132 (85.6%). IG-UST1 116/131 (88.5%). IG-UST3 119/132 (90.2%). IG-UST6 119/131 (90.8%). Of which (i) Contraindication to drug developed – CG-PBO 101/113 (89.4%). IG-UST1 105/116 (90.5%). IG-UST3 98/119 (82.4%). IG-UST6 97/119 (81.5%) Failure criteria met***. (i) Primary nonresponse – CG-PBO 44/132 (33.3%). IG-UST1 39/131 (29.8%). IG-UST3 41/132 (31.1%). IG-UST6 36/131 (27.5%). (ii) Secondary nonresponse – CG-PBO 91/132 (68.9%). IG-UST1 96/131 (73.3%). IG-UST3 98/132 (74.2%). IG-UST6 95/131 (72.5%). (iii) Unacceptable side effects – CG-PBO 41/132 (31.1%). IG-UST1 48/131 (36.6%). IG-UST3 40/132 (30.3%). IG-UST6 47/131 (35.9%). *Listed are all patients who received a full course of an immunomodulatory drug. Immunomodulatory drugs included azathioprine, mercaptopurine, and methotrexate **Glucocorticoid formulations included budesonide ***These failure criteria seem to relate to all drugs (i.e.both TNF antagonists and also other drugs such as Corticosteroids) combined. Separate data for TNF antagonists have not been reported. Patients may have reported more than one reason for	1%). (iv) Glucocorticoid** – CG-PBO 73/132 (55.3%). IG-UST1 59/131 (45.0%). IG-UST3 71/132 (53.8%). IG-UST6 59/131 (45.0%). (ivA) Baseline Corticosteroid dose, no., mg/day – CG-PBO 60, 20.0. IG-UST1 51, 15.0. IG-UST3 62, 20.0. IG-UST6 50, 20.0. (ivB) Baseline Budesonide dose, no., mg/day – CG-PBO 13, 9.0. IG-UST1 9, 9.0. IG-UST3 9, 9.0. IG-UST6 10, 9.0. (v) Antibiotics – CG-PBO 7/132 (5.3%). IG-UST1 12/131 (9.2%). IG-UST3 11/132 (8.3%). IG-UST6 12/131 (9.2%) *Listed are all patients who received a full course of an immunomodulatory drug. Immunomodulatory drugs included azathioprine, mercaptopurine, and methotrexate **Glucocorticoid formulations included budesonide
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				or treatment failure. Primary nonresponse refers to absence of an initial response. Secondary nonresponse refers to an initial response that was not maintained			
Sanborn 2012 (CERTIFI) - Induction (non-response)	Subcutaneous Ustekinumab 90mg at weeks 8 and 16	Subcutaneous Placebo at weeks 8 and 16. DOSE, and AGENT NOT REPORTED	Previous experience of biologics* – CG – 110/110 (100%). IG – 109/109 (100%) *Although not stated explicitly the proportion of patients with previous experience, it can be safely assumed to be 100% for all groups as it is a study looking at efficacy of UST in CD refractory to TNF treatment. It is stated in the main paper 'In this 36-week, randomized, double-blind, placebo-controlled phase 2b trial of ustekinumab (comprising 8-week induction and 28-week maintenance phases), we evaluated patients with moderate-to-severe Crohn's disease that was resistant to TNF antagonists.'	Patients were permitted to continue receiving stable doses of drugs for the treatment of Crohn's disease, including oral prednisolone (<=40 mg per day) or budesonide (<=9 mg per day), immunomodulators (e.g. azathioprine, mercaptopurine, or methotrexate), mesalamine, and antibiotics, if they had been taking the drugs for at least the prespecified period before study entry of 3 weeks, 4 weeks, 3 weeks, and 3 weeks, respectively. Patients had not received previous therapies targeting interleukin-12 or interleukin-23. Note – ‘Study entry’ here implies entry to the original induction phase of CERTIFI (i.e. week 0 to week 8 rather than week 8 to week 36) Proportions or numbers of patients per IG/CG per medication is NOT REPORTED for the week 8 to week 36 phase of CERTIFI (including non-responders induction study)	IV Glucocorticoids were not permitted at least 3 weeks before study entry TNF antagonists were not permitted at least 8 weeks before study entry Natalizumab was not permitted for at least 12 months before study entry Note – ‘Study entry’ here relates week 0 to week 8 induction phase. So 8 weeks should be added to the times stated	N/A - No protocol	Patients were permitted to continue receiving stable doses of drugs for the treatment of Crohn's disease, including oral prednisolone (<=40 mg per day) or budesonide (<=9 mg per day), immunomodulators (e.g. azathioprine, mercaptopurine, or methotrexate), mesalamine, and antibiotics, if they had been taking the drugs for at least the prespecified period before study entry of 3 weeks, 4 weeks, 3 weeks, and 3 weeks, respectively. Patients had not received previous therapies targeting interleukin-12 or interleukin-23. Note – ‘Study entry’ here implies entry to the original induction phase of CERTIFI (i.e. week 0 to week 8 rather than week 8 to week 36) Proportions or numbers of patients per IG/CG per medication is NOT REPORTED for the week 8 to week 36 phase of CERTIFI (including non-responders induction study)
Sanborn 2013 (GEMINI II) - Induction	Vedolizumab	Placebo					
Sanborn 2014	IGT1 – Tofacitinib 1mg oral twice daily. IGT5 – Tofacitinib 5mg oral twice daily. IGT15 – Tofacitinib 1	CG – Placebo oral twice daily (DOSE, and AGENT NOT REPORTED)	Anti-TNF(alpha) use within the previous 12 months [n (%)] – CG 1/34 (2.9%). IGT1 4/36 (11.1%). IGT5 1/34 (2.9%). IGT15 4/35 (11.4%)	The following at stable doses were permitted but not required: 5-acetylsalicylic acid or sulfasalazine (>=3 weeks before baseline and during treatment); Prednisolone 30mg or less per day or budesonide 9mg or less per	Azathioprine, 6-mercaptopurine, methotrexate – within 7 days of baseline prohibited Cyclosporine, mycophenolate, tacrolimus – within 4 weeks prohibited Interferon and anti-TNF(alpha) therapy – within 8 weeks prohibited	N/A – No protocol found	The following at stable doses were permitted but not required: 5-acetylsalicylic acid or sulfasalazine (>=3 weeks before baseline and during treatment); Prednisolone 30mg or less per day or b

	5mg oral twice daily.		Anti-TNF(alpha) use before within 12 months of baseline – NOT REPORTED Use of other biologics – NOT REPORTED	er day (>=2 weeks before baseline); Chronic treatment with antibiotics and rectally administered corticosteroids or 5-acetylsalicylic acid (>=2 weeks before baseline and during treatment) Patients remaining on immunosuppressant at screening [n (%)] – CG 0/34 (0.0%). IGT1 0/36 (0.0%). IGT5 0/34 (0.0%). IGT15 2/35 (5.7%) Number of patients on other medications at screening – NOT REPORTED Immunosuppressant use within the previous 12 months [n (%)] – CG 7/34 (20.6%). IGT1 8/36 (22.2%). IGT5 9/34 (26.5%). IGT15 15/35 (42.9%) Steroid use within the previous 12 months [n (%)] – CG 15/34 (44.1%). IGT1 16/36 (44.4%). IGT5 14/34 (41.2%). IGT15 16/35 (45.7%)		budesonide 9mg or less per day (>=2 weeks before baseline); Chronic treatment with antibiotics and rectally administered corticosteroids or 5-acetylsalicylic acid (>=2 weeks before baseline and during treatment) Patients remaining on immunosuppressant at screening [n (%)] – CG 0/34 (0.0%). IGT1 0/36 (0.0%). IGT5 0/34 (0.0%). IGT15 2/35 (5.7%) Number of patients on other medications at screening – NOT REPORTED	
Sanborn 20d (CELEST) - Induction	IG-U3B – Immediate-release oral formulation of Upadacitinib 3mg TWICE daily for 16 weeks (Week 0 to Week 16 of CELEST). IG-U6B – Immediate-release oral formulation of Upadacitinib 6mg TWICE daily for 16 weeks (Week 0 to Week 16 of CELEST). IG-U12B – Immediate-release oral formulation of Upadacitinib 12mg TWICE daily for 16 weeks (Week 0 to Week 16 of CELEST). IG-U24B – Immediate-release oral formulation of Upadacitinib	CG-PBO Placebo for 16 weeks (Week 0 to Week 16 of CELEST). DOSE, REGIMEN, ROUTE, and AGENT NOT REPORTED but it can be safely assumed that the Placebo was Oral and ONCE or TWICE daily doses for the maintenance of blinding	NOT REPORTED previous experience of biologic therapy as a whole but REPORTED previous experience of certain categories of biologics as follows: (i) Prior TNF antagonists (iA) 0 – CG-PBO 2/37 (5.4%). IG-U3B 2/39 (5.1%). IG-U6B 1/37 (2.7%). IG-U12B 2/36 (5.6%). IG-U24B 0/36 (0%). IG-U24Q 2/35 (5.7%). (iB) 1 – CG-PBO 15/37 (40.5%). IG-U3B 17/39 (43.6%). IG-U6B 12/37 (32.4%). IG-U12B 6/36 (16.7%). IG-U24B 10/36 (27.8%). IG-U24Q 10/35 (28.6%). (iC) 2 – CG-PBO 15/37 (40.5%). IG-U3B 16/39 (41.0%). IG-U6B 20/37 (54.1%). IG-U12B 24/36 (66.7%). IG-U24B 15/36 (41.7%). IG-U24Q 16/35 (45.7%). (iD) >=3 – CG-P	Patients could enter the study while receiving stable doses of aminosaliclates, oral corticosteroids (equivalent prednisone dose of <=30mg/d or budesonide of <=9mg/d), methotrexate, and/or CD-related antibiotics. Starting at week 2, patients receiving oral corticosteroids initiated a mandatory corticosteroid tapering following a protocol-specified schedule until discontinuation Baseline corticosteroid use, n (%) – CG-PBO 15/37 (40.5%). IG-U3B 21/39 (53.8%). IG-U6B 18/37 (48.6%). IG-U12B 17/36 (47.2%). IG-U24B 15/36 (41.7%). IG-U24Q 10/35 (28.6%) Baseline daily corticosteroid dose, mg [Median (Range)] – CG-PBO 20.0 (5-45). IG-U3B 20.0 (5-45). IG-U6B 22.5 (10-45). IG-U12B 20.0 (5-45). IG-U24B 20.0 (10-45). IG-U24Q 30.0 (10-45)NR	Patients had to discontinue Azathioprine or Mercaptopurine >=10 days before baseline	Not reported – No protocol	Note* - These are the same as medication up to study beginning Patients could enter the study while receiving stable doses of aminosaliclates, oral corticosteroids (equivalent prednisone dose of <=30mg/d or budesonide of <=9mg/d), methotrexate, and/or CD-related antibiotics. Starting at week 2, patients receiving oral corticosteroids initiated a mandatory corticosteroid tapering following a protocol-specified schedule until discontinuation Baseline corticosteroid use, n (%) – CG-PBO 15/37 (40.5%). IG-U3B 21/39 (53.8%). IG-U6B 18/37 (48.6%). IG-U12B 17/36 (47.2%). IG-U24B 15/36 (41.7%). IG-U24Q 10/35 (28.6%)

	b 24mg TWICE daily for 16 weeks (Week 0 to Week 16 of CELEST). IG-U24Q - Immediate-release oral formulation of Upadacitinib 24mg ONCE daily for 16 weeks (Week 0 to Week 16 of CELEST)		BO 5/37 (13.5%). IG-U3B 4/39 (10.3%). IG-U6B 4/37 (10.8%). IG-U12B 4/36 (11.1%). IG-U24B 9/36 (25.0%). IG-U24Q 7/35 (20.0%). (ii) Prior non-TNF antagonist biologics – CG-PBO 14/37 (37.8%). IG-U3B 15/39 (38.5%). IG-U6B 19/37 (51.4%). IG-U12B 15/36 (41.7%). IG-U24B 16/36 (44.4%). IG-U24Q 14/35 (40.0%)			Baseline daily corticosteroid dose, mg [Median (Range)] – CG-PBO 20.0 (5-45). IG-U3B 20.0 (5-45). IG-U6B 22.5 (10-45). IG-U12B 20.0 (5-45). IG-U24B 20.0 (10-45). IG-U24Q 30.0 (10-45)	
Sanborn 2022 - GALAXI 1	IG-G200 – Guselkumab 200mg Intravenous at weeks 0, 4, and, 8. IG-G600 – Guselkumab 600mg Intravenous at weeks 0, 4, and, 8. IG-G1200 – Guselkumab 1200mg Intravenous at weeks 0, 4, and, 8. IG-GC – this represents IG-G200, IG-G600, and, IG-G1200 (Guselkumab groups) combined. This is not a separate study arm by itself. IG-UST – Ustekinumab 6mg/kg Intravenous at week 0 AND Ustekinumab 90mg Subcutaneous at week 8	CG – Placebo (Agent, Dose, Regimen, and Route are NOT REPORTED)	History of biologic use [Number of patients/Total patients in given group (percentage)] – CG 42/61 (68.9%). IG-G200 36/61 (59.0%). IG-G600 39/63 (61.9%). IG-G1200 36/61 (59.0%). IG-GC 111/185 (60.0%). IG-UST 44/63 (69.8%) Patients with an inadequate response to, or intolerance to biologic therapy [Number of patients/Total patients in given group (percentage)] – CG 30/61 (49.2%). IG-G200 32/61 (52.5%). IG-G600 35/63 (55.6%). IG-G1200 34/61 (55.7%). IG-GC 101/185 (54.6%). IG-UST 37/63 (58.7%). Of which (i) Anti-TNF only – CG 25/61 (41.0%). IG-G200 26/61 (42.6%). IG-G600 27/63 (42.9%). IG-G1200 31/61 (50.8%). IG-GC 84/185 (45.4%). IG-UST 32/63 (50.8%). (ii) >=1 anti-TNF – CG 29/61 (47.5%). IG-G200 30/61 (49.2%). IG-G600 35/63 (55.6%). IG-G1200 33/61 (54.1%). IG-GC 98/185 (53.0%). IG-UST 37/63 (58.7%). (ii) i) Vedolizumab – CG 5/61 (8.2%). IG-G200 6/61 (9.8%). IG-G600 8/63 (12.7%). IG-G1200 3/61 (4.	Crohn's disease medication taken at baseline (YES) [Number of patients/Total patients in given group (percentage)] – CG 60/61 (98.4%). IG-G200 61/61 (100.0%). IG-G600 63/63 (100.0%). IG-G1200 61/61 (100.0%). IG-GC 185/185 (100.0%). IG-UST 63/63 (100.0%). Of which (i) >=1 medications for Crohn's disease – CG 45/61 (73.8%). IG-G200 44/61 (72.1%). IG-G600 47/63 (74.6%). IG-G1200 46/61 (75.4%). IG-GC 137/185 (74.1%). IG-UST 53/63 (84.1%). (ii) Immunomodulatory therapy – CG 26/61 (42.6%). IG-G200 15/61 (24.6%). IG-G600 18/63 (28.6%). IG-G1200 25/61 (41.0%). IG-GC 58/185 (31.4%). IG-UST 26/63 (41.3%). (iiia) Corticosteroids [Number of patients/Total patients in given group (percentage)] – CG 24/61 (39.3%). IG-G200 24/61 (39.3%). IG-G600 19/63 (30.2%). IG-G1200 20/61 (32.8%). IG-GC 63/185 (34.1%). IG-UST 26/63 (41.3%). (iiib) Corticosteroid dose (mg/day) [Median (IQR)] – CG 20.0 (10.0-30.0). IG-G200 20.0 (20.0-25.0). IG-G600 20.0 (10.0-25.0). IG-G1200 20.0 (15.0-22.5). IG-GC 20.0 (15.0-25.0). IG-UST 20.0 (15.0-32.5) Note – 'Immunomodulatory therapy' included azathioprine, mercaptopurine, and methotrexate. 'Corticosteroids' included bu	NOT REPORTED	NOT REPORTED – No protocol found	Crohn's disease medication taken at baseline (YES) [Number of patients/Total patients in given group (percentage)] – CG 60/61 (98.4%). IG-G200 61/61 (100.0%). IG-G600 63/63 (100.0%). IG-G1200 61/61 (100.0%). IG-GC 185/185 (100.0%). IG-UST 63/63 (100.0%). Of which (i) >=1 medications for Crohn's disease – CG 45/61 (73.8%). IG-G200 44/61 (72.1%). IG-G600 47/63 (74.6%). IG-G1200 46/61 (75.4%). IG-GC 137/185 (74.1%). IG-UST 53/63 (84.1%). (ii) Immunomodulatory therapy – CG 26/61 (42.6%). IG-G200 15/61 (24.6%). IG-G600 18/63 (28.6%). IG-G1200 25/61 (41.0%). IG-GC 58/185 (31.4%). IG-UST 26/63 (41.3%). (iiia) Corticosteroids [Number of patients/Total patients in given group (percentage)] – CG 24/61 (39.3%). IG-G200 24/61 (39.3%). IG-G600 19/63 (30.2%). IG-G1200 20/61 (32.8%). IG-GC 63/185 (34.1%). IG-UST 26/63 (41.3%). (iiib) Corticosteroid dose (mg/day) [Median (IQR)] – CG 20.0 (10.0-30.0). IG-G200 20.0 (20.0-25.0). IG-G600 20.0 (10.0-25.0). IG-G1200 20.0 (15.0-22.5). IG-GC 20.0 (15.0-25.0). IG-UST 20.0 (15.0-32.5).

			9%). IG-GC 17/185 (9.2%). IG-UST 5/63 (7.9%). (iv) Vedolizumab A ND >1 anti-TNF – CG 4/61 (6.6%). IG-G200 4/61 (6.6%). IG-G600 8/63 (12.7%). IG-G1200 2/61 (3.3%). IG-GC 14/185 (7.6%). IG-UST 5/63 (7.9%) Biologic-naïve [Number of patients/Total patients in given group (percent age)] – CG 19/61 (31.1%). IG-G200 25/61 (41.0%). IG-G600 24/63 (38.1%). IG-G1200 25/61 (41.0%). IG-GC 74/185 (40.0%). IG-UST 19/63 (30.2%) Note – ‘Biologics’ included infliximab, adalimumab, certolizumab pegol, or vedolizumab	desonide and beclomethasone dipropionate.			GC 20.0 (15.0-25.0). IG-UST 20.0 (15.0-32.5) Note – ‘Immunomodulatory therapy’ included azathioprine, mercaptopurine, and methotrexate. ‘Corticosteroids’ included budesonide and beclomethasone dipropionate.
Sands 2004 (ACENT II) Induction (Non-responder)	Infliximab 5mg/kg (Route NOT REPORTED) at weeks 14, 22, 30, 38, and 46. Beginning at week 2, patients who had a loss of response (defined by recurrence of draining fistulas, the need for additional therapy for persistent or worsening luminal disease activity, the need for a surgical procedure for Crohn’s disease, or the discontinuation of the study medication owing to a perceived lack of efficacy) were eligible to cross over to maintenance treatment with Infliximab 10mg/kg	Placebo (Agent, Dose, and Route NOT REPORTED) at weeks 14, 22, 30, 38, and 46. Beginning at week 22, patients who had a loss of response (defined by recurrence of draining fistulas, the need for additional therapy for persistent or worsening luminal disease activity, the need for a surgical procedure for Crohn’s disease, or the discontinuation of the study medication owing to a perceived lack of efficacy) were eligible to cross over to maintenance treatment with infliximab 5mg/kg	NR	NR	NR	NR	NR

Sands 2007	IG: Natalizumab 300mg at weeks 0,4, 8 + intravenous infliximab infusion (5 mg/kg) in week 6	CG: Placebo + intravenous infliximab infusion (5 mg/kg) in week 6	NR (other than infliximab that both groups needed to have)	NR Permitted CD medications included oral 5-aminosalicylic acid (5-ASA) compounds, if on a stable dose for at least 4 weeks; oral antibiotics if on a stable dose for at least 4 weeks; oral corticosteroids not exceeding 25 mg prednisolone or its equivalent for at least 4 weeks and at a stable dose for at least 2 weeks; and immunosuppressants (azathioprine, 6-mercaptopurine, or methotrexate) for at least 4 months before natalizumab and at a stable dose for at least 8 weeks.	Concurrent use of herbal preparations, rectal steroids, rectal 5-ASAs, tacrolimus, cyclosporine, mycophenolate mofetil, or any investigational or experimental agents was prohibited, as was prior treatment with natalizumab.	NR	Concomitant CD-related medications, n (%) 5-Aminosalicylate compounds CG 10 (37) IG 24 (46) Azathioprine, mercaptopurine, or methotrexate CG 15 (56) IG 26 (50) Oral steroids CG 8 (30) IG 14 (27) Antibiotics CG 5 (19) IG 10 (19)
Sands 2010	IG1 – Apilimod Mesylate 50mg Oral QD IG2 – Apilimod Mesylate 100mg	CG - Placebo Oral Daily (Agent, Dose, and Frequency NOT REPORTED)	Prior medication use [n (%)] of which, (i) Biologic agents – CG 38/73 (52%). IG1 47/73 (64%). IG2 45/74 (61%). (ii) Infliximab – CG 29/73 (40%). IG1 43/73 (59%). IG2 38/74 (41%). (iii) Adalimumab – CG 9/73 (12%). IG1 8/73 (11%). IG2 10/74 (14%). (iv) Certolizumab – CG 2/73 (3%). IG1 0/73 (0%). IG2 1/74 (1%). (v) Natalizumab – CG 9/73 (12%). IG1 13/73 (18%). IG2 12/74 (16%). (vi) CD P-571 – CG 1/73 (1%). IG1 0/73 (0%). IG2 0/74 (0%). (vii) Onercept – CG 0/73 (0%). IG1 1/73 (1%). IG2 0/74 (0%) Other biologics are NOT REPORTED	(i) Any [n (%)] – CG 53/73 (73%). IG1 50/73 (68%). IG2 55/74 (74%) (ii) Aminosalicylates (mesalamine) [n (%)] – CG 4/73 (5%). IG1 2/73 (3%). IG2 1/74 (1%) (iii) Antibiotics [n (%)] – CG 5/73 (7%). IG1 6/73 (8%). IG2 9/74 (12%) (iv) Systemic corticosteroids [n (%)] – CG 14/73 (19%). IG1 8/73 (11%). IG2 9/74 (12%) (v) Mercaptopurine/Azathioprine [n (%)] – CG 1/73 (1%). IG1 2/73 (3%). IG2 4/74 (5%) (vi) Methotrexate [n (%)] – CG 0/73 (0%). IG1 1/73 (1%). IG2 2/74 (3%) (vii) Biologic agents [n (%)] – CG 2/73 (3%). IG1 2/73 (3%). IG2 1/74 (1%)	NOT REPORTED	NOT REPORTED – No protocol. No mention of mandatory medications in the paper	Note – these are the same as medications up to study beginning (i) Any [n (%)] – CG 53/73 (73%). IG1 50/73 (68%). IG2 55/74 (74%) (ii) Aminosalicylates (mesalamine) [n (%)] – CG 4/73 (5%). IG1 2/73 (3%). IG2 1/74 (1%) (iii) Antibiotics [n (%)] – CG 5/73 (7%). IG1 6/73 (8%). IG2 9/74 (12%) (iv) Systemic corticosteroids [n (%)] – CG 14/73 (19%). IG1 8/73 (11%). IG2 9/74 (12%) (v) Mercaptopurine/Azathioprine [n (%)] – CG 1/73 (1%). IG1 2/73 (3%). IG2 4/74 (5%) (vi) Methotrexate [n (%)] – CG 0/73 (0%). IG1 1/73 (1%). IG2 2/74 (3%) (vii) Biologic agents [n (%)] – CG 2/73 (3%). IG1 2/73 (3%). IG2 1/74 (1%)
Sands 2014 (GEMIN I III)	Vedolizumab 300mg IV in 250 mL of 0.9% sodium chloride at weeks 0,2,6	Placebo administered intravenously in 250 mL of 0.9% sodium chloride at weeks 0, 2, and 6.	Prior TNF antagonist failure, n (%) CG 157 (76) - IG 158 (76) 1 prior TNF antagonist failure, n (%)b	NR	NR	NR	Corticosteroid use, n (%) CG 108 (52) IG 110 (53) Immunosuppressive use, n (%) CG 69 (33) IG 71 (34)

			CG 45 (22)c IG 59 (28)c 2 prior TNF antagonist failures, n (%) b CG 90 (43)c - IG 82 (39)c 3 prior TNF antagonist failures, n (%) b CG 21 (10)c IG 14 (7)c				Mesalamine use, n (%) a CG 61 (29) IG 68 (33)
Sands 2022 (SEAVUE)	Ustekinumab 6 mg/kg IV at BL then 90mg SC every 8 weeks	Adalimumab 160/80 mg SC at BL/W2, then 40mg SC every 2 weeks					
Schrabeir 2005	IG1: Subcutaneous injection Certolizumab 100 mg IG2: Subcutaneous injection Certolizumab 200 mg IG3: Subcutaneous injection Certolizumab 400 mg	Subcutaneous injection on placebo (saline)					
Schrabeir 2018a	receive subcutaneous injections of placebo weekly [QW], andecaliximab 150 mg every 2 weeks [Q2W], andecaliximab 150 mg QW, or andecaliximab 300 mg QW	Placebo	Prior exposure to TNF- α antagonist IG1 IG2 IG3 Yes IG1 46 [86.8] IG2 45 [84.9] IG3 43 [81.1] CG 24 [85.7] TOT 158 [84.5] No IG1 7 [13.2] IG2 8 [15.1] IG3 10 [18.9] CG 4 [14.3] TOT 29 [15.5] F	Concomitant use of oral corticosteroid at randomization, n [%] Yes 24 [45.3] 26 [49.1] 24 [45.3] 9 [32.1] 83 [44.4] Concomitant use of immunomodulator Yes 19 [35.8] 17 [32.1] 8 [15.1] 8 [28.6] 52 [27.8] N	NR	NR	Concomitant administration of the following was permitted: oral 5-aminosalicylate compounds; prednisone $\leq$ 30 mg/day or budesonide $\leq$ 9 mg/day at a stable dose for $\geq$ 2 weeks prior to screening; anti-diarrheals; azathioprine, 6-mercaptopurine or methotrexate at a stable dose for 4 weeks prior to screening; and antibiotics for treatment of CD at stable doses for $\geq$ 2 weeks prior to screening or doses consistent with the subject's standard lowdose regimen. Thiopurines or methotrexate could be initiated up to 4 weeks prior to screening
Schwartz 20	IG – Vedolizumab 300mg Intravenous at weeks	CG - Vedolizumab 300mg Intravenous at weeks 0, 2, 6, 14, and	Previous anti-TNF treatment [number of patients]	Concomitant treatment at baseline [number of patients/total]	NOT REPORTED		No protocol found. Note – These are the same as medications up to study beginning

21 - ENT ERP RIS E	0, 2, 6, 10, 14, and 22. If a seton was placed as part of the standard of care, it had to be removed by week 14. IGP – Pooled group which is a combination of IG and CG. It is not a separate study arm by itself	At week 10, patients received Placebo Intravenous (Agent NOT REPORTED). If a seton was placed as part of the standard of care, it had to be removed by week 14	s/total patients in group (percentage)] – CG 12/16 (75.0%). IG 13/16 (81.3%). IGP 25/32 (78.1%) Other biologics are NOT REPORTED	l patients in group (percentage)] of which: (i) Corticosteroids – CG 3/16 (18.8%). IG 3/16 (18.8%). IGP 6/32 (18.8%). (ii) Immunosuppressants – CG 5/16 (31.3%). IG 3/16 (18.8%). IGP 8/32 (25.0%)		All patients were prescribed companion antibiotics, per local label, from day 1 until week 6. Approved antibiotics were metronidazole, ciprofloxacin, amoxicillin clavulanate, and tinidazole per local label.	Concomitant treatment at baseline [number of patients/total patients in group (percentage)] of which: (i) Corticosteroids – CG 3/16 (18.8%). IG 3/16 (18.8%). IGP 6/32 (18.8%). (ii) Immunosuppressants – CG 5/16 (31.3%). IG 3/16 (18.8%). IGP 8/32 (25.0%)
Targan 1997	IG1: IV infusion 5 mg of ca2/kg IG2: IV infusion 10mg mg of ca2/kg IG3: IV infusion 20mg of ca2/kg	IV infusion placebo (agent: NR)	Patients were excluded if prior treatment with murine, chimeric or humanized monoclonal antibodies within four weeks before screening.	Patients who were receiving mesalamine, corticosteroids, azathioprine, or mercaptopurine before the study continued to receive a stable dose during the trial period	NR	NR	Prednisone equivalent < 20 mg/day orally: CG: 10 (40%) IG1: 8 (30%) IG2: 8 (29%) IG3: 10 (36%) Prednisone equivalent > 20 mg/day orally: CG: 6 (24%) IG1: 7 (26%) IG2: 8 (29%) IG3: 7 (25%) Mercaptopurine: CG: 4 (16%) IG1: 4 (15%) IG2: 4 (14%) IG3: 4 (14%) Azathioprine CG: 7 (28%) IG1: 5 (19%) IG2: 4 (14%) IG3: 8 (29%) Oral aminosalicylates CG: 17 (68%) IG1: 16 (59%)

							IG2: 18 (64%) IG3: 13 (46%)
Targan 2007 (ENCORE)	IV natalizumab 300 mg	IV infusion Placebo (exact agent and dosage: NR)	Patients who had received anti-tumor necrosis factor therapy within the previous 12 weeks, or had ever previously been treated with natalizumab were excluded	NR	Prior use of anti-tumor necrosis factor agents CG: 112 (45%) IG: 130 (50%)	NR	Concomitant Crohn's disease medication or diet, CG: 227 (91%) IG: 247 (95%) 5-ASA compounds CG: 120 (48%) IG: 128 (49%) Immunosuppressants CG: 96 (38%) IG: 97 (37%) Corticosteroids CG: 94 (38%) IG: 109 (42%) Antibiotics CG: 13 (5%) IG: 17 (7%) Diet CG: 4 (2%) IG: 3 (1%)
Loftus 2023 (U-EXCEL)	Upadacitinib 45 mg Oral daily (Frequency NOT REPORTED - Need full paper for this information) for 12 weeks	Placebo Oral daily for 12 weeks (Agent, Dose, and Frequency NOT REPORTED - Need full paper for this information)	NOT REPORTED - Need full paper for this information	NOT REPORTED - Need full paper for this information	NOT REPORTED - Need full paper for this information	According to the trial registration, female patients were required to have Contraception	NOT REPORTED - Need full paper for this information
Vermeire 2017 FITZROY - induction	Filgotinib 200mg oral once daily	Matching placebo or oral once daily (AGENT NOT REPORTED)	One of the exclusion criterion is as follows: 'Previous treatment with biological investigational medicinal products including murine, chimeric or humanized monoclonal antibodies or a chemokine receptor blocker within less than 5 half-lives prior to baseline. Previous treatment with a Janus kinase inhibitor is prohibited.'	Concurrent treatment with oral steroids (<=30 mg prednisolone or budesonide <=9 mg per day) or probiotics was allowed if dosages had been stable for at least 2 weeks before the first dose of study drug . Concurrent treatment with Crohn's disease-related antibiotics , or with mesalazine or olsalazine , was permitted if dosages had been stable for at least 4 weeks before the first dose of study drug . Previous exposure to sulfasalazine was allowed but had to be discontinued at least 4 weeks before screening in male patients	Previous exposure to sulfasalazine was allowed but had to be discontinued at least 4 weeks before screening in male patients Immunomodulators must have been discontinued at least 25 days before the first dose of the study drug Tube feeding, defined formula diets, or total parenteral alimentation was not allowed during the study IV corticosteroids were to be discontinued 14 days prior to screening Enemas or suppositories other than those required for colonoscopy were to be discontinued 7 days prior to screening Cyclosporine, mycophenolate, tacrolimus, or interferon were to be discontinued at least 10 weeks prior to screening	If using paracetamol at baseline , it should not be discontinued Contraception	Concurrent treatment with oral steroids (<=30 mg prednisolone or budesonide <=9 mg per day) or probiotics was allowed if dosages had been stable for at least 2 weeks before the first dose of study drug . Concurrent treatment with Crohn's disease-related antibiotics , or with mesalazine or olsalazine , was permitted if dosages had been stable for at least 4 weeks before the first dose of study drug . Previous exposure to sulfasalazine was allowed but had to

			Therefore, previous biologic (any biologic) exposure* (reported as 'previous anti-TNF exposure') – CG 28/44 (64%). IG 73/130 (56%) *The anti-TNF naïve group included four patients who were anti-TNF responders but who discontinued for financial reasons	s, whereas immunomodulators (e.g. thiopurines and methotrexate) must have been discontinued at least 25 days before the first dose of the study drug Oral corticosteroids – CG 23/44 (52%). IG 65/130 (50%). Daily Dose (mg/day) [Mean/Median (SD/IQR)] – CG* 21.3/20.0 (8.6/15.0-30.0). IG** 20.7/20.0 (8.6/15.0-30.0) *n=22 *n=63	Any prior lymphocyte depleting agent (e.g. Alemtuzumab) was prohibited. Lymphocyte apheresis or selective monocyte granulocyte apheresis was to be discontinued 12 months prior to screening Previous fecal microbiota transplant and stem cell transplants were prohibited Investigational chemical agents were to be discontinued 4 weeks before screening Previous treatment with biological investigational medicinal products including murine, chimeric or humanized monoclonal antibodies or a chemokine receptor blocker within less than 5 half-lives prior to baseline. Previous treatment with a janus kinase inhibitor is prohibited. Live vaccines must not have been administered within 90 days or an attenuated vaccine within 30 days of first dose of study drug as well as during the study duration until 6 weeks following last intake of GLPG0634 Patients currently on any therapy for chronic infection (such as pneumocystis, CMV, herpes simplex, herpes zoster, or atypical mycobacteria) were excluded from the study	be discontinued at least 4 weeks before screening in male patients, whereas immunomodulators (e.g. thiopurines and methotrexate) must have been discontinued at least 25 days before the first dose of the study drug Oral corticosteroids – CG 23/44 (52%). IG 65/130 (50%). Daily Dose (mg/day) [Mean/Median (SD/IQR)] – CG* 21.3/20.0 (8.6/15.0-30.0). IG** 20.7/20.0 (8.6/15.0-30.0) *n=22 *n=63	
Vermeir 2017 FORTIFY - induction non-responders	Filgotinib 200mg oral once daily	Matching placebo or oral once daily (AGENT NOT REPORTED). Placebo was presented as orally administered brown film-coated tablets that were identical in appearance to filgotinib and contained the same excipients	NOT REPORTED However, one of the exclusion criterion states that previous JAK inhibitor therapy was not allowed. Therefore, no patient had previous JAK inhibitors (CG – 0/13, IG – 0/39) but unable to comment on TNF inhibitors and hence on biologics as a whole	Note – the timepoints here apply to the original induction study (i.e. screening means week 0 rather than week 10, where the latter is where the maintenance phase began) Concurrent treatment with oral steroids (<=30 mg prednisolone or budesonide <=9 mg per day) or probiotics was allowed if dosages had been stable for at least 2 weeks before the first dose of study drug. Concurrent treatment with Crohn's disease-related antibiotics, or with mesalazine or olsalazine, was permitted if dosages had been stable for at least 4 weeks before the first dose of study drug. Previous exposure to sulfasalazine was allowed but had to be discontinued at least 4 weeks before screening in male patients, whereas immunomodulators (e.g. thiopurines and methotrexate) must have been discontinued at least 25 days before screening in male patients	Note – the timepoints here apply to the original induction study (i.e. screening means week 0 rather than week 10, where the latter is where the maintenance phase began) Previous exposure to sulfasalazine was allowed but had to be discontinued at least 4 weeks before screening in male patients Immunomodulators must have been discontinued at least 25 days before the first dose of the study drug Tube feeding, defined formula diets, or total parenteral alimentation was not allowed during the study IV corticosteroids were to be discontinued 14 days prior to screening Enemas or suppositories other than those required for colonoscopy were to be discontinued 7 days prior to screening Cyclosporine, mycophenolate, tacrolimus, or interferon were to be discontinued at least 10 weeks prior to screening Any prior lymphocyte depleting agent (e.g. Alemtuzumab) was prohibited. Lymphocyte apheresis or selective monocyte granulocyte apheresis was to be discontinued 12 months prior to screening Previous fecal microbiota transplant and stem cell transplants were prohibited	If using paracetamol at baseline, it should not be discontinued Contraception	Note – the timepoints here apply to the original induction study (i.e. screening means week 0 rather than week 10, where the latter is where the maintenance phase began) Concurrent treatment with oral steroids (<=30 mg prednisolone or budesonide <=9 mg per day) or probiotics was allowed if dosages had been stable for at least 2 weeks before the first dose of study drug. Concurrent treatment with Crohn's disease-related antibiotics, or with mesalazine or olsalazine, was permitted if dosages had been stable for at least 4 weeks before the first dose of study drug. Previous exposure to sulfasalazine was allowed but had to be discontinued at least 4 weeks before screening in male patients, whereas im

				nued at least 25 days before the first dose of the study drug Proportion of patients on each medication – NOT REPORTED for the maintenance phase	Investigational chemical agents were to be discontinued 4 weeks before screening Previous treatment with biological investigational medicinal products including murine, chimeric or humanized monoclonal antibodies or a chemokine receptor blocker within less than 5 half-lives prior to baseline. Previous treatment with a janus kinase inhibitor is prohibited. Live vaccines must not have been administered within 90 days or an attenuated vaccine within 30 days of first dose of study drug as well as during the study duration until 6 weeks following last intake of GLPG0634 Patients currently on any therapy for chronic infection (such as pneumocystis, CMV, herpes simplex, herpes zoster, or atypical mycobacteria) were excluded from the study		immunomodulators (e.g. thio purines and methotrexate) must have been discontinued at least 25 days before the first dose of the study drug Proportion of patients on each medication – NOT REPORTED for the maintenance phase
Watanabe 2012 - Induction	Adalimumab Adalimumab 80/40 mg Adalimumab 160/80 mg	Placebo	REPORTED under heading 'Crohn's disease-related medication prior to or at baseline of induction and maintenance trials'. Amino-salicylates CG 23 (100) II G1 27 (79.4) II G2 32 (97.0) ITO T 82 (91.1) Immunosuppressants CG 8 (34.8) II G1 11 (32.4) II G2 10 (30.3) ITOT 29 (32.2) Corticosteroids CG 5 (21.7) II G1 6 (17.6) II G2 8 (24.2) ITOT 19 (21.1) CD-related antibiotics CG 2 (8.7) II G1 1 (2.9) II G2 2 (6.1) ITOT 5 (5.6) Enteral nutrition CG 16 (69.6) II G1 22 (64.7) II G2 23 (69.7) ITO T 61 (67.8)	REPORTED under heading 'Crohn's disease-related medication prior to or at baseline of induction and maintenance trials'. Anti-TNF n(%) CG 13 (56.5) II G1 20 (58.8) II G2 19 (57.6) ITOT 52 (57.8)	Previous use of infliximab or biologic, if any, had to be discontinued at least 8 weeks before Baseline.	NR	Concomitant use of immunomodulators (azathioprine and 6-mercaptopurine), amino-salicylates, and Crohn's-related antibiotics, was permitted in the induction and maintenance trials, provided that the doses remained stable. Stable doses of corticosteroids (≤ 40 mg/day of prednisolone or equivalent), and stable enteral nutrition ≤ 1200 kcal/day were permitted. No changes of Crohn's-related concomitant therapies were allowed during the induction trial.
Watanabe 2020 - Induction	Vedolizumab 300 mg Intravenous infusion at Weeks 0, 2, and 6	Placebo by Intravenous infusion at Weeks 0, 2, and 6 (DOSE and AGENT NOT REPORTED)	Reported as 'Prior anti-TNF (alpha) treatment' [numbers (percentage)]: (i) No – CG 16/78 (20.5%). IG 18/79 (22.8%). (ii) Yes – CG 62/78 (79.5%). IG 61/79 (77.2%) Prior anti-TNF (alpha) failure [numbers (percentage)]	Patients were allowed concomitant treatment with oral 5-aminosalicylic acid, probiotics, antibiotics for CD, oral corticosteroids, immunomodulators and enteral nutrients (≤ 900 kcal/day) under specific conditions Concomitant medication for CD at baseline [numbers (percentage)]	These patients were excluded from the study (otherwise discontinued medication NOT REPORTED) – (i) Patients who started oral 5-ASAs, probiotics, antibiotics for CD treatment, or oral corticosteroids (≤ 30 mg/day) within 13 days before the first dose of the study drug. Or patients who changed dosage of or discontinued these drugs within 13 days before the first dose of the study drug if the patient had used these drugs for more than 14 days before the first dose of the study drug (ii) Patients who had received 5-ASA, corticosteroid enemas/suppositories, cortico	NOT REPORTED – No protocol found	Note – These were the same as Medications up to study beginning Patients were allowed concomitant treatment with oral 5-aminosalicylic acid, probiotics, antibiotics for CD, or oral corticosteroids, immunomodulators and enteral nu

			ge)]: (i) Overall – CG 61/78 (78.2%). IG 60/79 (75.9%) (ii) Inadequate response – CG 10/78 (12.8%). IG 14/79 (17.7%). (iii) Loss of response – CG 46/78 (59.0%). IG 45/79 (57.0%). (iv) Intolerance – CG 5/78 (6.4%). IG 1/79 (1.3%) Number of drugs of anti-TNF (alpha) failure [numbers (percentage)]: (i) None – CG 17/78 (21.8%). IG 19/79 (24.1%). (ii) One – CG 29/78 (37.2%). IG 29/79 (36.7%). (iii) Two – CG 32/78 (41.0%). IG 31/79 (39.2%) Worst prior treatment failure [numbers (percentage)]: (i) Prior anti-TNF (alpha) failure – CG 61/78 (78.2%). IG 60/79 (75.9%). (ii) Prior immunomodulators failure but not anti-TNF (alpha) failure – CG 9/78 (11.5%). IG 12/79 (15.2%)	ntage)]: (i) Enteral nutrient – CG 43/78 (55.1%). IG 38/79 (48.1%). (ii) 5-Aminosalicylic acid – CG 59/78 (75.6%). IG 64/79 (81.0%). (iii) Oral Corticosteroids AND no immunomodulators – CG 7/78 (9.0%). IG 13/79 (16.5%). (iv) No Oral Corticosteroids OR immunomodulators – CG 31/78 (39.7%). IG 30/79 (38.0%). (v) Oral Corticosteroids AND immunomodulators – CG 11/78 (14.1%). IG 9/79 (11.4%)	steroid IV infusion, oral corticosteroid at >30 mg/day, drugs for diarrhea-predominant irritable bowel syndrome, or Chinese herbal medicine for the CD treatment (e.g., Daikenchuto) within 13 days before the first dose of the study drug (iii) Patients who had received AZA, 6-MP, or MTX within 27 days before the first dose of the study drug. However, this did not apply to patients who had used these drugs for more than 83 days before the first dose of the study drug and continued the steady dose of the drugs for more than 27 days before the first dose of the study drug (iv) Patients who had received cyclosporine, tacrolimus, tofacitinib or any study drugs of low molecular compound for CD treatment within 27 days before the first dose of the study drug (v) Patients who had received adalimumab within 27 days before the first dose of the study drug or any biologics other than adalimumab within 55 days before the first dose of the study drug. However, this did not apply to patients who had received localized injections of these drugs (e.g., intraocular injection for treatment of age-related macular degeneration) (vi) Patients who had received any live-vaccinations within 27 days before the first dose of the study drug (vii) Patients who had a history or a complication of alcohol dependence or illicit drug use within one year before the first dose of the study drug. (viii) Patients who had received central venous nutrition therapy or enteral total nutrition therapy, or fasted within 20 days before the first dose of the study drug. (ix) Patients who had received an enteral nutrient of >900 kcal/day or who had started an enteral nutrient of ≤900 kcal/day within 20 days before the first dose of the study drug. Or patients who changed dosage of or discontinued the enteral nutrient within 20 days before the first dose of the study drug if the patient had received an enteral nutrient of ≤900 kcal/day more than 21 days before the first dose of the study drug		trients (<=900 kcal/day) under specific conditions Concomitant medication for CD at baseline [numbers (percentage)]: (i) Enteral nutrient – CG 43/78 (55.1%). IG 38/79 (48.1%). (ii) 5-Aminosalicylic acid – CG 59/78 (75.6%). IG 64/79 (81.0%). (iii) Oral Corticosteroids AND no immunomodulators – CG 7/78 (9.0%). IG 13/79 (16.5%). (iv) No Oral Corticosteroids OR immunomodulators – CG 31/78 (39.7%). IG 30/79 (38.0%). (v) Oral Corticosteroids AND immunomodulators – CG 11/78 (14.1%). IG 9/79 (11.4%)	
Winter 2004	Certolizumab (CDP870) single IV dose IG1 dose: 1.25 (n=2), IG2 dose = 5 (n=26), IG3 dose= 10 (n=17) or IG4= 20 mg/kg (n=23)	Placebo Normal Saline 100 ml	Previous anti-TNF therapy, n(%) CG= 3 (13), IG1=1 (50), IG2=6 (23) IG3=5 (29), IG4=7 (30)	Patients receiving aminosalicylate therapy, n(%) CG=10 (40) IG1=0 (0) IG2=12 (48) IG3=9 (53) IG4=9 (39) Patients receiving steroid therapy, n(%) CG=7 (28) IG1= 1 (50) IG2= 6 (24) IG3=6 (35) IG4=6 (26) Patients receiving immunosuppressive therapy, n(%) CG=11 (44) IG1=0 (0) IG2=11 (44) IG3=9 (53) IG4=10 (44)	NR		NR	Patients receiving aminosalicylate therapy, n(%) CG=10 (40) IG1=0 (0) IG2=12 (48) IG3=9 (53) IG4=9 (39) Patients receiving steroid therapy, n(%) CG=7 (28) IG1= 1 (50) IG2= 6 (24) IG3=6 (35) IG4=6 (26) Patients receiving immunosuppressive therapy, n(%) CG=11 (44) IG1=0 (0) IG2=11 (44) IG3=9 (53) IG4=10 (44)
					NR		NR	

Ye 2019	Crossover at week 30 Before week 30 IG: infliximab	Crossover at week 30 Before week 30 CG: CT-P13	IG: 84 (76%) CG: 80 (73%)	Corticosteroid use: IG:37 (33%) CG: 33 (30%)		IG: 111 randomly assigned to initiate CT-P13 , 56 to CT-P13–CT-P13 , 55 to CT-P13–infliximab CG: 109 randomly assigned to initiate infliximab , 54 to infliximab–infliximab, 55 to infliximab–CT-P13
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Table 3

Maintenance studies' characteristics

Study ID	Numbers randomised	Purine analogues use	Biologic naive or not	Mixed disease state or remission only
Buhl 2022 (STOP-IT)	CG(placebo) 56 IG(ifx) 59	Thiopurines 55% of all patients >50%	Not	Remission
Colombel 2007 (CHARM) - Maintenance (responders)	CG(placebo): 170 IG1(ada eow): 172 IG2(ada weekly): 157	AZA: 165/499 6-MP: 38/499 <50%	Not (the study had an induction phase with the biologic)	Mixed responders and remission
Colombel 2023 - LIBERTY-CD	CG(Placebo) 112 IG(CT-P13 SC) 231	NR	Not (the study had an induction phase with the biologic)	Mixed responders and remission
D'Haens 2022 (SERENE - Maintenance)	IG Ada CA 109 CG Ada TDM 109	Immunosuppressant use (n, %) IG 31 (33.7) CG 25 (27.2) <50%	Not (the study had an induction phase with the biologic)	Mixed responders and remission
Feagan 2015c (IM-UNITI)	CG(placebo)=133 IG(ust8wks)= 132 IG(ust12wks)=131	Immunosuppressants including azathioprine, mercaptopurine, and methotrexate, n(%) CG(placebo)= 47(35.3) IG(ust8wks)= 44(33.3) IG(ust12wks)= 52(39.4) <50%	Not	Mixed responders and remission
Ferrante 2022 - FORTIFY	CG(placebo) 179 IG1(ris180mg) 179 IG2(ris360mg) 184	Immunomodulator use, n (%) CG 40 (24) IG1 41 (26) IG2 41 (28) <50%	Not (the study recruited from two induction studies with the same biologics)	Mixed responders and remission
Hanauer 2002 (ACCENT I) - Maintenance (Responders)	CG(placebo) – 110 IG1(ifx5mg) – 113 IG2(ifx10mg) – 112	6CMP and AZA – 81/335 (24%) <50%	Not (the study had an induction phase with the biologic)	Mixed responders and remission
Jorgensen 2017 (NORSWITCH)	CG(ifx): 78 IG(CT-P13): 77	Use of immunosuppressives CG: 30/78 (38.5%) IG: 36/77 (46.8%) <50%	Mix 60/77 and 61/78 naive	Mixed responders and remission

Louis 2023 - SPARE	Group 1(comb): 71 Group 2(antimetabolite): 71 Group 3(ifx): 69	part of the intervention	Not	Remission
NCT00349752 (CO SPAR1)	CG(placebo) 87 IG(certolizumab) 87	NR	Not (extension of Sandborn 2010b (WELCOME))	Remission
Panes 2017 Maintenance	CG(placebo) 59 IG(tof5mg) 60 IG(tof10mg) 61	Patients receiving azathioprine, 6-mercaptopurine or methotrexate were required to stop these agents at least two weeks before randomisation <50%	Not (the study had an induction phase with the biologic)	Mixed responders and remission
Rutgeerts 1999	CG(placebo): 36 IG(ifx): 37	6CMP or AZA >6 months' duration at a stable dosage for 8 weeks was acceptable	Not (the study included patients that had responded to an initial infusion of infliximab or placebo)	Mixed responders and remission
Rutgeerts 2012 (EXTEND)	CG(placebo) 65 IG(ada) 64	Concomitant immunomodulators, n(%) CG 25 (38.5) IG 28 (43.8) <50%	Not (the study had an induction phase with the biologic)	Mixed responders and remission
Sandborn 2005a (ENACT 2)	CG(placebo) 179 responders IG(nat) 175 responders	Concomitant AZA and 6MP, n(%) AZA CG 45 (26) IG 42 (25) 6MP CG 7 (4) IG1 2(7) <50%	Not (the study had an induction phase with the biologic)	Mixed responders and remission
Sandborn 2007b (CLASSIC II)	CG(placebo): 18 IG1 (AdaEow): 19 IG2 (AdaWeekly): 18	Concomitant AZA and 6MP, n(%) AZA CG 1 (6) IG1 4 (21) IG2 2 (11) 6MP CG 1 (6) IG1 0 (0) IG2 3 (17) <50%	Not (the study had an induction phase with the biologic)	Remission
Sandborn 2012 (CERTIFI) - Maintenance	CG(placebo) 73 IG(ust) 72	Not given for the maintenance responder randomised population. For the total (n=526) induction randomised population 126 (24.0%) were receiving an immunomodulatory drug at baseline. <50%	Not	Mixed responders and remission
Sandborn 2013 (GEMINI II) - Maintenance	CG(placebo) 153 IG1 (VedE8w) 154 IG2 (VedE4w) 154	Stable doses of azathioprine or 6-mercaptopurine, n(%) CG(placebo) 152 (99.3) IG1 (VedE8w) 153 (99.4)	Not (the study had an induction phase with the biologic)	Mixed responders and remission

		IG2(VedE4w) 154 (100.0) >50%		
Sandborn 2020d (C ELEST) - Maintenance	IG(Upa3mg) 61 IG(Upa6mg) 23 IG(Upa12mg) 59 IG(Upa24mg) 37	Included patients had failed or inadequately responded to immunosuppressants	Not	Mixed responders and remission
Sandborn 2023 - BE RGAMOT Maintenance	CG (placebo): 217 IG (etro) 217 (one patient was randomised but left the study before receiving allocated medication, and the authors have not included them in these numbers)	Baseline use of immunosuppressants CG (placebo): 71 (33%) IG (etro): 67 (31%)	Not (the study had an induction phase with the biologic)	Mixed responders and remission
Sands 2004 (ACCE NT II) Maintenance (Responders)	CG(placebo): 99 IG(ifx): 96	6CMP or AZA CG 35/99 (35%) IG 29/96 (30%) <50%	Not (the study had an induction phase with the biologic)	Mixed responders and remission
Schreiber 2007 (PR ECISE 2)	CG(placebo) 212 IG(cert) 216	Immunosuppressive agents only, n(%) CG 52 (25) IG 59 (27) Glucocorticoids plus immunosuppressive agents, n(%) CG 34 (16) IG 28 (13) <50%	Not (the study had an induction phase with the biologic)	Mixed responders and remission
Schreiber 2021	CG(IV CT-P13) 25 IG(SC CT-P13) 28	AZA/6MCP/methotrexate use IG: 14/28 (50%) CG: 13/25 (52%) >50%	Not (the study had an induction phase with the biosimilar)	Mixed responders and remission
VanAssche 2012 (S WITCH)	CG(ifx) 37 IG(ADA) 36	AZA IG: 6/36 (16.7%) CG: 0/37 (0%) <50%	Not. Previous exposure to ADA, and receiving IFX doses >5 mg/kg intravenously were excluded	Mixed responders and remission
Vermeire 2017 FITZ ROY - maintenance responders	CG1(fil/pl) 14 IG1(fil100mg) 30 IG2(fil200mg) 30	Immunomodulators (eg, thiopurines and methotrexate) must have been discontinued at least 25 days before the first dose of the study drug <50%	Not (the study had an induction phase with the biologic)	Mixed responders and remission
Vermeire 2021 (VISI BLE 2)	CG(placebo): 135 IG(ved): 275	Immunosuppressive agents only, n(%) CG 34 (25.4) IG 51 (18.5) Corticosteroids plus immunosuppressive agents, n(%) CG 13 (9.7) IG 31 (11.3) <50%	Not (the study had an induction phase with the biologic)	Mixed responders and remission
	IG1 Filgotinib 100mg (n=105)	IG1/2 more than 20%	Not	

Vermeire 2025 - DIV ERSITY (maintenance)	IG 2 Filgotinib 200mg (n=118) CG1 Placebo (filgotinib 100 mg at induction) (n=56) CG1 Placebo (filgotinib 100 mg at induction) (n=56)	CG1/2 less than 20% <50%	(the study had an induction phase with the biologic)	Mixed clinical remission or endoscopic response at at end of induction
Volkers 2017 - SIMILAR	IG(biosimilar) NR CG(ifx) NR (total 47 participants)	NR	Not	Remission
Watanabe 2012 - Maintenance	CG(placebo) 25 IG(ada) 25	Immunosuppressants, n(%) CG 7 (28.0) IG 1 (44.0) <50%	Not (the study had an induction phase with the biologic)	Mixed responders and remission
Watanabe 2020 - Maintenance	CG(placebo) 12 IG(ved) 12	Immunomodulators, n(%) CG 3(25.0%) IG 2 (16.7%) Immunomodulators and corticosteroids, n(%) CG 3 (25.0) IG 1 (8.3) <50%	Not (the study had an induction phase with the biologic)	Mixed responders and remission
Young 2024 - iBaSS	IG: reference adalimumab (crossover to SB5) (n=57) CG: SB5 adalimumab biosimilar (crossover to reference adalimumab) (n=55)	IG n=24 (53.3%) CG n= 20 (46.5%) ~50%	Not	Remission [CD in remission or with mild disease activity (modified Harvey-Bradshaw Index (mHBI) score < 8)]

Table 4

Maintenance studies' intervention details

Study ID	Intervention medications IG	Intervention medications CG	Previous experience of biologic therapy	Medications up to study beginning	Medications that had to be discontinued prior to starting study	Mandatory medications per study protocol	Concomitant Medications during study
Buhl 2022 (STOP-IT)	Continue infliximab therapy at an unchanged dose for a duration of 48 weeks	Matching placebo for a duration of 48 weeks	Yes. All patients had been treated with standard IFX maintenance therapy for at least 1 year	Concomitant therapy with immune suppressants, except steroids, was allowed. The dosage and frequency must have been stable 3 months prior to inclusion, and must remain stable throughout the study period Continued concomitant therapy with stable doses of immunomodulators (thiopurines, methotrexate) was allowed (55% of patients)	No use of oral steroids within 3 months prior to inclusion	None	Thiopurines, methotrexate was allowed (55% of patients)

Col om bel 200 7 (C HA RM) - M aint ena nce (res pon der s)	IG1(eow): adali mumab 40mg o nce every other week, subcutan eous IG2(weekly): adalimumab 40 mg weekly, subc utaneous	Placebo (no fut her details)	Previous TN F-antagonist exposure: n (%) 238 (47. 7) out of 499 participants	Concurrent therapies for CD, including stable dosages (for at least 4 weeks before scree ning) of azathioprine, 6-merc aptopurine, methotrexate, 5-a minosalicylates, sulfasalazin e, oral mesalamine, and CD-r elated antibiotics, were permi tted, as were stable dosages (for at least 2 weeks before s creening) of prednisone (<=3 0 mg/day or equivalent) or bu desonide (<=9 mg/day) (patie nts could not be on both pred nisone and budesonide). Pati ents who had received inflix imab or any TNF antagonist o ther than adalimumab more t han 12 weeks before screenin g could be enrolled provided t hat they did not exhibit initial nonresponse to the agent (ie, no clinical response to first inj ection as judged by the invest igator). Female patients of chi ldbearing potential were requi red to use an effective form of birth control.	Patients could not be enrolled if : currently, on parenteral nutrition; had received investigational chemical agents w ithin 30 days or investigational biologic therapy within 3 months before screenin g; had received antibiotic treatment for non-CD-related infections within 3 week s before screening; had received treatment with adali-mumab or participated in an adalimumab clinical study; had received enema therapy within 2 weeks befor e screen-ing; had received cyclosporine, mycophenolate mofetil, ortacrolimus wi thin 8 weeks of screening	All patien ts entered a 2-we ek scree ning peri od befor e their ba seline as essmen ts. At the baseline visit (we ek 0), all eligible p atients re ceived o pen-label adalimu mab 80 mg subc utaneous ly followe d by a 40 -mg dose at week 2.	From all three groups n (%) out of 499 participant s Any corticosteroid: 210; p rednisone: 130; budesoni de: 48 Any immunosuppressive: 240; Azathioprine: 165; 6- mercaptopurine: 38; meth otrexate: 49 5-aminosalicylates: 206
Col om bel 202 3 - LIB ER TY- CD	Subcutaneous i njection of CT-P 13 SC	Subcutaneous i njection of place bo	NR	NR	NR	NR	NR
Fea gan 201 5c (IM- UNI TI)	IG1 (90mg/12wk s) IG2 (90mg/8w ks)	Placebo	No history of TNF antago nist treat-me nt — no. (%) CG = 52 (39. 1) IG1= 53 (40.2) IG2=5 2 (39.4)	NR	NR	NR	NR
Ferr ant e 2 022 - F OR TIF Y	IG1 SC Risankiz umab 180mg IG2 SC Risankiz umab 360mg	SC Placebo	Induction ph ase experien ce (induction population c haracteristic s in Table 1	(induction population charact eristics in Table 1	(induction population characteristics in Table 1	None oth er	Corticosteroid use IG1 3 2% IG2 30% CG 32% Immunomodulator use IG 1 26% IG2 28% CG 24%
Han aue	IG1 – Infliximab i nfusion, each inf	CG - Placebo - i dential in appe	Patients wer e excluded fr	'Patients receiving the followi ng treatments were eligible: 5	'Patients not receiving medical therapy had to have discontinued treatment for at least 4 weeks before screening'	None	'Patients receiving the foll owing treatments were eli

r 2002 (ACE NT I) - Maintenance (Responders)	usion 5 mg/kg. Infusions at week 2, week 6, and every 8 weeks thereafter until week 46. IG2 – Infliximab infusion, 5mg/kg infusions at week 2 and week 6. 10mg/kg every 8 weeks thereafter until week 46.	arance to Infliximab infusion. Infusions at week 2 (start point of maintenance study), week 6, and every 8 weeks thereafter until week 46.	om the study if they had received Infliximab in the past or any other agent targeting TNF	-aminosalicylates or antibiotics (if the dose remained constant for 4 weeks before the screening visit); corticosteroids (prednisone, prednisolone, or budesonide) at the equivalent of 40 mg per day of prednisone or less (stable dose for 3 weeks); azathioprine and 6-mercaptopurine (stable dose for 8 weeks); or methotrexate (stable dose for 6 weeks).' NOT REPORTED per IG/CG, the following data is based on responders as a whole. 5-Aminosalicylates – 159/335 (47%) 6-Mercaptopurine and Azathioprine – 81/335 (24%) Methotrexate – 10/335 (3%) Corticosteroids of which (i) Any – 175/335 (52%) (ii) >20mg per day – 61/335 (18%)			gible: 5-aminosalicylates or antibiotics (if the dose remained constant for 4 weeks before the screening visit); corticosteroids (prednisone, prednisolone, or budesonide) at the equivalent of 40 mg per day of prednisone or less (stable dose for 3 weeks); azathioprine and 6-mercaptopurine (stable dose for 8 weeks); or methotrexate (stable dose for 6 weeks).' NOT REPORTED per IG/CG, the following data is based on responders as a whole. 5-Aminosalicylates – 159/335 (47%) 6-Mercaptopurine and Azathioprine – 81/335 (24%) Methotrexate – 10/335 (3%) Corticosteroids of which (i) Any – 175/335 (52%) (ii) >20mg per day – 61/335 (18%)
Jorgen 2017 (NOR SWITC H)	IG: Patients were switched to biosimilar CT-P13 infusions on the same dose and intervals as their pre-randomisation infliximab regimen	CG: The dose and infusion intervals of patients' infliximab treatment regimens were kept unchanged from those before randomisation	IG: 60/77 and CG: 61/78 naïve	Immunosuppressive therapy: IG: 36/77 CG: 30/78 Prednisolone: IG: 0/77 CG: 2/78 Pre-infusion steroids IV: IG: 6/77 CG: 8/78	Initiation of systemic corticosteroids or an immunosuppressant or other medication on which according to the investigator would interfere with the stability of the disease was not allowed	None	Immunosuppressive therapy: IG: 36/77 CG: 30/78 Prednisolone: IG: 0/77 CG: 2/78 Pre-infusion steroids IV: IG: 6/77 CG: 8/78
NC T00349752 (CO SP AR 1)	IG: Certolizumab pegol 400 mg provided in a solution for subcutaneous injection (2 x 200 mg/mL) in single-use vials for administration at Weeks 0, 2, 4 and then every 4 weeks until Week 36	CG: Placebo provided for subcutaneous injection in 2 single-use vials for administration at Weeks 0, 2, 4 and then every 4 weeks until Week 36	All patients not naïve	NR	Subjects had to be receiving corticosteroids at a dose no higher than 30 mg/day prednisone or equivalent during the week prior to randomisation. Patients followed a corticosteroid forced-taper regimen after randomisation.	None	NR
					For the preceding induction study		

Pan es 2 017 Mai nten anc e	IG-T5 – Tofacitinib 5mg twice daily for 26 weeks (ROUTE NOT REPORTED but likely to be ORAL as it is twice daily over 26 weeks). IG-T10 – Tofacitinib 10mg twice daily for 26 weeks (ROUTE NOT REPORTED but likely to be ORAL as it is twice daily over 26 weeks)	CG – Placebo twice daily for 26 weeks (ROUTE, AGENT, and DOSE NOT REPORTED but ROUTE is likely to be ORAL as it is twice daily over 26 weeks)	Previous experience of biologic therapy as a whole (which includes JAKi) is NOT REPORTED Previous experience of TNFi – CG 39/59 (66.1%). IG-T5 48/60 (80.0%). IG-T10 48/61 (78.7%)	For the preceding induction study Concomitant corticosteroids were allowed up to oral prednisone-equivalent 30mg/day or budesonide 9mg/day, provided a stable dose had been taken for at least 2 weeks prior to baseline. Concomitant oral 5-ASA or sulfasalazine (stable dose for at least 4 weeks prior to baseline), chronic treatment for CD with antibiotics (e.g. metronidazole, rifaximin; stable dose for at least 2 weeks prior to baseline), rectally administered formulation of corticosteroids or 5-ASA (stable dose for at least 2 weeks prior to baseline) was also permitted but only data on corticosteroids is provided. Use of corticosteroids at entry to the maintenance phase – CG 18/59 (30.5%). IG-T5 18/60 (30.0%). IG-T10 23/61 (37.7%)	Patients receiving azathioprine, 6-mercaptopurine or methotrexate were required to stop these agents at least two weeks before randomisation Concomitant tumour necrosis factor inhibitor (TNFi) were not allowed, and a wash-out period of at least eight weeks prior to randomisation was required Cyclosporine, mycophenolate or tacrolimus were required to be stopped at least 4 weeks prior to baseline Intravenous Corticosteroids were required to be stopped at least 2 weeks prior to baseline Other investigational or marketed biologics with immunomodulatory properties were required to be stopped at least 3 months prior to baseline Treatment with Natalizumab or any anti-adhesion molecule was to be stopped at least 1 year prior to baseline Moderate to potent CYP3A inducers were prohibited within 28 days or 5 half-lives, whichever was longer, prior to first dose of study drug Moderate to potent CYP3A inhibitors were prohibited within 7 days or 5 half-lives whichever was longer prior to first dose of study drug	N/A – No protocol found	For the preceding induction study Concomitant corticosteroids were allowed up to oral prednisone-equivalent 30mg/day or budesonide 9mg/day, provided a stable dose had been taken for at least 2 weeks prior to baseline. Concomitant oral 5-ASA or sulfasalazine (stable dose for at least 4 weeks prior to baseline), chronic treatment for CD with antibiotics (e.g. metronidazole, rifaximin; stable dose for at least 2 weeks prior to baseline), rectally administered formulation of corticosteroids or 5-ASA (stable dose for at least 2 weeks prior to baseline) was also permitted but only data on corticosteroids is provided. In the maintenance study, a mandatory steroid taper algorithm was applied for patients receiving oral corticosteroids starting at baseline of the maintenance period with the dose decreased by 5mg prednisolone equivalent per week until the dose reached 20mg/day and then by 2.5mg/week to 10mg/day. Further taper was at the discretion of the investigator Use of corticosteroids at entry to the maintenance phase – CG 18/59 (30.5%). IG-T5 18/60 (30.0%). IG-T10 23/61 (37.7%)
Rut gee rts 199 9	IV 5, 10, or 20 mg/kg infliximab	IV infusion placebo	No (patients were induced with infliximab in a previous trial, one of the first)	For patients undergoing concomitant therapy for Crohn's disease, acceptable regimens for inclusion in the study were as follows: mesalamine 8 weeks' duration and at a stable	NR	None	For patients undergoing concomitant therapy for Crohn's disease, acceptable regimens for inclusion in the study were as follows: mesalamine 8 weeks' d

			on infliximab)	dosage for 4 weeks before screening; oral corticosteroids, 8 weeks duration at a stable dosage for 2 weeks, with a maximum dosage of 40 mg/day; and 6-mercaptopurine or azathioprine, 6 months duration at a stable dosage for 8 weeks			duration and at a stable dosage for 4 weeks before screening; oral corticosteroids, 8 weeks duration at a stable dosage for 2 weeks, with a maximum dosage of 40 mg/day; and 6-mercaptopurine or azathioprine, 6 months duration at a stable dosage for 8 weeks
Rutgers 2012 (EXTENDED)							
Sandborn 2005a (ENACT 2)	IV 300 mg Natalizumab every 4 weeks	IV infusion Placebo (exact agent and dosage: NR)	IG - Y 55 (33%), Refractory to such therapy 32 (58%) CG - Y 68 (40%), Refractory to such therapy 40 (23%)	NR	NR	No protocol	For both IG and CG, concurrent therapies, including stable doses of 5-aminosalicylates, prednisolone (25 mg per day or less) or equivalent, budesonide (6 mg per day or less), azathioprine, mercaptopurine, methotrexate, and antibiotics, were permitted. Corticosteroids - CG 76 (44%) IG 64 (38%). Prednisone - CG 54 (32%) IG 44 (26%). Budesonide CG 24 (14%) IG 21 (13%) Immunosuppressants - CG 60 (35%) IG 62 (37%). Azathioprine - CG 45 (26%) IG 42 (25%). Mercaptopurine - CG 7 (4%) IG 12 (7%). Methotrexate - CG 8 (5%) IG 8 (5%) Antibiotics (metronidazole, tinidazole, ciprofloxacin, and clarithromycin) - CG 10 (6%) IG 15 (9%) 5-Aminosalicylates (mesalamine, sulfasalazine, and olsalazine) - CG 93 (54%) IG 76 (45%) ≥1 Corticosteroids or immunosuppressants - CG 103 (60%) IG 96 (57%)

							Corticosteroids and immunosuppressants - CG 33 (19%) IG 30 (18%)
Sanborn 2007 (CLASSIC II)	IG1 (Subcutaneous Adalimumab 40 mg every other week): 2 (11) IG2 (Subcutaneous Adalimumab 40 mg weekly):	placebo not specified	all patients had received biologics in Classic I	NR	Patients' dosages of all concurrent drugs were required to remain constant, with the exception of corticosteroids. Steroid tapering was mandated for randomised patients at week 8 and was permitted in the open-label cohort for those patients who were responders (that is, who experienced a reduction of >70 points in CDAI score from week 0 in CLASSIC I). After week 8, daily doses for randomised patients receiving prednisone. 10 mg were reduced by 5 mg weekly until a dosage of 10mg/day was reached. Thereafter, dosage was reduced by 2.5 mg weekly to the point of discontinuation. Similarly, budesonide dosage was decreased by 3 mg every week until discontinuation.	NR	Concomitant drug treatment (n (%)) Any corticosteroid CG=10 (56) IG1=8 (47) IG2= 9 (50) Systemic corticosteroid CG=16 (33) IG1= 4 (21) IG2= 5 (28) Budesonide CG=4 (22) IG1= 4 (21) IG2=4 (22) Any immunosuppressive agent CG=3 (17) IG1=4 (21) IG2=5 (28) Azathioprine CG=1 (6) IG1= 4 (21) IG2= 2 (11) 6-Mercaptopurine CG= 1 (6) IG1=0 (0) IG2= 3 (17) Methotrexate CG=1 (6) IG1=0 (0) IG2= 0 (0) Crohn's-related antibiotics CG=1 (6) IG1= 0 (0) IG2=(0) 5-Aminosalicylates CG=8 (44) IG1=14 (74) IG2=12 (67)
Sanborn 2012 (CERTIFI) - Maintenance	Subcutaneous Ustekinumab 90mg at weeks 8 and 16	Subcutaneous Placebo at weeks 8 and 16. DOSE and AGENT NOT REPORTED	Previous experience of biologics* - CG - 110/110 (100%). IG - 109/109 (100%) *Although not stated explicitly the proportion of patients with previous experience, it can be safely assumed to be 100% for all groups as it is a study looking at efficacy of UST in CD refractory to TNF treatment. It is stated in the main paper 'In this 36-week, randomized, double-blind,	Patients were permitted to continue receiving stable doses of drugs for the treatment of Crohn's disease, including oral prednisolone (<=40 mg per day) or budesonide (<=9 mg per day), immunomodulators (e.g. azathioprine, mercaptopurine, or methotrexate), mesalamine, and antibiotics, if they had been taking the drugs for at least the prespecified period before study entry of 3 weeks, 4 weeks, 3 weeks, and 3 weeks, respectively. Patients had not received previous therapies targeting interleukin-12 or interleukin-23. Note - 'Study entry' here implies entry to the original induction phase of CERTIFI (i.e. week 0 to week 8 rather than week 8 to week 36) Proportions or numbers of patients per IG/CG per medication is NOT REPORTED for the week 8 to week 36 phase of CERTIFI (including responders maintenance study)	IV Glucocorticoids were not permitted at least 3 weeks before study entry TNF antagonists were not permitted at least 8 weeks before study entry Natalizumab was not permitted for at least 12 months before study entry Note - 'Study entry' here relates week 0 to week 8 induction phase. So, 8 weeks should be added to the times stated	Not reported - No protocol	Patients were permitted to continue receiving stable doses of drugs for the treatment of Crohn's disease, including oral prednisolone (<=40 mg per day) or budesonide (<=9 mg per day), immunomodulators (e.g. azathioprine, mercaptopurine, or methotrexate), mesalamine, and antibiotics, if they had been taking the drugs for at least the prespecified period before study entry of 3 weeks, 4 weeks, 3 weeks, and 3 weeks, respectively. Patients had not received previous therapies targeting interleukin-12 or interleukin-23. Note - 'Study entry' here implies entry to the original induction phase of CERTIFI (i.e. week 0 to week 8 rather than week 8 to week 36) Proportions or numbers of patients per IG/CG per medication is NOT REPORTED

			placebo-controlled phase 2b trial of ustekinumab (comprising 8-week induction and 28-week maintenance phases), we evaluated patients with moderate-to-severe Crohn's disease that was resistant to TNF antagonists.				RTED for the week 8 to week 36 phase of CERTIFI (including responders maintenance study)
Sandborn 2013 (GEMIN II) - Maintenance	VCG: Venolizumab responders placebo VIG1: Venolizumab responders Vedolizumab Every 8 Wk (n=154) VIG2: Vedolizumab Every 4 Wk (n=154) IG3: Vedolizumab Induction Nonresponders Every 4 Wk (n=506)	CG: placebo + concomitant medication	Prior Crohn's disease medications, n (%) Prior anti-TNF use VCG 82 (54) VIG1 88 (57) VIG2 83 (54) CG 72 (49) I G3 364 (72) Prior anti-TNF failure ≥1 failure VCG 78 (51) VIG1 82 (55) VIG2 77 (50) CG 70 (48) I G3 338 (67) Inadequate response VCG 35 (45) VIG1 37 (45) VIG2 31 (40) CG 41 (59) I G3 176 (52) Loss of response VCG 29 (37) VIG1 35 (43) VIG2 33 (43) CG 22 (31) I G3 132 (39)	Glucocorticoids were tapered in patients who had a response at week 6, according to a prespecified regimen; immunosuppressive agents were discontinued in patients at U.S. sites (see the Supplementary Appendix). The use of other concomitant medications remained constant.	Glucocorticoids were tapered in patients who had a response at week 6, according to a prespecified regimen; immunosuppressive agents were discontinued in patients at U.S. sites (see the Supplementary Appendix). The use of other concomitant medications remained constant.	NR	Concomitant CG: placebo VCG: Venolizumab responders placebo VIG1: Venolizumab responders Vedolizumab Every 8 Wk (n=154) VIG2: Vedolizumab Every 4 Wk (n=154) IG3: Vedolizumab Induction Nonresponders Every 4 Wk (n=506) Crohn's 52 disease medications, n (%) Corticosteroids only VCG 56 (37) VIG1 59 (38) VIG2 58 (38) CG 45 (30) I G3 163 (32) Immunosuppressives only** VCG 23 (15) VIG1 27 (18) VIG2 31 (20) CG 25 (17) IG3 75 (15) Corticosteroids and immunosuppressives VCG 26 (17) VIG1 23 (15) VIG2 22 (14) CG 26 (18) I G3 92 (18) No corticosteroids or immunosuppressives VCG 48 (31) VIG1 45 (29) VIG2 43 (28) CG 52 (35) I G3 176 (35)

			Intolerance V CG 14 (18) VI G1 10 (12) VI G2 13 (17) C G 7 (10) IG3 30 (9) ≥2 failures VCG 53 (35) VIG1 46 (30) VIG2 49 (32) CG 42 (28) I G3 208 (41)				
San dbo rn 2 020 d (C ELE ST) - M aint ena nce	IG-U6B Upadacitinib 6mg immediate-release twice daily for 36 weeks (ROUTE NOT REPORTED but likely to be ORAL as it is twice daily for 36 weeks). IG-U12B Upadacitinib 12mg immediate-release twice daily for 36 weeks (ROUTE NOT REPORTED but likely to be ORAL as it is twice daily for 36 weeks). IG-U24Q Upadacitinib 24mg immediate-release once daily for 36 weeks (ROUTE NOT REPORTED but likely to be ORAL as it is once daily for 36 weeks).	CG-U3B Upadacitinib 3mg immediate-release twice daily for 36 weeks (ROUTE NOT REPORTED but likely to be ORAL as it is twice daily for 36 weeks)	NOT REPORTED	NOT REPORTED per IG/CG for the maintenance phase For the preceding induction phase Patients could enter the study while receiving stable doses of aminosalicylates, oral corticosteroids (equivalent prednisone dose of ≤30mg/d or budesonide of ≤9mg/d), methotrexate, and/or CD-related antibiotics. Starting at week 2, patients receiving oral corticosteroids initiated a mandatory corticosteroid tapering following a protocol-specified schedule until discontinuation	Patients had to discontinue Azathioprine or Mercaptopurine ≥10 days before baseline in the induction study	Not reported – No protocol	NOT REPORTED per IG/CG for the maintenance phase For the preceding induction phase Patients could enter the study while receiving stable doses of aminosalicylates, oral corticosteroids (equivalent prednisone dose of ≤30mg/d or budesonide of ≤9mg/d), methotrexate, and/or CD-related antibiotics. Starting at week 2, patients receiving oral corticosteroids initiated a mandatory corticosteroid tapering following a protocol-specified schedule until discontinuation
San dbo rn 2 023 - BE RG AM OT Mai nten	IG - subcutaneous 105 mg certolizumab every 4 weeks for 52 weeks.	CG- placebo every 4 weeks for 52 weeks. Patients randomly assigned to placebo during induction who achieved CDAI-70 responses received	All patients went through an induction phase with certolizumab Experience with biologics at induction baseline is mentioned in	Patients must have had intolerance, inadequate response, or no response to one or more of corticosteroids, immunosuppressants, or anti-TNF therapy within 5 years of screening. Patients receiving stable doses of oral corticosteroids (≤20 mg per day prednisone or equivalent or ≤6 mg per day budesonide) for at le	Patients with previous exposure to antiadhesion molecule therapy were not allowed. Patients were excluded if they had taken one or more of adalimumab, certolizumab pegol, or infliximab within 8 weeks before randomisation or had taken ustekinumab within 14 weeks before randomisation.	Only the ones given as interventions	Baseline use of oral corticosteroids 42% in both groups. (Immunosuppressant use in Table 3).

anc e		blinded placebo during the maintenance phase after sham re-randomisation; these patients were not included in maintenance efficacy results	the induction tables for this study.	at least 2 weeks before screening or immunosuppressants (eg, azathioprine, 6-mercaptopurine, and methotrexate) for at least 8 weeks before screening were included.			
Sands 2004 (ACE NT II) Maintenance (Response)	Infliximab 5mg/kg at weeks 14, 22, 30, 38, and 46. Beginning at week 22, patients who had a loss of response (defined by recurrence of draining fistulas, the need for additional therapy for persistent or worsening luminal disease activity, the need for a surgical procedure for Crohn's disease, or the discontinuation of the study medication owing to a perceived lack of efficacy) were eligible to cross over to maintenance treatment with Infliximab 10mg/kg	Placebo at weeks 14, 22, 30, 38, and 46. Beginning at week 22, patients who had a loss of response (defined by recurrence of draining fistulas, the need for additional therapy for persistent or worsening luminal disease activity, the need for a surgical procedure for Crohn's disease, or the discontinuation of the study medication owing to a perceived lack of efficacy) were eligible to cross over to maintenance treatment with infliximab 5mg/kg	NR However, exclusion criteria state that if patients had received infliximab previously, they were excluded from the study. No mention of other biologics	Concurrent therapies for Crohn's disease, including stable doses of 5-aminosalicylates, oral corticosteroids, azathioprine, mercaptopurine, mycophenolate mofetil, methotrexate, and antibiotics, were permitted (i) 5-Aminosalicylates (oral or rectal) [n (%)] – CG 49/99 (49%). IG 41/96 (43%) (ii) Mercaptopurine or Azathioprine [n (%)] – CG 35/99 (35%). IG 29/96 (30%) (iii) Methotrexate [n (%)] – CG 2/99 (2%). IG 1/96 (1%) (iv) Antibiotics [n (%)] – CG 26/99 (26%). IG 28/96 (29%) (v) Corticosteroids. (va) Any [n (%)] – CG 30/99 (30%). IG 25/96 (26%). (vb) >20 mg per day [n (%)] – CG 8/99 (8%). IG 8/96 (8%)	NR	NR	Concurrent therapies for Crohn's disease, including stable doses of 5-aminosalicylates, oral corticosteroids, azathioprine, mercaptopurine, mycophenolate mofetil, methotrexate, and antibiotics, were permitted (i) 5-Aminosalicylates (oral or rectal) [n (%)] – CG 49/99 (49%). IG 41/96 (43%) (ii) Mercaptopurine or Azathioprine [n (%)] – CG 35/99 (35%). IG 29/96 (30%) (iii) Methotrexate [n (%)] – CG 2/99 (2%). IG 1/96 (1%) (iv) Antibiotics [n (%)] – CG 26/99 (26%). IG 28/96 (29%) (v) Corticosteroids. (va) Any [n (%)] – CG 30/99 (30%). IG 25/96 (26%). (vb) >20 mg per day [n (%)] – CG 8/99 (8%). IG 8/96 (8%)
Schreiber 2007 (PRECISE 2)	Subcutaneous injection Certolizumab 400 mg	Subcutaneous injection placebo (agent: NR)	Patients who had received any certolizumab pegol, who had received an anti-TNF agent or other biologic therapy within 3 months before enrollment, or who had a severe hypersensitivity	Glucocorticoids only: CG: 44 (21%) IG: 47 (22%) Immunosuppressive agents only: CG: 52 (25%) IG: 59 (27%) Glucocorticoids plus immunosuppressive agents: CG: 34 (16%) IG: 28 (13%)	NR	NR	Permitted concomitant therapies for Crohn's disease were stable doses of 5-aminosalicylates, 30 mg or less of prednisolone per day (or equivalent), azathioprine, 6-mercaptopurine, methotrexate, and antibiotics.

			ensitivity reaction or no clinical response after initial dosing with an anti-TNF were excluded	Neither glucocorticoids nor immunosuppressive agents CG: 80 (38%) IG: 81 (38%)			
Schreiber 2021	CT-P13 SC was administered via prefilled syringe containing 120 mg CT-P13 SC - SC Group	CT-P13 IV (5 mg/kg) was administered as a 2-hour (p15 minutes) IV infusion - IV Group	The study enrolled tumor necrosis factor or inhibitor-naïve patients	AZA/6MP/methotrexate use 14/28 and 13/25	Patient was ineligible if they had received or planned to receive any of following prohibited medications or treatments: - Any biological agents for the treatment of UC or CD - Parenteral corticosteroids for the treatment of UC or CD ≤ 2 weeks prior to screening - Antibiotics for the treatment of UC or CD ≤ 2 weeks prior to Day 0 - Alkylating agents ≤ 12 months prior to Day 0 - Thalidomide, tacrolimus, or cyclosporine ≤ 3 months prior to Day 0 - Live or live-attenuated vaccine ≤ 4 weeks prior to Day 0	Patient was either on stable doses or currently not receiving (during specified time frame) the following CD medication: - AZA or 6-MP for ≥ 8 weeks prior to Day 0 - Methotrexate for ≥ 6 weeks prior to Day 0 - Oral corticosteroids at the equivalent dose of ≤ 20 mg/day of prednisone for ≥ 2 weeks prior to Day 0 - Oral budesonide at the dose of ≤ 6 mg/day for ≥ 4 weeks prior to Day 0 5-ASA for ≥ 4 weeks prior to Day 0	AZA/6MP/methotrexate use 14/28 and 13/25

						eks prior to Day 0.	
Van Assche 2012 (S-WITCH)	IG-ADA 80mg Subcutaneous Adalimumab at inclusion and 40mg subcutaneous Adalimumab every other week for 54 weeks. Patients with disease flare were allowed dose intensification – step-up to 40mg every week. If complete loss of response, patients were allowed to switch over to the alternative treatment. Short (4-week) courses of steroids were also allowed per protocol	CG-IFX Continue Infliximab 5mg/kg Intravenously at 8-week intervals for 56 weeks. Patients with disease flare were allowed dose intensification – decrease of dosing interval with 2-week decrements. Short (4-week) courses of steroids were also allowed per protocol	Patient with previous exposure to ADA, and receiving IFX doses >5 mg/kg intravenously were excluded	Azathioprine – CG-IFX 0/37 (0.00%). IG-ADA 6/36 (16.7%) Methotrexate – CG-IFX 2/37 (5.41%). IG-ADA 0/36 (0.0%)	IFX doses >5 mg/kg intravenously were excluded	None	Azathioprine – CG-IFX 0/37 (0.00%). IG-ADA 6/36 (16.67%) Methotrexate – CG-IFX 2/37 (5.41%). IG-ADA 0/36 (0.00%)
Vermeire 2017 (FITZROY - maintenance responders)	IG1 - Filgotinib 100mg oral once daily. IG2 - Filgotinib 200mg oral once daily	Matching placebo oral once daily (AGENT NOT REPORTED). Placebo was presented as orally administered brown film-coated tablets that were identical in appearance to filgotinib and contained the same excipients	NOT REPORTED However, one of the exclusion criteria states that previous JAK inhibitor therapy was not allowed. Therefore, no patient had previous JAK inhibitors (CG – 0/15, IG1 – 0/30, IG2 – 0/31) but unable to comment on TNF inhibitors and hence on biologics as a whole	Note – the timepoints here apply to the original induction study (i.e. screening means week 0 rather than week 10, where the latter is where the maintenance phase began) Concurrent treatment with oral steroids (<=30 mg prednisolone or budesonide <=9 mg per day) or probiotics was allowed if dosages had been stable for at least 2 weeks before the first dose of study drug . Concurrent treatment with Crohn's disease-related antibiotics , or with mesalazine or olsalazine , was permitted if dosages had been stable for at least 4 weeks before the first dose of study drug . Previous exposure to sulfasalazine was allowed but had to be discontinued at least 4 weeks before screening in male patients, whereas immunomodulators (e.g. thiopurines and methotrexate) must have been discontinued at least 25 days before	Note – the timepoints here apply to the original induction study (i.e. screening means week 0 rather than week 10, where the latter is where the maintenance phase began) Previous exposure to sulfasalazine was allowed but had to be discontinued at least 4 weeks before screening in male patients Immunomodulators must have been discontinued at least 25 days before the first dose of the study drug Tube feeding, defined formula diets, or total parenteral alimentation was not allowed during the study IV corticosteroids were to be discontinued 14 days prior to screening Enemas or suppositories other than those required for colonoscopy were to be discontinued 7 days prior to screening Cyclosporine, mycophenolate, tacrolimus, or interferon were to be discontinued at least 10 weeks prior to screening Any prior lymphocyte depleting agent (e.g. Alemtuzumab) was prohibited . Lymphocyte apheresis or selective monocyte granulocyte apheresis was to be discontinued 12 months prior to screening Previous fecal microbiota transplant and stem cell transplants were prohibited Investigational chemical agents were to be discontinued 4 weeks before screening Previous treatment with biological investigational medicinal products including murine, chimeric or humanized monoclonal antibodies or a chemokine receptor	If using paracetamol at baseline , it should not be discontinued Contraception	Note – the timepoints here apply to the original induction study (i.e. screening means week 0 rather than week 10, where the latter is where the maintenance phase began) Concurrent treatment with oral steroids (<=30 mg prednisolone or budesonide <=9 mg per day) or probiotics was allowed if dosages had been stable for at least 2 weeks before the first dose of study drug . Concurrent treatment with Crohn's disease-related antibiotics , or with mesalazine or olsalazine , was permitted if dosages had been stable for at least 4 weeks before the first dose of study drug . Previous exposure to sulfasalazine was allowed but had to be discontinued at least 4 weeks before screening in male patients, where as immunomodulators

				the first dose of the study drug Proportion of patients on each medication – NOT REPORTED for the maintenance phase	blocker within less than 5 half-lives prior to baseline. Previous treatment with a janus kinase inhibitor is prohibited. Live vaccines must not have been administered within 90 days or an attenuated vaccine within 30 days of first dose of study drug as well as during the study duration until 6 weeks following last intake of GLPG0634 Patients currently on any therapy for chronic infection (such as pneumocystis, CMV, herpes simplex, herpes zoster, or atypical mycobacteria) were excluded from the study		(e.g. thiopurines and methotrexate) must have been discontinued at least 25 days before the first dose of the study drug Proportion of patients on each medication – NOT REPORTED for the maintenance phase
Vermeire 2021 (VIBILE 2)	vedolizumab 108 mg SC	SC Placebo (agent: NR)	Patients with previous exposure to approved or investigational anti-integrin antibodies (e.g., natalizumab, efalizumab, etrolizumab, abrilumab [AMG 181]), anti-mucosal addressin cell adhesion molecule-1 antibodies, or rituximab and vedolizumab were excluded Anti-TNF naïve CG: 64 [47.8%] IG: 110 [40.0%] Prior anti-TNF use: CG: 71 [53.0%] IG: 168 [61.1%] Prior use of IMM [only]: CG: 4 [3.0%] IG: 16 [5.8%] Prior use of oral CS [only]: CG: 23 [17.2%] IG: 67 [24.4%] Prior use of oral CS and IMM: CG: 103 [76.9%] IG: 189 [68.7%]	NR		NR	Only IMM: CG: 34 [25.4%] IG: 51 [18.5%] Only CS: CG: 31 [23.1%] IG: 64 [23.3%] IMM and CS: CG: 13 [9.7%] IG: 31 [11.3%]
Vermeire 2025 - DIVESTY (main)	Filgotinib 100 mg Filgotinib 200 mg Patients received their induction dose or placebo orally, once daily	Placebo (after receiving filgotinib 100mg at induction) Placebo (after receiving filgotinib 200mg at induction) Patients received their induction	All patients induced with the filgotinib at induction phase	About 50% of all patients had concomitant use of systemic corticosteroids, immunosuppressants or both	None	Vaccines, contraceptives, fertility medication	Only IMM (n): CG1: 9 CG2: 10 IG1: 23 IG2: 24 Only CS: CG1: 14

nan ce)		dose or placebo orally, once daily					CG2: 15 IG1: 27 IG2: 34 IMM and CS: CG1: 4 CG2: 4 IG1: 8 IG2: 8
Vol kers 201 7 - SIM ILA R	Infliximab biosimilar - Patients switched from infliximab-biological and received 4 to 6 doses of 5 mg/kg to 10 mg/kg of infliximab-biosimilar during the 30-week study period (Route and Regimen NOT REPORTED - Need full paper to find this information)	Infliximab biological - Patients continued infliximab-biological and received 4 to 6 doses of 5 mg/kg to 10 mg/kg of infliximab-biosimilar during the 30-week study period (Route and Regimen NOT REPORTED - Need full paper to find this information)	NR	NR	NR	NR	NR
Wat ana be 201 2 - Mai nten anc e							
Wat ana be 202 0 - Mai nten anc e	Vedolizumab 300mg intravenously at week 14, then every 8 weeks until week 54 (AGENT and DOSE NOT REPORTED)	Placebo intravenously at week 14, then every 8 weeks until week 54 (AGENT and DOSE NOT REPORTED)	Reported as 'Prior anti-TNF (alpha) treatment' [numbers (percentage)]: (i) No - CG 5/12 (41.7%). IG 4/12 (33.3%). (ii) Yes - CG 7/12 (58.3%). IG 8/12 (66.7%) Prior anti-TNF (alpha) failure [numbers (percentage)]: (i) Overall (percentage): (i) Overall	Patients were allowed concomitant treatment with oral 5-aminosalicylic acid, probiotics, antibiotics for CD, oral corticosteroids, immunomodulators and enteral nutrients (<=900 kcal/day) under specific conditions Concomitant medication for CD at baseline [numbers (percentage)]: (i) Enteral nutrient - CG 5/12 (41.7%). IG 8/12 (66.7%). (ii) 5-Aminosalicylic acid - CG 11/12 (91.7%). IG 8/12 (66.7%). (iii) Oral Corticosteroids AND no immunomodulators - CG 3/12 (25.0%). IG 2/12 (16.7%). (iv) No Oral C	These patients were excluded from the study (otherwise discontinued medication NOT REPORTED) - (i) Patients who started oral 5-ASAs, probiotics, antibiotics for CD treatment, or oral corticosteroids (<=30 mg/day) within 13 days before the first dose of the study drug . Or patients who changed dosage of or discontinued these drugs within 13 days before the first dose of the study drug if the patient had used these drugs for more than 14 days before the first dose of the study drug (ii) Patients who had received 5-ASA, corticosteroid enemas/suppositories, corticosteroid IV infusion, oral corticosteroid at >30 mg/day, drugs for diarrhea-predominant irritable bowel syndrome, or Chinese herbal medicine for the CD treatment (e.g., Daikenchuto) within 13 days before the first dose of the study drug (iii) Patients who had received AZA, 6-MP, or MTX within 27 days before the first dose of the study drug . However, this did not apply to patients who had used these drugs for more than 83 days before the first dose of the study drug and continued the steady dose of the drugs for more than 27 days before the first dose of the study drug (iv) Patients who had received cyclosporine, tacrolimus, tofacitinib or any study drugs of low molecular compound for CD treatment within 27 days before the first dose of the study drug (v) Patients who had received adalimumab within 27 days before the first dose of the study drug or a	NOT REPORTED - No protocol found	NOTE - These are the same as medications up to study beginning Patients were allowed concomitant treatment with oral 5-aminosalicylic acid, probiotics, antibiotics for CD, oral corticosteroids, immunomodulators and enteral nutrients (<=900 kcal/day) under specific conditions Concomitant medication for CD at baseline [numbers (percentage)]: (i) Enteral nutrient - CG 5/12 (41.7%). IG 8/12 (66.7%). (ii) 5-Aminosalicylic acid -

				II – CG 7/12 (58.3%). IG 8/12 (66.7%) (ii) Inadequate response – CG 1/12 (8.3%). IG 3/12 (25.0%) (iii) Loss of response – CG 6/12 (50.0%). IG 5/12 (41.7%) (iv) Intolerance – CG 0/12 (0.0%). IG 0/12 (0.0%) Number of drugs of anti-TNF (alpha) failure [numbers (percentage)]: (i) None – CG 5/12 (41.7%). IG 4/12 (33.3%). (ii) One – CG 5/12 (41.7%). IG 2/12 (16.7%). (iii) Two – CG 2/12 (16.7%). IG 6/12 (50.0%) Worst prior treatment failure [numbers (percentage)]: (i) Prior anti-TNF (alpha) failure – CG 7/12 (58.3%). IG 8/12 (66.7%). (ii) Prior immunomodulators failure but not anti-TNF (alpha) failure – CG 2/12 (16.7%). IG 11/12 (91.7%)	orticosteroids OR immunomodulators – CG 3/12 (25.0%). IG 1/12 (8.3%). (v) Oral Corticosteroids AND immunomodulators – CG 0/12 (0.0%). IG 3/12 (25.0%) ny biologics other than adalimumab within 55 days before the first dose of the study drug. However, this did not apply to patients who had received localized injections of these drugs (e.g., intraocular injection for treatment of age-related macular degeneration) (vi) Patients who had received any live-vaccinations within 27 days before the first dose of the study drug (vii) Patients who had a history or a complication of alcohol dependence or illicit drug use within one year before the first dose of the study drug. (viii) Patients who had received central venous nutrition therapy or enteral total nutrition therapy, or fasted within 20 days before the first dose of the study drug. (ix) Patients who had received an enteral nutrient of >900 kcal/day or who had started an enteral nutrient of ≤900 kcal/day within 20 days before the first dose of the study drug. Or patients who changed dosage of or discontinued the enteral nutrient within 20 days before the first dose of the study drug if the patient had received an enteral nutrient of ≤900 kcal/day more than 21 days before the first dose of the study drug NOTE – First dose of the study drug refers to Week 0 dose during the induction phase (i.e. not Week 0 of Maintenance phase which is Week 14)	CG 11/12 (91.7%). IG 8/12 (66.7%). (iii) Oral Corticosteroids AND no immunomodulators – CG 3/12 (25.0%). IG 2/12 (16.7%). (iv) No Oral Corticosteroids OR immunomodulators – CG 3/12 (25.0%). IG 1/12 (8.3%). (v) Oral Corticosteroids AND immunomodulators – CG 0/12 (0.0%). IG 3/12 (25.0%)	
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			G 3/12 (25.0%)				
Young 2024 - iBaSS	Reference adalimumab according to existing regimen	SB5 adalimumab biosimilar according to existing regimen	All patients were induced with adalimumab or biosimilar Other biologicals: IG n=14 (31.1%), CG n=11 (25.6%)	Currently taking concomitant immunosuppressive therapy at baseline, n (%) IG 24 (53.3) CG 20 (46.5)	NR	None	NR

Table 5

Induction studies' primary and secondary outcomes

Study ID	I.a Clinical remission	I.b Clinical response	I.c Endoscopic remission	I.d Withdrawals due to adverse events	I.e Serious adverse events	I.f Total numbers of patients with adverse events
Chen 2020	IG 38/102, CG 7/103 at 4 weeks	Clinical response (decrease in CDAI $\geq$ 70 from baseline) CG 28/103, IG 69/102	NR	IG 3/102, CG 5/103	IG 2/102, CG 1/103	IG 38/102, CG 38/103
Colombel 2007 (CHARM) - Induction (non-responders)	Week 12: CG (Plb) NR/91 IG1 (Adalimumab) 25/88 [calculated from 28%] IG2 (Adalimumab weekly) NR/100 <i>Need to contact authors to get further details on non-responders clinical remission.</i>	<i>Need to contact authors for more details on clinical response CR-70 in non-responders</i>	NR	<i>Need to contact authors to separate information for non-responders and responders</i>	<i>Need to contact authors to separate information for non-responders and responders</i>	<i>Need to contact authors to separate information for non-responders and responders</i>
Colombel 2010 (SONIC)	 By week 26 CG(AZA) 54/170 IG1(IFX) 81/169 IG2(Combo) 102/169 By week 50 CG 41/170 IG1 64/169 IG2 80/169	 CDAI 70 Response (wk 26): CG 71/170 IG1 95/169 IG2 113/169 CDAI 70 Response (wk 50): CG 56/170 IG1 75/169 IG2 88/169 CDAI 100 response (wk 26): CG 64/170 IG1 92/169 IG2 105/169 CDAI 100 Response (wk 50): CG 47/170 IG1 70/169 IG2 85/169	 Mucosal healing (wk 26): CG 18/170 IG1 28/169 IG2 47/169 Randomised patients not assessed with endoscopy were counted as failures	 At week 54: CG 42/170 IG1 29/169 IG2 37/169	 At week 54: CG 43/170 IG1 39/169 IG2 27/169	 Through week 30: CG 63/170 IG1 41/169 IG2 39/169 Through week 50: CG 69/170 IG1 53/169 IG2 53/169

D'Haens 1999 (refractory CD)	NR	NR as dichotomous CDAI mean(SEM) at week 4: CG: 261.3(33.3) IG1(5mg): 122.8(26.1) IG2(10mg): 220.5(63.4) IG3(20mg): 161.9(34.5)	NR as dichotomous CDEIS mean(SEM) at week 4: CG: 7.5(5.4) IG1(5mg): 6.4(5.1) IG2(10mg): 4.3(5.4) IG3(20mg): 5.2(2.8)	The follow-up ileocolonoscopy could not be performed in 2 CG patients: 1 due to surgery, 1 due to abdominal pain In 3 patients with ileitis, the ileocecal valve could not be intubated so that the ileum could not directly be visualized, but not explained in which groups they belonged	NR (except for 1 infliximab-treated patient with exclusive rectosigmoidal Crohn's disease developed a new rectal stricture at the site of earlier severe ulceration. This stricture needed multiple endoscopic dilatations in combination with stool softeners.)	NR
D'Haens 2008	Week 14 CG (corticosteroids) 21/66 IG (combined) 43/67 (taken from graph) After this time, infliximab was given to the control group and therefore no further data has been reported	NR	NR	At end of study CG 14/66 IG 14/67	CG 19/66 IG 20/67 <i>Not known at whether at end of trial - we have assumed that these occurred at 26 weeks</i>	<i>Need to contact authors for number of patients with AE as Table 2 only provides number of adverse events.</i> UNCLEAR
D'Haens 2022 (ADVANCE)	CG(pl) 44/186 IG1(ris600) 152/373 IG2(ris1200) 141/372	NR	CG(pl) 16/186 IG1(ris600) 81/373 IG2(ris1200) 81/372	CG 14/186 IG1 9/373 IG2 7/372	Combined severe and serious, serious infections and death CG 55/186 IG1 52/373 IG2 34/372	CG 105/186 IG1 210/373 IG2 191/372
D'Haens 2022 (SERENITY - Induction)						
Duan 2013	Clinical remission at week 26 - decrease in CDAI <70 points but a total CDAI score of <150 CG (AZA) 3/8 IG1 (IFX) 4/8 IG2 (Combo - AZA + IFX) 5/8	Clinical efficacy at week 26 - decrease in CDAI >70 points or a decrease of ≥25% of the total CDAI score CG (AZA) 2/8 IG1 (IFX) 2/8 IG2 (Combo - AZA + IFX) 2/8	"Fully healed": CG (AZA) 3/8 IG1 (IFX) 1/8 IG2 (Combo - AZA + IFX) 4/8 Basically healing: CG (AZA) 1/8 IG1 (IFX) 1/8 IG2 (Combo - AZA + IFX) 1/8	CG (AZA) 1/8 IG1 (IFX) 1/8 IG2 (Combo - AZA + IFX) 0/8	NR	NR
Feagan 2008	Day 57 (CDAI ≤150) CG: 21%, n=12 IG1(0.5mg): 30%, n=19 IG2(2mg): 37%, n=24	Day 57 ≥70-point decrement in CDAI from baseline CG: 41%, n=24 IG1(0.5mg): 49%, n=30 IG2(2mg): 53%, n=34	NR	CG:0 IG1(0.5mg): 1 (aggravated CD) IG2(2mg): 1 (aggravated CD)	SAEs: CG:10 IG1(0.5mg): 6 IG2(2mg): 10 BUT "Severe AEs were experienced by 37 (29%) MLN0002-treated and 19 (33%) placebo-treated patients"	CG:50 IG1(0.5mg): 58 IG2(2mg): 59

		Day 57 $\geq$100-point decrement in CDAI from baseline CG: 31%, n=18 IG1(0.5mg): 43%, n=27 IG2(2mg): 47%, n=31 Day 180 $\geq$100-point decrement in CDAI from baseline CG: 27%, n=16 IG1(0.5mg): 32%, n=20 IG2(2mg): 43%, n=28 (days 8, 15, 29, 43 illustrated in a graph)				
Feagan 2015a (UNIT 1-1)	Clinical remission (CAI < 150) at week 8: CG (Plb) 18/247 IG1 (Ust 130) 39/245 IG2 (Ust 6) 52/249	100-point clinical response at week 6: CG (Plb) 53/247 IG1 (Ust 130) 84/245 IG2 (Ust 6) 84/249 100-point clinical response at week 8: CG (Plb) 50/247 IG1 (Ust 130) 82/245 IG2 (Ust 6) 94/249 70-point clinical response at week 3: CG (Plb) 67/247 IG1 (Ust 130) 94/245 IG2 (Ust 6) 101/249 70-point clinical response at week 6: CG (Plb) 75/247 IG1 (Ust 130) 113/245 IG2 (Ust 6) 109/249	NR	CG (Plb) 10/247 IG1 (Ust 130) 9/245 IG2 (Ust 6) 14/249 <i>Need to contact authors to describe reasons for withdrawal and loss to follow-up further.</i>	CG (Plb) 15/247 IG1 (Ust 130) 12/245 IG2 (Ust 6) 18/249	CG (Plb) 159/247 IG1 (Ust 130) 159/245 IG2 (Ust 6) 164/249
Feagan 2015b (UNIT 1-2)	Clinical remission (CAI < 150) at week 8: CG (Plb) 41/210 IG1 (Ust 130) 64/209 IG2 (Ust 6) 84/209	100-point clinical response at week 6: CG (Plb) 60/210 IG1 (Ust 130) 108/209 IG2 (Ust 6) 116/209 100-point clinical response at week 8: CG (Plb) 67/210 IG1 (Ust 130) 99/209 IG2 (Ust 6) 121/209	NR	CG (Plb) 12/210 IG1 (Ust 130) 9/209 IG2 (Ust 6) 2/209 <i>Need to contact authors to describe reasons for withdrawal and loss to follow-up further.</i>	CG (Plb) 12/210 IG1 (Ust 130) 10/209 IG2 (Ust 6) 6/209	CG (Plb) 113/210 IG1 (Ust 130) 106/209 IG2 (Ust 6) 115/209

		70-point clinical response at week 3: CG (Plb) 66/210 IG1 (Ust 130) 103/209 IG2 (Ust 6) 106/209 70-point clinical response at week 6: CG (Plb) 81/210 IG1 (Ust 130) 123/209 IG2 (Ust 6) 135/209				
Feagan 2017	Clinical remission defined as 'CDAI score <150' Week 4 In clinical remission [number of patients/total patients in given group (percentage)] – CG 3/39 (7.7%). IG-R200 4/41 (9.8%). IG-R600 8/41 (19.5%) Week 8 In clinical remission [number of patients/total patients in given group (percentage)] – CG 1/39 (2.6%). IG-R200 7/41 (17.1%). IG-R600 10/41 (24.4%) Week 12 (primary) In clinical remission [number of patients/total patients in given group (percentage), Difference vs placebo (95% CI, p value)] – CG 6/39 IG-R200 10/41 IG-R600 15/41	Clinical response defined as 'either CDAI score <150 or a CDAI reduction of >=100 from baseline' Week 4 In clinical response CG 6/39 IG-R200 10/41 IG-R600 13/41 Week 8 In clinical response CG 5/39 IG-R200 13/41 IG-R600 13/41 Week 12 In clinical response CG 8/39 IG-R200 15/41 IG-R600 17/41	Endoscopic remission defined as 'CDEIS score of <=4 at week 12 (<=2 for patients with initial isolated ileitis) Week 12 In endoscopic remission [number of patients/total patients in given group (percentage)] CG 1/39 (3%) IG-R200 6/41 (15%), 12.1%. IG-R600 8/41 (20%), 16.8%	Through week 12 Withdrawals per IG/CG [number of patients withdrawing/total patients in given group (percentage)] – CG 6/39 (15.38%). IG-R200 6/41 (14.63%). IG-R600 1/41 (2.44%)	Through week 12 Serious adverse events [number of patients/total patients in given group (percentage)] – CG 12/39 (31%). IG-R200 9/41 (22%). IG-R600 3/41 (7%) A serious adverse event was defined as any that results in death, is immediately life-threatening, results in persistent or significant disability or incapacity, requires or prolongs patient hospital stay, is a congenital anomaly or birth defect, or is an important medical event, based upon appropriate medical judgement that might jeopardise the patient and might require medical or surgical intervention Note – Severe adverse events were reported as a subcategory of adverse events whereas Serious adverse events were a category of their own. It is unclear how many patients had both severe and serious adverse events	Through week 12 Total number of patients with adverse events [number of patients/total patients in given group (percentage)] – CG 32/39 (82%). IG-R200 32/41 (78%). IG-R600 31/41 (76%).
Ghosh 2003	Clinical remission (CDAI <150) Week 6 (PRIMARY END-POINT): CG (Plb) 17/63 IG1 (Nat 1 of3) 20/68 IG2 (Nat 2 of3) 29/66 IG3 (Nat 2 of6) 16/51	70-point clinical response Week 2 CG (Plb) 19/63 IG1 (Nat 1 of3) 31/68 IG2 (Nat 2 of3) 36/66 IG3 (Nat 2 of6) 22/51 Week 4 CG (Plb) 18/63 IG1 (Nat 1 of3) 32/68 IG2 (Nat	NR	CG (Plb) 7/63 IG1 (Nat 1 of3) 1/68 IG2 (Nat 2 of3) 5/66 IG3 (Nat 2 of6) 4/51 <i>These numbers were based on withdrawal due to lack of efficacy and adverse events. Authors need to be contacted to provide clear numbers on withdrawal numbers and reasons.</i>	CG (Plb) 7/63 IG1 (Nat 1 of3) 7/68 IG2 (Nat 2 of3) 6/66 IG3 (Nat 2 of6) 6/51	CG (Plb) 51/63 IG1 (Nat 1 of3) 50/68 IG2 (Nat 2 of3) 57/66 IG3 (Nat 2 of6) 40/51

		2of3) 41/66 IG3 (Nat 2 of6) 27/51 Week 6 CG (Plb) 24/63 IG1 (Nat 1of3) 40/68 IG2 (Nat 2of3) 47/66 IG3 (Nat 2 of6) 29/51 Week 8 CG (Plb) 22/63 IG1 (Nat 1of3) 38/68 IG2 (Nat 2of3) 44/66 IG3 (Nat 2 of6) 28/51 Week 12 CG (Plb) 27/63 IG1 (Nat 1of3) 34/68 IG2 (Nat 2of3) 40/66 IG3 (Nat 2 of6) 33/51				
Gordon 2001	Clinical remission (cdai < 150) at week 2 (primary end-point): CG (Plb) 1/12 IG (Nat) 7/18	At week 2: CG - mean CDAI reduction of 11 IG - mean CDAI reduction of 45 (unknown SD) from 258 (range, 122-436) to 213 (range, 46-413) Need to contact authors for more information on the clinical response observed in each group.	NR	CG (Plb) 2/12 IG (Nat) 1/18 Need to contact the authors for further clarity on withdrawal information.	Need to contact authors for full clarity on what serious adverse events occurred.	Need to contact the author as information provided only speaks about most common adverse events and not all events.
Hanauer 2002 (ACCENT I) - Induction (no n-response)	NR	Authors did not assess for co-primary end-points	NR	Authors did not assess for co-primary end-points	Need to contact author for separate safety information for responders and non-responders	Need to contact author for separate safety information for responders and non-responders
Hanauer 2006 (CLASSIC I)	Week 1: CG (Plb) 7/74 IG1 (Ada 40) 16/75 IG2 (Ada 80) 13/75 IG3 (Ada 160) 16/76 Week 2: CG (Plb) 14/74 IG1 (Ada 40) 14/75 IG2 (Ada 80) 20/75 IG3 (Ada 160) 24/76 Week 4 (primary):	70-point clinical response Week 1: CG (Plb) 24/74 IG1 (Ada 40) 37/75 IG2 (Ada 80) 40/75 IG3 (Ada 160) 32/76 Week 2: CG (Plb) 30/74 IG1 (Ada 40) 44/75 IG2 (Ada 80) 40/75 IG3 (Ada 160) 37/76	NR	CG (Plb) 5/74 IG1 (Ada 40) 1/75 IG2 (Ada 80) 2/75 IG3 (Ada 160) 2/76 Need to contact authors for further clarity on 'other' and 'withdrawn consent' reasons.	CG (Plb) 3/74 IG1 (Ada 40) 0/75 IG2 (Ada 80) 1/75 IG3 (Ada 160) 3/76	CG (Plb) 55/74 IG1 (Ada 40) 50/75 IG2 (Ada 80) 51/75 IG3 (Ada 160) 57/76

		CG (Plb) 12/74 IG1 (Ada 40) 18/75 IG2 (Ada 80) 24/75 IG3 (Ada 160) 36/76 0) 55/75 IG3 (Ada 160) 45/76 Week 4: CG (Plb) 37/74 IG1 (Ada 40) 54/75 IG2 (Ada 80) 59/75 IG3 (Ada 160) 59/76 100-point clinical response Week 1: CG (Plb) 16/74 IG1 (Ada 40) 23/75 IG2 (Ada 80) 25/75 IG3 (Ada 160) 21/76 Week 2: CG (Plb) 15/74 IG1 (Ada 40) 21/75 IG2 (Ada 80) 37/75 IG3 (Ada 160) 31/76 Week 4: CG (Plb) 25/74 IG1 (Ada 40) 34/75 IG2 (Ada 80) 40/75 IG3 (Ada 160) 50/76				
Hanauer 2021 (VOLT-AIRE-CD)	Clinical remission at week 24 IG1 (BI 695501) 46/72 CG (Ada) 54/75	70-point Clinical Response Week 4 (primary end-point): IG1 (BI 695501) 61/72 CG (Ada) 68/75 Week 24 (secondary end-point): IG1 (BI 695501) 55/72 CG (Ada) 59/75 <i>Exploratory end-points included other weeks - 12 and 48</i>	NR	IG1 (BI 695501) 15/72 CG (Ada) 16/75 <i>Need to contact author for further clarity on 'withdrawal by patient', 'lost to follow-up' and 'physician decision' reasons for discontinuation of study.</i>	Week 0 - 24: IG1 (BI 695501) 6/72 CG (Ada) 8/75 Week 24 - 56: IG1 (BI 695501) 2/72 CG (Ada) 9/75	Week 0 - 24: IG1 (BI 695501) 45/72 CG (Ada) 42/75 Week 24 - 56: IG1 (BI 695501) 31/72 CG (Ada) 34/75
Leman 2006	Week 12: CG (Plb) 22/58 IG (IFX) 43/57 Week 24 (primary): CG (Plb) 17/58 IG (IFX) 32/57 Week 52: CG (Plb) 13/58	NR	CDEIS Decrease from baseline (median [interquartile range]): Week 24: CG (Plb) 1.2 [-1.5-4.4] IG (IFX) 6.9 [4.1-9.5]	CG (Plb) 5/58 IG (IFX) 2/57	CG (Plb) 3/58 IG (IFX) 3/57 Table 2 describes "Serious adverse event in 5 cases (infliximab, n=3; placebo, n=3)	CG (Plb) 28/58 IG (IFX) 29/57

	IG (IFX) 23/57					
Allez 2023 (TRIDENT- Part 1)	Week 12 CG(placebo) 7/72 IG(Tesnatilimab) 15/73	>100 CDAI reduction Week 12 CG(placebo) 11/72 IG(Tesnatilimab) 21/73		CG(placebo) 14/72 IG(Tesnatilimab) 25/73 (of which one was death)	CG(placebo) 1/72 IG(Tesnatilimab) 8/73 (of which one was death)	CG(placebo) 24/72 IG(Tesnatilimab) 45/73 (of which one was death)
Panacione 2022 (MOTIVATE)	CG(pl) 37/187 IG1(ris600) 81/191 IG2(ris1200) 77/191	NR		CG(pl) 2/187 IG1(ris600) 5/191 IG2(ris1200) 16/191	CG(pl) 24/187 IG1(ris600) 9/191 IG2(ris1200) 24/191	CG(pl) 124/187 IG1(ris600) 90/191 IG2(ris1200) 113/191
Panes 2017 Induction	Week 8: CG (Plb) 33/92 IG1 (Tof 5) 37/86 IG2 (Tof 10) 37/86 IG3 (Tof 15) 7/16	<u>>=70-point decrease clinical response</u> Week 8: CG (Plb) 56/92 IG1 (Tof 5) 65/86 IG2 (Tof 10) 64/86 IG3 (Tof 15) 13/16 <u>>=100-point decrease clinical response</u> Week 8: CG (Plb) 49/92 IG1 (Tof 5) 60/86 IG2 (Tof 10) 59/86 IG3 (Tof 15) 12/16	NR	Need to contact authors to: - confirm contents of reasons such as 'no longer willing to participate', 'study terminated by sponsor', 'other reasons'. - and to confirm discontinuation due to AEs as there are discrepancies between Table 3 and Figure 2 flowchart	Patients with Serious and severe adverse events CG (Plb) 11/92 IG1 (Tof 5) 8/86 IG2 (Tof 10) 17/86 IG3 (Tof 15) 1/16 Need to contact authors for total number of patients that experienced serious and severe adverse events.	CG (Plb) 55/92 IG1 (Tof 5) 50/86 IG2 (Tof 10) 52/86 IG3 (Tof 15) 9/16
Present 1999	complete response (defined as the absence of any draining fistulas at two consecutive visits CG: 4/31 IG1: 17/31 IG2: 12/32	a reduction of 50 percent or more from baseline in the number of draining fistulas observed at two or more consecutive study visits CG : 8/31 IG1: 21/31 IG2: 18/32	NR	CG: 0 IG1: 1 IG2:1	5 in total IG1 1/31 IG2 4/31 CG 0/32	CG: 12/31 IG1: 10/31 IG2: 26/32
Sandborn 2001a	clinical remission (CDAI <150) at each visit Week 24 Placebo 8 weekly 1/27 Placebo 12 weekly 1/31 CDP57 8 weekly 6/57 CDP57 12 weekly 6/54	week 2 CDAI 70 response 15/58 50/111 week 2 CDAI 100 response 8/58 33/111	NR	placebo 8 weekly, 10 mg/kg CDP57 8 weekly, placebo 12 weekly, and 10 mg/kg CDP57 12 weekly Withdrawal due to adverse events information was combined in Table 2. Need to contact authors for separation of data per group.	placebo 8 weekly, 10 mg/kg CDP57 8 weekly, placebo 12 weekly, and 10 mg/kg CDP57 12 weekly Need to contact authors for no. of patients experiencing serious adverse events per group as information was not provided in tables or texts.	placebo 8 weekly, 10 mg/kg CDP57 8 weekly, placebo 12 weekly, and 10 mg/kg CDP57 12 weekly Need to contact the authors for no. of patients experiencing adverse events as information was not presented in tables or text.
Sandborn 2001b	CDAI <150 at week 4 CG: 4/20 IG: 2/23 week 2: CG: 3/20	<u>>=70-point decrease clinical response at week 4</u> CG: 9/20 IG: 9/23 week 2: CG: 3/20	NR	CG: 9/20 IG: 14/23	SAEs: CG: 2/20 IG: 1/23 Severe: CG: 3/20	CG: 10/20 IG: 17/23

	IG: 2/ 23 week8: CG: 5/20 IG: 3/ 23	CG: 5/20 IG: 11/ 23 week8: CG: 6/20 IG: 7/ 23			IG: 1/23	
Sandborn 2005a (ENACT 1)	CDAI <150 at week 10 CG: 55/181 IG: 267/724 week 2 % CG: 10 IG: 14 week 4 % CG: 19 IG: 23 week 6 % CG: 23 IG: 33 week 8 % CG: 28 IG: 34 week 12 % CG: 31 IG: 40	<u>>=70-point decrease clinical response at week 10</u> CG: 88/181 IG: 408/724 week 2 % CG: 33 IG: 40 week 4 % CG: 45 IG: 51 week 6 % CG: 53 IG: 58 week 8 % CG: 50 IG: 57 week 12 % CG: 51 IG: 61	NR	CG: 13/181 IG: 59/724	CG: 12/181 IG: 52/724	CG: 153/181 IG: 626/724
Sandborn 2007a	CDAI <150 at week 4 CG: 12/166 IG: 34/159 week 1 CG: 6/166 IG: 10/159 week 2 CG: 10/166 IG: 34/159	<u>>=70-point decrease clinical response at week 4</u> CG: 56/166 IG: 82/159 week 1 CG: 34/166 IG: 55/159 week 2 CG: 54/166 IG: 83/159 <u>>=100-point decrease clinical response at week 4</u> CG: 41/166 IG: 61/159	NR	CG: 5/166 IG: 3/159	CG: 8/166 IG: 2/159	CG: 121/166 IG: 91/159

		week 1 CG: 20/166 IG: 31/159 week 2 CG: 30/166 IG: 58/159				
Sandborn 2007c (PRECISE 1)	CDAI <150 at week 6 CG: 57/329 IG: 71/333 CDAI <150 at week 26 CG: 32/329 IG: 47/333	>=100-point decrease clinical response at week 6 CG: 87/329 IG: 115/333 >=100-point decrease clinical response at week 26 CG: 52/329 IG: 75/333	NR	CG: 151/329 IG: 126/333	CG: 23/329 IG: 34/333	CG: 260/329 IG: 269/333
Sandborn 2008 (Population 1)	CDAI <150 at week 8 CGsub: 6/26 IGsub: 6/25 GCiv: 3/27 IGiv: 7/26 week 2 CGsub: 3/26 IGsub: 6/25 GCiv: 2/27 IGiv: 5/26 week 4 CGsub: 4/26 IGsub: 6/25 GCiv: 4/27 IGiv: 7/26 week 6 CGsub: 6/26 IGsub: 7/25 GCiv: 3/27 IGiv: 6/26	a reduction of 25% or more and 70 points or more from the baseline CDAI score at week 8 CGsub: 13/26 IGsub: 12/25 GCiv: 8/27 IGiv: 13/26 week 2 CGsub: 11/26 IGsub: 11/25 GCiv: 6/27 IGiv: 10/26 week 4 CGsub: 8/26 IGsub: 13/25 GCiv: 8/27 IGiv: 14/26 week 6 CGsub: 10/26 IGsub: 13/25 GCiv: 6/27 IGiv: 14/26 >=100-point decrease clinical response at week 8	NR	CGsub: 2/26 IGsub: 0/25 GCiv: 3/27 IGiv: 2/26	CGsub: 2/26 IGsub: 0/25 GCiv: 1/27 IGiv: 2/26	CGsub: 22/26 IGsub: 17/25 GCiv: 19/27 IGiv: 20/26

		CGsub: 9/26 IGsub: 12/25 GCiv: 7/27 IGiv: 13/26 week 2 CGsub: 6/26 IGsub: 9/25 GCiv: 6/27 IGiv: 8/26 week 4 CGsub: 7/26 IGsub: 11/25 GCiv: 7/27 IGiv: 11/26 week 6 CGsub: 9/26 IGsub: 12/25 GCiv: 4/27 IGiv: 13/26				
Sandborn 2008 (Population 2)	CDAI <150 at week 8 IGsub: 3/14 IGiv: 4/13 week 2 IGsub: 0/14 IGiv: 1/13 week 4 IGsub: 1/14 IGiv: 3/13 week 6 IGsub: 2/14 IGiv: 4/13	<u>a reduction of 25% or more and 70 points or more from the baseline CDAI score at week 8</u> IGsub: 6/14 IGiv: 7/13 week 2 IGsub: 1/14 IGiv: 5/13 week 4 IGsub: 3/14 IGiv: 8/13 week 6 IGsub: 5/14 IGiv: 8/13 <u>>=100-point decrease clinical response at week 8</u> IGsub: 5/14 IGiv: 5/13 week 2 IGsub: 0/14	NR	IGsub: 1/14 IGiv: 0/13	IGsub: 2/14 IGiv: 2/13	IGsub: 12/14 IGiv: 10/13

		IGiv: 65/13 week 4 IGsub: 2/14 IGiv: 6/13 week 6 IGsub: 4/14 IGiv: 7/13				
Sandborn 2011	CDAI <150 at week 6 CG: 53/216 IG: 68/223 week 2 CG: 33/216 IG: 50/223 week 4 CG: 40/216 IG: 57/223	<u>>=100-point decrease clinical response at week 8</u> CG: 71/216 IG: 87/223 week 2 CG: 42/216 IG: 71/223 week 4 CG: 55/216 IG: 76/223	NR	CG: 24/216 IG: 16/223	CG: 8/216 IG: 12/223	CG: 100/216 IG: 114/223
Sandborn 2012 (CE RTIFI) - Induction	Secondary outcome is remission at week 6 and week 22 Week 4 - CG (Plb) 12/132 IG1 (Ust 1) 14/131 IG2 (Ust 3) 25/132 IG3 (Ust 6) 16/131; Week 6 (primary) - CG (Plb) 14/132 IG1 (Ust 1) 21/131 IG2 (Ust 3) 21/132 IG3 (Ust 6) 16/131; Week 8 - CG (Plb) 14/132 IG1 (Ust 1) 23/131 IG2 (Ust 3) 24/132 IG3 (Ust 6) 24/131	Primary outcome is CD AI100 6 weeks and secondary outcome at week 4 Week 4 - CG (Plb) 33/132 IG1 (Ust 1) 54/131 IG2 (Ust 3) 61/132 IG3 (Ust 6) 53/131; Week 6 - CG (Plb) 38/132 IG1 (Ust 1) 57/131 IG2 (Ust 3) 57/132 IG3 (Ust 6) 62/131; Week 8 - CG (Plb) 33/132 IG1 (Ust 1) 56/131 IG2 (Ust 3) 59/132 IG3 (Ust 6) 73/131	NR	CG (Plb) 19/132 IG1 (Ust 1) 10/131 IG2 (Ust 3) 12/132 IG3 (Ust 6) 8/131	CG (Plb) 11/132 IG1 (Ust 1) 6/131 IG2 (Ust 3) 8/132 IG3 (Ust 6) 9/131	CG (Plb) 94/132 IG1 (Ust 1) 89/131 IG2 (Ust 3) 88/132 IG3 (Ust 6) 80/131
Sandborn 2012 (CE RTIFI) - Induction (no n-resp onse)	Week 8 CG (Plb) 7/110 IG (Ust) 3/109 Week 22 (primary) CG (Plb) 7/110 IG (Ust) 12/109	Week 8 CG (combined Plb) 15/110 IG (combined Ust) 16/109 Week 22 CG (combined Plb) 20/110 IG (combined Ust) 22/109	NR	CG (Plb) 22/110 IG1 (Ust) 17/109 <i>IG2(ust270/90) 10/85</i>	CG (Plb) 21/110 IG1 (Ust 90) 22/109	CG (Plb) 89/110 IG1 (Ust)86/109

	Week 36 CG (Plb) 10/110 IG (Ust) 7/109	Week 36 CG (combined Plb) 18/110 IG (combined Ust) 16/109				
Sandborn 2013 (GE MINI II) - Induction	CDAI <150 at week 6 CG: 10/148 IG: 32/220	>=100-point decrease clinical response at week 6 CG: 38/148 IG: 69/220	NR	CG: 11/148 IG: 21/220	CG: 9/148 IG: 20/220	CG: 88/148 IG: 124/220
Sandborn 2014	CDAI <150 at week 4 CG: 7/34 IG1(1mg): 11/36 IG2(5mg): 8/34 IG3(15mg): 5/35	>=70-point decrease clinical response at week 4 CG: 16/34 IG1(1mg): 13/36 IG2(5mg): 19/34 IG3(15mg): 16/35 >=100-point decrease clinical response at week 4 CG: 10/34 IG1(1mg): 11/36 IG2(5mg): 15/34 IG3(15mg): 13/35	NR	CG: 8/34 IG1(1mg): 2/36 IG2(5mg): 2/34 IG3(15mg): 1/35	CG: 5/34 IG1(1mg): 4/36 IG2(5mg): 4/34 IG3(15mg): 1/35	CG: 22/34 IG1(1mg): 18/36 IG2(5mg): 21/34 IG3(15mg): 22/35
Sandborn 2023 - BE RGAM OT (cohort 1)	CDAI <150 at week 14 CG(pl) 10/59 IG1(etr105) 28/120 IG2(etr210) 35/121	NR		NR	NR	NR
Sandborn 2020d (CELEST) - Induction	Clinical remission 1.5/1.0 (defined as average daily Stool Frequency of <=1.5 and AP score of <=1.0, with neither worse than the baseline value) at week 16 CG: 4/37 IG1(3mg): 5/39 IG2(6mg): 10/37 IG3(12mg): 4/36 IG4(24mg): 8/36 IG5(24mgQD): 5/35	Clinical response [CDAI <150 and decrease in CDAI from baseline >= 70 points (CR-70)] at week 16 CG: 2/37 IG1(3mg): 8/39 IG2(6mg): 11/37 IG3(12mg): 14/36 IG4(24mg): 11/36 IG5(24mgQD): 7/35	Endoscopic remission at week 12/16 (defined as SES-CD of <=4 and a >=2-point reduction from baseline, with no subscore>1) at week 12/16 CG: 0/37 IG1(3mg): 4/39 IG2(6mg): 3/37 IG3(12mg): 3/36 IG4(24mg): 8/36 IG5(24mgQD): 5/35	CG: 9/37 IG1(3mg): 5/39 IG2(6mg): 4/37 IG3(12mg): 9/36 IG4(24mg): 6/36 IG5(24mgQD): 4/35	CG: 2/37 IG1(3mg): 5/39 IG2(6mg): 2/37 IG3(12mg): 10/36 IG4(24mg): 3/36 IG5(24mgQD): 7/35	CG: 27/37 IG1(3mg): 34/39 IG2(6mg): 29/37 IG3(12mg): 29/36 IG4(24mg): 30/36 IG5(24mgQD): 29/35
			NR	Through week 12	Through week 12	Through week 12

Sandborn 2022 - GAXI 1	Clinical remission defined as 'CDAI score <150' Week 12 A. In clinical remission – CG 10/61 IG-G200 35/61 IG-G600 35/63 IG-G1200 28/61 IG-UST 29/63	Clinical response defined as '>=100-point reduction from baseline in CDAI score or CDAI score <150' Week 12 A. In clinical response CG 15/61 IG-G200 43/61 IG-G600 42/63 IG-G1200 37/61 IG-UST 42/63		Patients with adverse event(s) (AE) leading to withdrawal CG 11/70 (15.71%). IG-G200 14/73 (19.18%). IG-G600 12/73 (16.44%). IG-G1200 14/73 (19.18%). IG-GC 40/219 (18.26%). IG-UST 8/71 (11.27%)	Patients with >=1 serious adverse event (SAE) CG 4/70 (5.7%). IG-G200 3/73 (4.1%). IG-G600 4/73 (5.5%). IG-G1200 1/73 (1.4%). IG-GC 8/219 (3.7%). IG-UST 4/71 (5.6%)	Patients with >=1 adverse event (AE) CG 42/70 (60.0%). IG-G200 32/73 (43.8%). IG-G600 37/73 (50.7%). IG-G1200 31/73 (42.5%). IG-GC 100/219 (45.7%). IG-UST 36/71 (50.7%)
Sands 2004 (ACCENT II) Induction (Non-responders)	NOT REPORTED	A response was defined as a reduction of at least 50 percent from baseline in the number of draining fistulas at consecutive visits four or more weeks apart. Time-point of response is NOT REPORTED Patients who achieved response [n (%)] – CG: 7/44 (16%). IG: 9/43 (21%)	NOT REPORTED	NOT REPORTED – They provide combined data for the responders and non-responders but no separate information. NEED TO CONTACT AUTHORS TO REQUEST SEPARATE DATA FOR RESPONDERS AND NON-RESPONDERS PER IG/CG Adverse events leading to discontinuation of study agent (combined data for both the responders and non-responders) [n (%)] – CG 12/144 (8%). IG 5/138 (4%)	NOT REPORTED – They provide combined data for the responders and non-responders but no separate information. NEED TO CONTACT AUTHORS TO REQUEST SEPARATE DATA FOR RESPONDERS AND NON-RESPONDERS PER IG/CG Serious adverse events (combined data for both the responders and non-responders) [n (%)] – CG 33/144 (23%). IG1 19/138 (14%)	NOT REPORTED – They provide combined data for the responders and non-responders but no separate information. NEED TO CONTACT AUTHORS TO REQUEST SEPARATE DATA FOR RESPONDERS AND NON-RESPONDERS PER IG/CG Adverse events (combined data for both the responders and non-responders) [n (%)] – CG 132/144 (92%). IG 123/138 (89%)
Sands 2007	CDAI <150 at week 10 CG: 8/27 IG: 19/52 Week 8 CG: 8/27 IG: 17/52 Week 6 CG: 7/27 IG: 12/52 Week 4 CG: 3/27 IG: 9/52 Week 2 CG: 2/27 IG: 8/52	>=70-point decrease clinical response at week 10 CG: UNCLEAR/27 IG: UNCLEAR/52	NR	CG: 4/27 IG: 7/52	CG: 1/27 IG: 1/52	CG: 27/27 IG: 48/52
Sands 2010	Clinical remission defined as 'CDAI score of <150 points' Day 29 Patients in Clinical Remission [n (%)] –	Clinical response defined as 'decrease in CDAI score of >=100 points from baseline' Day 29	NR	Time-points for adverse events, serious adverse events, and withdrawals due to adverse events are NOT REPORTED (NEED TO CONTACT AUTHORS FOR MORE INFORMATION). They report this data for induction (randomised) and maintenance (non-randomised) phases combined	Time-points for adverse events, serious adverse events, and withdrawals due to adverse events are NOT REPORTED (NEED TO CONTACT AUTHORS FOR MORE INFORMATION). They report this data for induction (randomised) and maintenance (non-randomised) and maintenance (non-randomised) phases combined	Time-points for adverse events, serious adverse events, and withdrawals due to adverse events are NOT REPORTED (NEED TO CONTACT AUTHORS FOR MORE INFORMATION). They report this data for induction (randomised) and maintenance (non-randomised) and maintenance (non-randomised) phases combined

	CG 10/73 (13.7%). IG1 10/73 (13.7%). IG2 13/74 (17.6%) Day 43 Patients in Clinical Remission [n (%)] – CG 14/73 (19.2%). IG1 8/73 (11%). IG2 11/74 (14.9%)	Patients in Clinical Response [n (%)] – CG 21/73 (28.8%). IG1 18/73 (24.7%). IG2 19/74 (25.7%) Day 43 Patients in Clinical Response [n (%)] – CG 22/73 (30.1%). IG1 10/73 (13.7%). IG2 16/74 (21.6%)		ned per IG/CG which makes it difficult to know how many had adverse events, serious adverse events, or had withdrawn due to adverse events by day 43. However, they do report overall how many patients completed the induction phase but they do not specify why those patients who did not complete induction failed to do so. Patients not completing induction phase [n (%)] – CG 19/73 (26%). IG1 16/73 (22%). IG2 16/74 (22%) As they have not specified the reasons for failure to complete induction, it should be assumed the above figures represent withdrawals due to adverse events as a worst-case scenario for the induction phase	domised) phases combined per IG/CG which makes it difficult to know how many had adverse events, serious adverse events, or had withdrawn due to adverse events by day 43. They report the following for the study overall: Number of patients experiencing serious adverse events [n (%)] – CG 8/73 (11%). IG1 6/73 (8%). IG2 4/74 (5%) As they do not specify what time-point do these figures apply to but are likely to represent the induction and maintenance phases combined, these can be considered as figures for the worst-case scenario for the induction phase alone	n-randomised) phases combined per IG/CG which makes it difficult to know how many had adverse events, serious adverse events, or had withdrawn due to adverse events by day 43. They report the following for the study overall: Number of patients experiencing adverse events [n (%)] – CG 59/73 (81%). IG1 53/73 (73%). IG2 59/74 (80%) As they do not specify what time-point do these figures apply to but are likely to represent the induction and maintenance phases combined, these can be considered as figures for the worst-case scenario for the induction phase alone
Sands 2014 (GEMINI III)	CDAI <150 at week 10 CG(fail): 19/157 IG(fail): 42/158 CG(naive): 8/50 IG(naive): 18/51 week 6(primary) CG(fail): 19/157 IG(fail): 24/158 CG(naive): 6/50 IG(naive): 16/51	<u>>=100-point decrease clinical response at week 10</u> CG(fail): 39/157 IG(fail): 74/158 CG(naive): 11/50 IG(naive): 26/51 week 6 CG(fail): 35/157 IG(fail): 62/158 CG(naive): 12/50 IG(naive): 20/51	NR	CG: 15/207 IG: 13/209	CG: 16/207 IG: 13/209	CG: 124/207 IG: 117/209
Sands 2022 (SEAVUE)	CDAI <150 at week 52 (primary, but not used in our analysis) CG: 119/195 IG: 124/191 week 16 (used in our analysis) CG: 117/195 IG: 109/191	<u>>=100-point decrease clinical response at week 52</u> CG: 129/195 IG: 138/191	ES-CD score <=3/0 for patients with BL score=3 at week 52 CG: 55/195 IG: 51/191	CG: 22/195 IG: 12/191	CG: 32/195 IG: 25/191	CG: 152/195 IG: 153/191
Schreiber 2005	CDAI <150 at week 12 CG: 17/73 IG1: 20/74 IG2: 14/72 IG3: 19/73	<u>>=100-point decrease clinical response at week 12</u> CG: 26/73 IG1: 27/74 IG2: 26/72 IG3: 32/73	NR	CG: 32/73 IG1: 36/74 IG2: 32/72 IG3: 32/73	CG: 6/73 IG1: 7/74 IG2: 10/72 IG3: 6/73	CG: 51/73 IG1: 57/74 IG2: 55/72 IG3: 48/73

Schreiber 2018a	CDAI <150 at week 8 CG: 6/28 IG1(150x2): 11/53 IG2(150): 9/53 IG3(300): 6/53	liquid or very soft stool frequency and abdominal pain composite score ≤ 8 at week 8 CG: 4/28 IG1(150x2): 9/53 IG2(150): 7/53 IG3(300): 6/53	NR	CG: 1/28 IG1(150x2): 1/53 IG2(150): 5/53 IG3(300): 6/53	CG: 3/28 IG1(150x2): 1/53 IG2(150): 6/53 IG3(300): 8/53	CG: 19/28 IG1(150x2): 32/53 IG2(150): 33/53 IG3(300): 37/53
Schwartz 2021 - ENTERPRISE	NR	NOT REPORTED. They report 'fistulae response' Fistulae response defined as '≥50% decrease from baseline in the number of draining perianal fistulae at the visit, assessed by gentle finger compression during clinical examinations. Patients with missing data at the visit were classed as nonresponders' Week 30 Fistulae response [Number of patients/Total patients in group (percentage)] – CG 9/14 (64.3%). IG 6/14 (42.9%). IGP 15/28 (53.6%) Week 22 and 30 Fistulae response [Number of patients/Total patients in group (percentage)] – CG 8/14 (57.1%). IG 5/14 (35.7%). IGP 13/28 (46.4%)	NOT REPORTED	Adverse events leading to discontinuation [Number of patients/Total patients in group (percentage)] – CG 1/16 (6.3%). IG 3/18 (16.7%). IGP 4/34 (11.8%)	Serious adverse events [Number of patients/Total patients in group (percentage)] – CG 4/16 (25.0%). IG 3/18 (16.7%). IGP 7/34 (20.6%)	Adverse events [Number of patients/Total patients in group (percentage)] – CG 15/16 (93.8%). IG 17/18 (94.4%). IGP 32/34 (94.1%)
Targan 1997	CDAI <150 at week 4 CG: 1/25 IG(5): 19/27 IG(10): 11/28 IG(20): 11/28 week 2 CG: 1/25 IG(5): 16/27 IG(10): 10/28	≥70-point decrease in clinical response at week 4 CG: 4/25 IG(5): 22/27 IG(10): 14/28 IG(20): 18/28	NR	UNCLEAR	UNCLEAR	UNCLEAR

	IG(20): 10/28 (taken from graph)					
Targan 2007 (ENCO RE)	CDAI <150 at week 12 CG: 62/250 IG: 98/259 week 8 CG: 52/250 IG: 83/259 week 4 CG: 40/250 IG: 62/259	<u>>=70-point decrease clinical response at week 12</u> CG: 110/250 IG: 155/259 week 8 CG: 100/250 IG: 145/259 week 4 CG: 92/250 IG: 132/259 <u>>=100-point decrease clinical response at week 12</u> CG: 77/250 IG: 127/259 week 8 CG: 82/250 IG: 124/259 week 4 CG: 54/250 IG: 101/259	NR	CG: 42/250 IG: 36/259	CG: 24/250 IG: 13/259	CG: 206/250 IG: 222/259
Vermeire 2017 FITZROY - induction	CDAI <150 at week 10 CG: 10/44 IG: 60/130 week 6 CG: 12/44 IG: 53/130 week 4 CG: 8/44 IG: 44/130 week 2 CG: 9/44 IG: 29/130	<u>>=100-point decrease clinical response at week 10</u> CG: 18/44 IG: 76/130	SES-CD ≤4, ulcerated surface subscore of 1 or less in all five segments at week 10 CG: 3/44 IG: 18/130	CG: 7/44 IG: 31/152 (more people because 22 were re-randomised from placebo to filgotinib)	CG: 8/44 IG: 33/152 (more people because 22 were re-randomised from placebo to filgotinib)	CG: 31/44 IG: 128/152 (more people because 22 were re-randomised from placebo to filgotinib)
Vermeire 2017 FITZROY - induction non-r	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

responders						
Watanabe 2012 - Induction	CDAI <150 at week 4 CG: 3/23 IG1: 6/34 IG2: 11/33 week 2 CG: 1/23 IG1: 5/34 IG2: 6/33	<u>>=70-point decrease clinical response at week 4</u> CG: 7/23 IG1: 20/34 IG2: 23/33 <u>>=100-point decrease clinical response at week 4</u> CG: 4/23 IG1: 17/34 IG2: 15/33	NR	CG: 1/23 IG1: 2/34 IG2: 1/33	CG: 2/23 IG1: 3/34 IG2: 1/33	CG: 12/23 IG1: 20/34 IG2: 17/33
Watanabe 2020 - Induction	CDAI <150 at week 10 CG: 8/78 IG: 14/79 week 6 CG: 10/78 IG: 11/79 week 2 CG: 4/78 IG: 5/79	<u>>=100-point decrease clinical response at week 10</u> CG: 13/78 IG: 21/79 week 6 CG: 10/78 IG: 19/79 week 2 CG: 5/78 IG: 13/79	NR	CG: 12/78 IG: 3/79	CG: 10/78 IG: 8/79	CG: 42/78 IG: 49/79
Winter 2004	CDAI <150 at week 4 CG: 10/25 IG1(5): 9/25 IG2(10): 5/19 IG3(20): 4/23	<u>>=100-point decrease clinical response at week 4</u> CG: 14/25 IG1(5): 15/25 IG2(10): 11/19 IG3(20): 10/23	NR	CG: 5/25 IG: 31/67	CG: 2/25 IG: 7/67	CG: 15/25 IG: 43/67
Ye 2019	clinical remission at weeks 6, 14, and 30 Week 6 (primary) IG: 47 CG: 49 Week 14 IG: 59 CG: 60 Week 30 IG: 61 CG: 62	Week 6 CDAI-70 IG: 77 CG: 81 CDAI-100 IG: 67 CG: 70 Week 14 CDAI-70 IG: 96	NR	<i>up to 30 weeks</i> CG: 21/109 IG : 17/111	<i>up to 30 weeks</i> CG: 9/109 IG : 6/111	<i>up to 30 weeks</i> CG: 70/109 IG : 63/111

		CG: 96 CDAI-100: IG: 78 CG: 83 Week 30 CDAI-70 IG: 85 CG: 82 CDAI-100 IG: 80 CG: 80				
Loftus 2023 (U-EXCEL)	Clinical Remission defined as 'CDAI <150' OR 'Clinical remission per SF (stool frequency)/AP (abdominal pain) (also referred to as PRO-2) is defined as average daily very soft or liquid stool frequency ≤ 2.8 AND average daily abdominal pain score ≤1.0, and both not greater than baseline' Week 12 Clinical Remission per CDAI [n (%)] – CG 51/176 (29%). IG 172/350 (49%) Clinical Remission per SF/AP [n (%)] – CG 39/176 (22%). IG 178/350 (51%)	Clinical Response is NOT REPORTED in the press release version. Full paper may provide this information	Endoscopic Remission is NOT REPORTED in the press release version. Full paper may provide this information. The press release version does report Endoscopic Response Endoscopic response is defined as 'a decrease in simple endoscopic score for Crohn's disease (SES-CD) of >50 percent from baseline (or at least a 2-point reduction from baseline for subjects with a baseline SES-CD of 4), as scored by central reviewer.' Week 12 Endoscopic Response [n (%)] – CG 23/176 (13%). IG 161/350 (46%)	NOT REPORTED – Need full paper for this information	Serious adverse events [%] – CG 6.8%. IG 6.9% Note – Time-points of measurement are NOT REPORTED and number randomised per IG/CG are NOT REPORTED therefore it is not possible at this stage to convert the percentage to numbers. The full paper may provide this information	NOT REPORTED – Need full paper for this information

Table 6

Maintenance studies' primary and secondary outcomes

Study ID	M.a Clinical relapse	M.b Clinical loss of response	M.c Endoscopic relapse	M.d Withdrawals due to adverse events	M.e Serious adverse events	M.f Total numbers of patients with adverse events
Buhl 2022 (STOP-IT)	Week 48 (reported + withdrawals counted as treatment failures) CG 31/56 IG 5/59	NR	CG 42/56 IG 17/59	CG 8/56 IG 4/59	CG 2/56 IG 2/59	NR
Colombel 2007 (CHAR)	(Data collected from Figure 2 and calculated from clinical remission)	<70-point decrease CDAI Score	NR			

M) - Maintenance (responders)	Week 26 - CG (Plb) 141/170 IG1 (Ada eow) 104/172 IG2 (Ada weekly) 84/157 Week 56 - CG (Plb) 150/170 IG1 (Ada eow) 110/172 IG2 (Ada weekly) 92/157	Week 26 - CG 122/170 IG1 79/172 IG2 69/157 Week 56 - CG 140/170 IG1 98/172 IG2 80/157 <100-point decrease CDAI Score Week 26 - CG 125/170 IG1 83/172 IG2 75/157 Week 56 - CG 142/170 IG1 101/172 IG2 82/157		Need to contact author for separation of safety data from Table 4 for responders and non-responders of each group.	Need to contact author for separation of safety data from Table 4 for responders and non-responders of each group.	Need to contact author for separation of safety data from Table 4 for responders and non-responders of each group.
Colombel 2023 - LIBERTY-CD	Week 54 CG(placebo) 87/231 IG(CT-P13 SC) 76/112	Week 54 CG(placebo) 79/231 IG(CT-P13 SC) 69/112	Week 54 CG(placebo) 151/231 IG(CT-P13 SC) 100/112	NR	CG(placebo) 8/105 IG(CT-P13 SC) 16/238	CG(placebo) 65/105 IG(CT-P13 SC) 172/238
D'Haens 2022 (SERENITY - Maintenance)	ada vs ada					
Feagan 2015c (IM-UNITI)	Calculated from clinical remission information in table Week 44: CG (Plb) 86/133 IG1 (Ust q12w) 69/132 IG2 (q8w) 64/132	Calculated from sustained 100-point clinical response at week 44 from table Week 44: CG (Plb) 75/133 IG1 (Ust q12w) 57/132 IG2 (q8w) 56/132	NR	CG (Plb) 13/133 IG1 (Ust q12w) 9/132 IG2 (q8w) 14/132 Need to contact the authors for further clarity on 'terminated study' individuals described in the supplemental figure.	CG (Plb) 20/133 IG1 (Ust q12w) 16/132 IG2 (q8w) 13/132	CG (Plb) 111/133 IG1 (Ust q12w) 106/132 IG2 (q8w) 107/132
Ferrante 2022 - FORTIFY	Week 52 CG(placebo) 117/184 IG1(ris180mg) 105/179 IG2(ris360mg) 92/179	NR	Week 52 CG(placebo) 163/184 IG1(ris180mg) 132/179 IG2(ris360mg) 124/179	CG(placebo) 10/184 IG1(ris180mg) 10/179 IG2(ris360mg) 17/179	CG(placebo) 23/184 IG1(ris180mg) 24/179 IG2(ris360mg) 22/179	CG(placebo) 135/184 IG1(ris180mg) 129/179 IG2(ris360mg) 128/179
Hanauer 2002 (ACCENT I) - Maintenance (Responders)	Week 30: CG (Placebo) 87/110 IG1 (IFX 5mg) 69/113 IG2 (IFX 5-10mg) 62/112	Need to contact authors for exact proportion of patients with 70-point clinical response at week 30 and 54 to calculate clinical loss of response.	NR	Need to contact the authors to provide separate information for the safety information for responders and non-responders.	Need to contact the authors to provide separate information for the safety information for responders and non-responders.	Need to contact the authors to provide separate information for the safety information for responders and non-responders.
Jorgensen 2017 (NORSWITCH)	Harvey-Bradshaw Index remission (score less than or equal to 4): CG (IFX) 37/78 IG1 (CT-P13) 31/77	Disease worsening was defined by worsening in Harvey-Bradshaw Index (HBI) for CD (a change from baseline of 4 points or more and a total score of 7 points or greater) CG (IFX) 38/78 IG1 (CT-P13) 25/77	NR	CG (IFX) 2/78 IG1 (CT-P13) 1/77	CG (IFX) 8/78 IG1 (CT-P13) 8/77	CG (IFX) 57/78 IG1 (CT-P13) 49/77
Louis 2023 - SPARE	39 in total before retreatment but NR per group (2/23/3 patients were retreated)	NR	NR	NR	Group 1: 10 Group 2: 8 Group 3: 13	NR
NCT00349752 (COSPAR1)	CG(placebo): 68/87 IG(certolizumab): 64/87	NR	NR	NR	CG(placebo): 8/87 IG(certolizumab): 9/87	NR
		Loss of Clinical Response-100	NR			

Panes 2017 Maintenance	CG (Plb) 47/59 IG1 (Tof5) 44/60 IG2 (Tof10) 43/61	Week 26: CG (Plb) 44/59 IG1 (Tof5) 44/60 IG2 (Tof10) 37/61		CG (Plb) 28/59 IG1 (Tof5) 26/60 IG2 (Tof10) 19/61	Patients with serious and severe AEs: CG (Plb) 13/59 IG1 (Tof5) 11/60 IG2 (Tof10) 14/61 <i>Need to contact authors for or combined data on patients experiencing serious and severe AEs.</i>	CG (Plb) 44/59 IG1 (Tof5) 50/60 IG2 (Tof10) 48/61
Rutgeerts 1999	Week 44 (randomisation at week 12) CG (placebo): 23/36 IG (ifx): 15/37	Week 44 (randomisation at week 12) CG (placebo): 23/36 IG (ifx): 14/37	NR	CG (Plb) 12/36 IG (Ifx) 10/37	<i>Need to contact authors for or numbers of patients with serious adverse events.</i>	CG (Plb) 35/36 IG (Ifx) 35/37
Rutgeerts 2012 (EXTEND)	Week 12 (8 weeks after the randomisation): CG (Plb) 47/65 IG (Ada) 34/64 Week 52: CG (Plb) 59/65 IG (Ada) 43/64	NR	Patients without mucosal healing (Mucosal ulceration was considered present if the final outcome of the ileocolonoscopy review process determined that 1 or more of the 5 segments of the ileocolon had ulceration): Week 12: CG (Plb) 57/65 IG (Ada) 47/64 Week 52: CG (Plb) 65/65 IG (Ada) 49/64 Patients without CDEIS Remission (remission defined as score of 4 or less) Week 12: CG (Plb) 47/65 IG (Ada) 31/64 Week 52: CG (Plb) 63/65 IG (Ada) 46/64	From flowchart: CG (Plb) 4/65 IG (Ada) 8/64 From table: CG (Plb) 5/65 IG (Ada) 7/64 <i>Discrepancies in the numbers of discontinuations due to adverse events between table and flowchart.</i>	CG (Plb) 5/65 IG (Ada) 4/64	CG (Plb) 55/65 IG (Ada) 61/64
Sandborn 2005a (ENACT 2)	Week 36 (randomisation at week 12): CG (Plb) 89/214 (26% of 120 had remission) IG (Nat) 73/214 (44% of 130 had remission) Week 60: CG (Plb) 102/214 (15% of 120 had remission) IG (Nat) 79/214 (39% of 130 had remission)	Patients without CDAl-70 response at week 36: CG (Plb) 122/214 (28% of 170 had sustained response) IG (Nat) 66/214 (61% of 168 had sustained response) Patients without CDAl-70 response at week 60: CG (Plb) 136/214 (20% of 170 had sustained response) IG (Nat) 77/214 (54% of 168 had sustained response) <i>This may be a loss of response as the values reported are sustained response. What do you think?</i>	NR	CG (Plb) 61/214 IG (Nat) 29/214	CG (Plb) 21/214 IG (Nat) 18/214	CG (Plb) 207/214 IG (Nat) 194/214

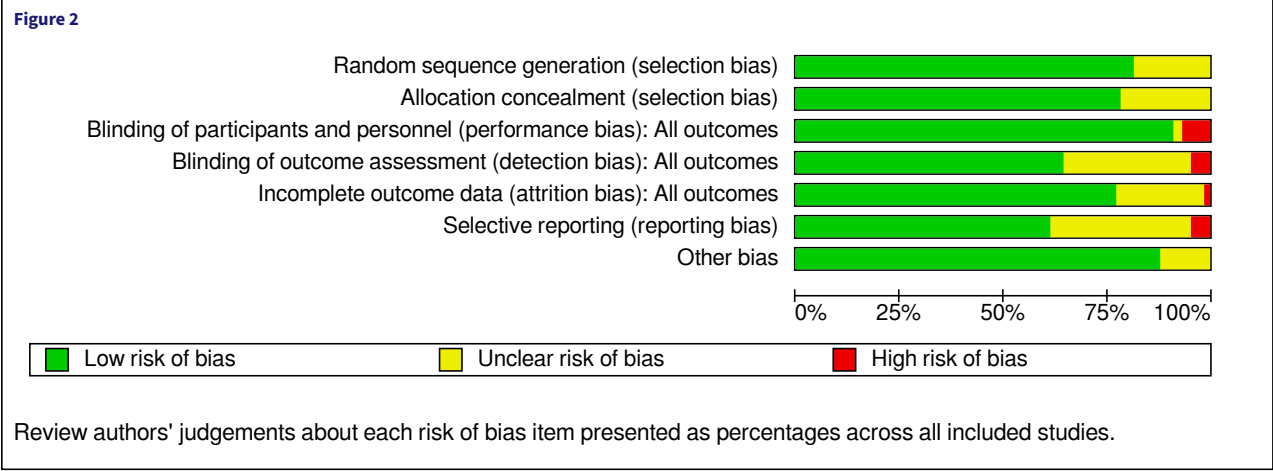
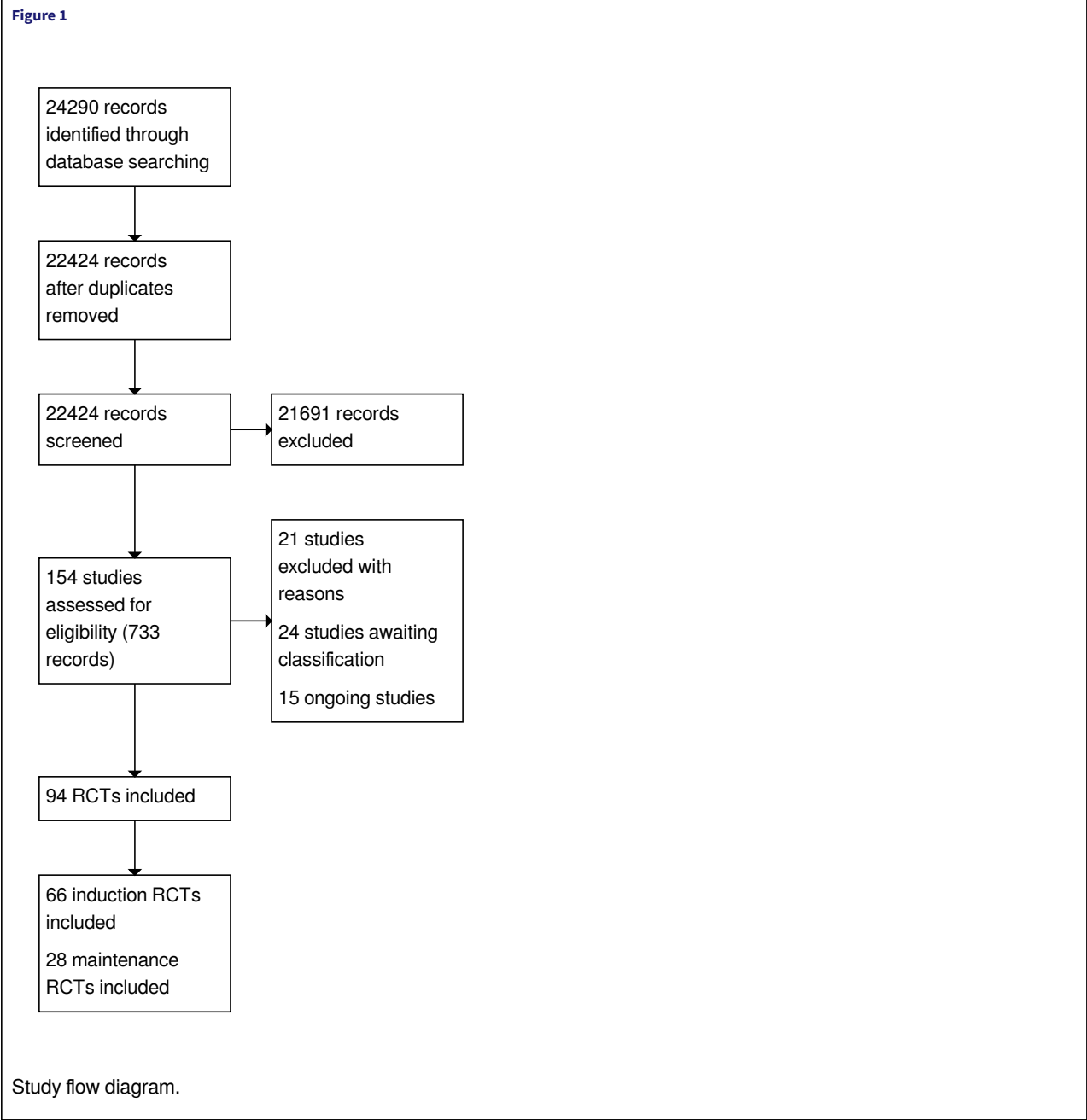
Sandborn 2007b (CLASIS II)	Week 24: CG (Plb) 9/18 (50%) IG1 (Ada eow) 3/19 (16%) IG2 (Ada weekly) 1/18 (6%) Week 56: CG (Plb) 10/18 (56%) IG1 (Ada eow) 4/19 (21%) IG2 (Ada weekly) 3/18 (17%)	Patients with <70-point clinical response Week 24: CG (Plb) 3/18 IG1 (Ada eow) 1/19 IG2 (Ada weekly) 1/18 Week 56: CG (Plb) 5/18 IG1 (Ada eow) 4/19 IG2 (Ada weekly) 2/18 Patients with <100-point clinical response Week 24: CG (Plb) 7/18 IG1 (Ada eow) 3/19 IG2 (Ada weekly) 1/18 Week 56: CG (Plb) 2/18 IG1 (Ada eow) 4/19 IG2 (Ada weekly) 8/18	NR	CG (Plb) 2/18 IG1 (Ada eow) 2/19 IG2 (Ada weekly) 1/18	CG (Plb) 2/18 IG1 (Ada eow) 1/19 IG2 (Ada weekly) 0/18	CG (Plb) 18/18 IG1 (Ada eow) 15/19 IG2 (Ada weekly) 14/18
Sandborn 2012 (CERTIFI) - Maintenance	(Results collected and calculated from clinical remission in patients in remission at week 6 in Table S6 - ustekinumab responders in maintenance phase) Week 22 - CG (Plb) 57/73 IG1 (Ust 90) 50/72	(Results collected and calculated from sustained 70-point clinical response in Table S6 - ustekinumab responders in maintenance phase) Week 22 - CG (Plb) 49/73 IG1 (Ust 90) 32/72	NR	Maintenance only CG (Plb) 10/73 IG1 (Ust 90) 5/72 <i>will need to contact authors to clarify "unsatisfactory therapeutic effect" but considering worst-case scenario these numbers were included)</i>	Induction and maintenance phases added up CG(Plb) 33/183 IG(Ust) 31/181	Induction and maintenance phases added up CG(Plb) 151/183 IG(Ust) 140/181
Sandborn 2013 (GEMINI II) - Maintenance	Week 52 (Randomisation occurred at week 6): CG (Plb) 120/153 (21.6% maintained remission from week 6) IG1 (Ved q4w) 98/154 (36.4% maintained remission) IG2 (Ved q8w) 94/154 (39.0% maintained remission) <i>(reported as proportion of patients at remission at week 6)</i>	Patients without CDAI-100 response Week 52: CG (Plb) 107/153 (30.1% with response) IG1 (Ved q4w) 84/154 (45.5% with response) IG2 (Ved q8w) 87/154 (43.5% with response)	NR	CG (Plb) 81/153 IG1 (Ved q4w) 60/154 IG2 (Ved q8w) 73/154	CG (Plb) 23/153 IG1 (Ved q4w) 25/154 IG2 (Ved q8w) 28/154	CG (Plb) 128/153 IG1 (Ved q4w) 130/154 IG2 (Ved q8w) 135/154
Sandborn 2020d (CELEST) - Maintenance	Authors need to be contacted to separate data for remission and clinical responders.	Authors need to be contacted to separate data for remission and clinical responders.	Authors need to be contacted to separate data for remission and clinical responders.	Authors need to be contacted to separate data for remission and clinical responders.	Authors need to be contacted to separate data for remission and clinical responders.	Authors need to be contacted to separate data for remission and clinical responders.
Sandborn 2023 - BERGAMOT Maintenance	CG (placebo): 151/217 IG (etrolizumab): 134/217	NR	CG (placebo): 204/217 IG (etrolizumab): 191/217	CG: 19/217 IG: 27/217	CG: 9/217 IG: 9/217	CG: 190/217 IG: 189/217
Sands 2004 (ACCENT II) Maintenance (Responders)	NR	A response was defined as a reduction of at least 50 percent from base line (week 0) in the number of draining fistulas at cons	NR	NEED TO CONTACT AUTHORS TO REQUEST SEPARATE DATA FOR RESPONDERS AND NON-RESPONDERS PER IG/CG	NEED TO CONTACT AUTHORS TO REQUEST SEPARATE DATA FOR RESPONDERS AND NON-RESPONDERS AN	NEED TO CONTACT AUTHORS TO REQUEST SEPARATE DATA FOR RESPONDERS AND NON-RESPONDERS PER IG/CG

		ecutive visits four or more weeks apart A complete response was defined by – the absence of draining fistulas Loss of Response [n (%)] as read from Figure 2A Week 14 (for reference) CG: 0/98 (0%). IG: 0/91 (0%) Week 22 CG: 31/98 (32%). IG: 14/91 (15%) Week 30 CG: 56/98 (57%). IG: 26/91 (29%) Week 38 CG: 65/98 (66%). IG: 32/91 (35%) Week 46 CG: 66/98 (67%). IG: 35/91 (38%) Week 54 CG: 68/98 (69%). IG: 39/91 (43%) Loss of Response as stated in text [n (%)] Week 54 CG: 75/98 (77%). IG: 49/91 (54%) Loss of Complete Response [n (%)] as read from Figure 2B Week 14 (for reference) CG: 28/98 (29%). IG: 23/91 (25%) Week 22 CG: 58/98 (59%). IG: 40/91 (44%). Week 30 CG: 71/98 (72%). IG: 47/91 (52%) Week 38 CG: 76/98 (78%). IG: 49/91 (54%) Week 46	Adverse events leading to discontinuation of study agent (combined data for both the responders and non-responders) [n (%)] – CG 12/144 (8%). IG 5/138 (4%)	D NON-RESPONDERS PER IG/CG Serious adverse events (combined data for both the responders and non-responders) [n (%)] – CG 33/144 (23%). IG 19/138 (14%)	Adverse events (combined data for both the responders and non-responders) [n (%)] – CG 132/144 (92%). IG 123/138 (89%)	
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		CG: 78/98 (80%). IG: 52/91 (57%) Week 54 CG: 79/98 (81%). IG: 57/91 (63%)				
Schreiber 2007 (PRE CISE 2)	Week 26 (randomisation at week 6): CG (Plb) 152/212 IG (Cert) 113/216	Patients without CDAI-100 response who had response at wk6 Week 26: CG (Plb) 140/212 (34% had response) IG (Cert) 82/216 (62% had response) Patients without CDAI-100 response Week 26: CG (Plb) 136/212 (36% had response) IG (Cert) 80/216 (63% had response) <i>Need to clarify</i>	NR	From AEs in induction and mainten phases: CG (Plb) 112/212 IG (Cert) 69/216 From AEs in mainten phase: CG (Plb) 111/212 IG (Cert) 66/216 <i>Numbers of patients with AEs that withdrew differs between flowchart and table. Need to contact authors for clarity on these numbers.</i>	CG (Plb) 14/212 IG (Cert) 12/216	CG (Plb) 143/212 IG (Cert) 140/216
Schreiber 2021	Week 22 CDAI <150 SC: 17/28 IV: 15/25	Week 22 CDAI reduction >=100 SC: 21/28 IV: 20/25	Week 22 SES-CD score =< 2 points SC: 5/28 IV: 1/25	SC - 6/28 IV - 7/25	SC - 6/66 IV - 10/65 (CD and UC combined)	SC - 50/66 IV - 27/65 (CD and UC combined)
VanAssche 2012 (SWITCH)	NR	Patients without CDAI-100 response Week 54 (randomisation occurred at week 0): CG (Ada) 10/36 IG (Ifx) 7/37	NR	CG (Ada) 10/36 IG (Ifx) 1/37	CG (Ada) 5/36 IG (Ifx) 0/37	CG (Ada) 30/36 IG (Ifx) 27/37
Vermeire 2017 FITZROY - maintenance responders	Placebo: /15 FIL200toPL: /14 FIL200to100: /30 FIL200: /30 NR have asked authors	PLtoFIL100: /22 FIL200toPL: /9 FIL200: /25 NR have asked authors	NR have asked authors	NR	NR	NR
Vermeire 2021 (VISIBLE 2)	Week 52 (randomisation at week 6): CG (Plb) 88/135 IG (Ved) 143/275	Patients without CDAI-100 clinical response at Week 52 (randomisation at week 6): CG (Plb) 75/135 IG (Ved) 132/275	NR	CG (Plb) 56/135 IG (Ved) 106/275	CG (Plb) 14/135 IG (Ved) 23/275	CG (Plb) 102/135 IG (Ved) 202/275
Vermeire 2025 - DIVERSITY (maintenance)	FIL100 82/105 FIL200 70/118 Placebo 85/112	FIL100 72/105 FIL200 67/118 Placebo 78/112	NR	FIL100 17/105 FIL200 18/118 Placebo 7/112	FIL100 14/104 FIL200 13/118 Placebo 8/111	FIL100 75/104 FIL200 80/118 Placebo 71/111
Volkers 2017 - SIMILAR	NR	NR	NR	NR	NR	NR
Watanabe 2012 - Mai	<i>Estimated from graphs in Figure 5</i>	<i>Estimated from graphs in Figure 5</i>	NR	CG (Plb) 23/25 IG1 (ADA 40) 15/25 IG2	CG (Plb) 6/25 IG1 (ADA 40) 0/25	CG (Plb) 23/25 IG (ADA 40) 20/25

[illegible]

Figures



	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias): All outcomes	Blinding of outcome assessment (detection bias): All outcomes	Incomplete outcome data (attrition bias): All outcomes	Selective reporting (reporting bias)	Other bias
Allez 2023 (TRIDENT- Part 1)	+	+	+	+	?	+	+
Allez 2023 (TRIDENT- Part 2)	+	+	+	+	+	+	+
Buhl 2022 (STOP-IT)	+	+	+	+	+	?	+
Chen 2020	+	+	+	+	+	+	+
Chen 2025	?	+	?	?	?	+	?
Colombel 2007 (CHARM) - Induction (non-responders)	+	+	+	+	?	-	?
Colombel 2007 (CHARM) - Maintenance (responders)	+	+	+	+	?	+	?
Colombel 2010 (SONIC)	+	+	+	+	+	+	+
Colombel 2023 - LIBERTY-CD	?	?	+	?	?	+	?
D'Haens 1999 (refractory CD)	+	+	+	+	+	?	+
D'Haens 2008	+	+	-	-	+	+	+
D'Haens 2022 (ADVANCE)	+	+	+	+	+	+	+
Duan 2013	?	?	?	?	+	?	+
Feagan 2008c	?	?	+	?	+	+	+
Feagan 2015a (UNITI-1)	+	+	+	?	?	+	+
Feagan 2015b(UNITI-2)	+	+	+	?	?	+	+
Feagan 2015c (IM-UNITI)	+	+	+	?	+	+	+
Feagan 2017	+	+	+	+	+	+	+
Ferrante 2022 - FORTIFY	+	+	+	+	?	?	+
Ferrante 2024 (VIVID-1)	+	+	+	+	?	+	+
Ghosh 2003	+	+	+	+	+	?	+
Gordon 2001	?	+	+	+	+	?	+
Hanauer 2002 (ACCENT I) - Induction (non-response)	+	+	+	+	?	?	?
Hanauer 2002 (ACCENT I) - Maintenance (Responders)	+	+	+	+	+	?	?
Hanauer 2006 (CLASSIC I)	+	+	+	+	+	?	+
Hanauer 2021 (VOLTAIRE-CD)	+	+	+	+	+	+	+
Hart 2025 (GRAVITI)	+	+	+	+	?	+	+
Jairath 2025 (RELIEVE UCCD)	?	?	+	?	?	?	+
Jorgensen 2017 (NORSWITCH)	+	+	+	+	+	+	+
Lemann 2006	+	+	+	+	+	?	+
Loftus 2023 (U-ENDURE)	+	+	+	?	+	+	+
Loftus 2023 (U-EXCEED)	+	+	+	?	+	+	+

Loftus 2023 (U-EXCEL)	+	+	+	?	+	+	+
Louis 2023 - SPARE	+	+	-	-	+	+	+
Matsumoto 2016 (DIAMOND)	+	+	-	-	+	+	+
Panaccione 2022 (MOTIVATE)	+	+	+	+	+	+	+
Panaccione 2024 (GALAXI-2)	+	?	+	+	+	?	+
Panaccione 2024 (GALAXI-3)	+	?	+	+	+	?	+
Panes 2017 Induction	+	+	+	+	+	+	+
Panes 2017 Maintenance	+	+	+	+	+	+	+
Peyrin-Biroulet 2024 - SEQUENCE	?	?	-	+	?	?	+
Present 1999	?	+	+	?	+	-	+
Röder 2021	+	?	+	?	+	?	?
Rutgeerts 1999	+	?	+	+	+	?	+
Rutgeerts 2006	+	+	+	?	?	?	+
Rutgeerts 2012 (EXTEND)	?	?	+	+	+	+	+
Sandborn 2001a	+	+	+	+	+	?	+
Sandborn 2001b	+	+	+	?	+	?	+
Sandborn 2005a (ENACT 1)	+	+	+	+	+	?	+
Sandborn 2005a (ENACT 2)	+	+	+	+	?	?	+
Sandborn 2007a	+	+	+	+	+	+	+
Sandborn 2007b (CLASSIC II)	?	+	+	+	+	+	+
Sandborn 2007c (PRECISE 1)	+	?	+	+	+	+	+
Sandborn 2008 (Population 1)	+	+	+	?	+	+	+
Sandborn 2011	+	+	+	?	+	?	+
Sandborn 2012 (CERTIFI) - Induction	+	+	+	+	+	+	+
Sandborn 2012 (CERTIFI) - Induction (non-response)	+	+	+	+	+	?	+
Sandborn 2012 (CERTIFI) - Maintenance	+	+	+	+	+	+	+
Sandborn 2013 (GEMINI II) - Induction	+	+	+	+	+	+	+
Sandborn 2013 (GEMINI II) - Maintenance	+	+	+	+	+	+	+
Sandborn 2014	?	+	+	+	+	+	+
Sandborn 2020d (CELEST) - Induction	+	+	+	+	+	+	+
Sandborn 2022 - GALAXI 1	+	+	+	+	+	+	+
Sandborn 2023 - BERGAMOT (cohort 1)	+	+	+	+	?	+	?
Sandborn 2023 - BERGAMOT (cohort 3)	+	+	+	+	+	+	+
Sandborn 2023 - BERGAMOT Maintenance	+	+	+	?	+	+	+
Sands 2004 (ACCENT II) Induction (Non-responders)	+	+	+	?	+	-	+
Sands 2004 (ACCENT II) Maintenance (Responders)	+	+	+	?	+	-	+
Sands 2007	?	?	+	?	+	?	+
Sands 2010	+	+	+	+	+	+	+
Sands 2014 (GEMINI III)	+	+	+	+	+	+	+
Sands 2022 (SEAVUE)	+	+	+	+	+	+	+
Sands 2022 (SERENITY)	+	+	+	?	+	+	+
Schreiber 2005	+	+	-	+	+	+	+
Schreiber 2007 (PRECISE 2)	+	+	+	+	-	+	+
Schreiber 2018a	?	?	+	+	+	+	+
Targan 1997	+	+	+	+	+	?	+
Targan 2007 (ENCORE)	+	+	+	+	+	?	+
VanAssche 2012 (SWITCH)	+	+	-	-	?	?	+
Vermeire 2017 FITZROY - induction	+	+	+	+	+	+	+
Vermeire 2017 FITZROY - induction non-responders	+	+	+	+	+	?	+
Vermeire 2017 FITZROY - maintenance responders	+	+	+	+	+	?	+

Vermeire 2021 (VISIBLE 2)	+	+	+	?	+	+	+
Vermeire 2025 - DIVERSITY (maintenance)	+	?	+	+	?	+	?
Vermeire 2025 - DIVERSITY A	+	?	+	+	+	+	+
Vermeire 2025 - DIVERSITY B	+	?	+	+	+	+	+
Volkers 2017 - SIMILAR	?	?	+	?	?	?	?
Watanabe 2012 - Induction	?	?	+	?	+	+	+
Watanabe 2012 - Maintenance	?	?	+	?	+	+	+
Watanabe 2020 - Induction	+	+	+	?	+	+	+
Watanabe 2020 - Maintenance	+	+	+	?	+	+	+
Winter 2004	?	?	+	?	+	?	+
Ye 2019	+	+	+	+	+	+	+
Young 2024 - iBaSS	+	+	+	+	?	?	?

Review authors' judgments about each risk of bias item for each included study.

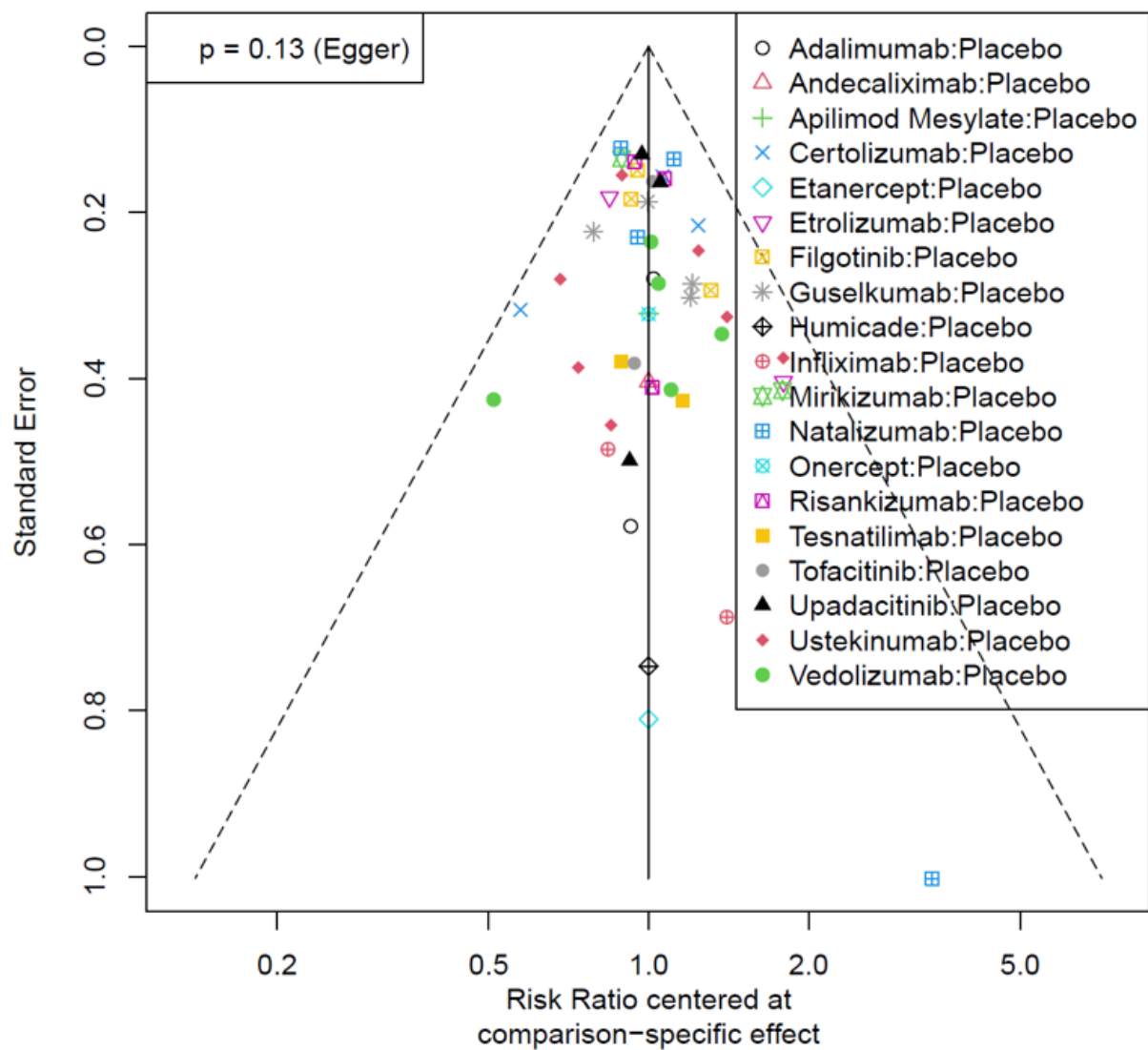
Figure 4

Clinical remission: Treatment vs. Placebo (Random effects Effects Model)



Gordon plot for clinical remission for biologics for induction of remission in Crohn's Disease, with placebo as reference treatment.

Figure 5



Comparison-adjusted funnel plot for induction of clinical remission

Figure 6

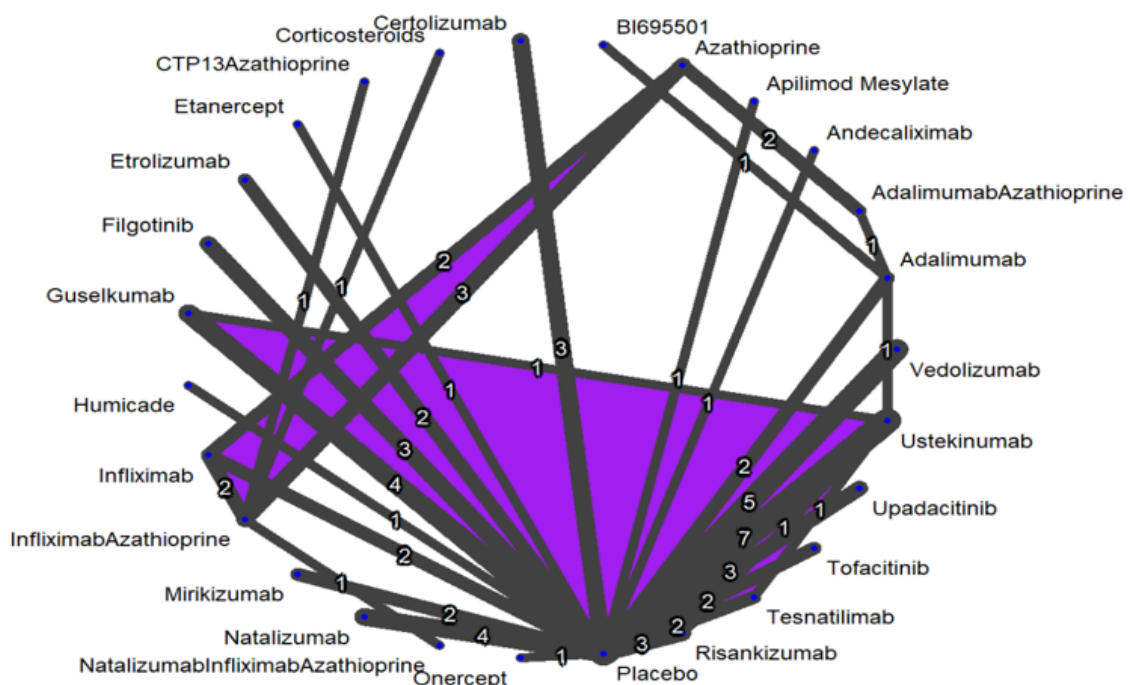
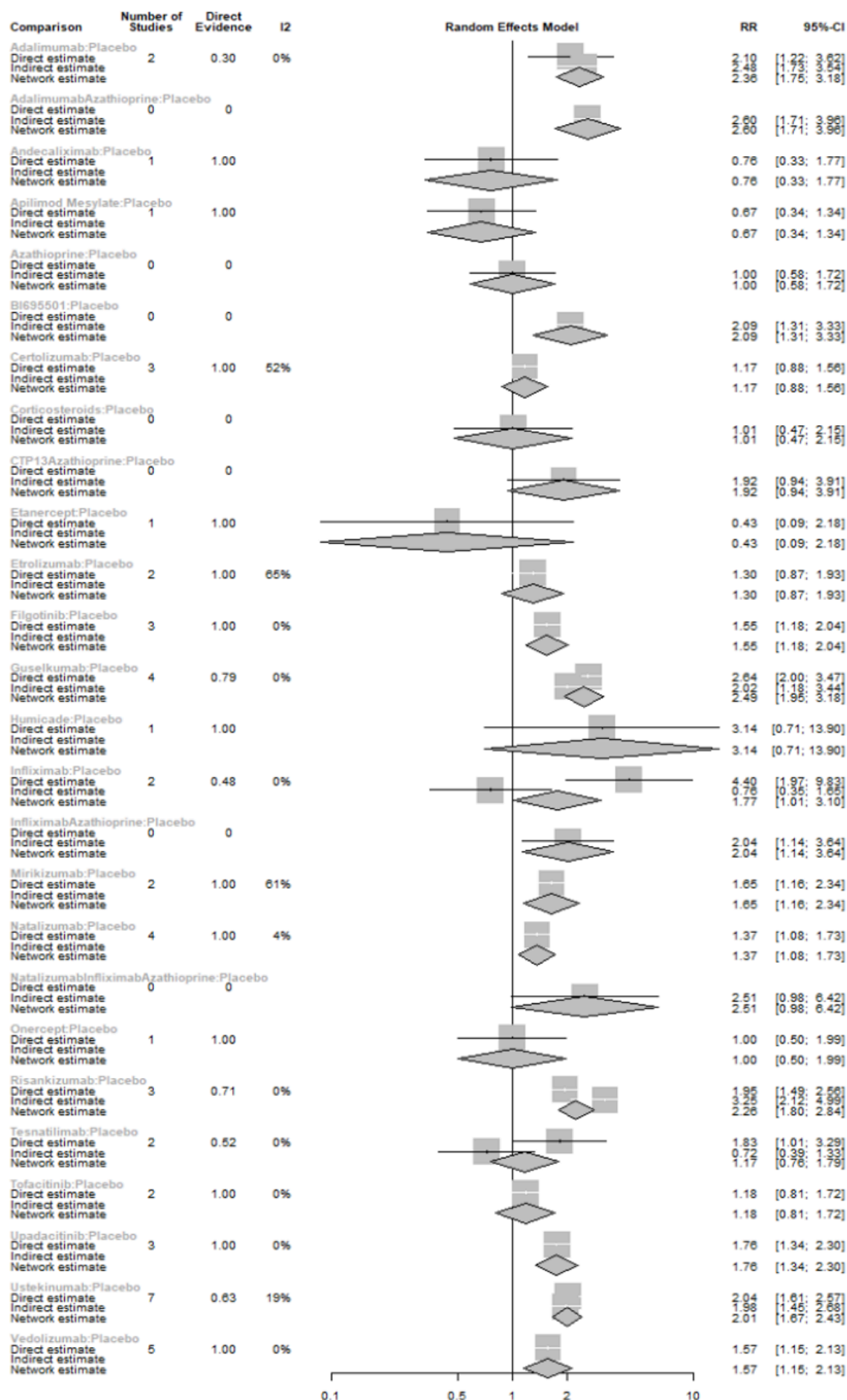
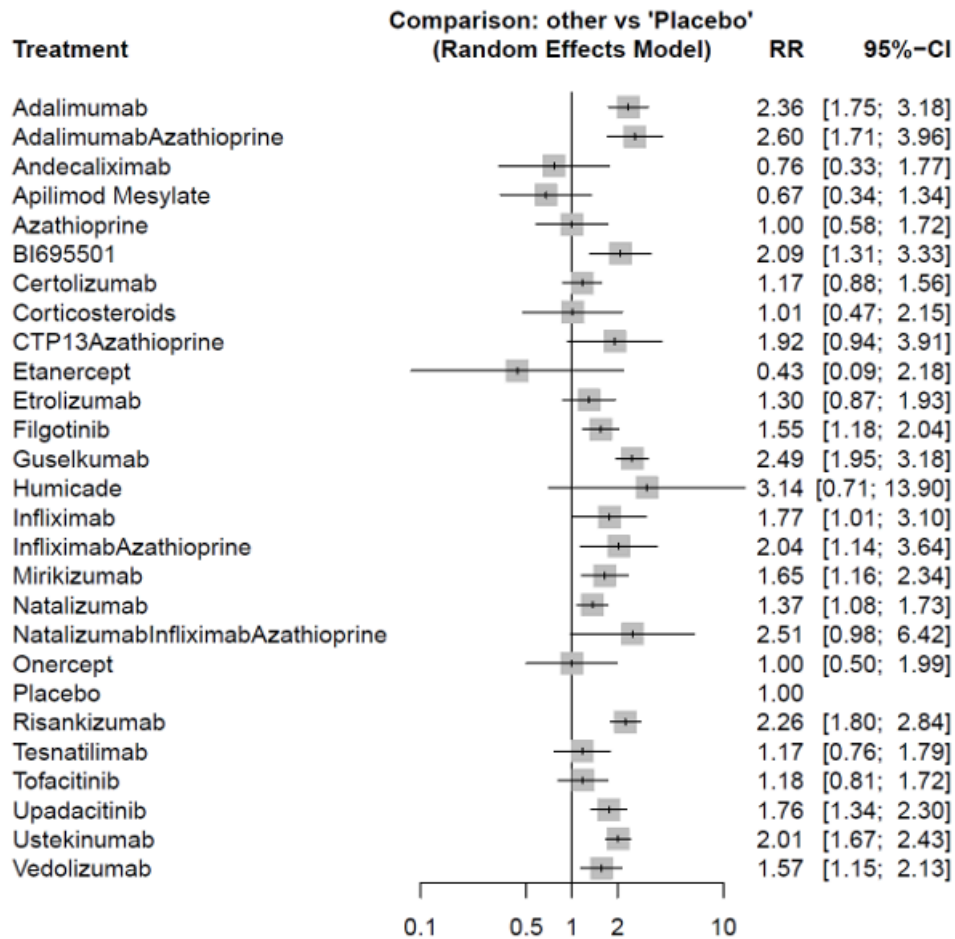


Figure 7



Direct, indirect and network estimates, number of direct studies vs placebo, contribution of direct evidence to the network estimate, and I^2 for pairwise comparisons for induction of clinical remission.

Figure 8



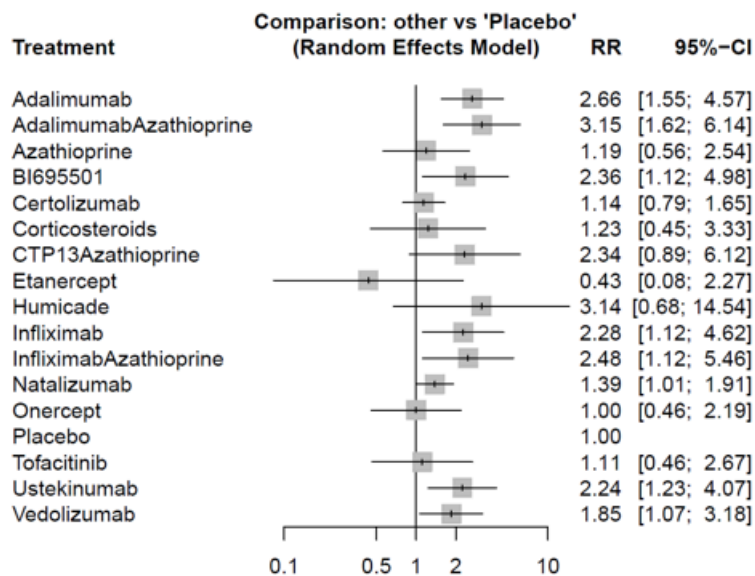
Forest plot for induction of clinical remission

Figure 9

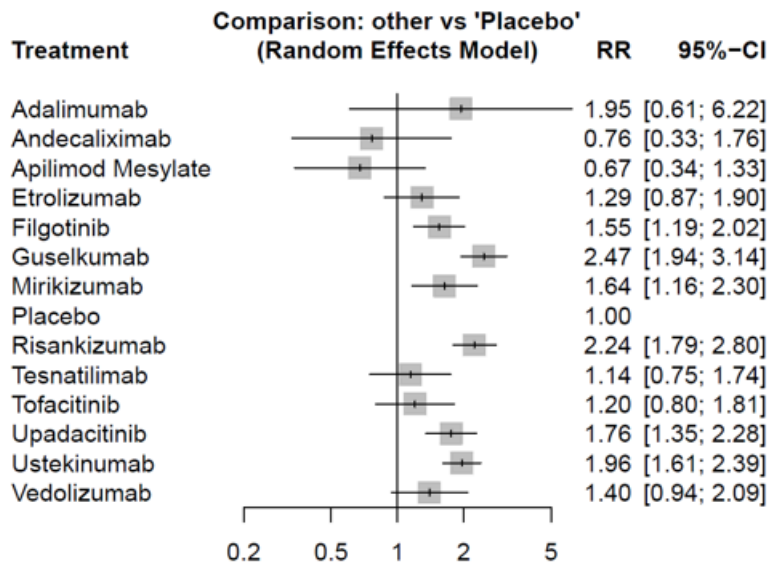
	SUCRA (common)	SUCRA (random)
AdalimumabAzathioprine	0.8323	0.8777
Guselkumab	0.9185	0.8673
Adalimumab	0.8508	0.8481
Humicade	0.8258	0.8415
Risankizumab	0.8858	0.8169
NatalizumabInfliximabAzathioprine	0.7215	0.8000
Ustekinumab	0.7519	0.7385
BI695501	0.7369	0.7250
InfliximabAzathioprine	0.6488	0.7100
CTP13Azathioprine	0.5950	0.6477
Infliximab	0.5000	0.5781
Upadacitinib	0.6785	0.5758
Mirikizumab	0.5827	0.5592
Filgotinib	0.5523	0.5158
Vedolizumab	0.5708	0.5042
Natalizumab	0.4331	0.4188
Etrolizumab	0.3665	0.3762
Tesnatilimab	0.2500	0.2992
Tofacitinib	0.3177	0.2985
Certolizumab	0.3450	0.2938
Corticosteroids	0.1819	0.2469
Onercept	0.2731	0.2362
Azathioprine	0.1492	0.2212
Placebo	0.2077	0.1727
Andecaliximab	0.1204	0.1258
Etanercept	0.0946	0.1150
Apilimod Mesylate	0.1092	0.0900
- based on 100 simulations		
SUCRA rankings for induction of clinical remission		

Figure 10

>=50% naïve



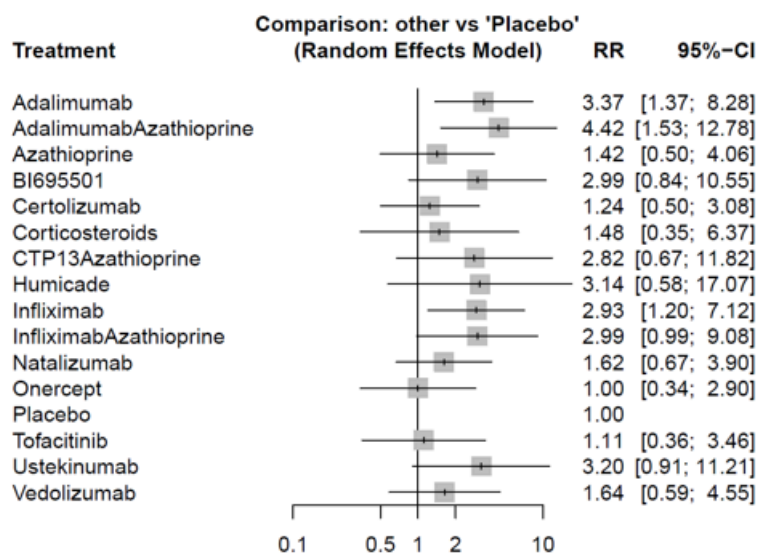
<50% naïve



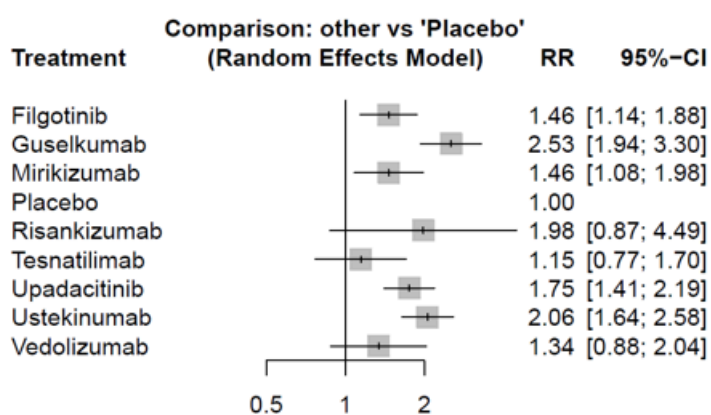
Subgroup analysis for studies with more and less than 50% of participants naïve to biologics for induction of clinical remission.

Figure 11

exclusively naïve

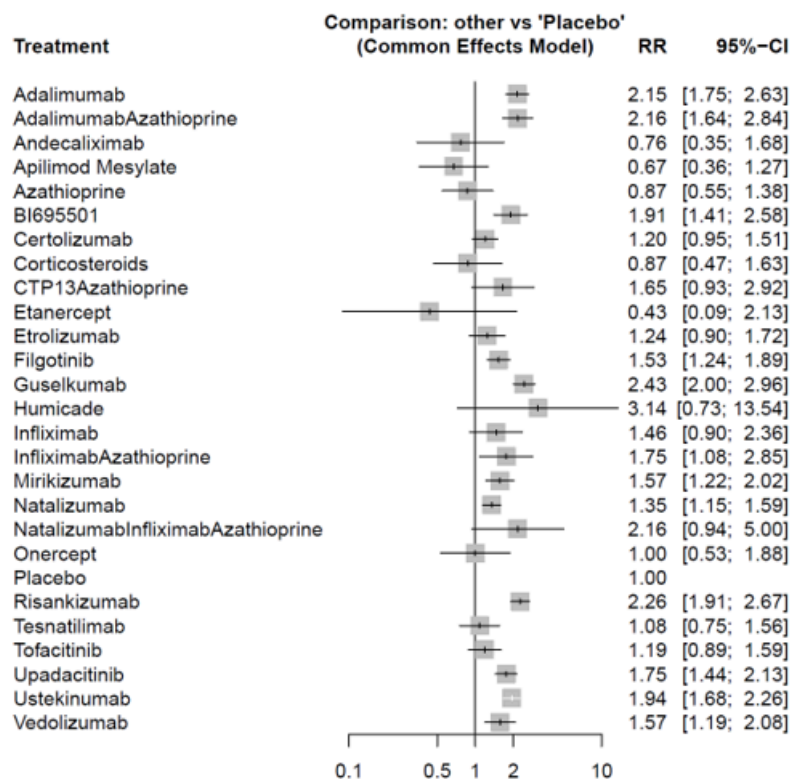


exclusively not naïve



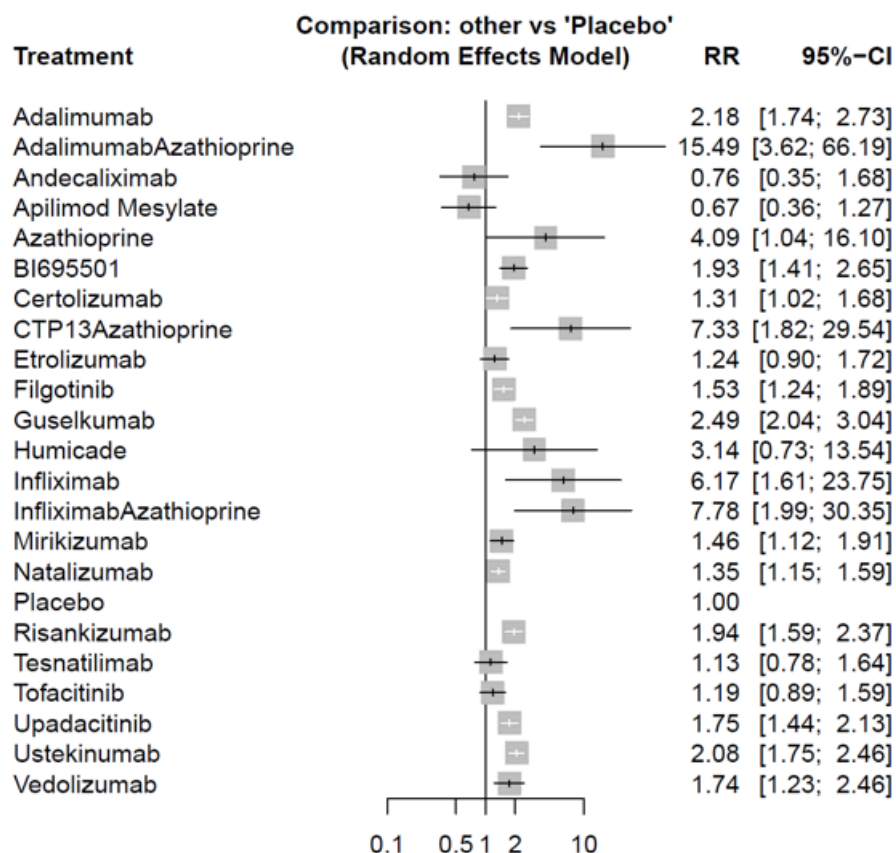
Subgroup analysis for studies with participants exclusively naïve or not naïve to biologics for induction of clinical remission.

Figure 12



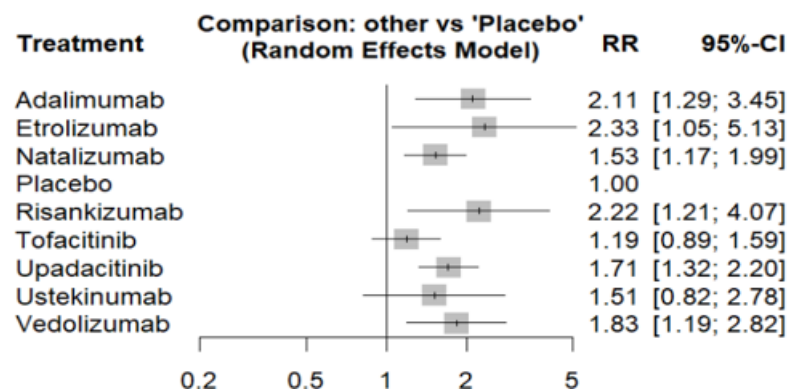
Common (fixed) effects sensitivity analysis for induction of remission

Figure 13



Sensitivity analysis for risk of bias (removal of high RoB studies)

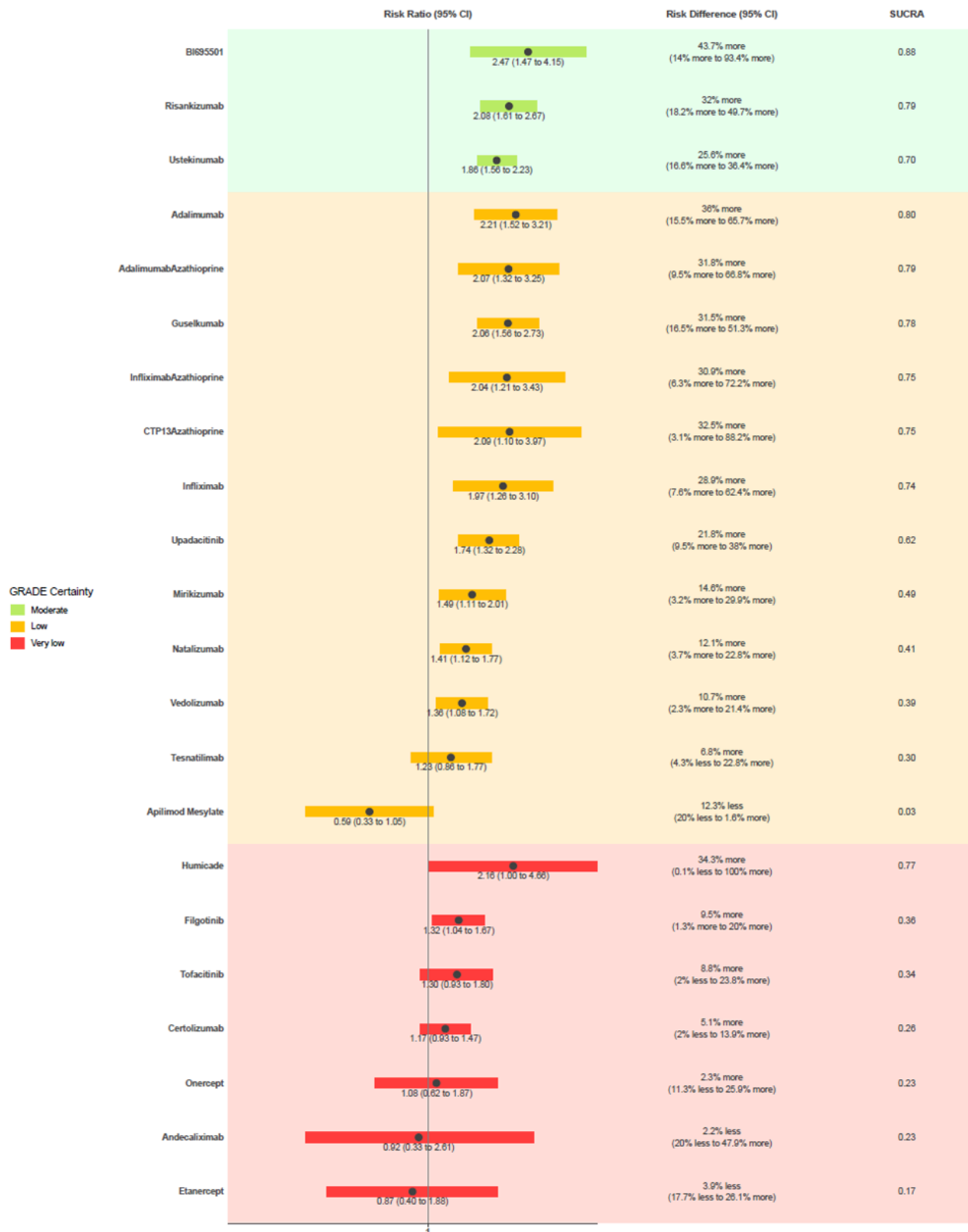
Figure 14



Sensitivity analysis for studies with less than 20% concomitant purine analogues for induction of remission (removal of studies where the population is mixed regarding the use of purine analogues)

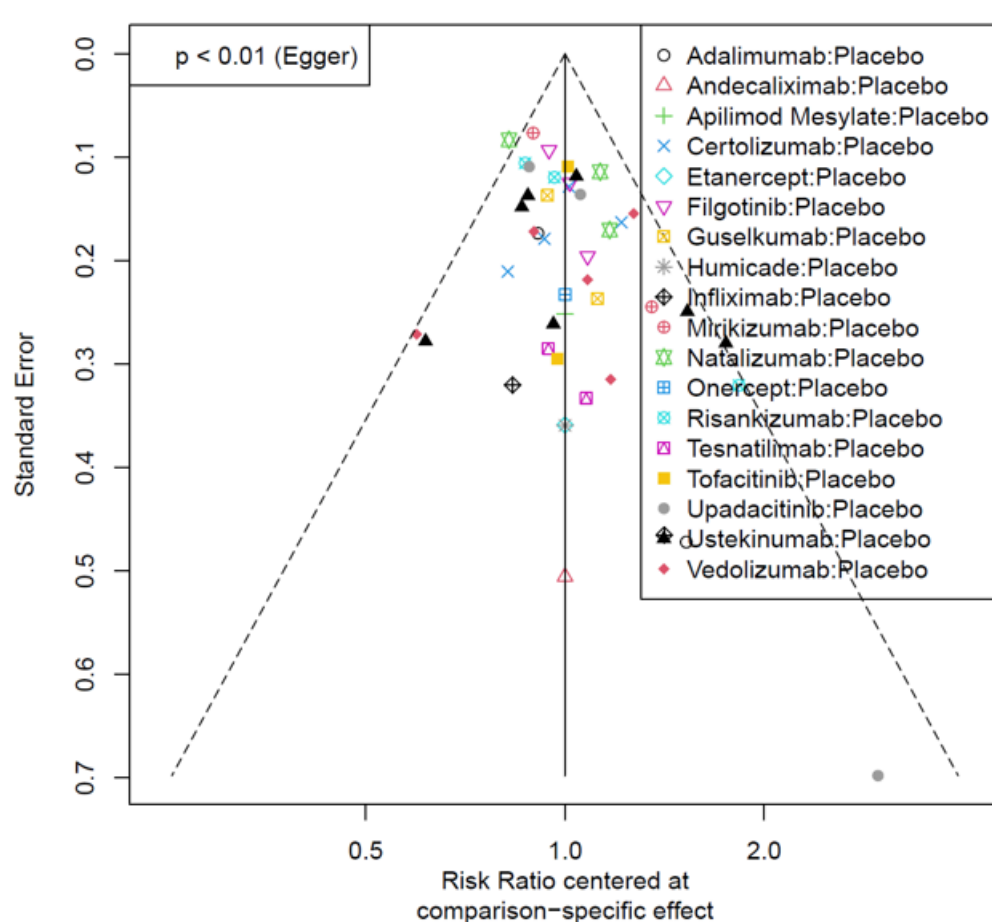
Figure 15

Clinical response: Treatment vs. Placebo (Random effects Effects Model)



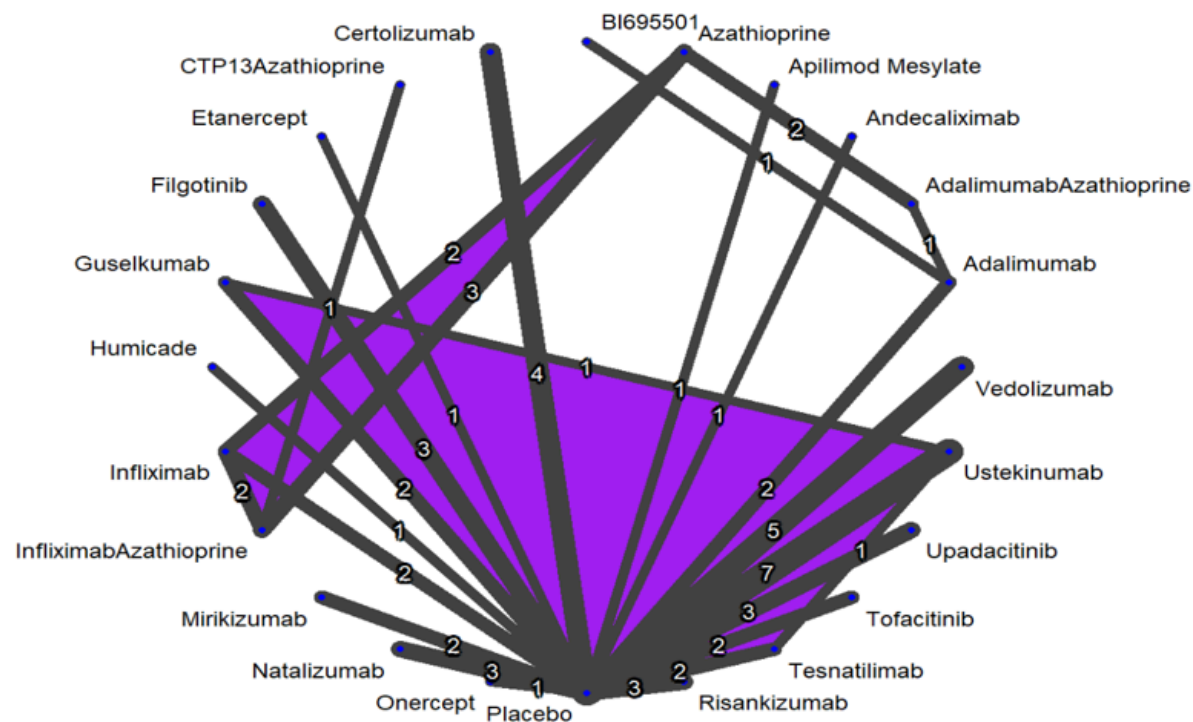
Gordon plot for clinical response for biologics for induction of remission in Crohn's Disease, with placebo as reference treatment.

Figure 16



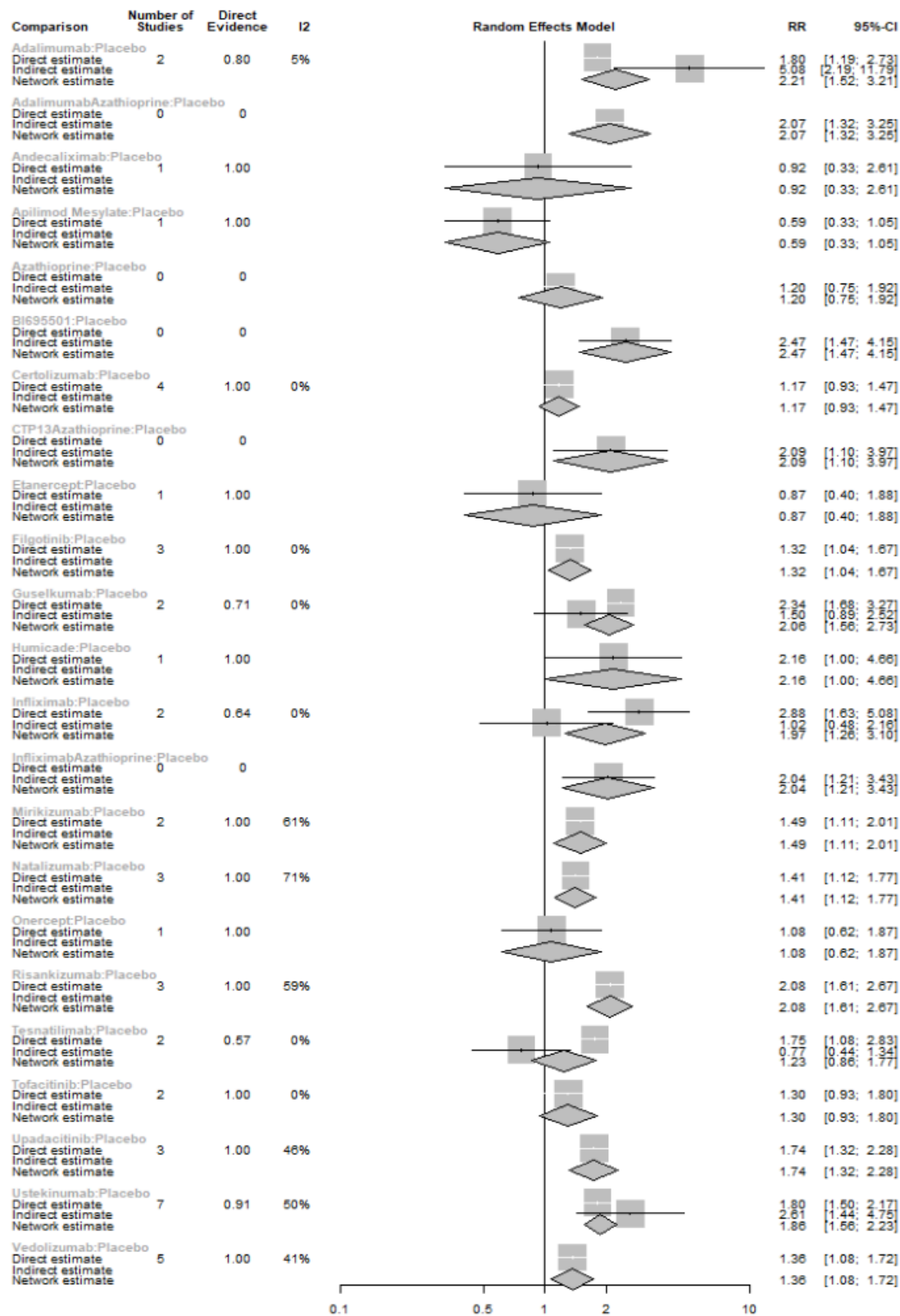
Comparison-adjusted funnel plot for induction of clinical response

Figure 17



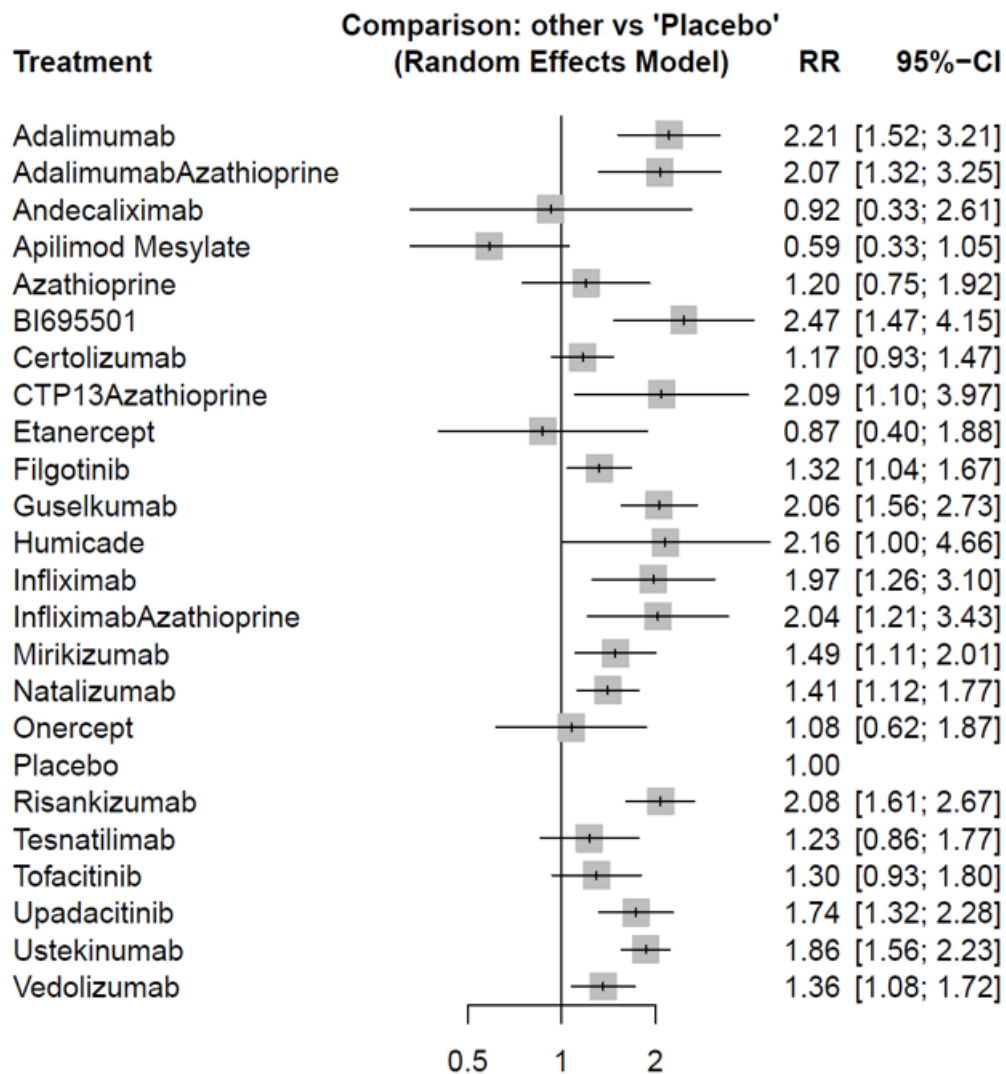
Network plot for induction of clinical response (shaded regions denote multi-arm studies)

Figure 18



Direct, indirect and network estimates, number of direct studies vs placebo, contribution of direct evidence to the network estimate, and I² for pairwise comparisons for induction of clinical response.

Figure 19



Forest plot for induction of clinical response

Figure 20

	SUCRA (common)	SUCRA (random)
BI695501	0.9248	0.9083
Adalimumab	0.8783	0.8417
Risankizumab	0.7943	0.7783
AdalimumabAzathioprine	0.7391	0.7735
Humicade	0.7991	0.7683
Guselkumab	0.8330	0.7613
InfliximabAzathioprine	0.7291	0.7470
CTP13Azathioprine	0.7391	0.7348
Infliximab	0.6478	0.7257
Ustekinumab	0.7383	0.6970
Upadacitinib	0.6365	0.6274
Mirikizumab	0.4539	0.4965
Natalizumab	0.4130	0.4165
Vedolizumab	0.4417	0.3804
Filgotinib	0.3809	0.3522
Tofacitinib	0.3817	0.3235
Tesnatilimab	0.2191	0.3157
Azathioprine	0.2009	0.2896
Certolizumab	0.2639	0.2787
Onercept	0.2326	0.2235
Andecaliximab	0.2296	0.2204
Etanercept	0.1522	0.1652
Placebo	0.1457	0.1383
Apilimod Mesylate	0.0252	0.0365
- based on 100 simulations		
SUCRA rankings for induction of clinical response		

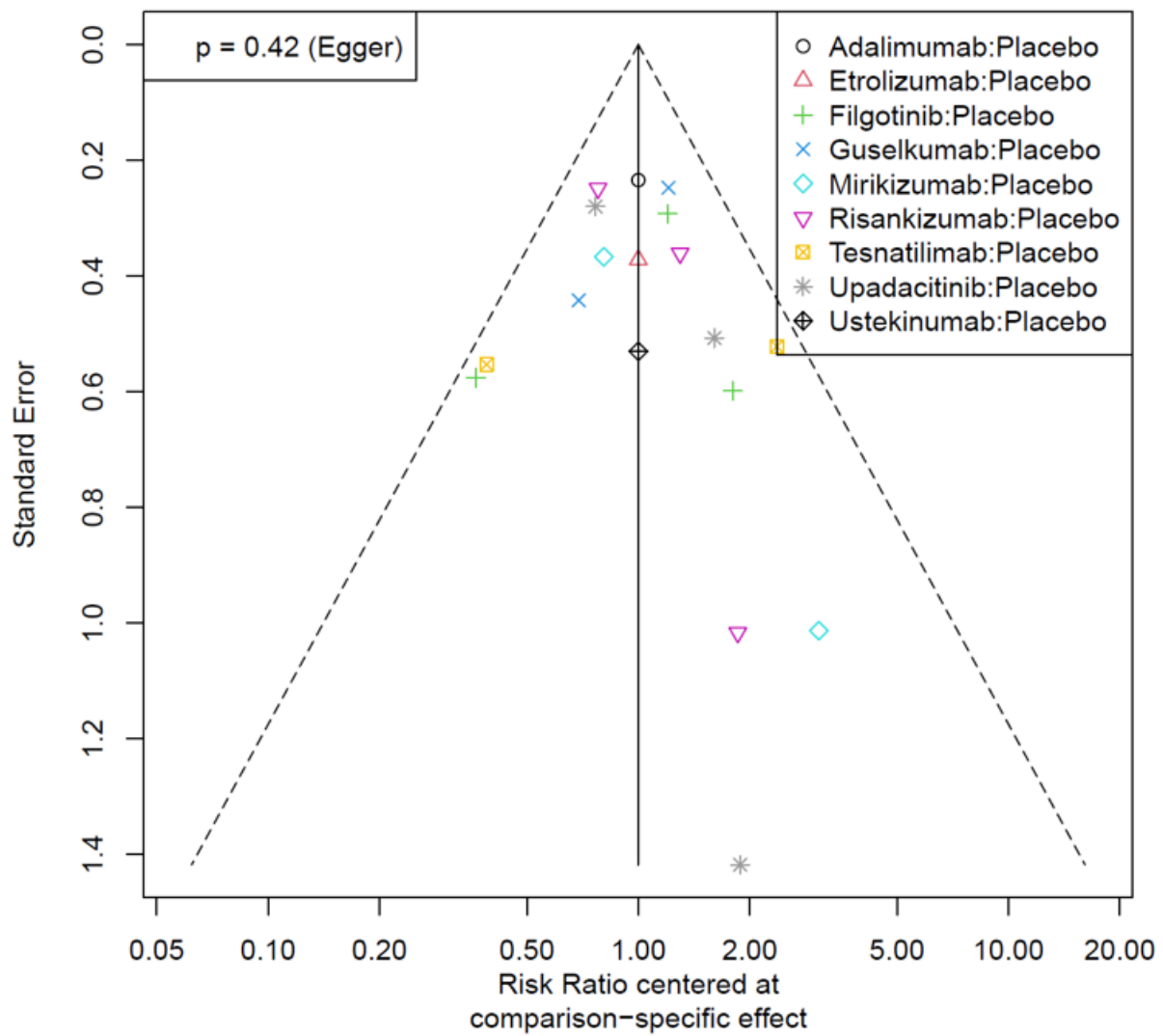
Figure 21

Endoscopic remission: Treatment vs. Placebo (Random effects Effects Model)



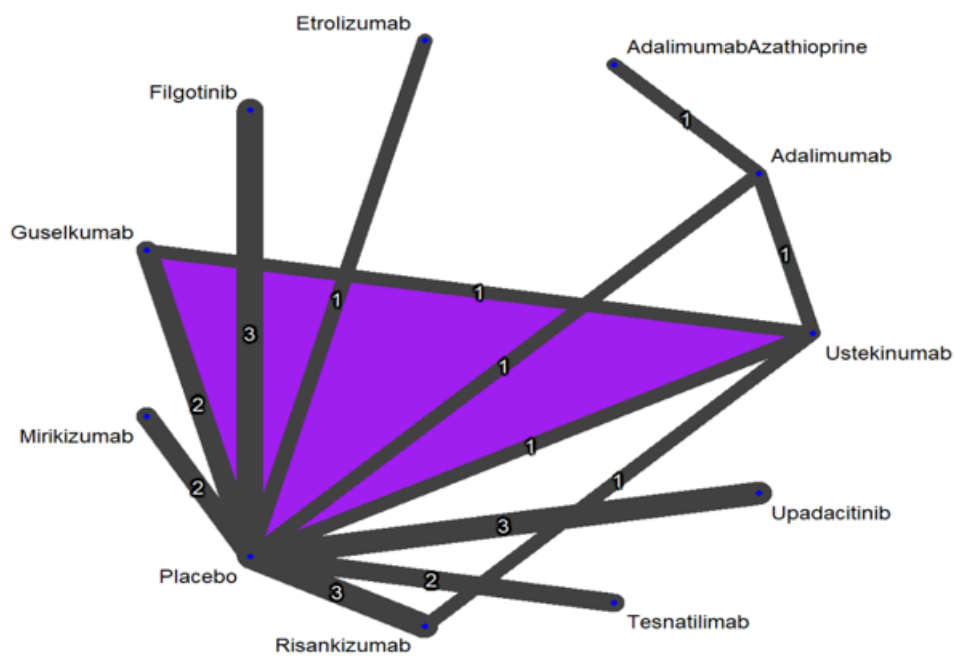
Gordon plot for endoscopic remission for biologics for induction of remission in Crohn's Disease, with placebo as reference treatment.

Figure 22



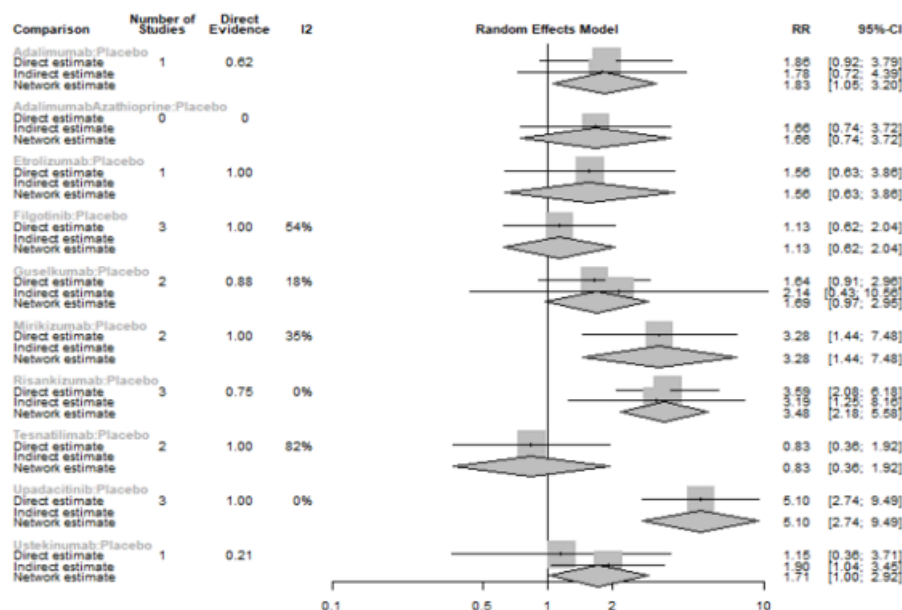
Comparison-adjusted funnel plot for induction of endoscopic remission

Figure 23



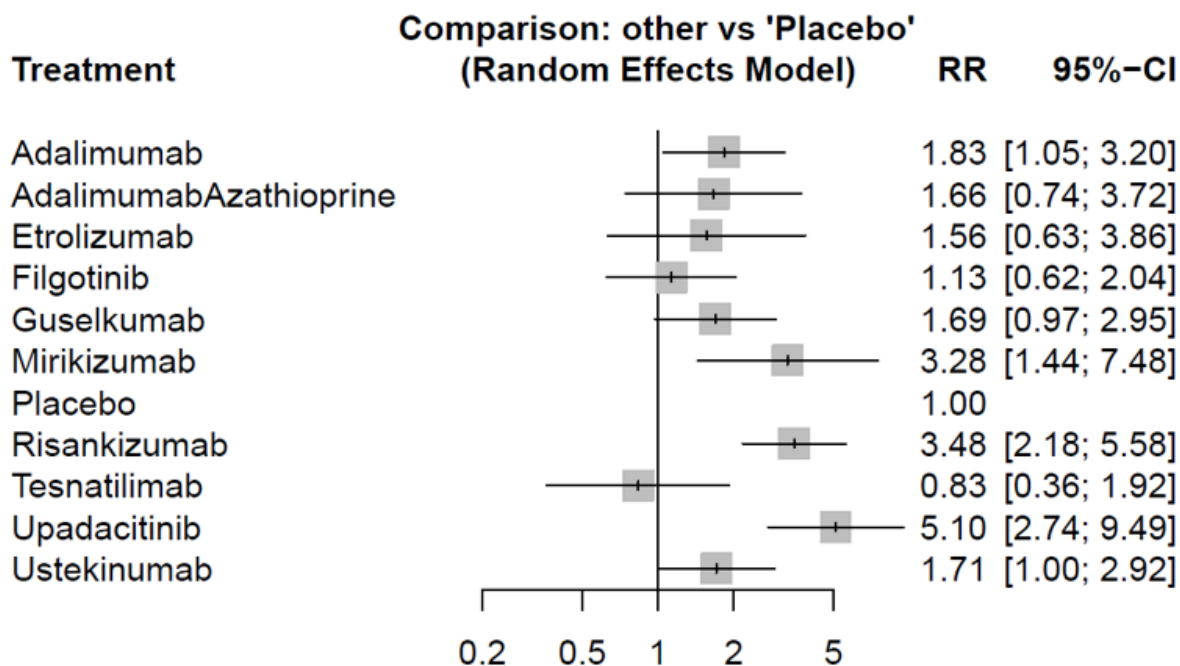
Network plot for induction of endoscopic remission (shaded regions denote multi-arm studies)

Figure 24



Direct, indirect and network estimates, number of direct studies vs placebo, contribution of direct evidence to the network estimate, and I² for pairwise comparisons for induction of endoscopic remission.

Figure 25



Forest plot for induction of endoscopic remission

Figure 26

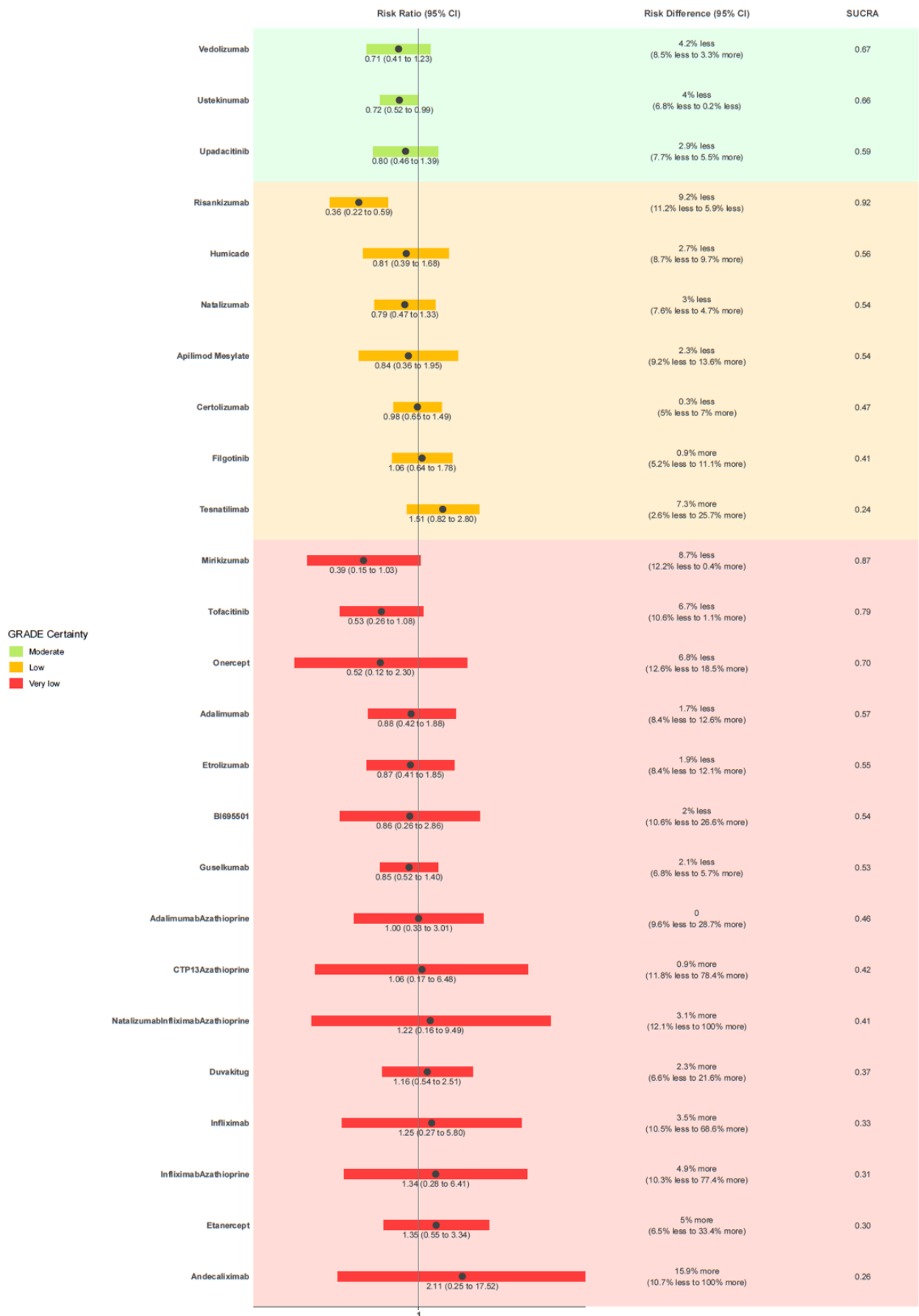
	SUCRA (common)	SUCRA (random)
Upadacitinib	0.978	0.948
Risankizumab	0.860	0.853
Mirikizumab	0.817	0.823
Adalimumab	0.571	0.556
Ustekinumab	0.506	0.510
AdalimumabAzathioprine	0.439	0.486
Guselkumab	0.485	0.461
Etrolizumab	0.432	0.413
Filgotinib	0.244	0.211
Placebo	0.104	0.132
Tesnatilimab	0.064	0.107

- based on 100 simulations

SUCRA rankings for induction of endoscopic remission

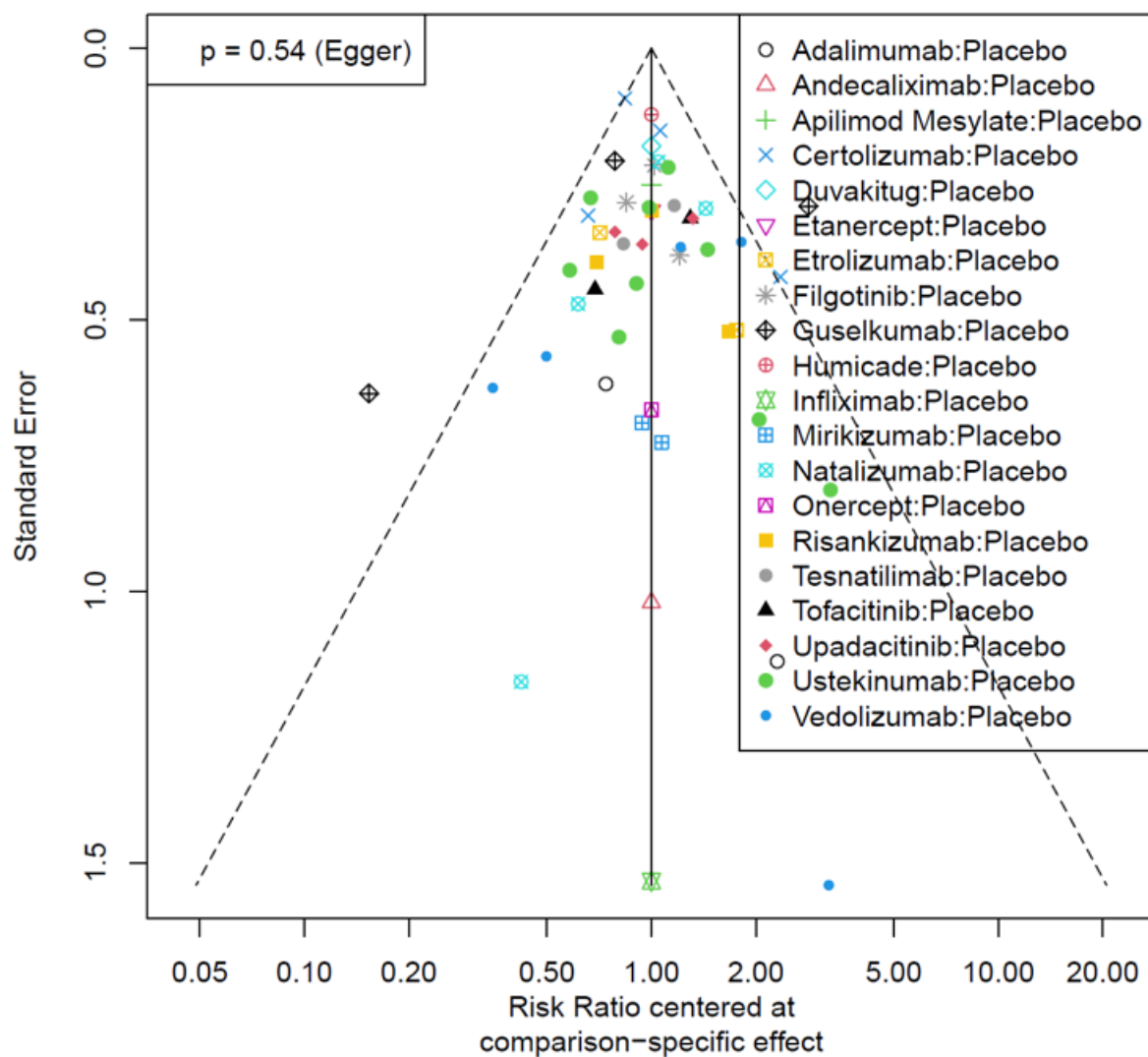
Figure 27

Treatment vs. Placebo (Random effects Effects Model)



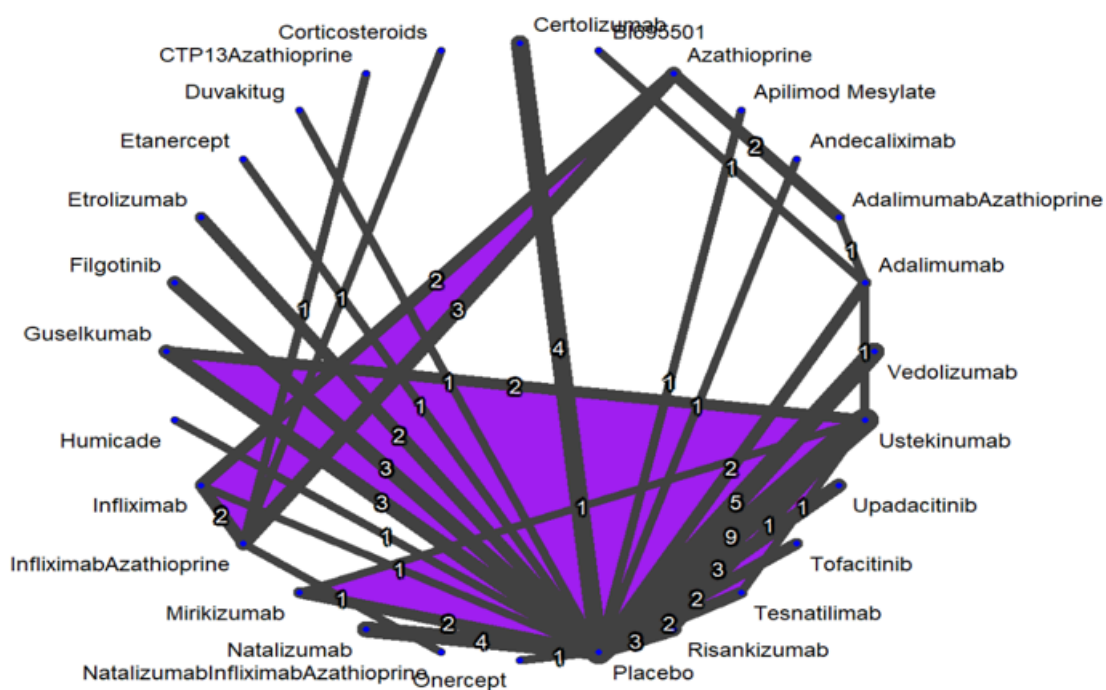
Gordon plot for withdrawals due to adverse events for biologics for induction of remission in Crohn's Disease, with placebo as reference treatment.

Figure 28



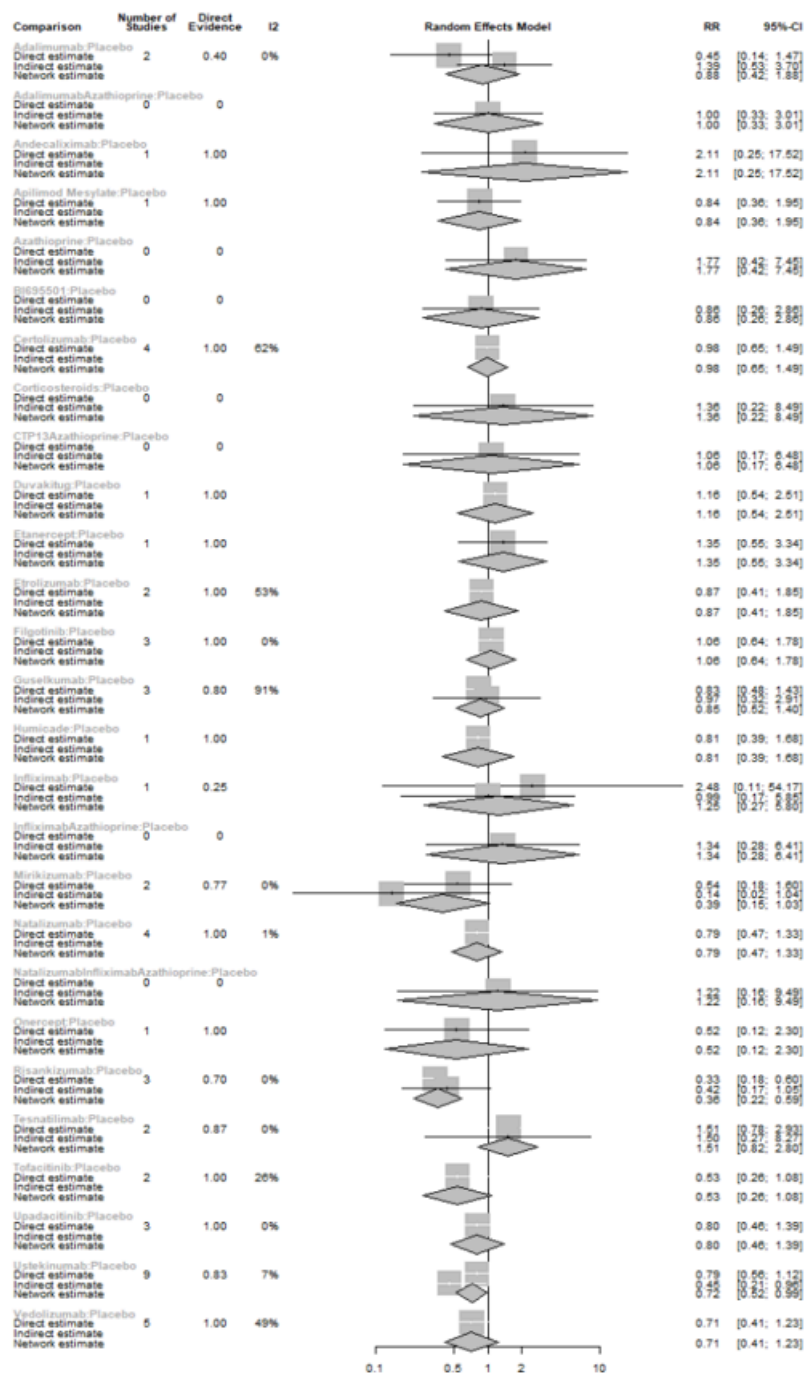
Comparison-adjusted funnel plot for withdrawals due to adverse events during induction.

Figure 29



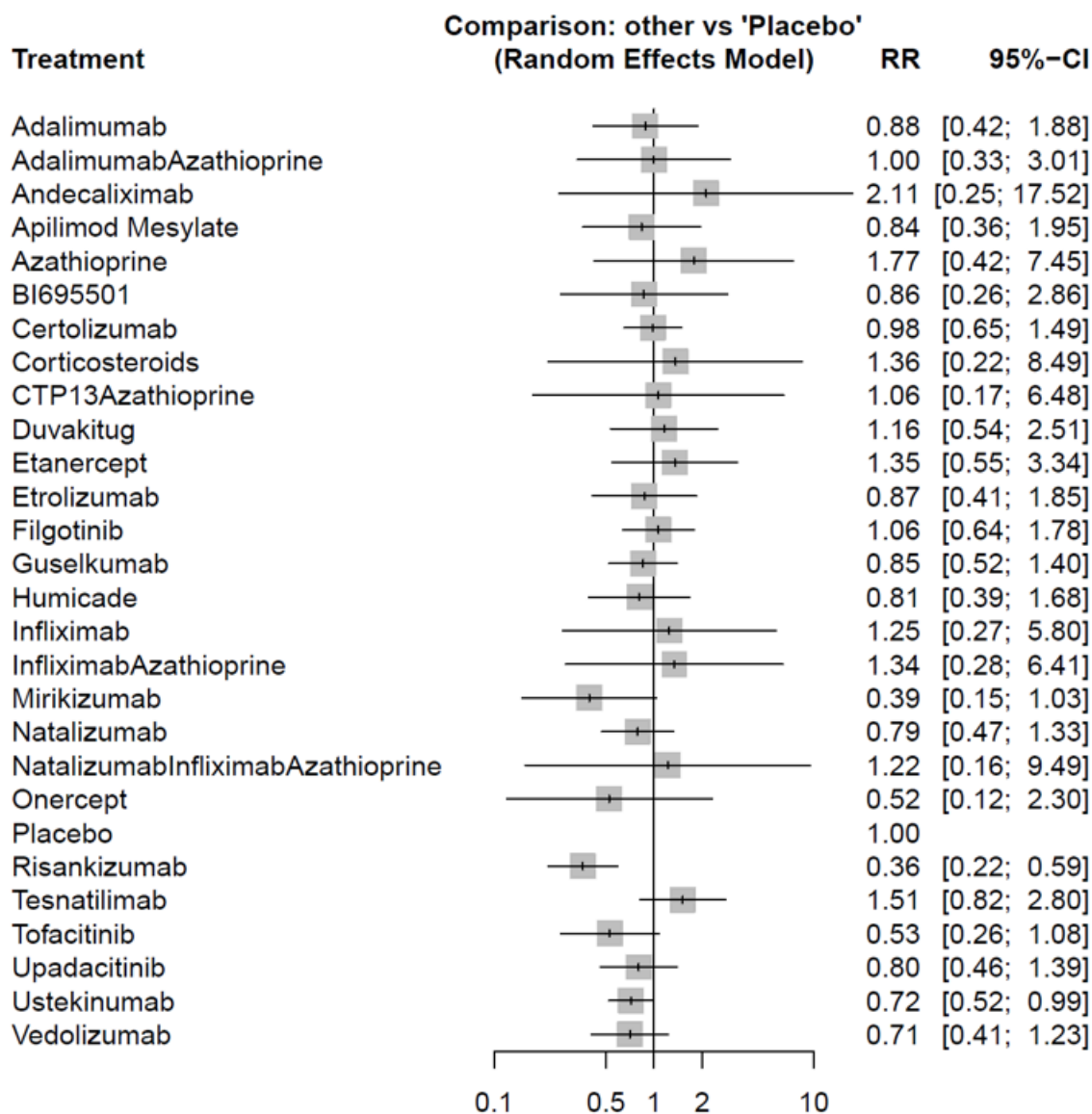
Network plot for withdrawals due to adverse events during induction (shaded regions denote multi-arm studies)

Figure 30



Direct, indirect and network estimates, number of direct studies vs placebo, contribution of direct evidence to the network estimate, and I² for pairwise comparisons for withdrawals due to adverse events during induction.

Figure 31



Forest plot for withdrawals due to adverse events during induction

Figure 32

	SUCRA (common)	SUCRA (random)
Risankizumab	0.9626	0.9252
Mirikizumab	0.9007	0.8411
Tofacitinib	0.8278	0.7863
Onercept	0.7385	0.7593
Ustekinumab	0.7148	0.6663
Vedolizumab	0.6570	0.6485
Natalizumab	0.5811	0.5985
Upadacitinib	0.6033	0.5707
Adalimumab	0.4656	0.5604
Humicade	0.6311	0.5589
Guselkumab	0.5937	0.5419
Apilimod Mesylate	0.5548	0.5374
Etrolizumab	0.6004	0.5344
BI695501	0.4667	0.5159
AdalimumabAzathioprine	0.4085	0.5119
Certolizumab	0.5922	0.4670
Placebo	0.4293	0.4400
CTP13Azathioprine	0.4496	0.4011
Filgotinib	0.4078	0.3981
NatalizumabInfliximabAzathioprine	0.3419	0.3807
InfliximabAzathioprine	0.2107	0.3626
Infliximab	0.3167	0.3507
Duvakitug	0.3937	0.3470
Etanercept	0.2922	0.3000
Corticosteroids	0.2581	0.2959
Andecaliximab	0.2493	0.2733
Tesnatilimab	0.1996	0.2541
Azathioprine	0.1522	0.1726

- based on 100 simulations

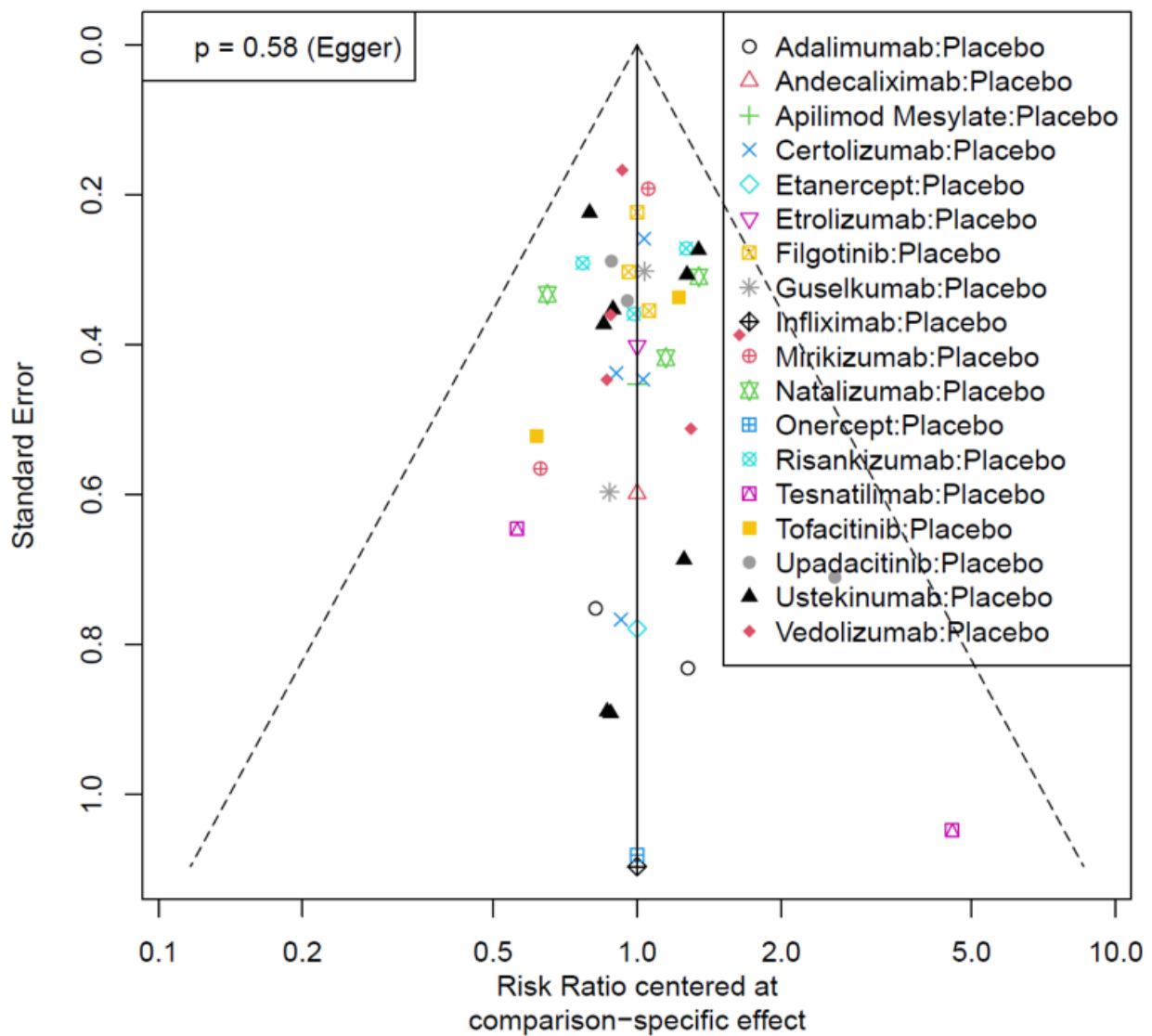
SUCRA rankings for withdrawals due to adverse events during induction

Figure 33



Gordon plot for serious adverse events for biologics for induction of remission in Crohn's Disease, with placebo as reference treatment.

Figure 34



Comparison-adjusted funnel plot for serious adverse events during induction.

Figure 35

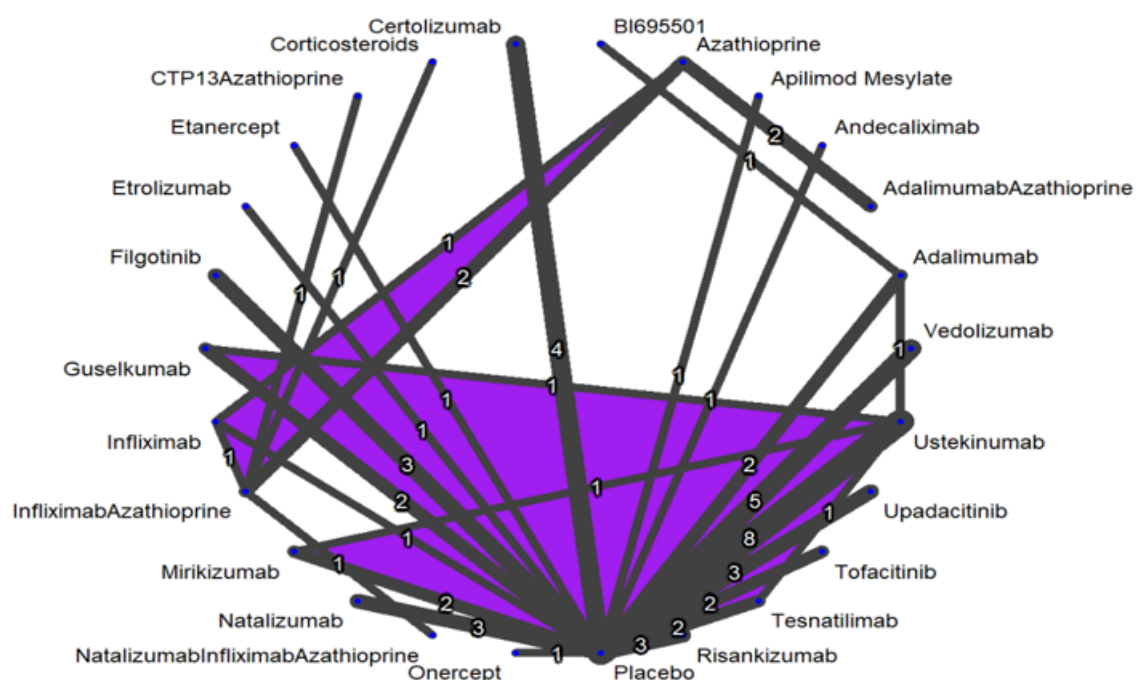
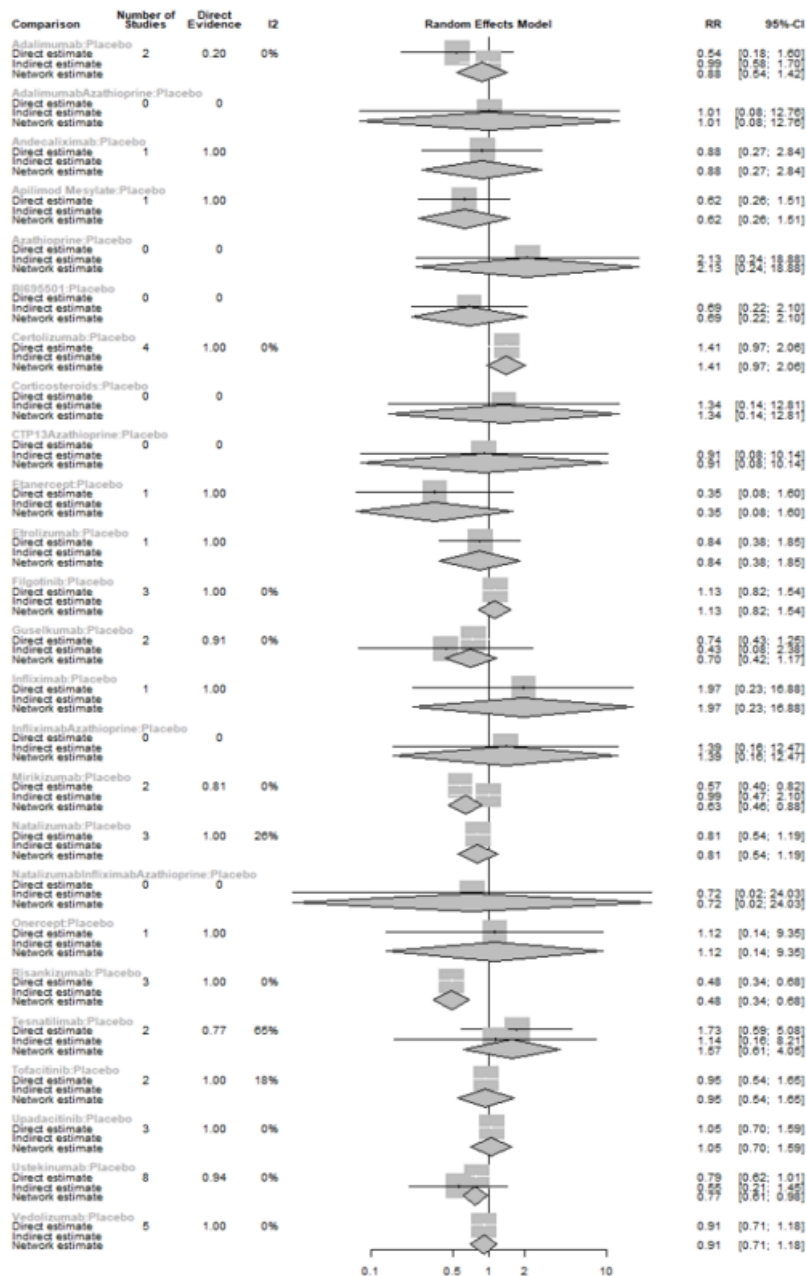
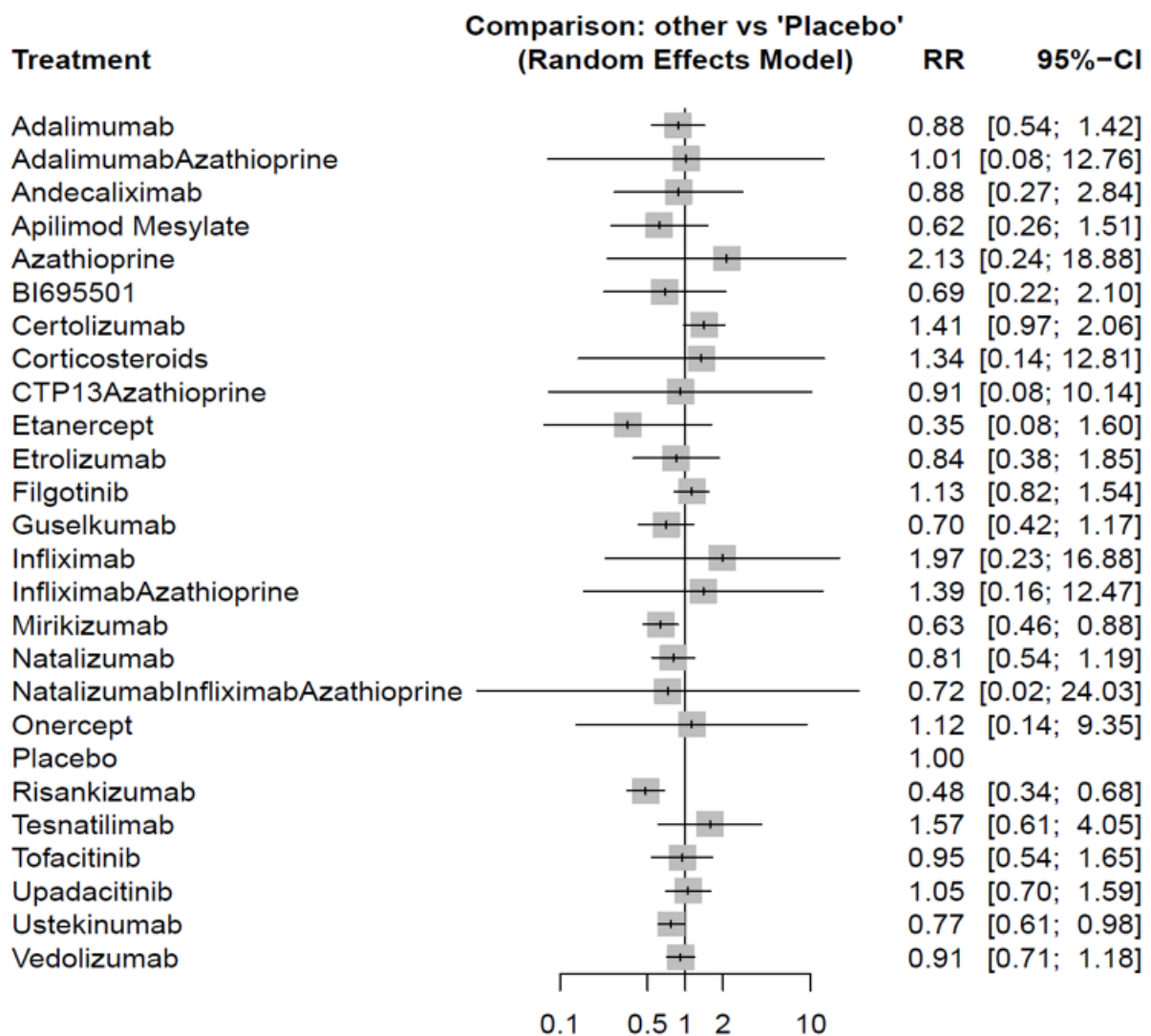


Figure 36



Direct, indirect and network estimates, number of direct studies vs placebo, contribution of direct evidence to the network estimate, and I² for pairwise comparisons for serious adverse events during induction.

Figure 37



Forest plot for serious adverse events during induction

Figure 38

	SUCRA (common)	SUCRA (random)
Risankizumab	0.8496	0.8340
Etanercept	0.8220	0.7688
Mirikizumab	0.6856	0.7172
Guselkumab	0.6352	0.6508
Apilimod Mesylate	0.6712	0.6424
Ustekinumab	0.5960	0.6052
BI695501	0.6264	0.5924
Natalizumab	0.5888	0.5640
NatalizumabInfliximabAzathioprine	0.5148	0.5492
Etrolizumab	0.5264	0.5212
CTP13Azathioprine	0.4820	0.5156
Vedolizumab	0.5104	0.5096
Adalimumab	0.5108	0.5036
Tofacitinib	0.5192	0.4988
Andecaliximab	0.5392	0.4848
Onercept	0.4116	0.4744
AdalimumabAzathioprine	0.4148	0.4452
Placebo	0.4396	0.4356
Filgotinib	0.4288	0.4244
Upadacitinib	0.4556	0.4228
InfliximabAzathioprine	0.3612	0.4076
Corticosteroids	0.4024	0.3832
Tesnatilimab	0.2380	0.2932
Certolizumab	0.2828	0.2688
Infliximab	0.2584	0.2500
Azathioprine	0.2292	0.2372

- based on 100 simulations

SUCRA rankings for serious adverse events during induction

Figure 39

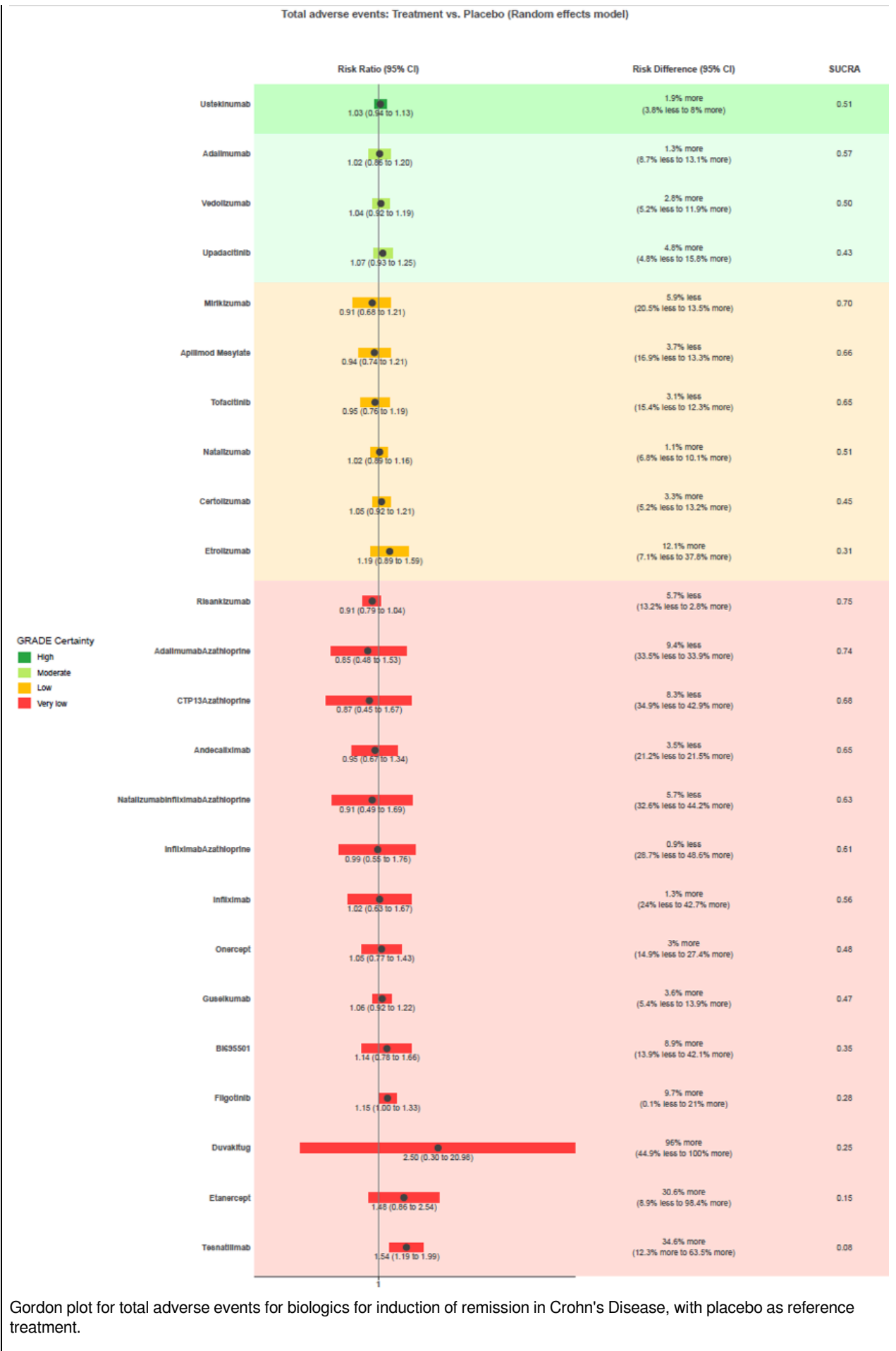
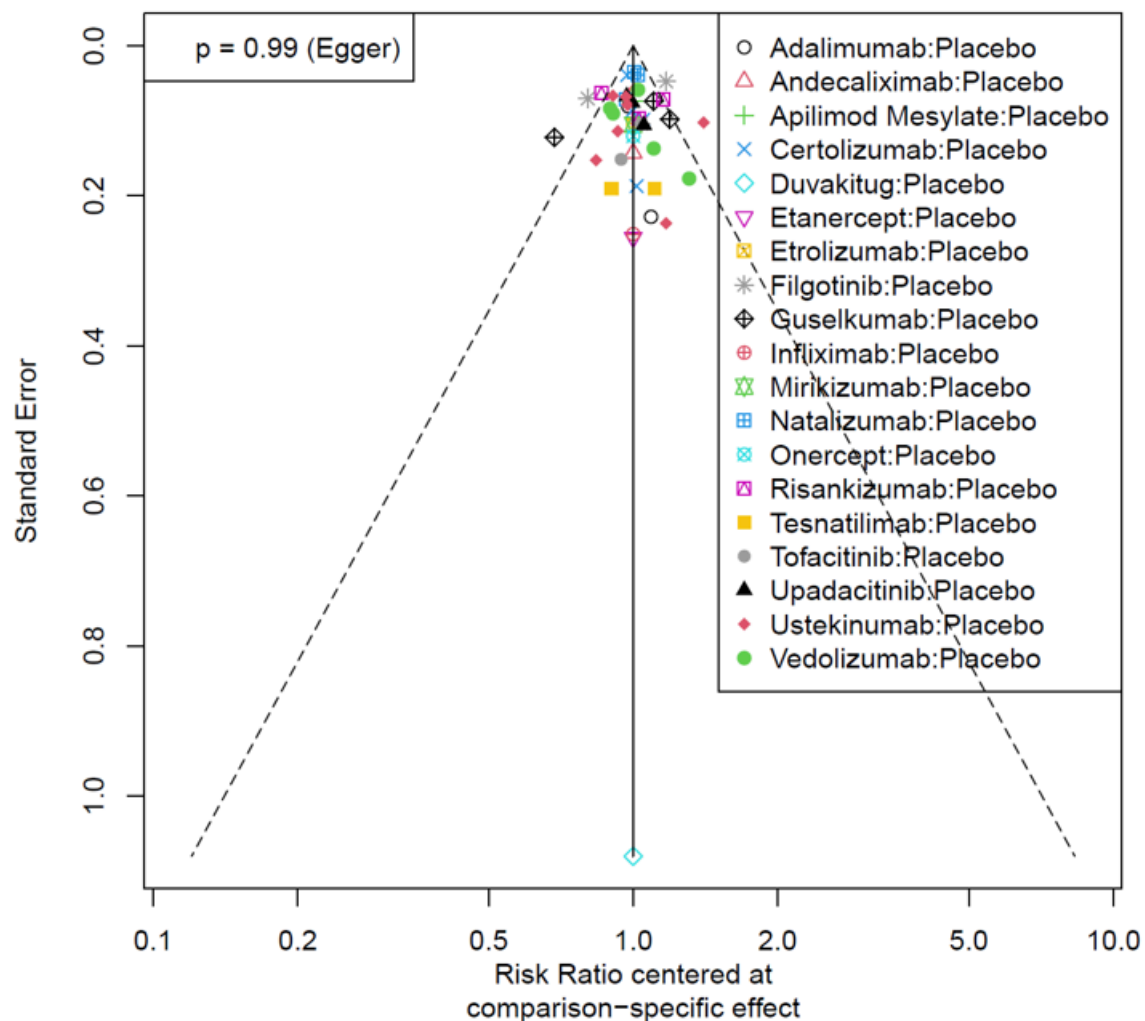
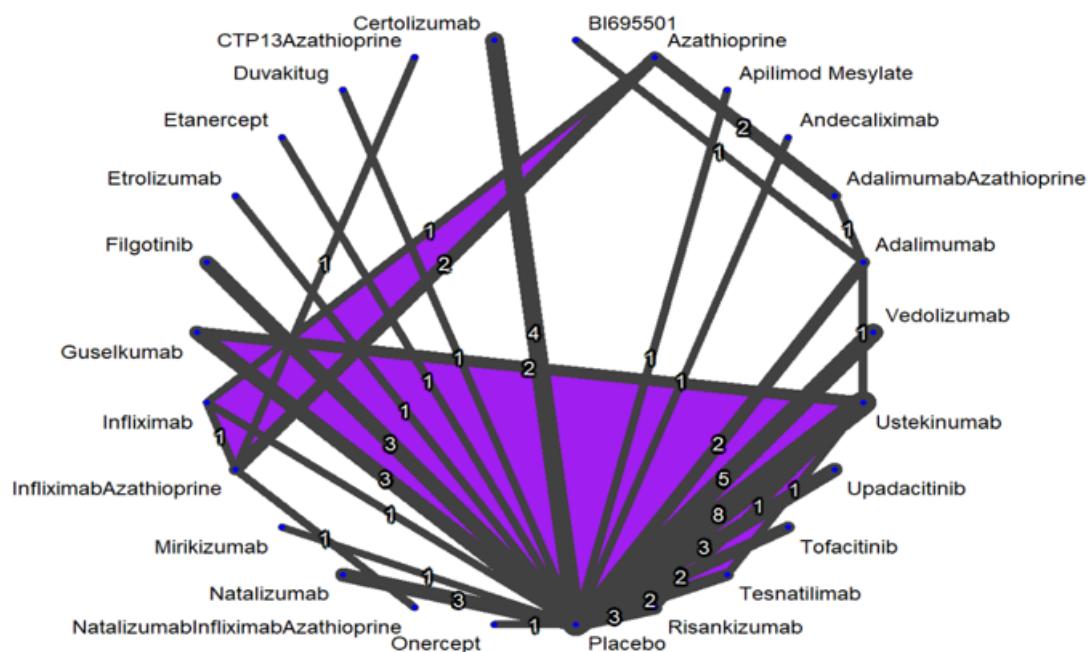


Figure 40



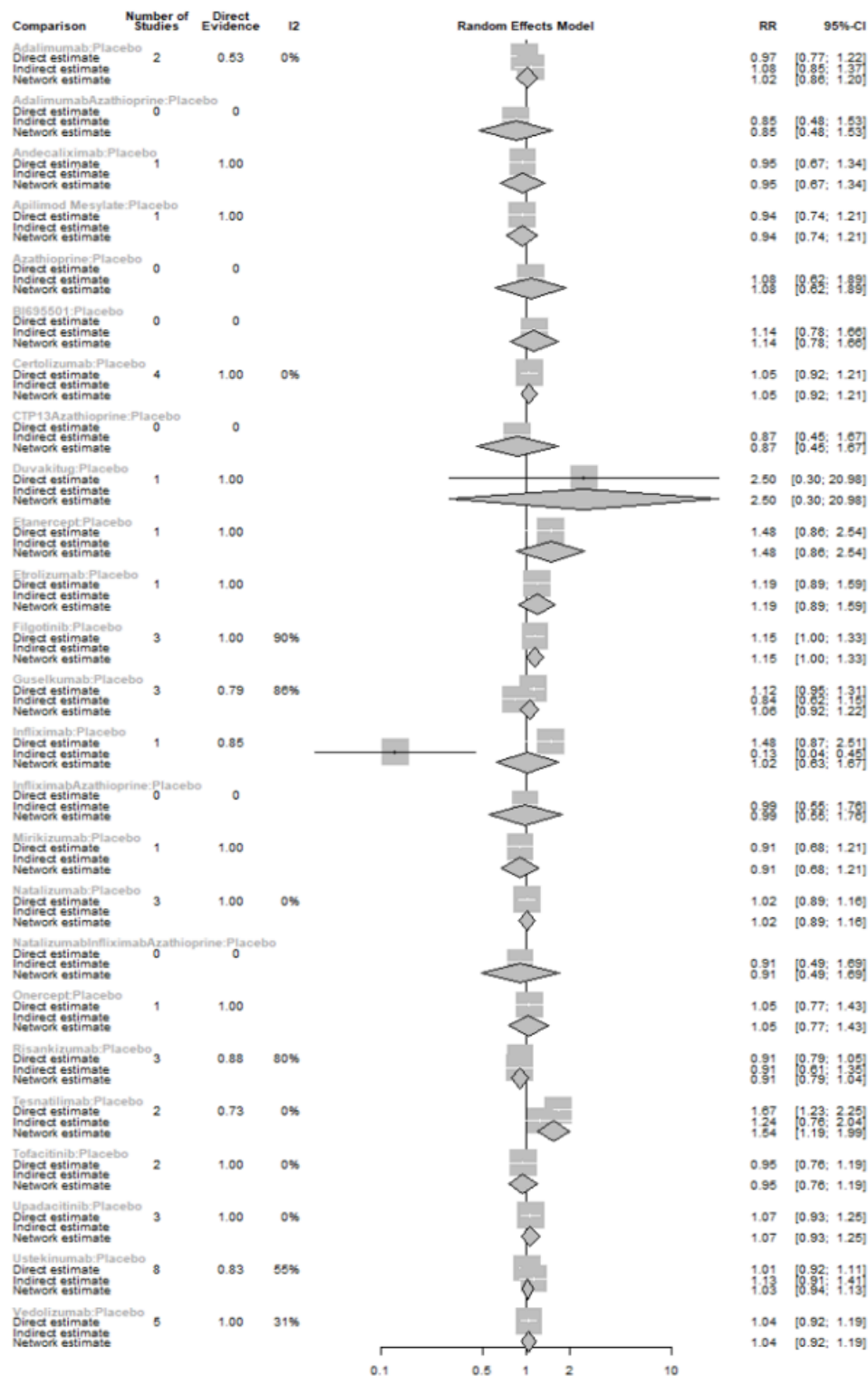
Comparison-adjusted funnel plot for total adverse events during induction.

Figure 41



Network plot for total adverse events during induction (shaded regions denote multi-arm studies)

Figure 42



Network plot for total adverse events during induction.

Figure 43

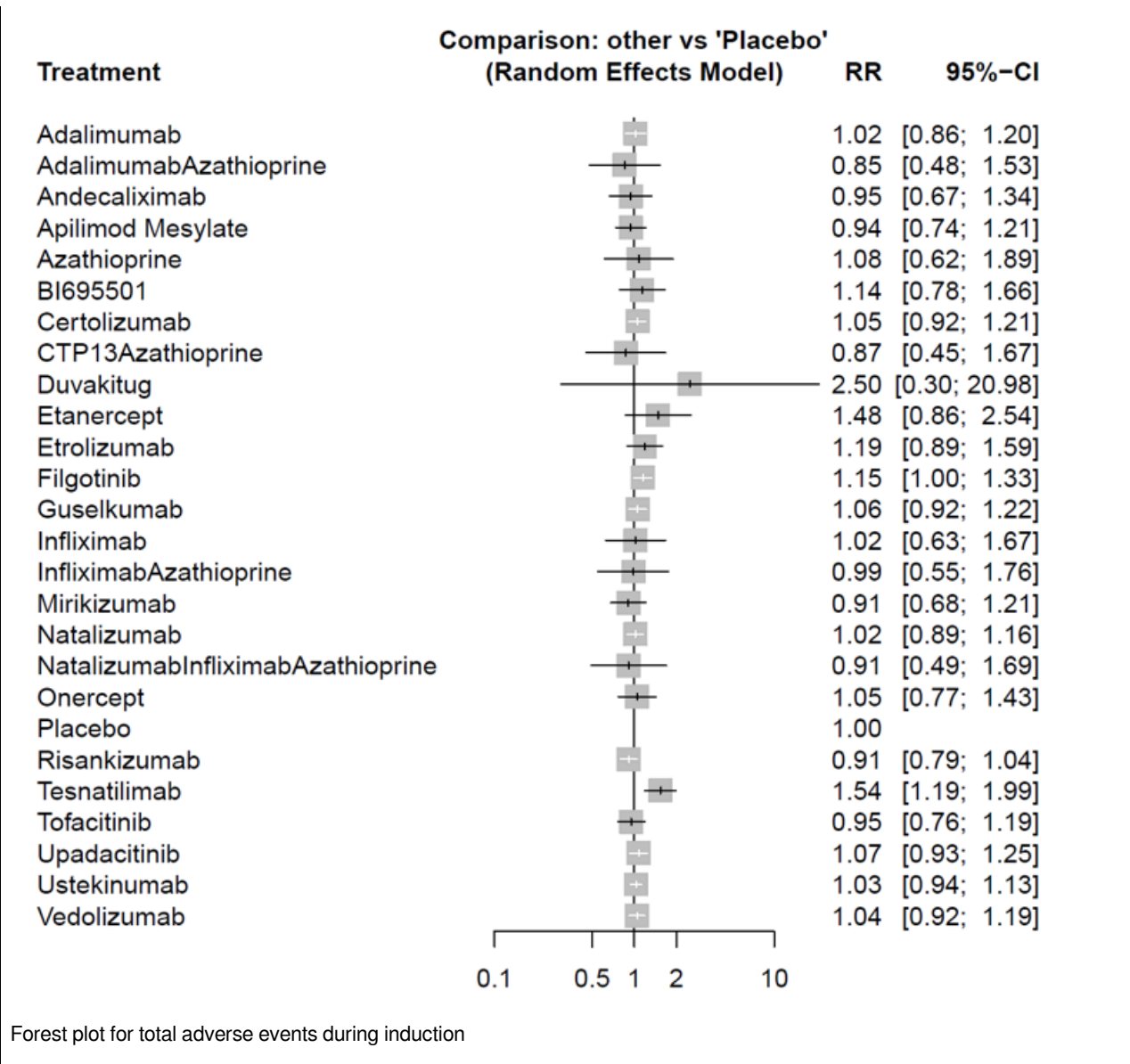


Figure 44

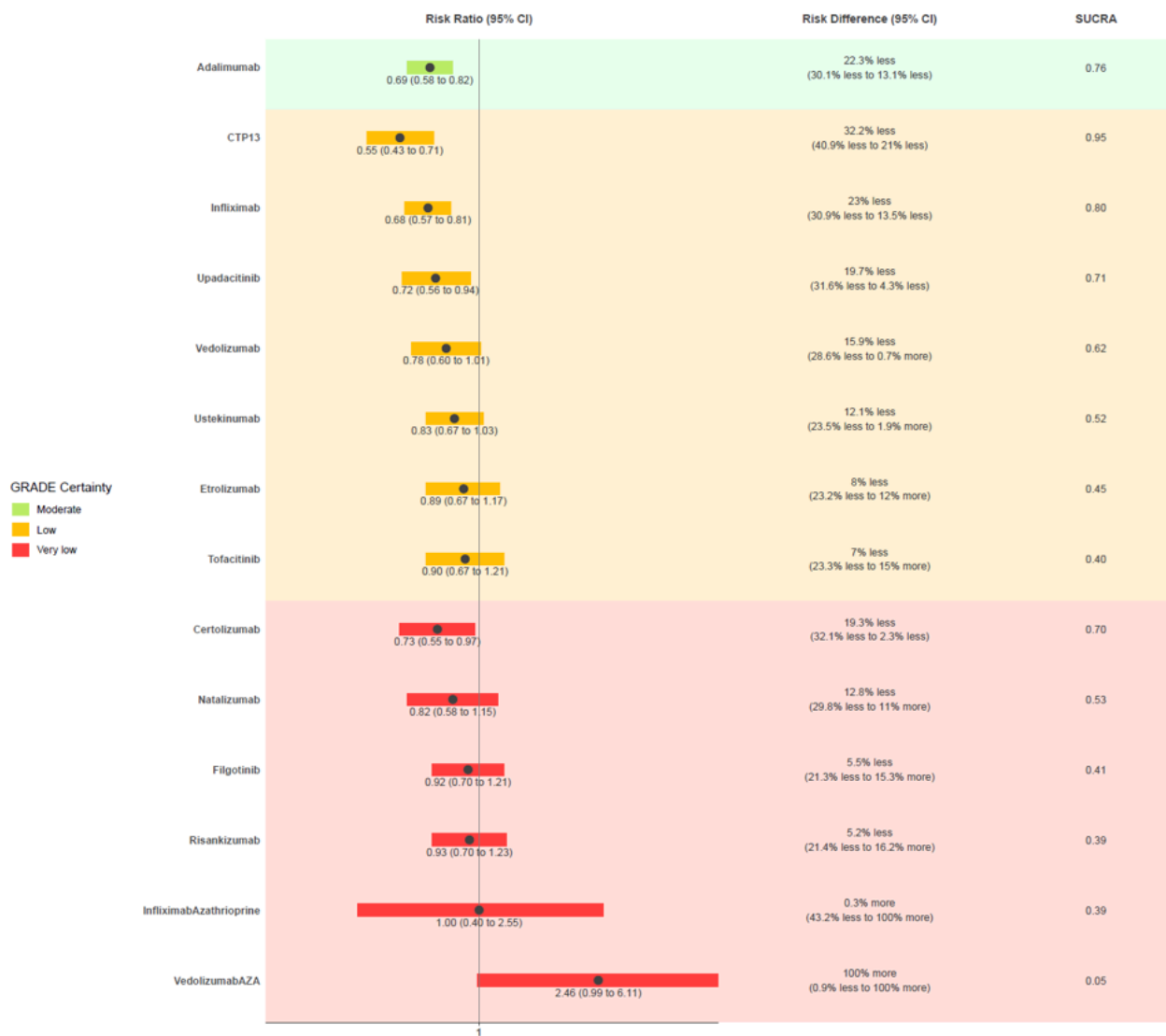
	SUCRA (common)	SUCRA (random)
Risankizumab	0.8240	0.7636
AdalimumabAzathioprine	0.6608	0.7520
Mirikizumab	0.7744	0.7332
Tofacitinib	0.7128	0.6844
NatalizumabInfliximabAzathioprine	0.6264	0.6576
Andecaliximab	0.6648	0.6536
Apilimod Mesylate	0.7128	0.6484
CTP13Azathioprine	0.6876	0.6344
Placebo	0.6104	0.5956
Infliximab	0.4852	0.5728
InfliximabAzathioprine	0.4692	0.5524
Natalizumab	0.5160	0.5496
Ustekinumab	0.5484	0.5328
Adalimumab	0.6060	0.5248
Onercept	0.4896	0.4836
Vedolizumab	0.5068	0.4820
Guselkumab	0.4840	0.4672
Certolizumab	0.4972	0.4560
Upadacitinib	0.4676	0.4308
Azathioprine	0.3068	0.4304
BI695501	0.4188	0.3900
Filgotinib	0.2272	0.3152
Etrolizumab	0.2668	0.2876
Duvakitug	0.1948	0.1836
Etanercept	0.1772	0.1464
Tesnatilimab	0.0644	0.0720

- based on 100 simulations

SUCRA rankings for total adverse events during induction

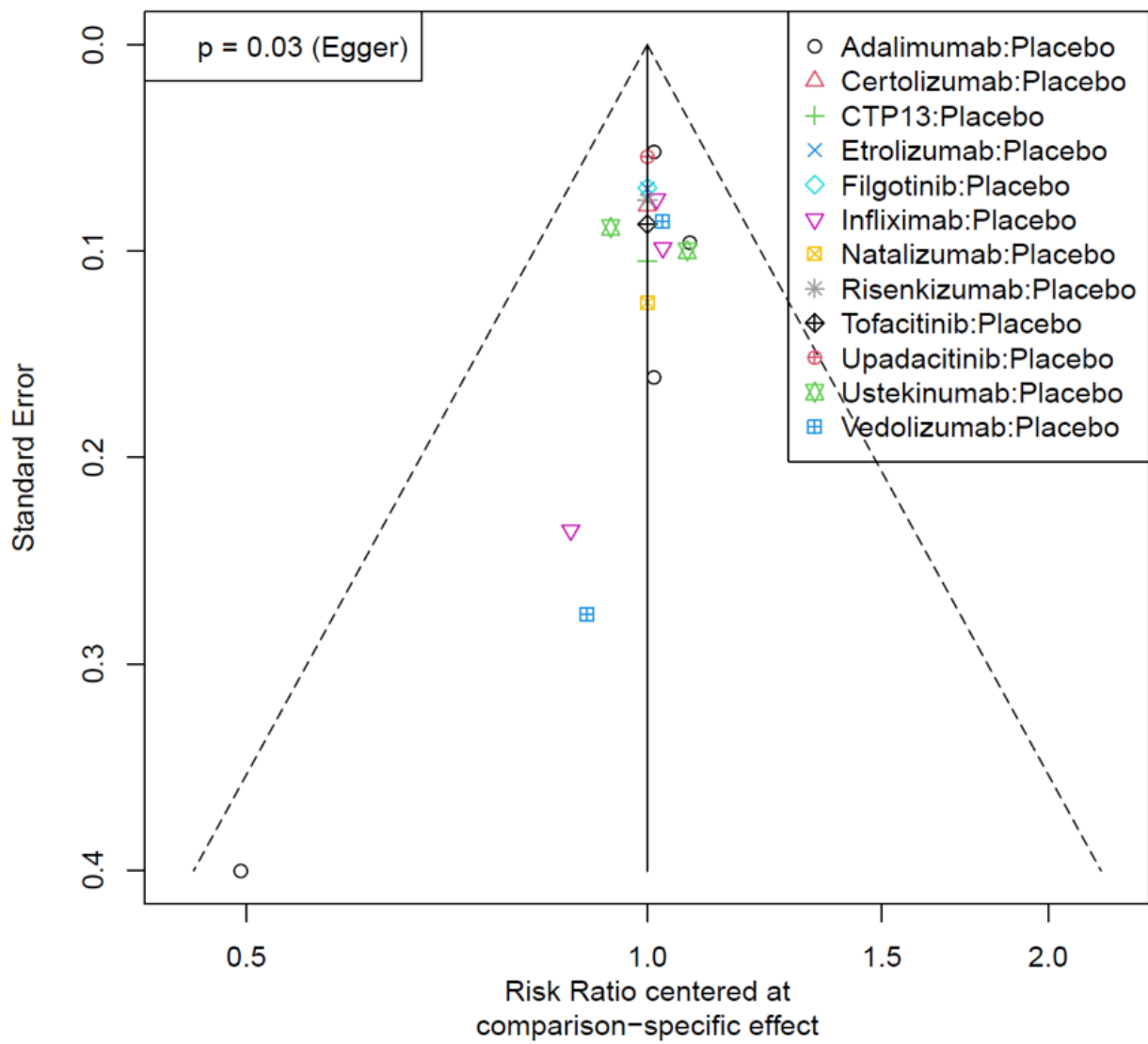
Figure 45

Clinical relapse: Treatment vs. Placebo (Random effects model)



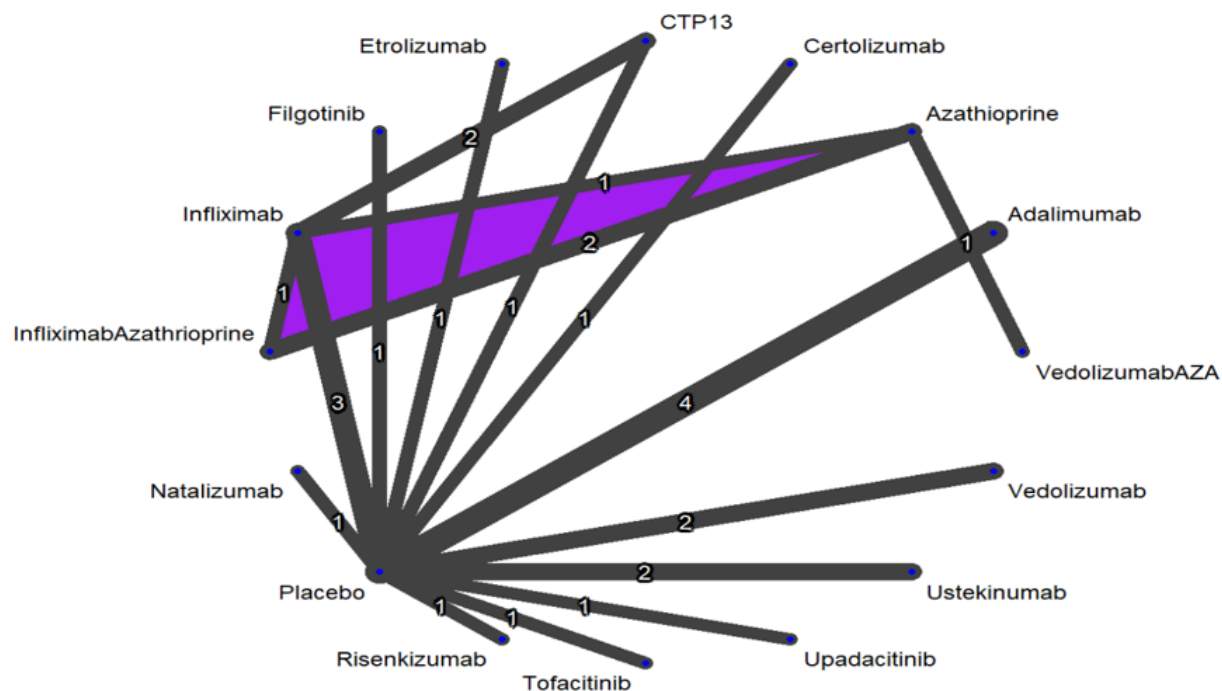
Gordon plot for clinical relapse for biologics for maintenance of remission in Crohn's Disease, with placebo as reference treatment.

Figure 46



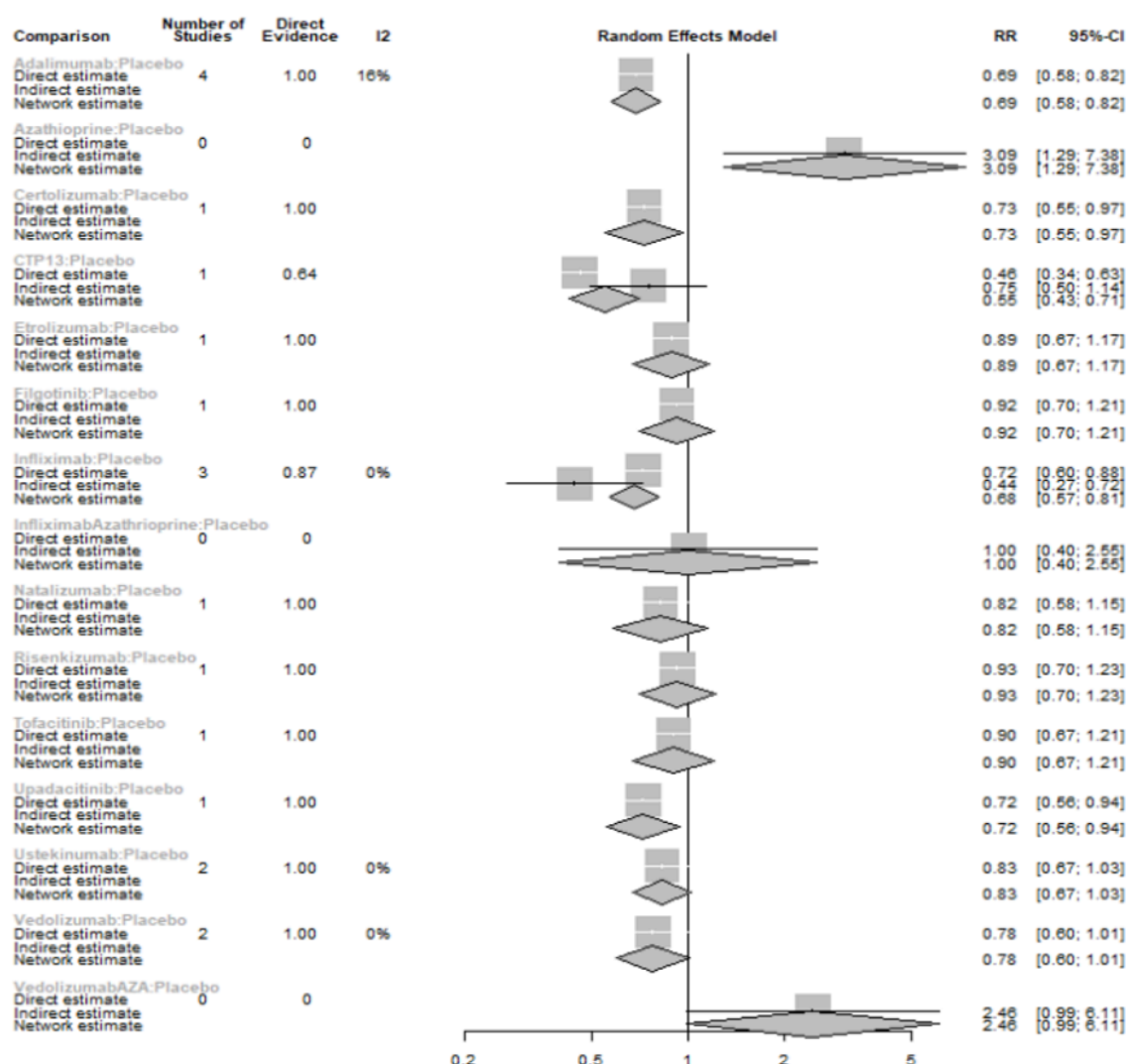
Comparison-adjusted funnel plot for clinical relapses during maintenance of clinical remission

Figure 47



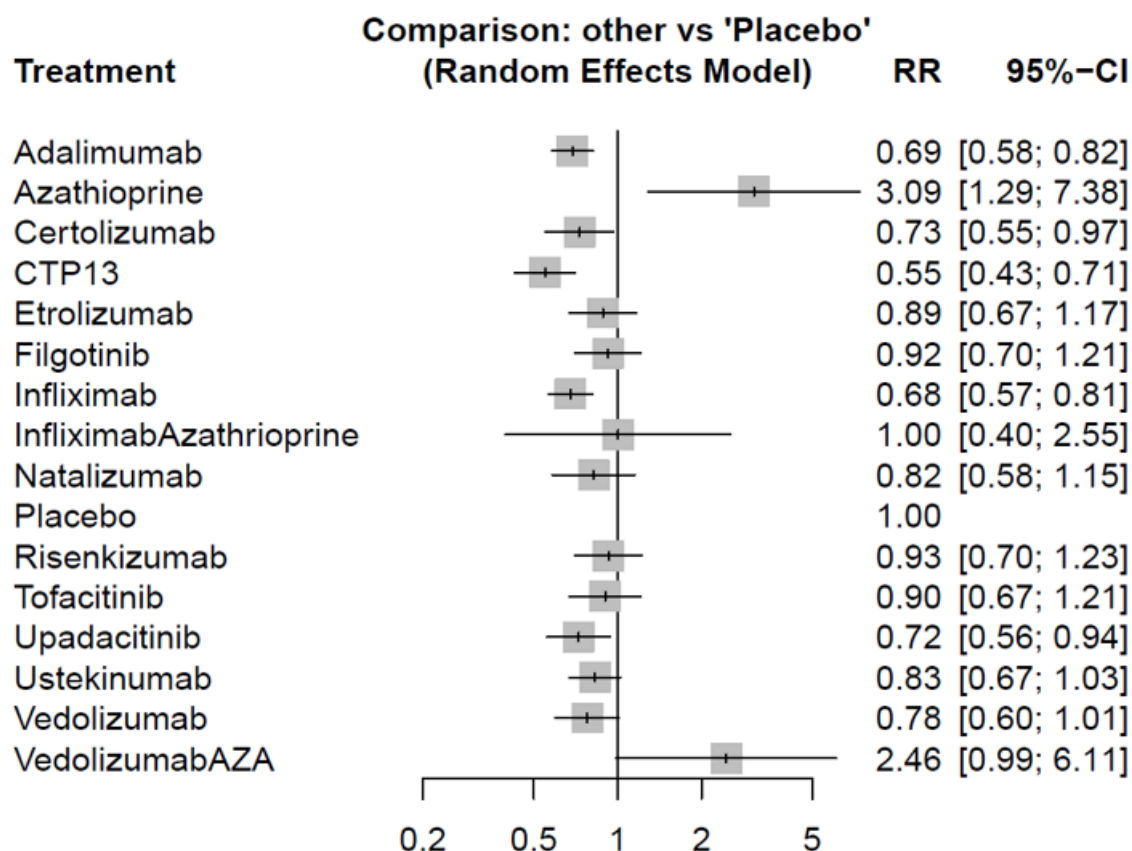
Network plot for maintenance of clinical remission (shaded regions denote denotes multi-arm studies)

Figure 48



Direct, indirect and network estimates, number of direct studies vs placebo, contribution of direct evidence to the network estimate, and I² for pairwise comparisons for maintenance of clinical remission.

Figure 49



Forest plot for clinical relapse during maintenance of clinical remission

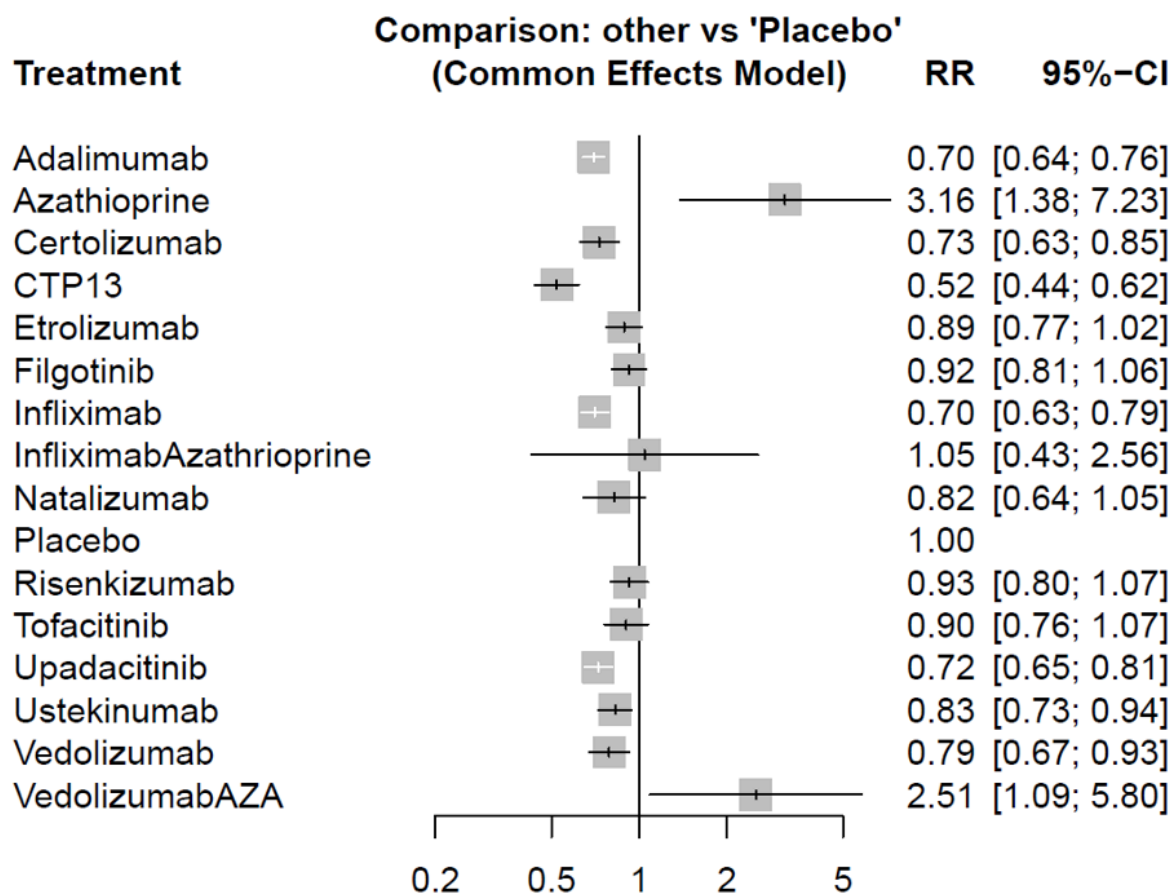
Figure 50

	SUCRA (common)	SUCRA (random)
CTP13	0.9960	0.9600
Infliximab	0.7907	0.8020
Adalimumab	0.8100	0.7820
Certolizumab	0.7580	0.7193
Upadacitinib	0.7553	0.6687
Vedolizumab	0.6040	0.6107
Natalizumab	0.5253	0.5680
Ustekinumab	0.5140	0.5000
Etrolizumab	0.4507	0.4540
Tofacitinib	0.4207	0.4433
Risenkizumab	0.3673	0.3893
Filgotinib	0.3793	0.3813
InfliximabAzathioprine	0.3160	0.3713
Placebo	0.2407	0.2780
VedolizumabAZA	0.0480	0.0493
Azathioprine	0.0240	0.0227

- based on 100 simulations

SUCRA rankings for maintenance of clinical remission

Figure 51



Common (fixed) effects sensitivity analysis for maintenance of clinical remission

Figure 52

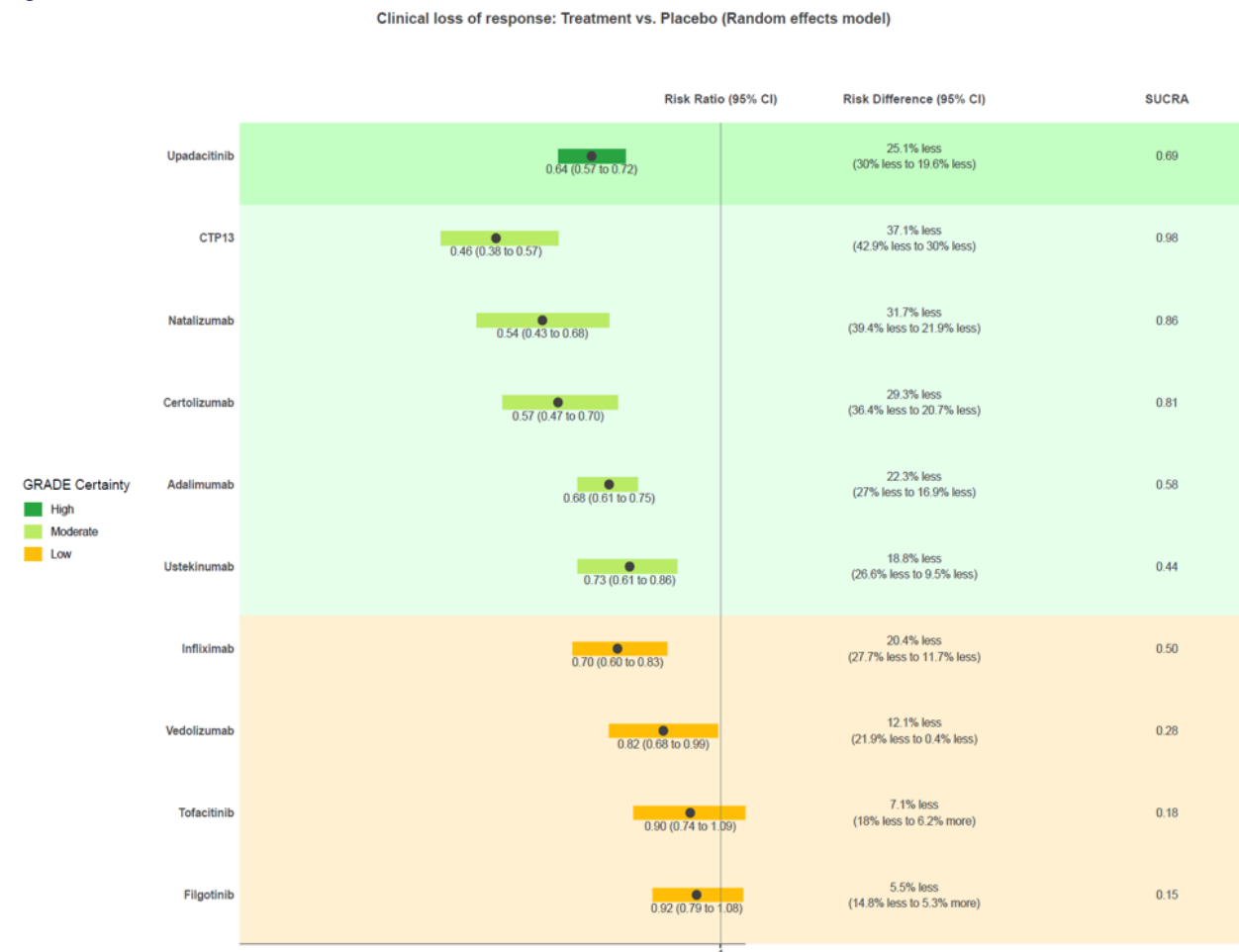
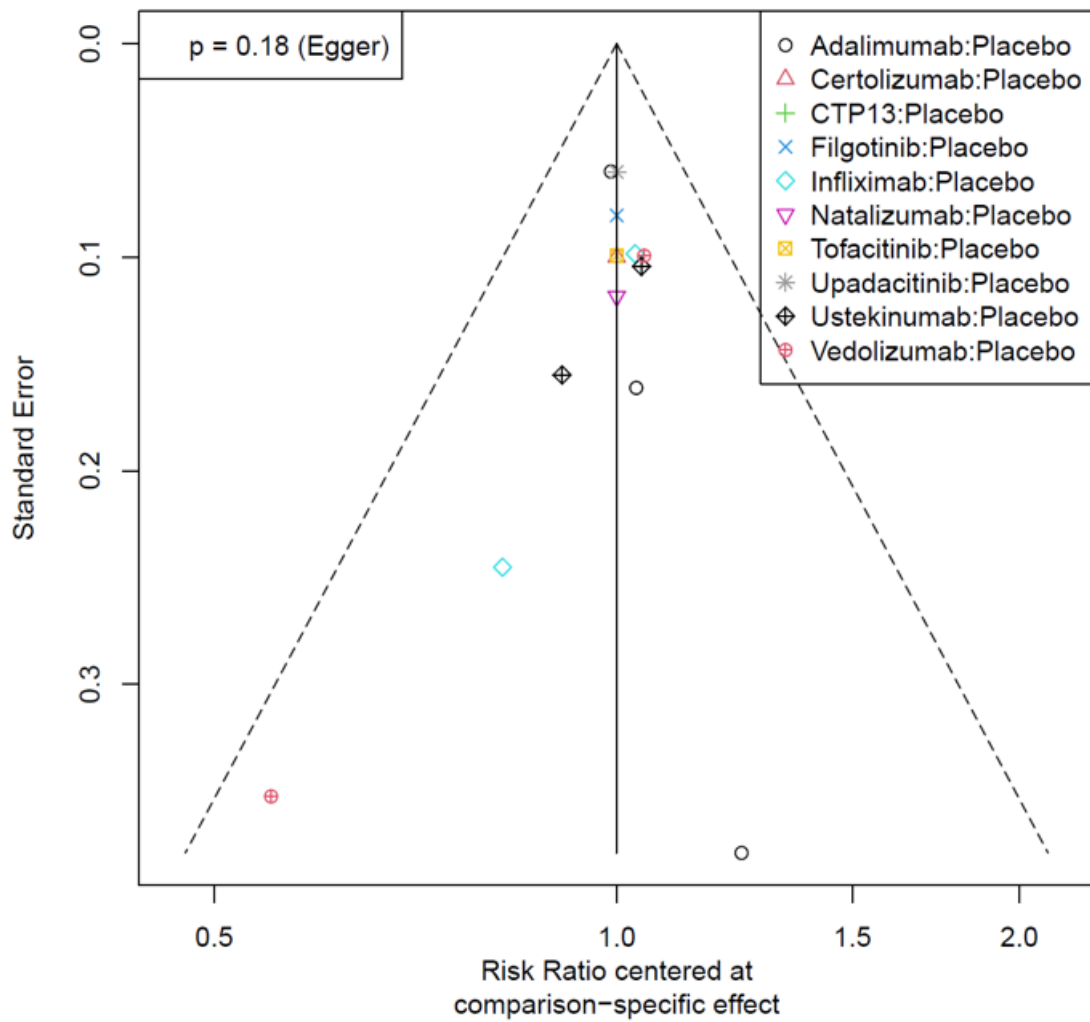
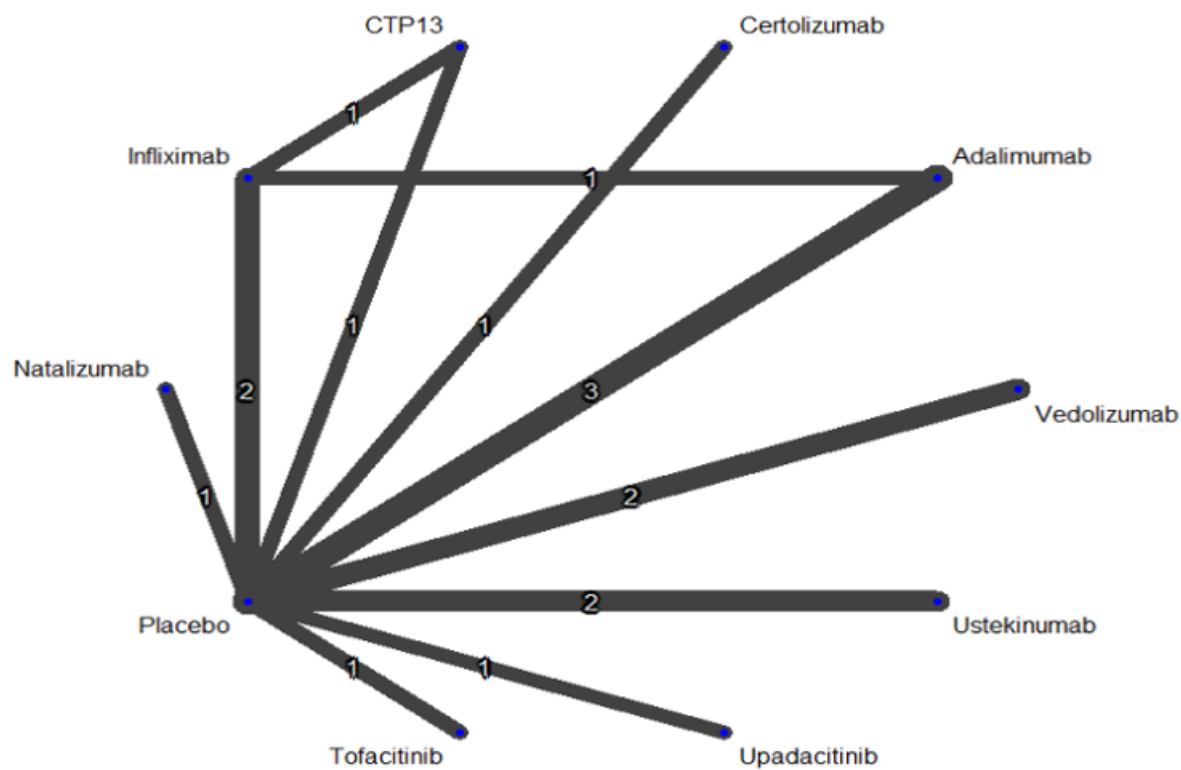


Figure 53



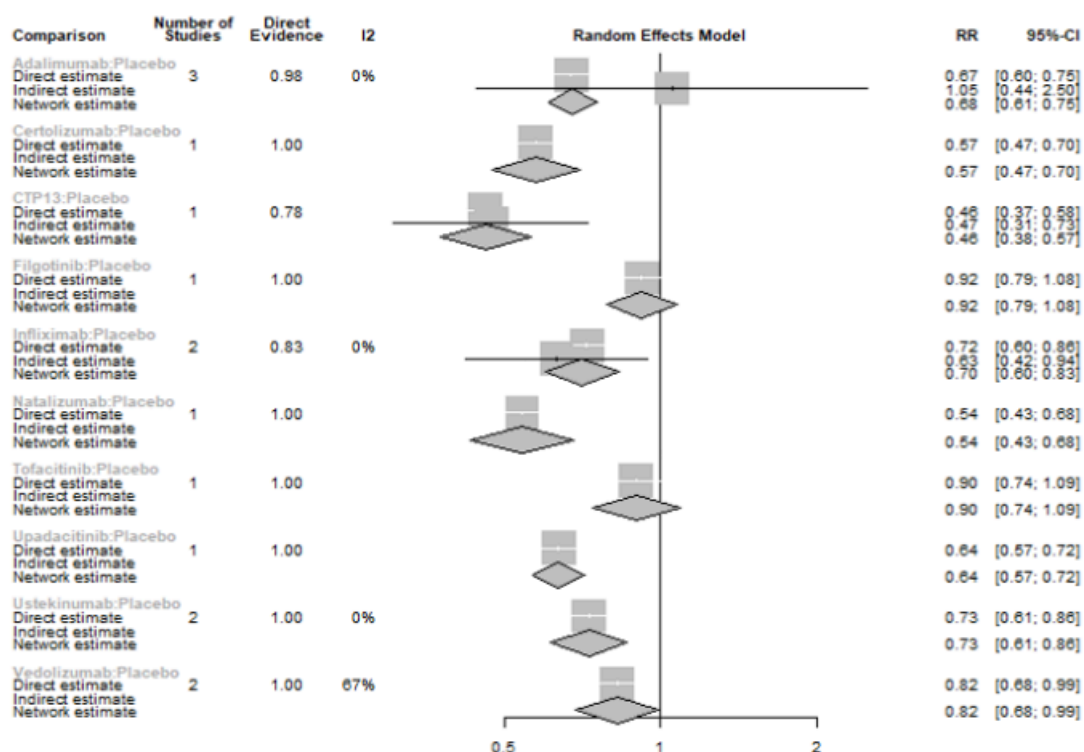
Comparison-adjusted funnel plot for loss of clinical response during maintenance

Figure 54



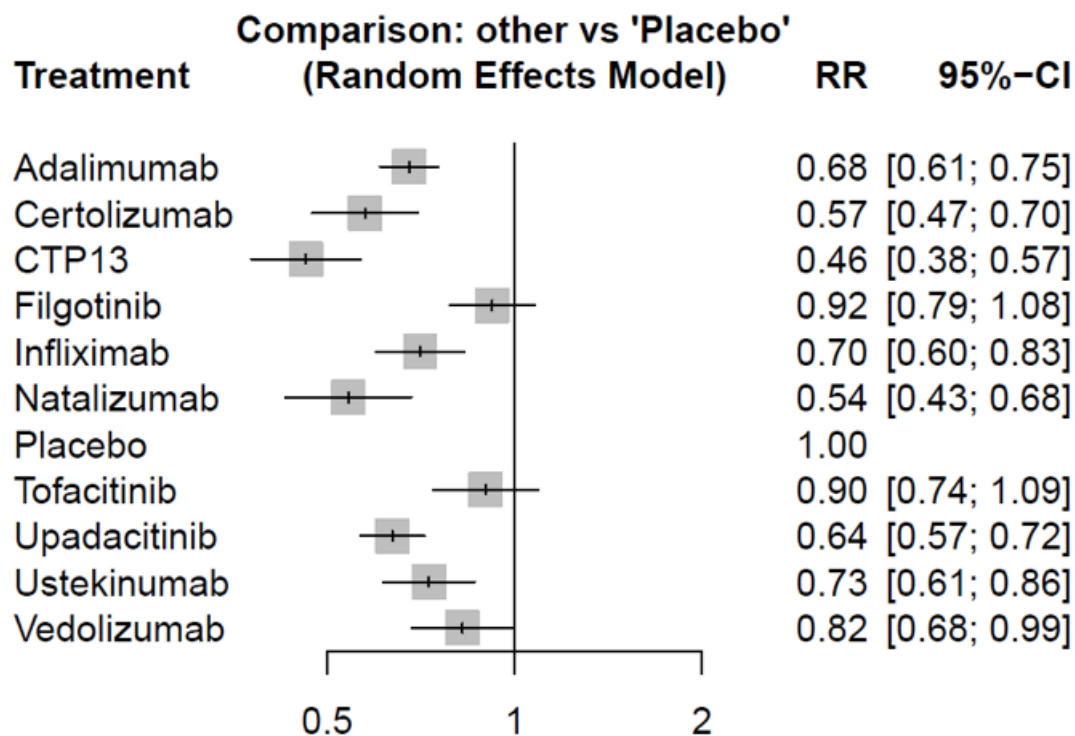
Network plot for maintenance of clinical response

Figure 55



Direct, indirect and network estimates, number of direct studies vs placebo, contribution of direct evidence to the network estimate, and I² for pairwise comparisons for maintenance of clinical response.

Figure 56



Forest plot for loss of clinical response during maintenance

Figure 57

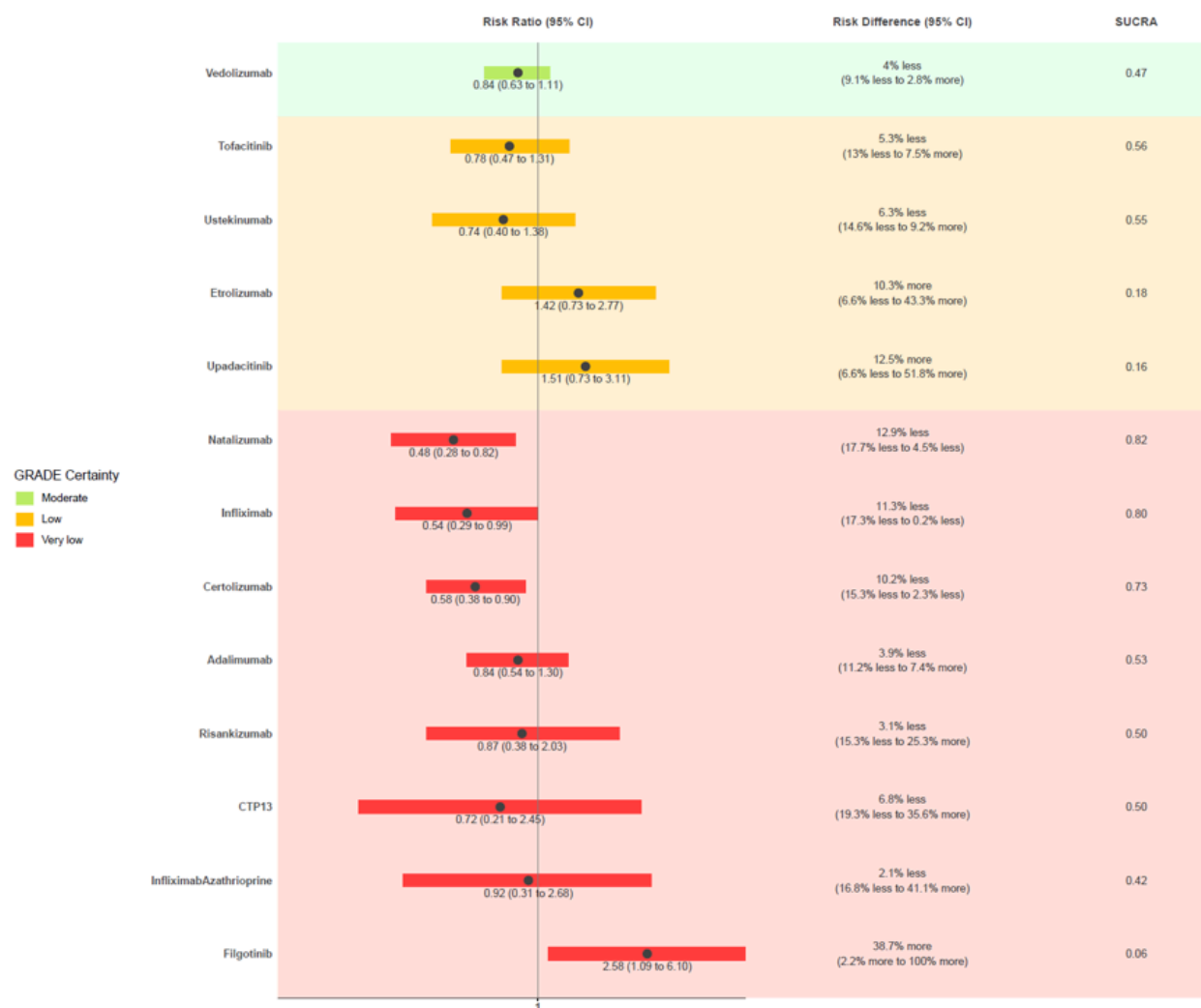
	SUCRA (common)	SUCRA (random)
CTP13	0.981	0.972
Natalizumab	0.860	0.867
Certolizumab	0.793	0.809
Upadacitinib	0.666	0.664
Adalimumab	0.582	0.562
Infliximab	0.503	0.535
Ustekinumab	0.477	0.457
Vedolizumab	0.280	0.286
Tofacitinib	0.185	0.182
Filgotinib	0.138	0.138
Placebo	0.035	0.028

- based on 100 simulations

SUCRA rankings for maintenance of clinical response

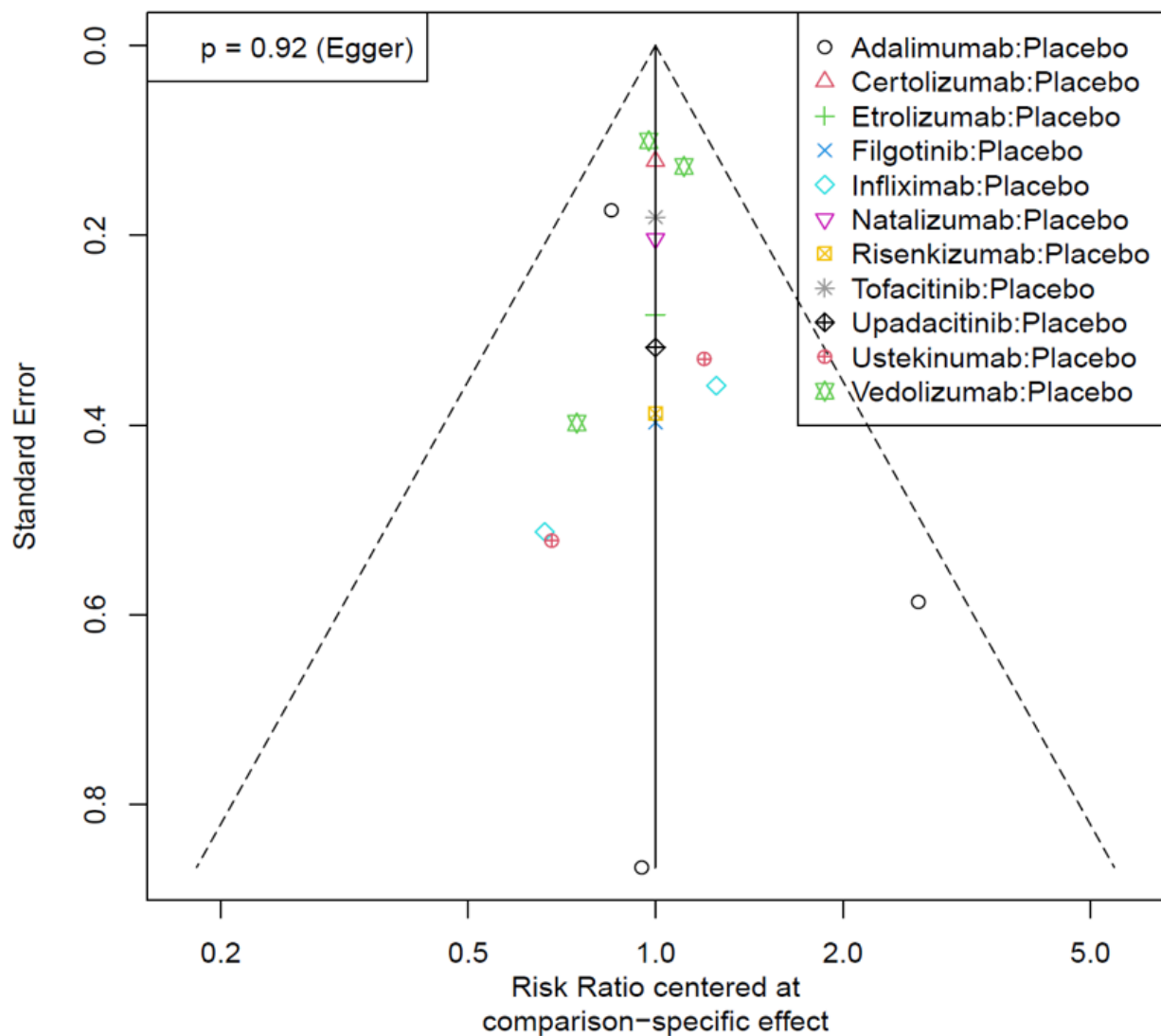
Figure 58

Withdrawals due to adverse events: Treatment vs. Placebo (Random effects model)



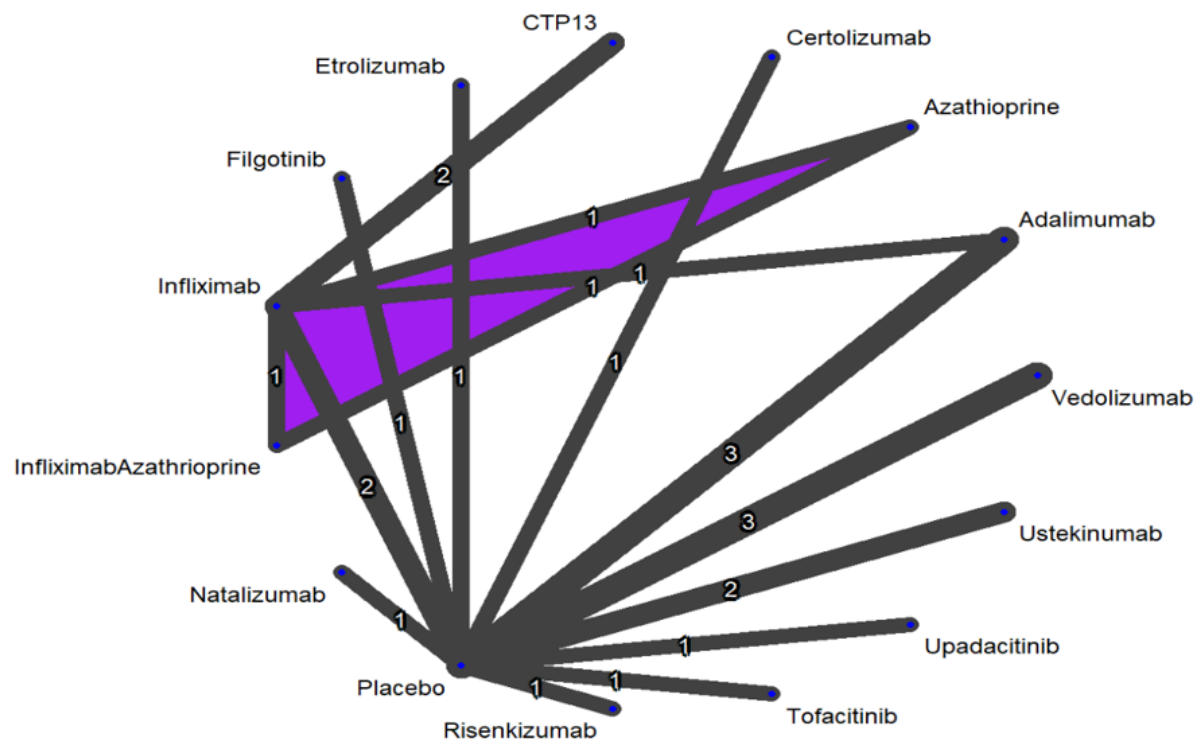
Gordon plot for withdrawals due to adverse events for biologics for maintenance of remission in Crohn's Disease, with placebo as reference treatment.

Figure 59



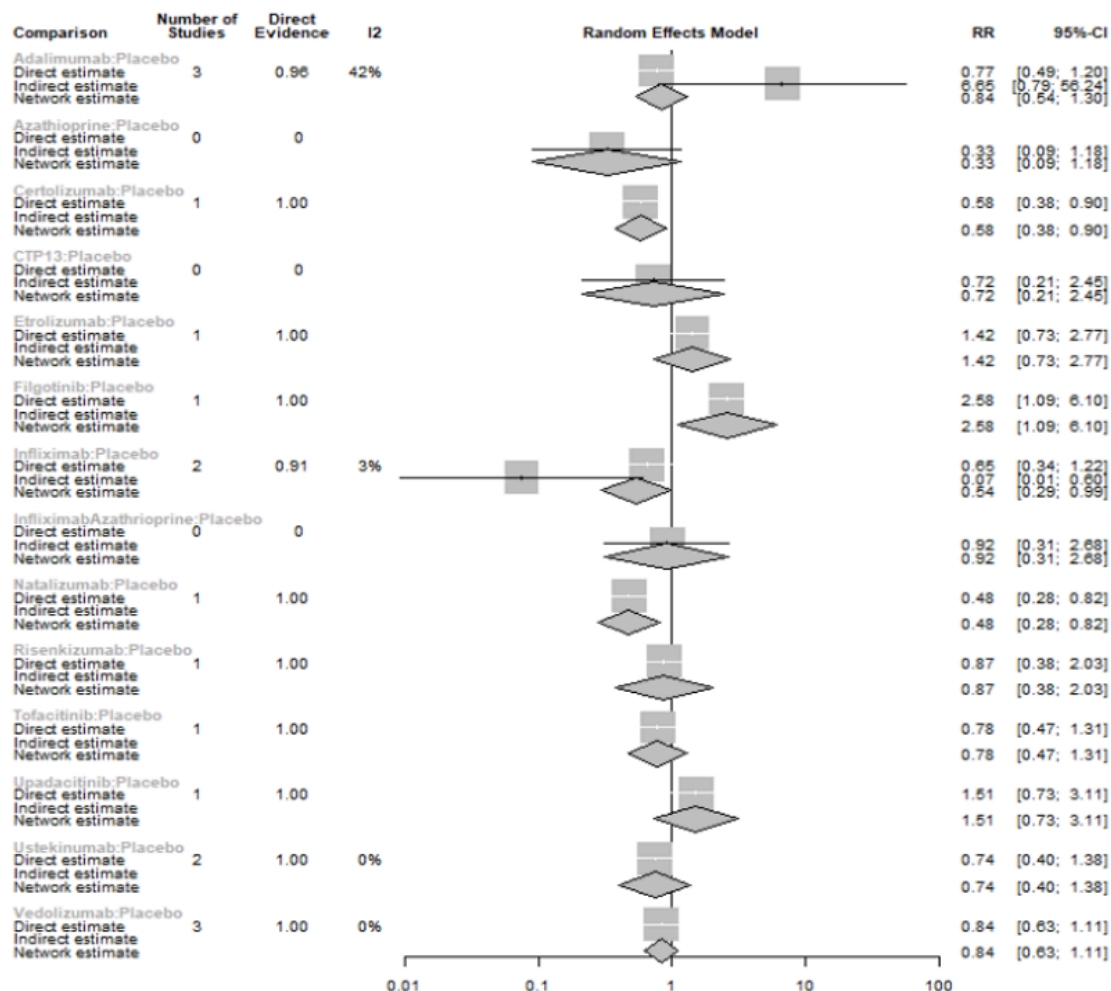
Comparison-adjusted funnel plot for withdrawals due to adverse events during maintenance

Figure 60



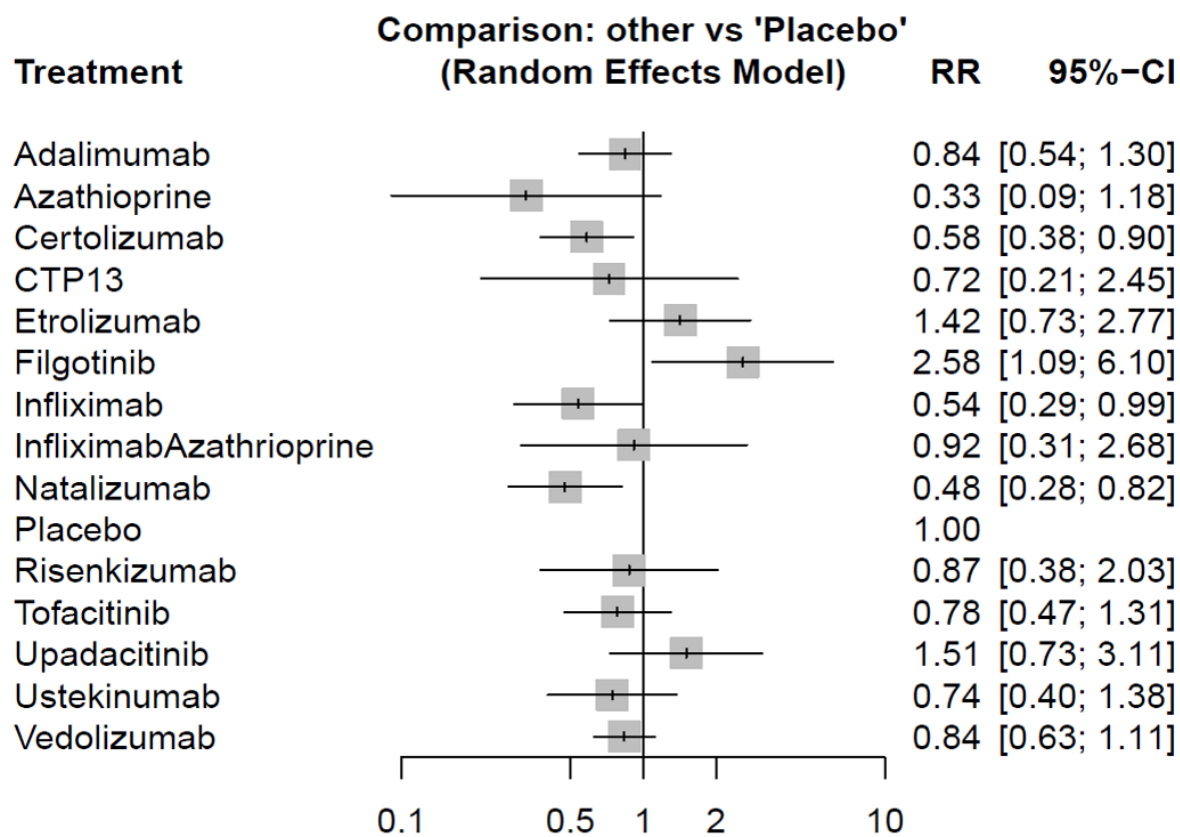
Network plot for withdrawals due to adverse events during maintenance (shaded region denotes multi-arm studies)

Figure 61



Direct, indirect and network estimates, number of direct studies vs placebo, contribution of direct evidence to the network estimate, and I² for pairwise comparisons for withdrawals due to adverse events during maintenance

Figure 62



Forest plot for withdrawals due to adverse events during maintenance

Figure 63

	SUCRA (common)	SUCRA (random)
Azathioprine	0.9064	0.8707
Natalizumab	0.8586	0.8507
Infliximab	0.7850	0.7671
Certolizumab	0.7643	0.7329
CTP13	0.5607	0.5964
Ustekinumab	0.5621	0.5600
Tofacitinib	0.5057	0.5500
Adalimumab	0.5479	0.4829
Vedolizumab	0.4671	0.4743
InfliximabAzathrioprine	0.4336	0.4650
Risenkizumab	0.4536	0.4650
Placebo	0.3079	0.3314
Etrolizumab	0.1821	0.1657
Upadacitinib	0.1336	0.1579
Filgotinib	0.0314	0.0300

- based on 100 simulations

SUCRA rankings for withdrawals due to adverse events during maintenance

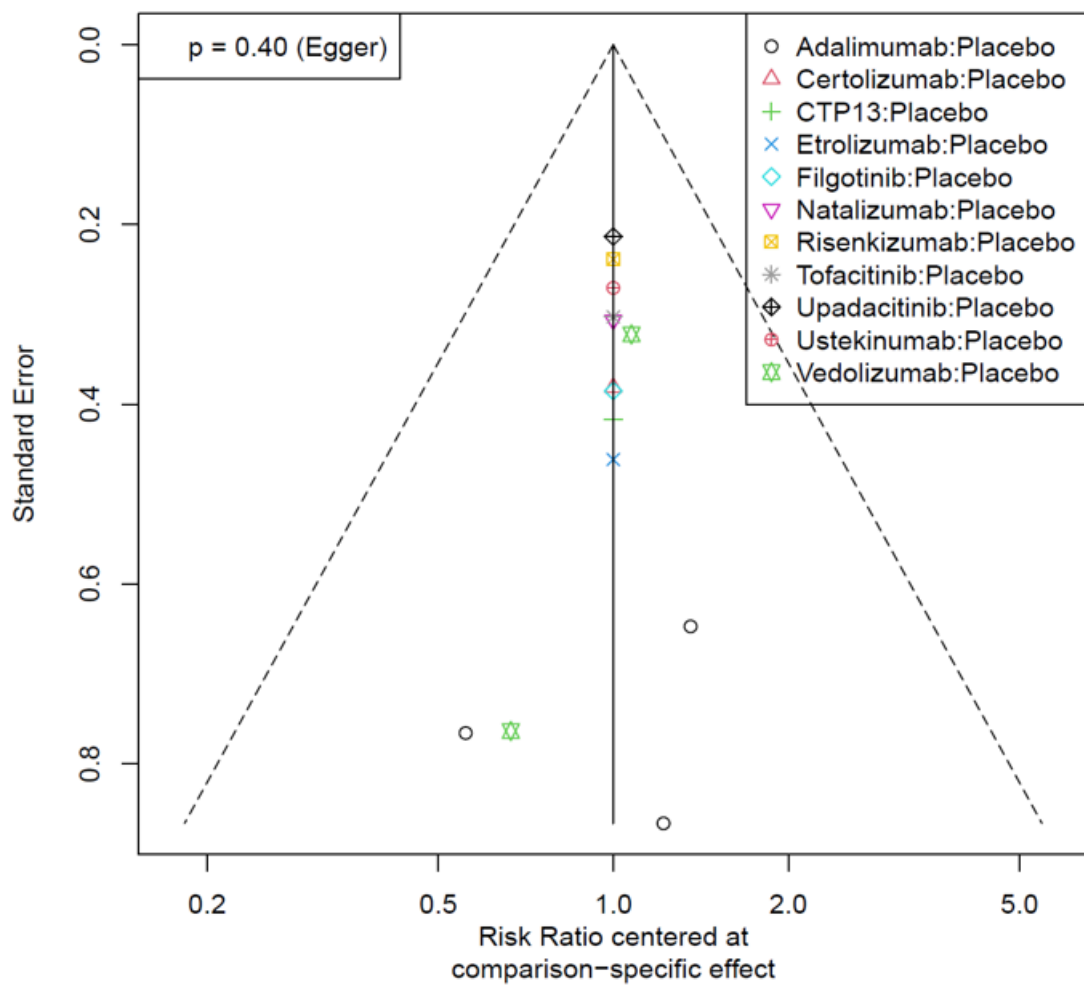
Figure 64

Serious adverse events: Treatment vs. Placebo (Random effects model)



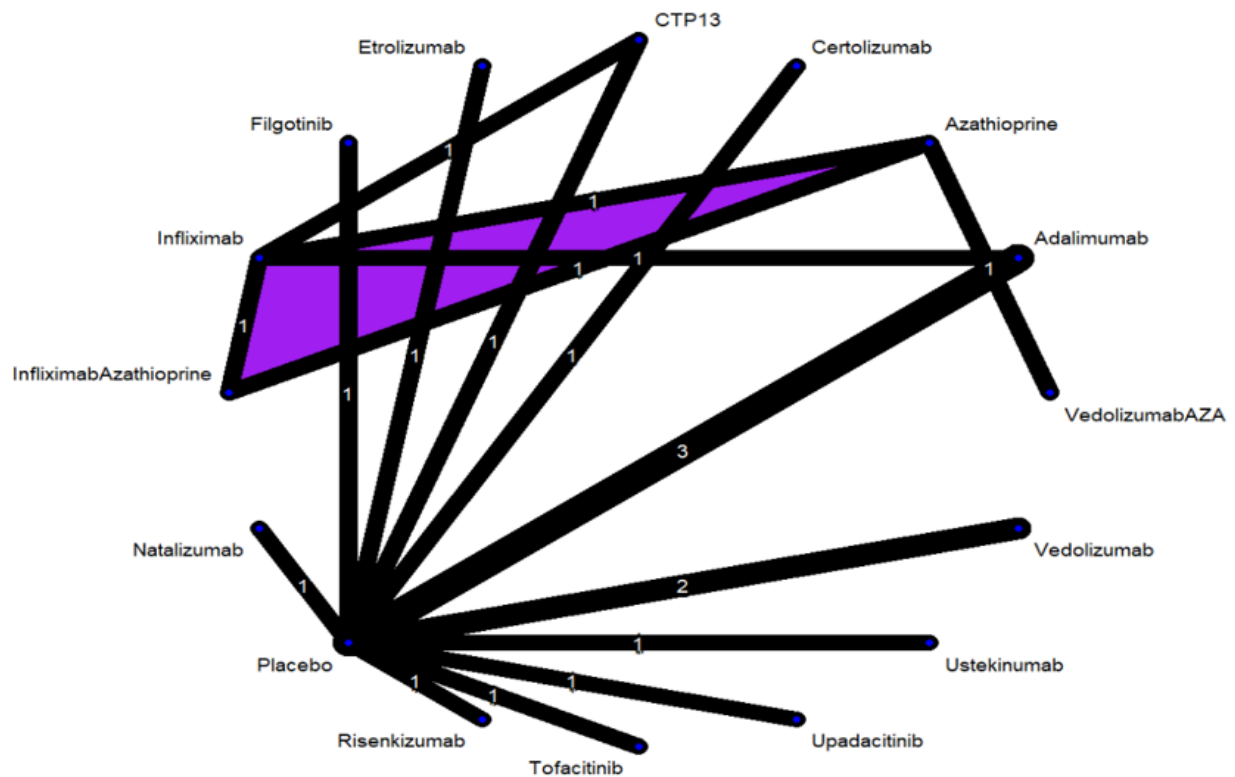
Gordon plot for serious adverse events for biologics for maintenance of remission in Crohn's Disease, with placebo as reference treatment.

Figure 65



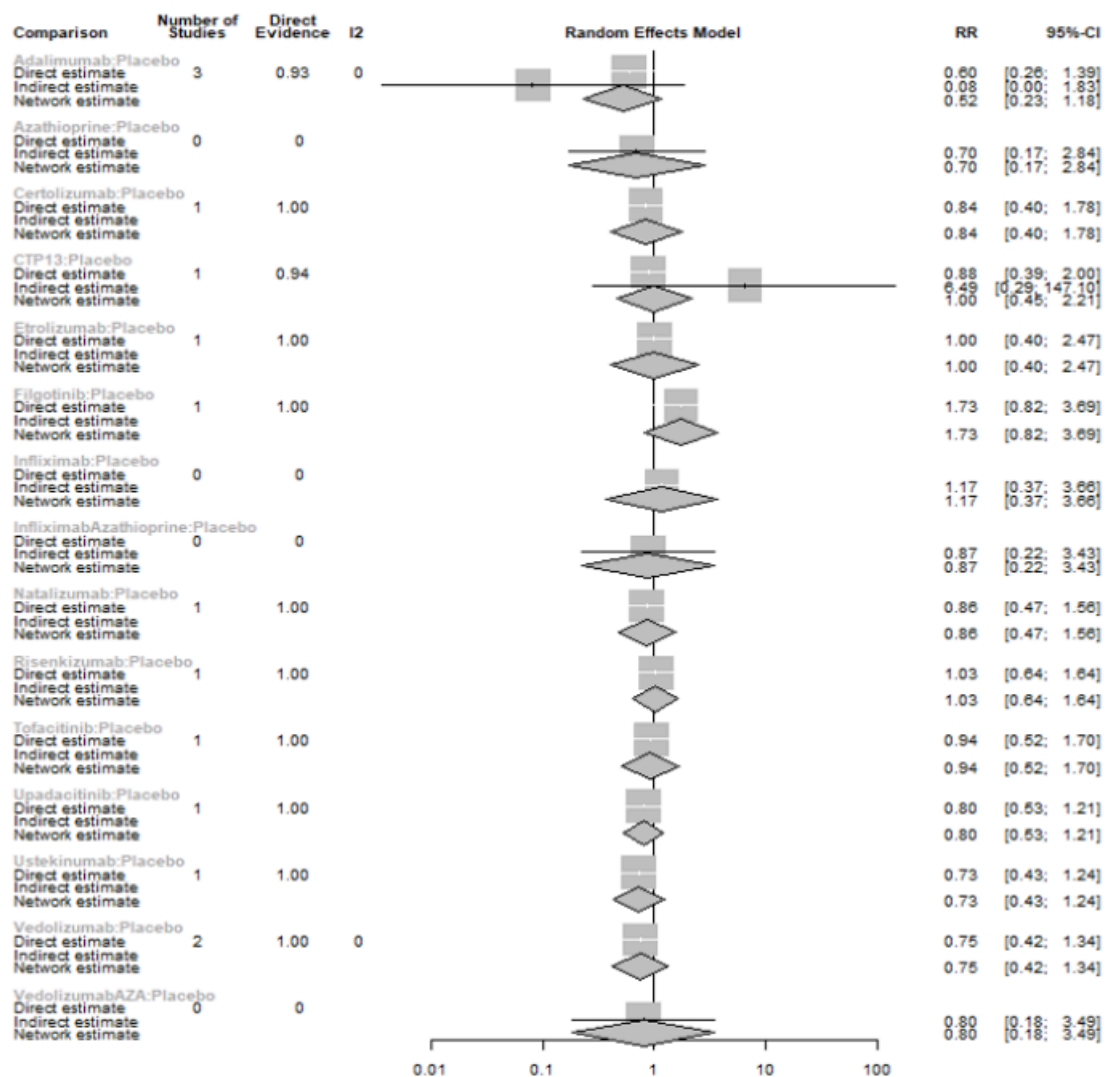
Comparison-adjusted funnel plot for serious adverse events during maintenance

Figure 66



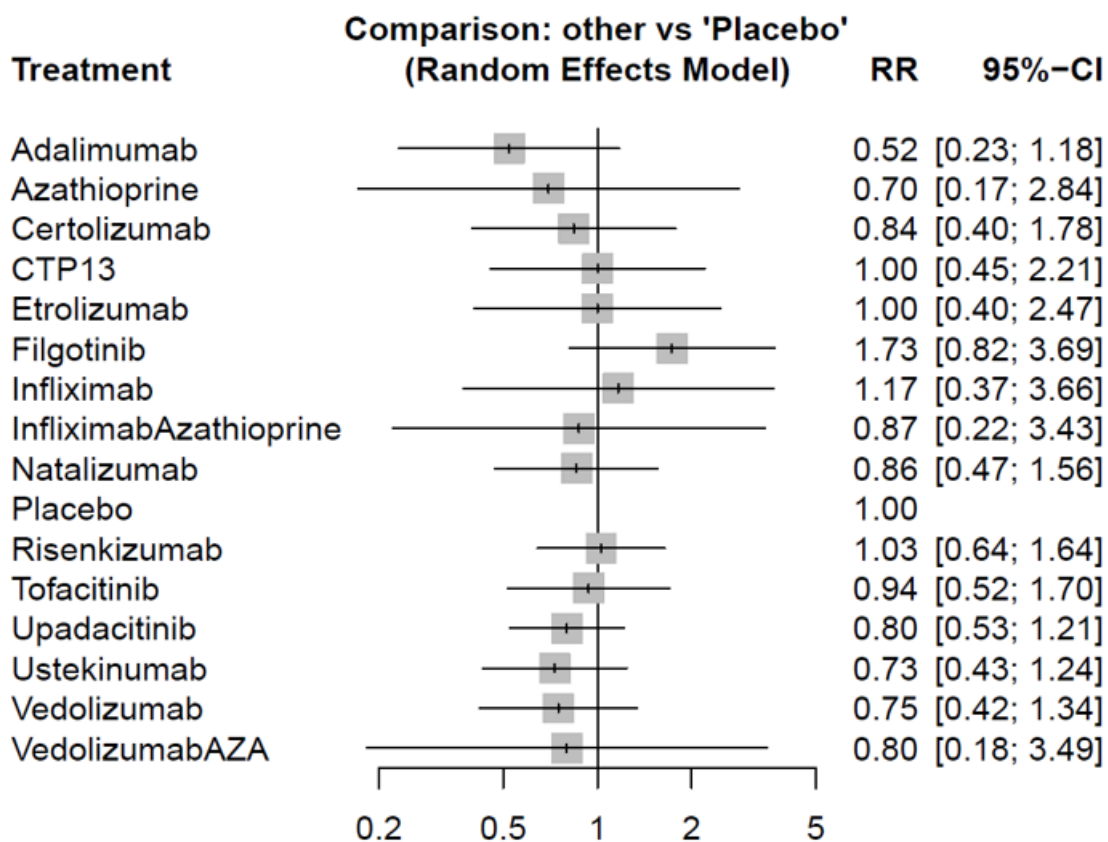
Network plot for serious adverse events during maintenance (shaded region denotes multi-arm studies)

Figure 67



Direct, indirect and network estimates, number of direct studies vs placebo, contribution of direct evidence to the network estimate, and I² for pairwise comparisons for serious adverse events during maintenance

Figure 68



Forest plot for serious adverse events during maintenance

Figure 69

	SUCRA (common)	SUCRA (random)
Adalimumab	0.8380	0.8320
Ustekinumab	0.6487	0.6553
Vedolizumab	0.6460	0.6227
Upadacitinib	0.6047	0.6087
Azathioprine	0.6020	0.6007
InfliximabAzathioprine	0.5567	0.5633
VedolizumabAZA	0.5180	0.5373
Certolizumab	0.5253	0.5187
Natalizumab	0.4933	0.4893
Tofacitinib	0.4667	0.4673
Etrolizumab	0.4367	0.4500
CTP13	0.4053	0.4087
Placebo	0.3793	0.3800
Risenkizumab	0.4247	0.3713
Infliximab	0.3347	0.3327
Filgotinib	0.1200	0.1620

SUCRA rankings for serious adverse events during maintenance

Figure 70

Total adverse events: Treatment vs. Placebo (Random effects model)



Gordon plot for total adverse events for biologics for maintenance of remission in Crohn's Disease, with placebo as reference treatment.

Figure 71

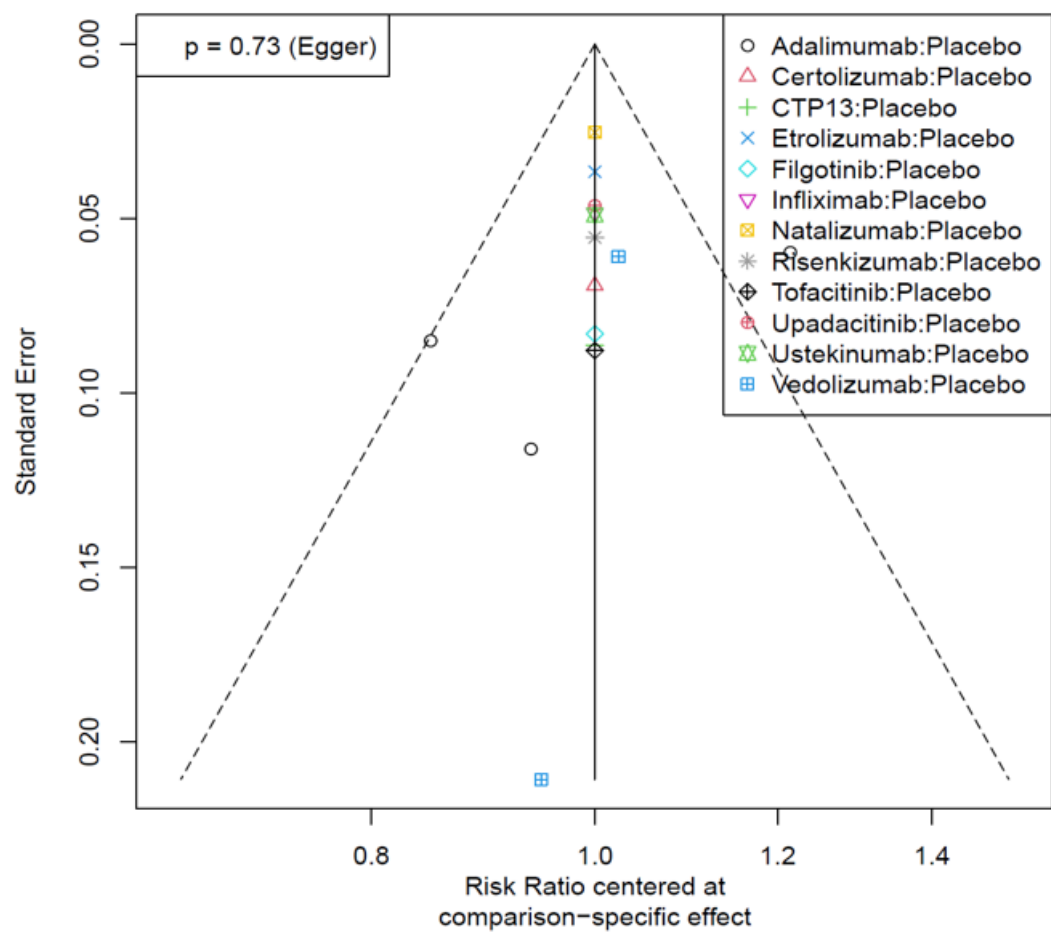


Figure 72

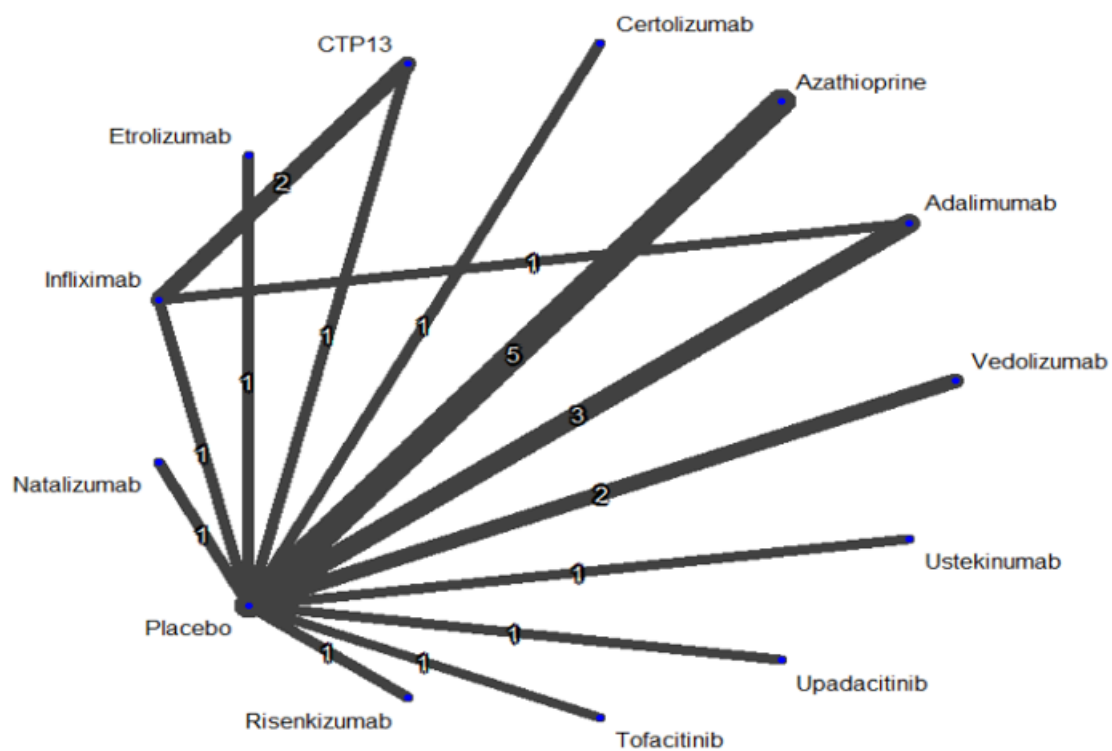
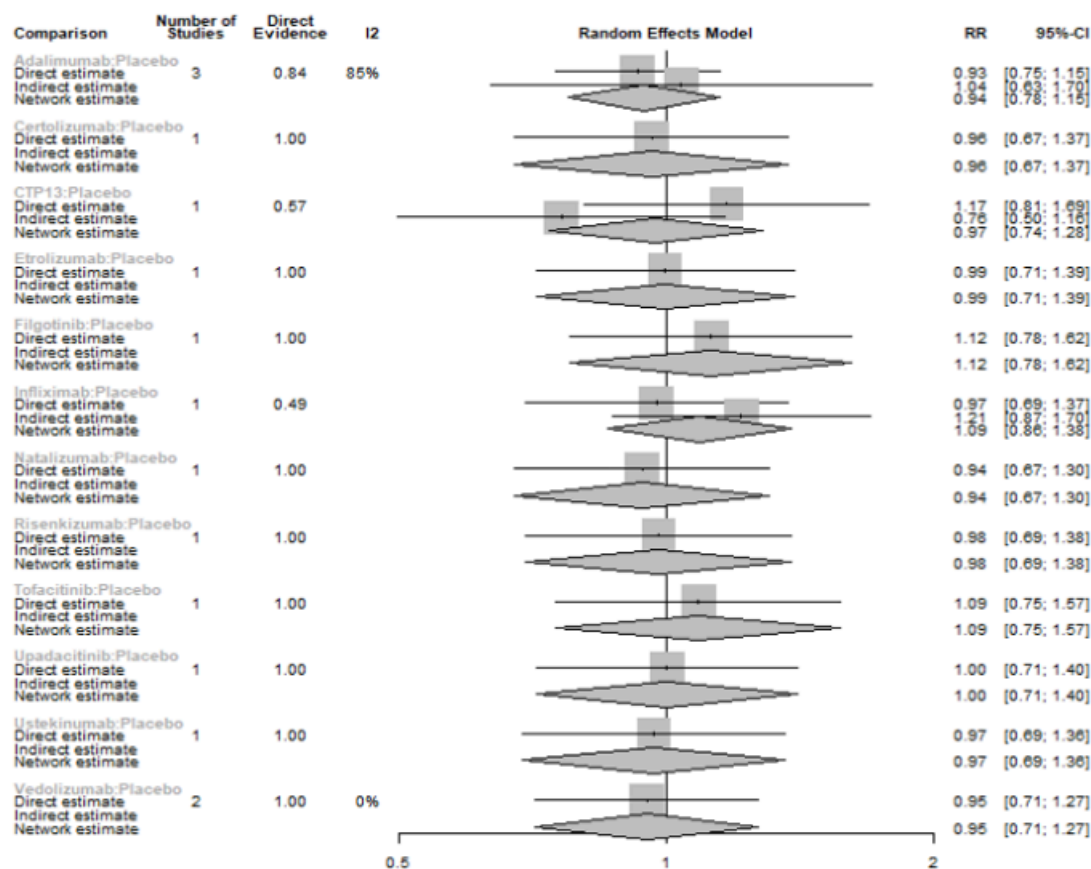
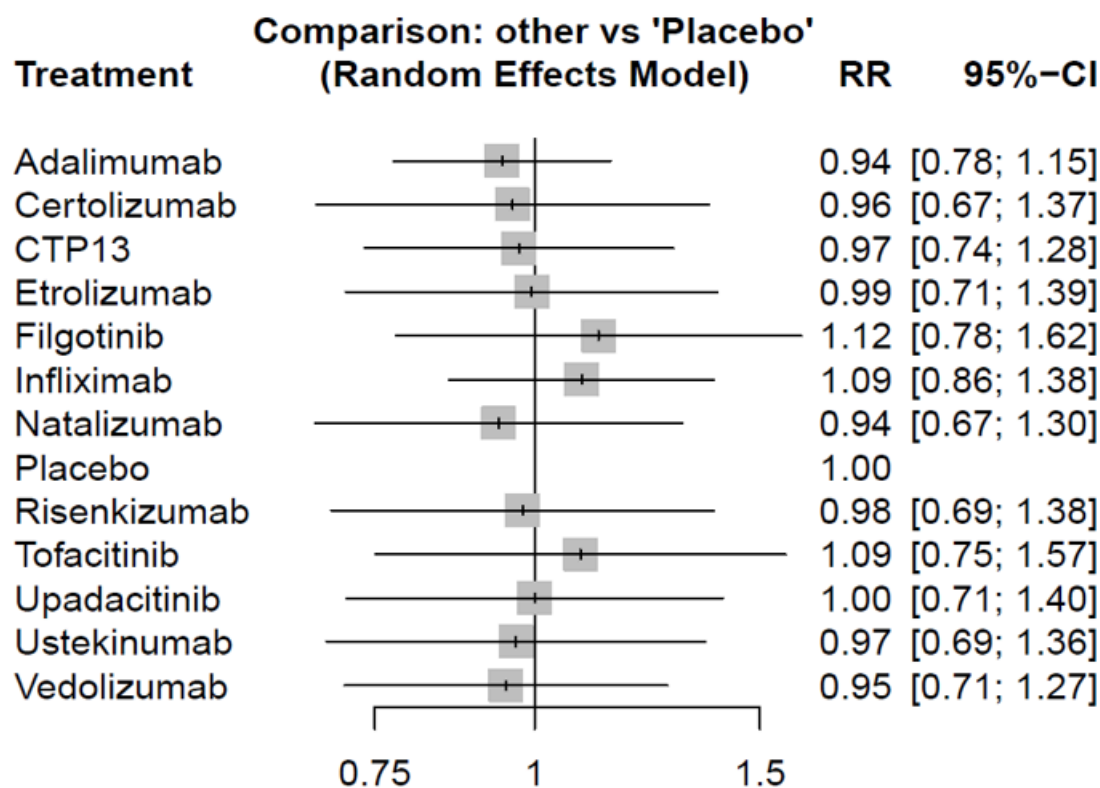


Figure 73



Direct, indirect and network estimates, number of direct studies vs placebo, contribution of direct evidence to the network estimate, and I² for pairwise comparisons for total adverse events during maintenance

Figure 74



Forest plot for total adverse events during maintenance

Figure 75

	SUCRA (common)	SUCRA (random)
Adalimumab	0.6000	0.6617
Natalizumab	0.8492	0.6342
Certolizumab	0.6683	0.5875
CTP13	0.4108	0.5642
Vedolizumab	0.6250	0.5450
Ustekinumab	0.6083	0.5192
Placebo	0.4458	0.5133
Risenkizumab	0.6125	0.5092
Upadacitinib	0.5683	0.5025
Etrolizumab	0.4808	0.4683
Filgotinib	0.0942	0.3458
Tofacitinib	0.1908	0.3417
Infliximab	0.3458	0.3075

- based on 100 simulations

SUCRA rankings for total adverse events during maintenance