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SYSTEMATIC REVIEWS AND META-ANALYSES

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Comparative Efficacy of Advanced Therapies for Achieving Endoscopic Outcomes in Crohn's Disease: A Systematic Review and Network Meta-Analysis

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BACKGROUND & AIMS: **We conducted a network meta-analysis to compare the efficacy of advanced therapies for achieving endoscopic outcomes in patients with moderate-to-severely active Crohn's disease.**

METHODS: **MEDLINE, Embase, and Cochrane CENTRAL databases were searched from inception to August 2, 2023 to identify phase II and III randomized controlled trials (RCTs) in adults (≥18 years) with moderate-to-severe Crohn's disease treated with tumor necrosis factor (TNF) antagonists, etrolizumab, vedolizumab, anti-interleukin (IL)12/23p40, anti-IL23p19, or Janus kinase-1 (JAK1) inhibitors, compared with placebo/active comparator, for induction and/or maintenance of remission and reported endoscopic outcomes. Primary outcome was endoscopic response after induction therapy, and endoscopic remission after maintenance therapy. We performed a random-effects network meta-analysis using a frequentist approach, and estimated relative risk (RRs), 95% confidence interval (CI) values, and *P* score for ranking agents. We used GRADE to ascertain certainty of evidence.**

RESULTS: **A total of 20 RCTs (19 placebo-controlled and 1 head-to-head trial; 5592 patients) were included out of which 12 RCTs reported endoscopic outcomes for the induction phase, 5 reported for the maintenance phase, and 3 reported for both induction and maintenance phases. JAK1 inhibitors (RR, 3·49 [95% CI, 1·48–8·26]) and anti-IL23p19 (RR, 2·30 [95% CI, 1·02–5·18]) agents were more efficacious than etrolizumab (moderate certainty of evidence), and JAK1 inhibitors (RR, 2·34 [95% CI, 1·14–4·80]) were more efficacious than anti-IL12/23p40 agents for inducing endoscopic response (moderate certainty of evidence). JAK1 inhibitors and anti-IL23p19 ranked highest for induction of endoscopic response. There was paucity of RCTs of TNF antagonists reporting endoscopic outcomes with induction therapy. On network meta-analysis of 6 RCTs, all agents except vedolizumab (RR, 1.89 [95% CI, 0.61–5.92]) were effective in maintaining endoscopic remission compared with placebo. TNF antagonists, IL12/23p40, and JAK1 inhibitors were ranked highest.**

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Abbreviations used in this paper: CD, Crohn's disease; CI, confidence interval; IL, interleukin; JAK1, Janus kinase 1; RCT, randomized controlled trial; RR, relative risk; TNF, tumor necrosis factor.

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CONCLUSIONS: **On network meta-analysis, JAK1 inhibitors and anti-IL23p19 agents may be the most effective among non-TNF-targeting advanced therapies for inducing endoscopic response. Future head-to-head trials will further inform positioning of different therapies for the management of Crohn's disease.**

Keywords: Mucosal Healing; Infliximab; Ustekinumab; Positioning.

Crohn's disease (CD) is a chronic inflammatory bowel disease that occurs in genetically susceptible individuals in response to unknown environmental triggers, which can result in lifelong gastrointestinal complications with a high burden to patients and health care systems.[1] The therapeutic targets of management of CD have evolved from focusing only on symptom control to treating to clinical remission, and the resolution of intestinal ulcers.[2] Regulatory authorities, such as the Food and Drug Administration, recommend a coprimary end point of clinical and endoscopic remission for efficacy assessment in clinical trials of CD.[3] However, there is a poor correlation between clinical symptoms and endoscopic disease activity in patients with CD. For example, post hoc analysis of the SONIC trial suggested that approximately half of patients with CD in clinical remission have persistent intestinal ulcers.[4] Achievement of endoscopic remission is associated with superior long-term outcomes including sustained clinical remission, low risk of surgery and hospitalizations, and disease complications.[5–7]

In the past 2 decades, the development of several classes of advanced therapies targeting distinct pathways of inflammation including biologics targeting tumor necrosis factor (TNF)-α, $\alpha_4\beta_7$ integrins, interleukin (IL)12/23 and IL23, and oral small molecule drugs, such as Janus kinase 1 (JAK1) inhibitors, have made endoscopic remission a more achievable therapeutic target in patients with moderate-to-severely active CD. Recent network meta-analyses comparing biologics and oral small molecules in patients with CD have focused on achieving clinical outcomes.[8,9] However, their comparative efficacy in achieving these endoscopic outcomes is unknown.

Hence, we conducted a systematic review and network meta-analysis comparing biologics and oral small molecule drugs for achieving endoscopic outcomes in patients with moderate-to-severely active CD and used GRADE to appraise the certainty of evidence.

Methods

This systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension statement for systematic reviews incorporating network meta-analyses[10] and was conducted following an a priori developed protocol. We followed good research practices outlined in the International Society for Pharmacoeconomics and Outcomes Research report on interpreting indirect treatment comparisons and network meta-analysis for health care decision-making.[11]

Study Eligibility Criteria

Eligible studies were phase II or III randomized controlled trials (RCTs) fulfilling the following criteria. (1) Patients: adults ($\geq$ 18 years) with moderate-to-severely active CD. (2) Intervention and comparator: treatment with TNF antagonists (infliximab originator or biosimilar, adalimumab originator or biosimilar, certolizumab pegol), anti-integrin (vedolizumab, etrolizumab), anti-IL12/23p40 (ustekinumab), anti-IL23p19 agents (risankizumab, guselkumab, mirikizumab), or JAK1 inhibitors (upadacitinib, filgotinib). (3) Outcomes: reported endoscopic response, endoscopic remission, and/or ulcer-free endoscopic healing (mucosal healing). Minimum duration for induction trials was 2 weeks, and 4 months for maintenance trials. We excluded the following studies: trials focusing exclusively on fistulizing disease; hospitalized patients with CD; trials of probiotics, antibiotics, and complementary therapies; trials comparing a combination of advanced therapies with immunosuppressive treatments, such as thiopurine or methotrexate versus monotherapy with either (because of inability to obtain data on concomitant immunosuppressive therapy from trials of advanced therapies); and trials of advanced therapies in early phases of development, without a planned phase III trial. There were no language restrictions for our study.

Data Sources, Search Strategy, and Study Selection

MEDLINE, EMBASE, and Cochrane CENTRAL Register of Controlled trials were searched from inception to August 2, 2023 (Supplementary Methods). Citations and abstracts of potentially relevant studies were screened and selected, and completed manuscripts were retrieved to assess for eligibility by 2 reviewers independently (SKV and TMN). Disagreements were resolved by consensus and discussion with a third author (VJ). Abstracts from Digestive Disease Week, annual meetings of the European Crohn's and Colitis Organization and of the American College of Gastroenterology, and the United European Gastroenterology Week from inception to August 2023 were hand searched to identify additional studies that meet the inclusion criteria.

Data Extraction and Quality Assessment

Data were independently extracted into a Microsoft Excel spreadsheet. Intention-to-treat numbers were used to assess the main outcomes. Trial design features extracted included: (1) trial design and participant characteristics (number of treatment arms, trial development phase, year of publication, number of participants, study duration, number of participants analyzed, disease activity score used at inclusion, mean age, gender ratio), (2) type of intervention (drug class and concomitant therapies), (3) criteria for enrollment and outcome assessment including use of endoscopy and minimum endoscopic score on enrollment and outcome assessment (endoscopic remission, response, and ulcer-free endoscopic healing), and (4) disease severity and duration. A risk of bias assessment was performed in the included trials using the Cochrane Risk of Bias Tool for Randomized Trials.

Outcomes

The primary outcome was the comparative efficacy of different classes of advanced therapies for inducing endoscopic response (induction therapy), and maintenance of endoscopic remission (maintenance therapy), as defined by the original trial. Secondary outcomes of interest were induction of endoscopic remission and ulcer-free endoscopic healing, and maintenance of endoscopic response and ulcer-free endoscopic healing. If data from multiple time points were reported, this outcome was preferentially extracted at 8 weeks for induction trials (range, week 8–14) and 52 weeks (range, week 44–66) for maintenance trials. If data for multiple doses were available, we used Food and Drug Administration–approved dosing regimen for approved therapies; for drugs that are still in development, the efficacy of combined doses was included in the analysis. Given the strong impact of prior TNF antagonist exposure on key clinical outcomes in patients with CD, we conducted subgroup analyses comparing endoscopic outcomes in biologic-naive versus biologic-exposed patients, where feasible.

Statistical Analysis

Direct or pairwise meta-analysis to calculate pooled relative risk (RR) and 95% confidence intervals (CI) was performed using the DerSimonian-Liard random effects model. Class-specific comparisons were performed because there were limited data on individual drugs. Although there is a partial overlap in mechanism of action of etrolizumab and vedolizumab, the data were analyzed separately because of the differences in their molecular targets. A random effects model was selected given the anticipated differences between trials with respect to patient populations and interventions. Between-study heterogeneity was assessed using the I^2 statistic, with 30%–60% representing moderate heterogeneity, 61%–75% representing substantial heterogeneity, and >75% representing considerable heterogeneity.[12] Small study effects and publication bias were examined by assessing for funnel plot asymmetry. Direct comparisons were performed using Review Manager 5.4 (Cochrane Collaboration, Copenhagen, Denmark). We performed a network meta-analysis using the frequentist approach, with the statistical package "netmeta" version 0.9-0 (https://cran.r-project.org/web/packages/netmeta/index.html) in R version 4.0.2.[13] We examined local incoherence in each node by comparing the results of head-to-head estimates and indirect estimates. We provide the *P* score to rank the efficacy of treatments, which is analogous to the surface under the cumulative ranking curve. The *P* score ranges from a value between 0 (worst) to 1 (best), and is determined solely on the point estimates and standard errors of the network estimates under the normality assumption.[14]

Certainty of the Evidence

The Grading of Recommendations Assessment, Development and Evaluation criteria was used to appraise confidence in estimates derived from the direct and indirect comparisons of efficacy outcomes. In this approach, direct evidence from RCTs starts at high

What You Need to Know

Background

Endoscopic remission is a recommended treatment target for patients with Crohn's disease (CD).

Findings

On comparison of five drug classes in 20 randomized controlled trials (RCTs) in our network meta-analysis, all classes of medications except etrolizumab were effective in inducing endoscopic response and/or remission. Janus kinase1 (JAK1) inhibitors and anti-interleukin (IL)23p19 ranked highest for induction of endoscopic response. All drug classes except vedolizumab were effective for maintenance of endoscopic remission. There is paucity of RCT of tumor necrosis factor (TNF) antagonists reporting endoscopic outcomes with induction therapy.

Implications for patient care

Our study suggests that JAK1 inhibitors and anti-IL23p19 agents are probably more effective amongst non-TNF-targeting advanced therapies for induction of endoscopic outcomes. Endoscopic outcomes with TNF antagonists and vedolizumab have not been well-studied in comparative RCTs. The findings assist in making well-informed decisions when choosing advanced therapies for patients with CD and highlights the gaps in existing literature.

confidence, and is rated down by risk of bias, indirectness, imprecision, inconsistency/heterogeneity, and/or publication bias to moderate, low, and very low confidence. Indirect evidence starts at the lowest rating of the 2 pairwise estimates that contribute as first-order loops to the indirect estimate but can be further downrated for imprecision or intransitivity between the direct and indirect comparisons.

Results

The search yielded 21,227 citations from the databases and 12 records handpicked from other sources. After removing the duplicates, the remaining 13,103 records were screened, and 668 full-text articles were selected and reviewed for eligibility. A total of 20 RCTs recruiting 5592 participants were included. Out of them, 19 were placebo-controlled and 1 was head-to-head trial (SEAVUE)[15] comparing IL12/23p40 antagonist (ustekinumab) and TNF antagonist (adalimumab). In the phase 2 GALAXI-1 study, patients randomized to the reference ustekinumab arm were also included in the analysis (Figure 1). Out of the 20 included trials, 12 reported outcomes for the induction phase,[16–24] 5 reported for the maintenance phase,[15,17,23,25,26] and 3 reported outcomes for both the induction and maintenance phases.[27–29] Data for vedolizumab were available only for the maintenance of endoscopic remission outcome. There were 14 phase III and 6 phase II trials. All studies except 2 (CERTIFI and VISIBLE 2)[16,25] reported using the central reading for endoscopic assessment.

Definitions of Endoscopic Outcomes

All except 2 trials defined endoscopic response using the SES-CD score (at least 50% decrease, with additional criteria in some studies); and 2 trials defined endoscopic response using the CDEIS score.[18,28] There were 4 different definitions of endoscopic remission. Five studies defined endoscopic remission as an SES-CD score $\leq$2, 10 studies defined it as an SES-CD score $\leq$4 with additional criteria, 1 study used an SES-CD score of $\leq$3,[15] and 2 studies defined endoscopic remission by a CDEIS score $\leq$4.[18,28] Ulcer-free endoscopic healing was defined

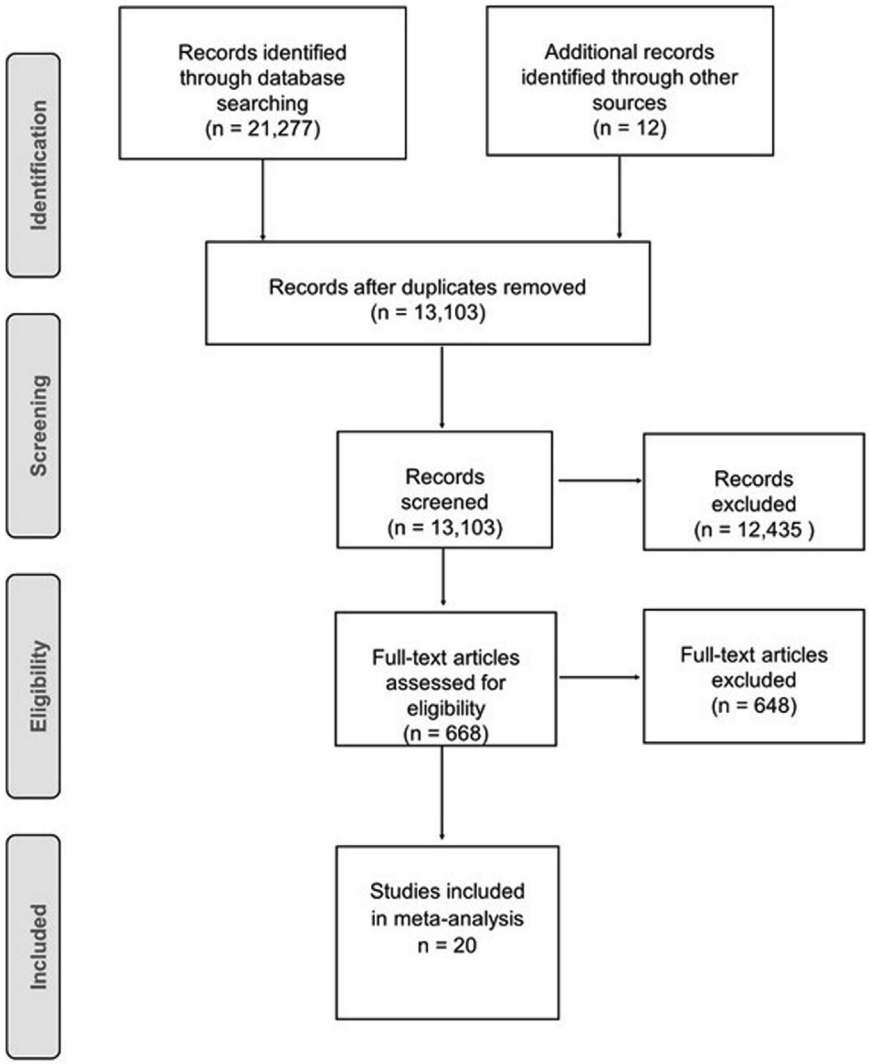

Figure 1. PRISMA diagram showing study selection.

as an absence of ulcers on ileocolonoscopy. The details of the definitions used in the included trials are listed in Supplementary Table 1. For primary outcome (endoscopic response) of induction studies, the timing of assessment was Week 12 for most of the studies (9/13). For the remaining studies, it was reported at Week 8 (2 studies), 10 (1 study), and 14 (1 study). Among the 6 maintenance studies, the primary outcome (endoscopic remission) was reported at Week 52 in all studies except 1 (BERGAMOT at Week 66).

Endoscopic Outcomes: Induction Therapy

Endoscopic response. Thirteen trials[17–24,28,29] including 4159 participants assessed efficacy of reported endoscopic response. Figure 2*A* shows the network geometry for the endoscopic response outcome. Data on endoscopic response with TNF antagonists were available for only 1 trial with 64 patients on adalimumab. Pairwise comparisons of induction outcomes were presented in Supplementary Figure 1. On network meta-analysis, JAK1 inhibitors (RR, 4·21 [95% CI, 2·68–6·78]), IL23p19 (RR, 2·81 [95% CI, 1·95–4·05]) and anti-IL12/23p40 (RR, 1·82 [95% CI, 1·05–3·16]) antagonists were superior to placebo (Table 1). On comparing active therapies, JAK1 inhibitors (RR, 3·49 [95% CI, 1·48–8·26]) and anti-IL23p19 (RR, 2·30 [95% CI, 1·02–5·18]) agents were superior to etrolizumab (moderate certainty of evidence), and JAK1 inhibitors (RR, 2·34 [95% CI, 1·14–4·80) were superior to anti-IL12/23p40 for inducing endoscopic response (moderate certainty of evidence) (Table 1). Overall JAK1 inhibitors ranked highest (P = 0·97) followed by anti-IL23p19 agents (P = 0·77) for inducing endoscopic response (Supplementary Figure 2); however, there was paucity of data on efficacy of TNF antagonists and vedolizumab in inducing endoscopic response. GRADE certainty of evidence for all comparisons on network meta-analysis are shown in Supplementary Table 2.

Induction endoscopic response and remission for biologic-naive patients were reported in 4 trials (JAK1 inhibitor in 1, IL23p19 antagonist in 2, IL12/23p40 antagonist in 1).[20–22,24] On network meta-analysis, anti-IL12/23p40 (RR, 4·31 [95% CI, 2·21–8·41]) and anti-IL23p19 agents (RR, 3·87 [95% CI, 2·38–6·30]) were more efficacious than placebo in inducing endoscopic response (Supplementary Table 3). No agent was superior to others for achieving endoscopic response. Induction endoscopic response and remission for biologic-experienced patients were reported in 9 trials of JAK1 inhibitors, anti-IL23p19 and anti-IL12/23p40 classes.[17–24] On network meta-analysis, JAK1 inhibitors (RR, 6·43 [95% CI, 3·64–11·37]) and anti-IL23p19 (RR, 2·71 [95% CI, 2·01–3·64]), but not anti-IL12/23p40 were superior to placebo for inducing endoscopic response (Supplementary Table 4). Among active comparisons, JAK1 inhibitor was more effective compared with anti-IL12/23p40 (RR, 3·91 [95% CI, 1·46–10·47]) and anti-IL23p19 (RR, 2·38 [95% CI, 1·25–4·51]) in inducing endoscopic response in patients with prior exposure to biologics.

Endoscopic remission. Induction of endoscopic remission was assessed in 13 trials[17–24,28,29] including 4918 participants. Figure 2*B* shows the network geometry for the induction of endoscopic remission outcome. On network meta-analysis, all agents except etrolizumab were superior to placebo (Table 1). On comparing active therapies, JAK1 inhibitors were superior to etrolizumab (odds ratio, 2·83 [95% CI, 1·15–6·98]) therapy and TNF antagonists (RR, 2·35 [95% CI, 1·61–4·74]) for inducing endoscopic remission (Table 1). JAK1 inhibitors ranked highest (P = 0·94) in inducing endoscopic remission followed by anti-IL23p19 agents (P = 0·77) (Supplementary Figure 3).

Among biologic-naive patients, on network meta-analysis, anti-IL23p19 (RR, 2·53 [95% CI, 1·44–4·43]) was more efficacious than placebo in inducing remission

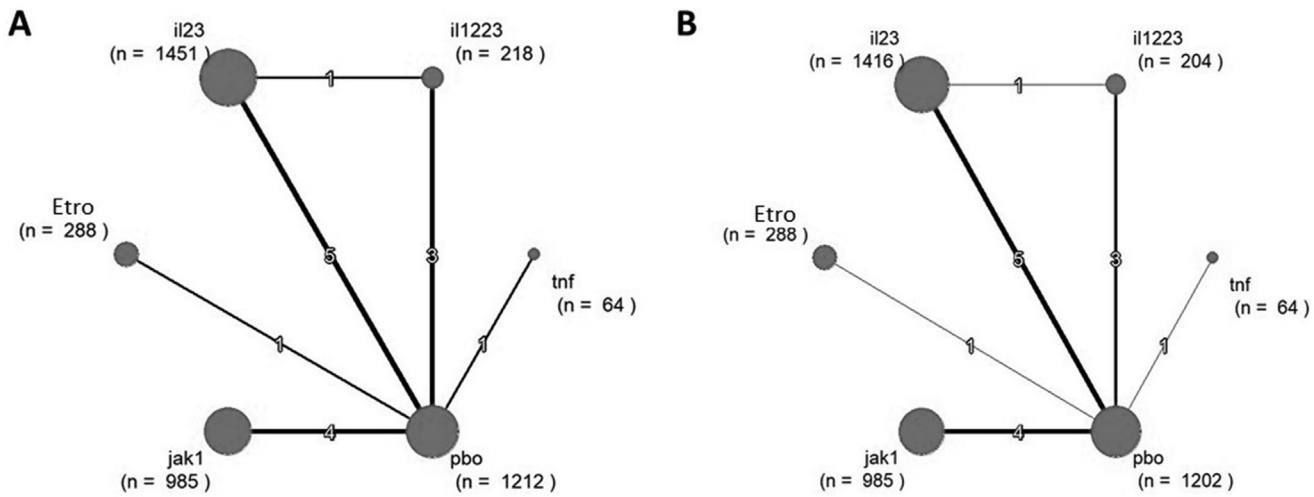

Figure 2. Network plot showing included studies for assessing the efficacy of pharmacotherapeutic classes in inducing (*A*) endoscopic response and (*B*) endoscopic remission.

Table 1. Comparative Efficacy of Biologic Agents and Oral Small Molecules for Induction of Endoscopic Response and Endoscopic Remission in Patients With Moderate-to-Severe Crohn's Disease Using Network Meta-Analysis, Expressed as RR with 95% Confidence Intervals

		Induction of endoscopic response, all patients					
Induction of endoscopic remission, all patients	JAK1 inhibitors	1·52 (0·84–2·74)	**2·34 (1·14–4·80)**	2·43 (0·90–6·59)	**3·49 (1·48–8·26)**	—	**4·21 (2·68–6·78)**
	1·33 (0·72–2·44)	IL23 antagonists	1·54 (0·87–2·71)	1·60 (0·62–4·16)	**2·30 (1·02–5·18)**	—	**2·81 (1·95–4·05)**
	1·66 (0·72–3·82)	1·25 (0·64–2·45)	IL12/23 antagonists	1·04 (0·37–2·94)	1·49 (0·60–3·71)	—	**1·82 (1·05–3·16)**
	2·35 (1·61–4·74)	1·77 (0·92–3·40)	1·41 (0·60–3·35)	TNF antagonists	1·44 (0·46–4·50)	—	1·75 (0·73–4·24)
	2·83 (1·15–6·98)	2·14 (0·90–5·07)	1·70 (0·61–4·78)	1·21 (0·48–3·06)	Etrolizumab	—	1·22 (0·59–2·52)
	—	—	—	—	—	Vedolizumab	—
	4·37 (2·73–6·99)	**3·30 (2·23–4·87)**	**2·63 (1·32–5·22)**	**1·86 (1·10–3·14)**	1·54 (0·71–3·33)	—	Placebo

NOTE. Comparisons read from left-to-right; RR for comparisons in the cell in common between column- and row-defining treatment. RR >1 favors row-defining treatment. For induction of endoscopic remission, RR >1 favors row-defining treatment. For induction of endoscopic response, RR >1 favors column-defining treatment. Values highlighted in bold are statistically significant.
IL, interleukin; JAK1 inhibitors, Janus kinase 1 inhibitors; RR, risk ratio; TNF, tumor necrosis factor.

(Supplementary Table 3). In biologic-experienced patients, JAK1 inhibitors, anti-IL23p19, and anti-IL12/23p40 were more efficacious than placebo in inducing endoscopic remission (Supplementary Table 4).

Ulcer-free endoscopic healing. Induction of ulcer-free endoscopic healing was reported in 10 trials.[16–18,20,21,24,27,28] On network meta-analysis, anti-IL23p19, anti-IL12/23p40, and TNF antagonists were superior to placebo (Supplementary Table 5). No agent was superior to others on active comparisons.

Endoscopic Outcomes: Maintenance Therapy

Endoscopic response. Six trials of maintenance therapy reported endoscopic response outcome, with 1780 patients, including 1 head-to-head trial (SEAVUE).[15,17,23,26,28,29] Five trials were designed as rerandomization of responders to induction therapy rolling into maintenance therapy, whereas SEAVUE was a treat-straight-through clinical trial. Supplementary Figure 4 shows the network geometry for the maintenance of endoscopic response outcome.

Pairwise comparison of maintenance outcomes is presented in Supplementary Figure 5. On network meta-analysis, all classes were superior to placebo (Table 2). On comparison of active therapies, anti-IL12/23p40 agents (RR, 5·87 [95% CI, 1·36–25·28]), TNF antagonists (RR, 4·80 [95% CI, 1·12–20·68]), and JAK1 inhibitors (RR, 3·18 [95% CI, 1·68–6·03), were superior to etrolizumab for maintaining endoscopic response. JAK1 inhibitors were more efficacious than anti-IL23p19 agents (RR, 2·17 [95% CI, 1·14–4·15]) for maintaining endoscopic response (Table 2). Overall IL12/23p40 ranked highest ($P = 0·93$) in maintenance of endoscopic response followed by TNF antagonists ($P = 0·75$) and JAK1 inhibitors ($P = 0·70$) (Supplementary Figure 6).

Endoscopic remission. Maintenance of endoscopic remission was assessed in 6 trials[15,23,25,26,28,29] recruiting 1821 participants. Figure 3 shows the network geometry for the maintenance of endoscopic remission outcome. On network meta-analysis, all classes of medications except vedolizumab (RR, 1.89 [95% CI, 0.61–5.92]) were superior to placebo. Among active comparisons, there was no difference among the different classes of drugs (Table 2). Overall TNF antagonists ranked highest ($P = 0·88$), followed by anti-IL12/23p40 agents ($P = 0·83$) and JAK1 inhibitors ($P = 0·72$) (Supplementary Figure 7). GRADE certainty of evidence for all comparisons on network meta-analysis and risk of bias are shown in Supplementary Tables 2 and 6 respectively.

Discussion

Outcome measures and treatment targets in CD clinical trials have evolved over time, from symptom-based assessment to targeting more objective endoscopic end points. Achieving and maintaining endoscopic remission

Table 2. Comparative Efficacy of Biologic Agents and Oral Small Molecules for Maintenance of Endoscopic Response and Endoscopic Remission in Patients With Moderate-to-Severe Crohn's Disease Using Network Meta-Analysis, Expressed as RR With 95% Confidence Intervals

Maintenance of endoscopic response, all patients							
Maintenance of endoscopic remission, all patients	JAK1 inhibitors	**2·17 (1·14–4·15)**	0·54 (0·12–2·52)	0·66 (0·14–3·08)	**3·18 (1·68–6·03)**	—	**4·65 (2·64–8·18)**
	1·85 (0·81–4·22)	IL23 antagonists	0·25 (0·06–1·08)	0·30 (0·07–1·32)	1·46 (0·95–2·26)	—	**2·14 (1·57–2·93)**
	0·58 (0·11–3·01)	0·31 (0·07–1·47)	IL12/23 antagonists	1·22 (0·89–1·67)	**5·87 (1·36–25·28)**	—	**8·58 (2·05–35·83)**
	0·54 (0·11–2·64)	0·29 (0·07–1·29)	0·93 (0·60–1·45)	TNF antagonists	**4·80 (1·12–20·68)**	—	**7·02 (1·68–29·31)**
	2·49 (0.95–6·40)	1·34 (0·62–2·88)	4·26 (0·84–21·52)	4·57 (0.96–21·67)	Etrolizumab	—	**1·46 (1·08–1·97)**
	2.61 (0.69–9.95)	1.41 (0.42–4.75)	4.50 (0.69–29.26)	4.82 (0.78–29.72)	1.05 (0.29–3.89)	Vedolizumab	—
	4·96 (2·46–10·00)	**2·67 (1·74–4·11)**	**8·53 (1·93–37·75)**	**9·14 (2·21–37·80)**	**1·97 (1·13–3·45)**	1.89 (0.61–5.92)	Placebo

NOTE. Comparisons read from left-to-right; RR for comparisons in the cell in common between column- and row-defining treatment. RR >1 favors row-defining treatment. For induction of endoscopic remission, RR >1 favors row-defining treatment. For induction of endoscopic response, RR >1 favors column-defining treatment. Values highlighted in bold are statistically significant.
IL, interleukin; JAK1 inhibitors, Janus kinase 1 inhibitors; RR, risk ratio; TNF, tumor necrosis factor.

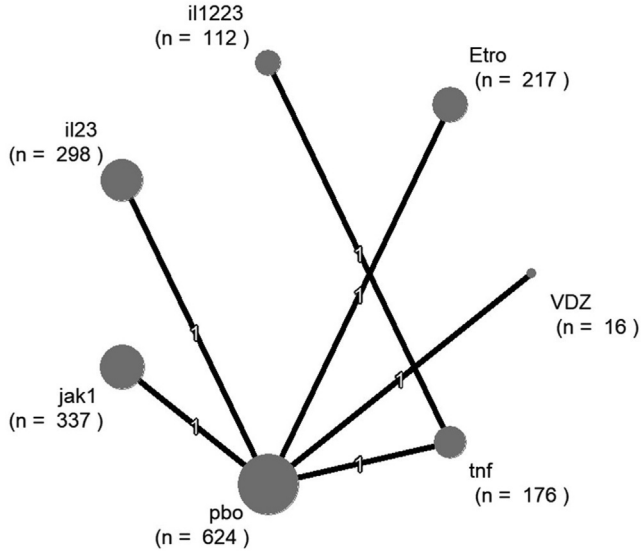

Figure 3. Network plot showing included studies for assessing the efficacy of pharmacotherapeutic classes in maintaining endoscopic remission.

has been associated with a reduction in CD-related complications, but there are limited data on comparative efficacy of available CD therapies in inducing and maintaining these outcomes. In this network meta-analysis, we combined the available direct and indirect evidence from 20 RCTs including 1 head-to-head trial to evaluate the efficacy of different pharmacologic therapeutic classes for induction and maintenance of endoscopic outcomes. There are several key findings from this study. First, all classes of medications except etrolizumab were effective in inducing endoscopic response and/or remission; however, there were no trials of vedolizumab reporting endoscopic outcomes with induction therapy. Second, JAK1 inhibitors may be more effective than TNF antagonists, anti-IL12/23p40, and etrolizumab for inducing endoscopic response and/or remission, although there was only 1 small trial of endoscopic outcomes with induction therapy with TNF antagonists. Specifically focusing on patients with prior biologic exposure, JAK1 inhibitors may be more effective than anti-IL23p19 and anti-IL12/23p40 agents for inducing endoscopic response. Third, for maintenance of endoscopic remission and/or response outcomes there was no difference among different classes. JAK1 inhibitors may be more effective than anti-IL23p19 agents in maintaining endoscopic response. There are 2 important caveats when interpreting these findings. First, there is considerable paucity of RCT-level data on the efficacy of TNF antagonists in inducing endoscopic outcomes. This is in stark contrast to the well-established effectiveness of TNF agents in achieving endoscopic outcomes in real-world studies. Hence, most analyses for TNF antagonists should be interpreted with caution. It is very unlikely that there will be future clinical trials of TNF antagonists in CD, unless they are used as comparator arms in future trials. Second, there were limited data on efficacy of

vedolizumab in inducing and maintaining endoscopic outcomes. The VISIBLE2 trial of subcutaneous vedolizumab compared with placebo for maintenance of remission included only 29 patients who volunteered to undergo ileocolonoscopies for whom endoscopic remission end points were reported. With these caveats, overall, these findings add new information to prior findings on the efficacy of JAK1 inhibitors, anti-IL23p19, and TNF antagonists for induction and maintenance of clinical remission and/or response in patients with moderate-to-severely active CD and demonstrate the relative superiority of these agents for endoscopic outcomes, compared with other classes similar to findings for clinical remission outcome.

Prior network meta-analyses have identified TNF antagonists, particularly infliximab and adalimumab, as 1 of the most effective biologics for inducing clinical outcomes (ie, remission and response) in patients with moderate-to-severely active CD. However, early clinical trials in CD did not incorporate endoscopic outcomes, leading to paucity of data on efficacy of TNF antagonists for this network meta-analysis. There are limited data on the efficacy of infliximab on endoscopic response and data predominantly arise from adalimumab (EXTEND trial). Earlier RCTs assessing the efficacy of infliximab with a small group of patients in the late 1990s showed significant improvement in the CDEIS score.[30] Although a substudy from the ACCENT-1 trial showed improvement in ulcer-free endoscopic healing and change in the CDEIS score with standard 3-dose induction therapy compared with a single dose at Week 10, the outcomes defined by SES-CD or CDEIS scores were not evaluated.[30] A recent RCT (SERENE-CD) evaluating a dose optimization strategy of adalimumab showed endoscopic response (>50% decrease from baseline in SES-CD or a ≥2 point reduction in patients with a baseline SES-CD score of 4) in 39% of patients receiving a standard dose of adalimumab at Week 12, which is comparable with endoscopic response rates observed with newer biologics.[31] However, only approximately 18% had failed prior infliximab therapy. Similarly in the CALM trial, mucosal healing (CDEIS <4 and no deep ulcers) was observed in 30% of biologic-naive patients with CD randomized to the clinical management group receiving adalimumab with dose adjustment driven by CDAI and prednisolone use.[32] These results suggest that TNF antagonists are effective in induction and maintenance of endoscopic outcomes.

On analysis of maintenance studies, all classes of therapies except vedolizumab were effective compared with placebo and overall TNF antagonists ranked highest. Among the anti-integrins, although etrolizumab showed superior efficacy during maintenance phase (BERGAMOT trial), the drug failed to show promising results in the phase 3 program and therefore further efforts to develop this drug have been abandoned. There are limited data on efficacy of vedolizumab for the induction and maintenance of endoscopic outcomes from clinical trials. In the open-label single-arm VERSIFY trial endoscopic remission was observed in only 17.9% of patients receiving vedolizumab standard dosing schedule at Week 52 with considerably lower remission rates in the TNF antagonist-exposed patients (8.3%) compared with TNF antagonist-naive patients (25%).[33] Another open-label trial (LOVE-CD) showed higher endoscopic remission rates than were observed in the VERSIFY trial at Week 52 (36%), which could be because of the fact that more than 60% of participants in this trial had received an additional induction dose at Week 10 and additionally, there was also evidence of a dose-response relationship.[34]

Given lack of adequate head-to-head control trials and limited data, positioning of advanced therapies in the management algorithm of CD is extremely difficult. However, the available data suggest that TNF antagonist therapy is effective in inducing and maintaining endoscopic outcomes similar to the observations for clinical outcomes. In a recent patient level data pooled analysis from 4 clinical trials including 299 patients comparing the efficacy of adalimumab, infliximab, ustekinumab, and vedolizumab in achieving endoscopic healing (SES-CD <3), Narula et al[35] observed that adalimumab and infliximab had higher rates of endoscopic healing at 1 year compared with vedolizumab, after adjusting for disease duration, concomitant corticosteroid use, and prior TNF antagonist failure. A recent head-to-head RCT (SEAVUE) comparing efficacy of adalimumab and ustekinumab showed similar endoscopic remission rates with both agents at Week 52 (31% vs 29%; $P = .63$) in biologic-naive patients with CD.[15] Nonetheless, newer biologics, such as JAK1 inhibitors and IL12/23 antagonists, fared better especially in patients who failed prior biologics. Results from a head-to-head controlled trial (SEQUENCE) comparing risankizumab (IL23p19 antagonist) and ustekinumab (IL12/23p40 antagonist) in patients who failed prior TNF antagonist therapy were recently made available in a press release.[36] In this study, considerably higher proportions of patient receiving risankizumab achieved endoscopic response (45% vs 22%) and steroid-free endoscopic remission (31% vs 15%) at Week 48 compared with ustekinumab.

Our study has several strengths. To our knowledge, this is one of the first meta-analyses in patients with moderate-to-severe CD evaluating the comparative efficacy of different advanced therapies for inducing and maintaining endoscopic outcomes specifically. We incorporated the data on novel therapies that are in advanced phases of drug development, including obtaining data from clinical trial registries. We also acknowledge there are several limitations of this network meta-analysis. First, class-specific comparisons were made instead of drug-specific comparisons because of the limited availability of individual drugs included in the meta-analysis. For some agents, such as TNF antagonists, there was considerable paucity of data because endoscopic outcomes were not for regulatory approval of these medications. Second, there were limited data

available exploring the additional advantage of combining immunomodulators with TNF antagonists. In the subpopulation of patients with baseline mucosal ulcerations in SONIC trial, a higher number of study participants receiving the combination of infliximab and azathioprine achieved mucosal healing compared with infliximab monotherapy but it was not statistically superior (43.9% vs 30.1%; $P = .06$).[37] Third, there was paucity of data on efficacy of different agents in biologic-naive and biologic-experienced patients, particularly in patients who are refractory to different classes of biologics and/or oral small molecules. Patients in contemporary trials are more likely to be multidrug refractory. Fourth, most of the data informing the network were derived from placebo-controlled trials. Fifth, there was variability in the definition of endoscopic remission across trials. However, the definition of endoscopic response was fairly similar across trials, and was centrally read by expert endoscopists, allowing reliable comparison across the studies. Our study also underscores the gaps within the current literature and provides direction for future studies that can better inform therapeutic choices for patients with CD.

In conclusion, based on a network meta-analysis of 20 RCTs of advanced therapies in patients with moderate-to-severely active CD, JAK1 inhibitors and anti-IL23p19 agents may be superior to other non-TNF-targeting biologics, particularly patients who failed prior biologics for achieving favorable endoscopic outcomes. Although there is paucity of data on endoscopic outcomes with TNF antagonists in RCT settings, real-world evidence suggests high effectiveness with these agents. Future head-to-head trials with clinical and endoscopic outcomes will inform positioning of different therapies for the management of moderate-to-severely active CD.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://doi.org/10.1016/j.cgh.2023.12.023.

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Tran M. Nguyen (Data curation: Equal; Formal analysis: Lead; Methodology: Equal; Writing – review & editing: Equal)

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Guangyong Zou (Methodology: Supporting; Writing – review & editing: Equal)

Jeffrey D. McCurdy (Writing – review & editing: Equal)

Laurent Peyrin-Biroulet (Writing – review & editing: Equal)

Silvio Danese (Writing – review & editing: Equal)

Christopher Ma (Writing – review & editing: Equal)

Siddharth Singh (Conceptualization: Lead; Data curation: Equal; Supervision: Lead; Validation: Lead; Writing – review & editing: Lead)

Vipul Jairath, BSc, MbChB (hons), DPhil (Conceptualization: Lead; Supervision: Lead; Validation: Lead; Writing – review & editing: Lead)

Conflicts of interest

These authors disclose the following: Neeraj Narula has been a speaker or advisor for Janssen, AbbVie, Takeda, Pfizer, Merck, Sandoz, Fresenius Kabi, Innomar, Iterative Scopes, Bristol Myers Squibb, Viatris, and Ferring. Talat Bessissow acted as a speaker or advisor for AbbVie, Alimentiv (formerly Robarts Inc), Amgen, Bristol-Myers-Squibb, Ferring, Fresenius Kabi, Gilead, Janssen, Pendopharm, Merck, Pentax, Pfizer, Roche, Sandoz, Takeda, and Viatris. Guangyong Zou and his institution have received consulting/advisory board fee from Alimentiv Inc. Jeffrey D. McCurdy received consulting fees and or speaker honorarium from AbbVie, Bristol Myers Squibb, Fresenius Kabi, Ferring, Janssen, Takeda, and Pfizer. Laurent Peyrin-Biroulet received consulting fees from AbbVie, Alimentiv, Alma Bio Therapeutics, Amgen, Applied Molecular Transport, Arena, Biogen, BMS, Celltrion, CONNECT BioPharm, Cytoki Pharma, Enthera, Ferring, Fresenius Kabi, Galapagos, Genentech, Gilead, Gossamer Bio, GSK, HAC-Pharma, IAG Image Analysis, Index Pharmaceuticals, Inotrem, Janssen, Lilly, Medac, Mopac, Morphic, MSD, Norgine, Novartis, OM Pharma, ONO Pharma, OSE Immunotherapeutics, Pandion Therapeutics, Pfizer, Prometheus, Protagonist, Roche, Sandoz, Takeda, Theravance, Thermo Fisher, Tigenix, Tillots, Viatris, Vifor, Ysopia, and Abivax; received grants from Takeda, Fresenius Kabi, and Cell Trion; and received speaker fees from Galapagos, AbbVie, Janssen, Genentech, Ferring, Tillots, Celltrion, Takeda, Pfizer, Sandoz, Biogen, MSD, Amgen, Vifor, Arena, Lilly, Gilead, Viatris, and Medac. Silvio Danese has received consultancy fees from AbbVie, Alimentiv, Allergan, Amgen, AstraZeneca, Athos Therapeutics, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Celltrion, Dr Falk Pharma, Eli Lilly, Enthera, Ferring Pharmaceuticals Inc, Gilead, Hospira, Inotrem, Janssen, Johnson & Johnson, MSD, Mundipharma, Mylan, Pfizer, Roche, Sandoz, Sublimity Therapeutics, Takeda, TiGenixa, UCB Inc, and Vifor; and lecture fees from AbbVie, Amgen, Ferring Pharmaceuticals Inc, Gilead, Janssen, Mylan, Pfizer, and Takeda. Christopher Ma has received consulting fees from AbbVie, Alimentiv, Amgen, AVIR Pharma Inc, BioJAMP, Bristol Myers Squibb, Celltrion, Ferring, Fresenius Kabi, Janssen, McKesson, Mylan, Takeda, Pendopharm, Pfizer, Roche, Sanofi; speaker's fees from AbbVie, Amgen, AVIR Pharma Inc, Alimentiv, Bristol Myers Squibb, Ferring, Fresenius Kabi, Janssen, Takeda, Pendopharm, and Pfizer; royalties from Springer Publishing; and research support from Ferring, Takeda, and Pfizer. Siddharth Singh has received institutional research support from Pfizer. Vipul Jairath has received has received consulting/advisory board fees from AbbVie, Alimentiv Inc, Arena Pharmaceuticals, Asahi Kasei Pharma, Asieris, Astra Zeneca, Bristol Myers Squibb, Celltrion, Eli Lilly, Ferring, Flagship Pioneering, Fresenius Kabi, Galapagos, GlaxoSmithKline, Genentech, Gilead, Janssen, Merck, Mylan, Pandion, Pendopharm, Pfizer, Protagonist, Reistone Biopharma, Roche, Sandoz, Second Genome, Takeda, Teva, Topivert, Ventyx, and Vividion; and speaker's fees from, AbbVie, Ferring, Galapagos, Janssen Pfizer Shire, Takeda, and Fresenius Kabi. The remaining authors disclose no conflicts.

Supplementary Material

Search Strategies include the following:

MEDLINE (Inception–August 2, 2023)

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2 factorial$.tw.
3 (crossover$ or cross over$ or cross-over$).tw.
4 placebo$.tw.
5 single blind.mp.
6 double blind.mp.
7 triple blind.mp.
8 (singl$ adj blind$).tw.
9 (double$ adj blind$).tw.
10 (tripl$ adj blind$).tw.
11 assign$.tw.
12 allocat$.tw.
13 randomized controlled trial/
14 or/1-13
15 exp Crohn disease/ or crohn*.mp.
16 14 and 15
17 limit 16 to humans

EMBASE (Inception–August 2, 2023)

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3 (crossover$ or cross over$ or cross-over$).tw.
4 placebo$.tw.
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7 triple blind.mp.
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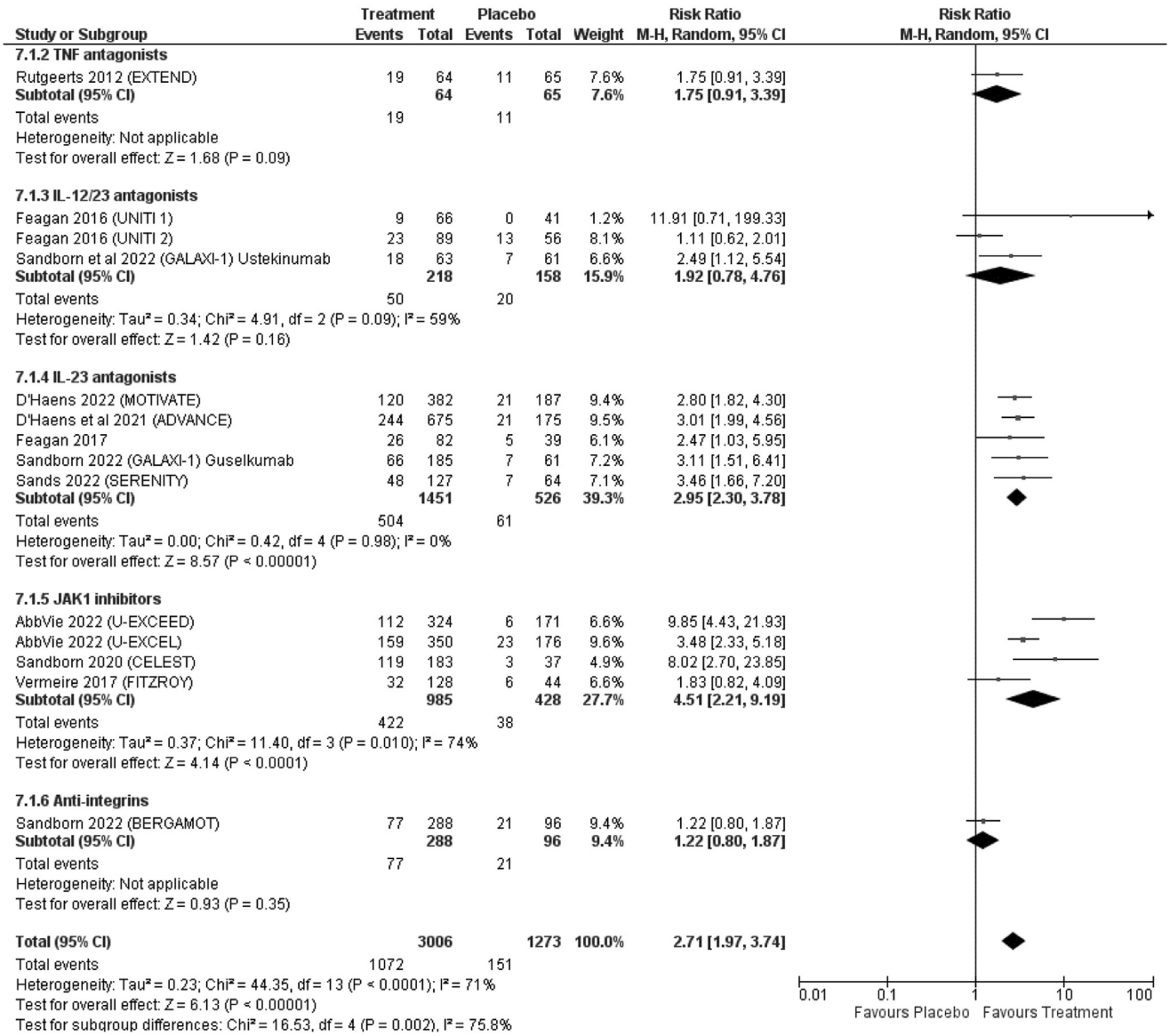
9 (double$ adj blind$).tw.
10 (tripl$ adj blind$).tw.
11 assign$.tw.
12 allocat$.tw.
13 crossover procedure/
14 double blind procedure/
15 single blind procedure/
16 triple blind procedure/
17 randomized controlled trial/
18 or/1-17
19 exp Crohn disease/ or crohn*.mp.
20 18 and 19
21 limit 20 to humans

Cochrane Library (CENTRAL) (Inception–August 2, 2023)

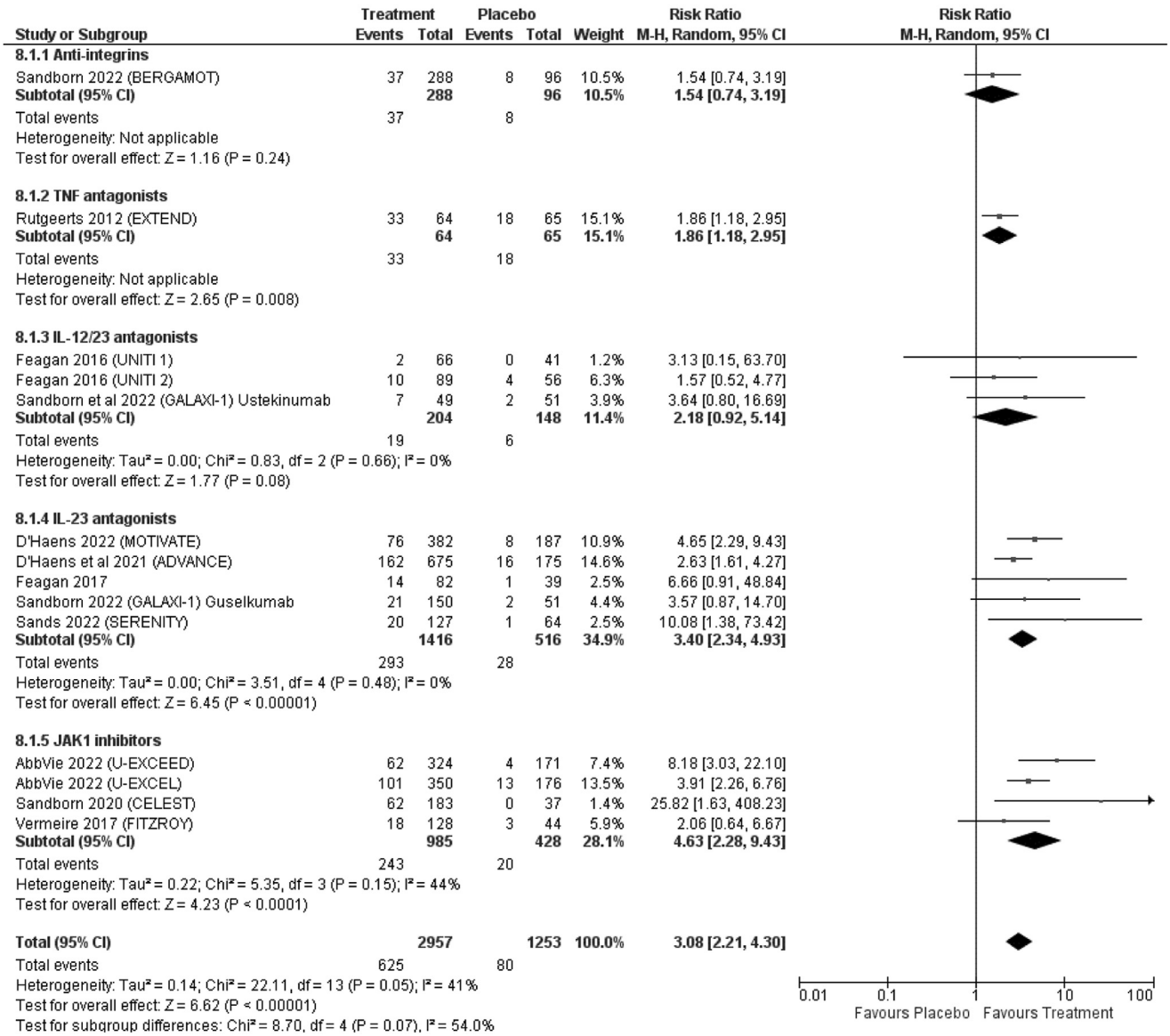
Crohn

A



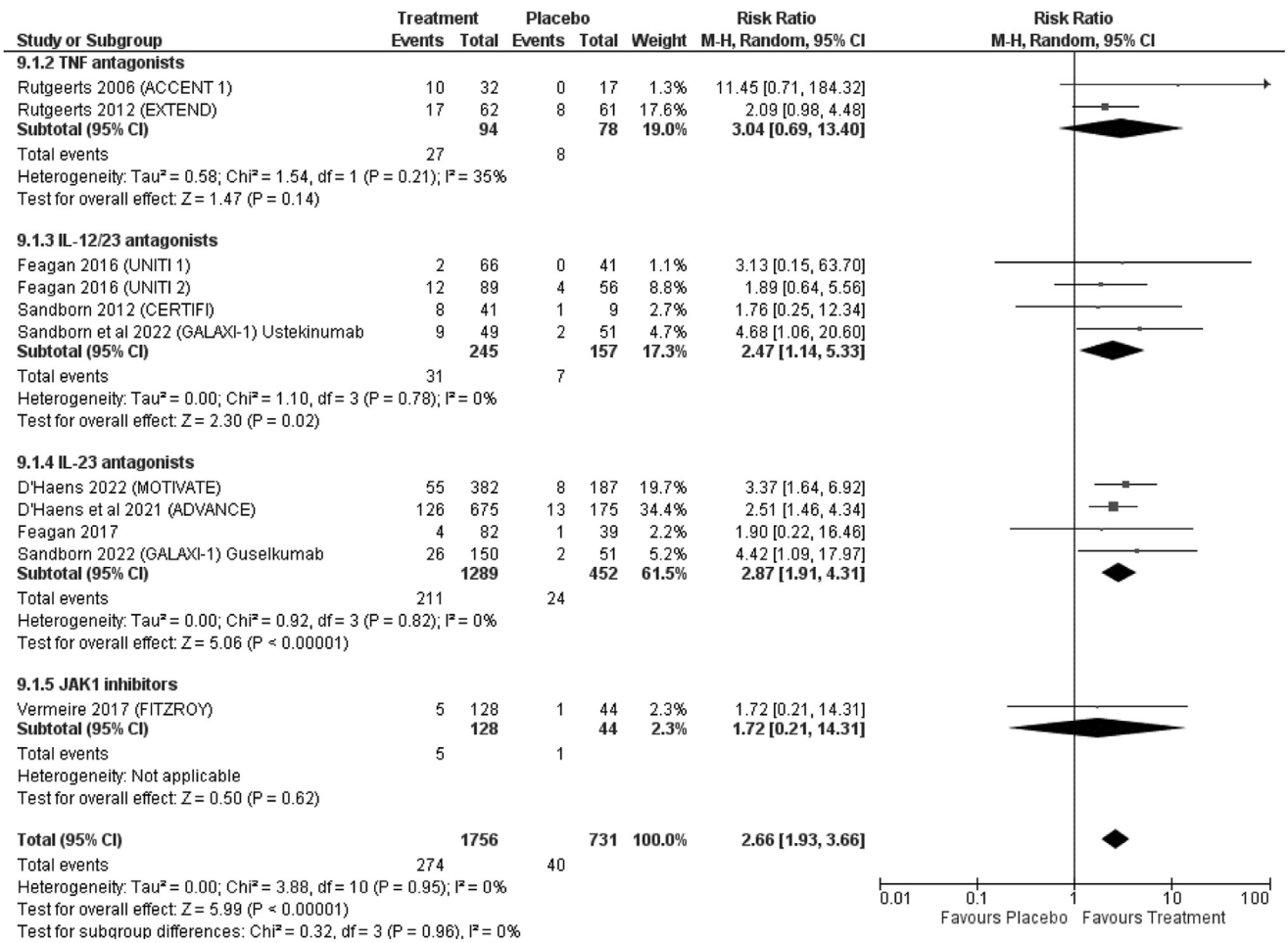
Supplementary Figure 1. Pairwise comparison showing the efficacy of different advanced therapies for the induction of (*A*) endoscopic response, (*B*) endoscopic remission, and (*C*) ulcer-free endoscopic healing.

B

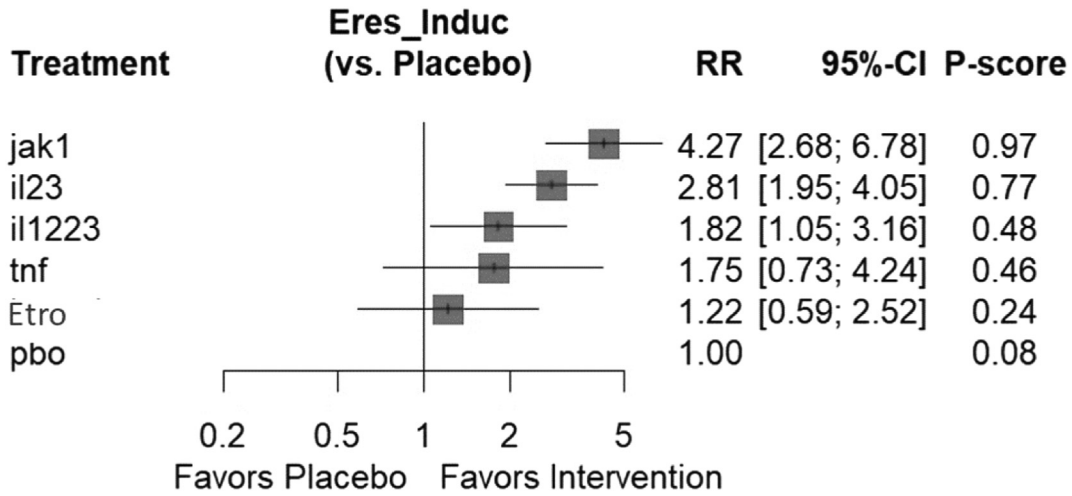


Supplementary Figure 1. (*continued*).

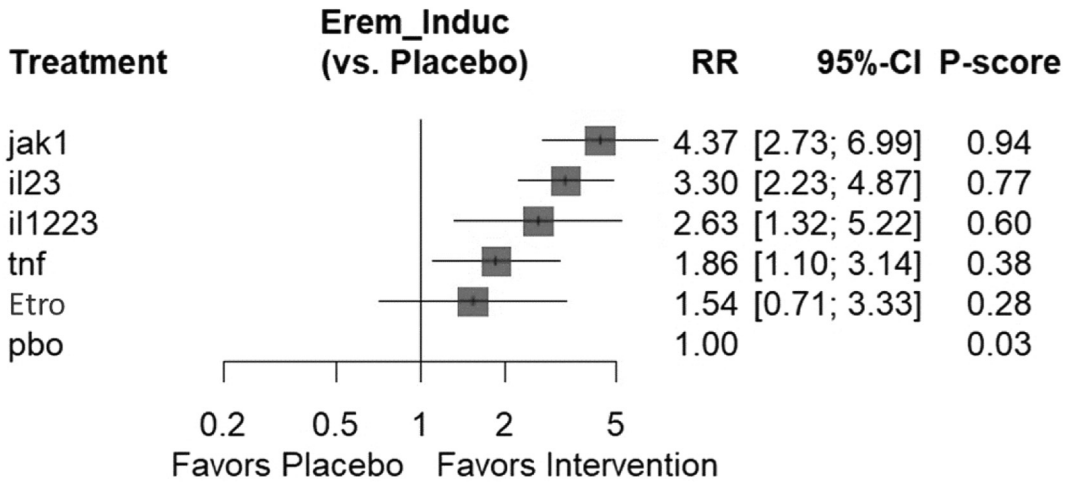
C



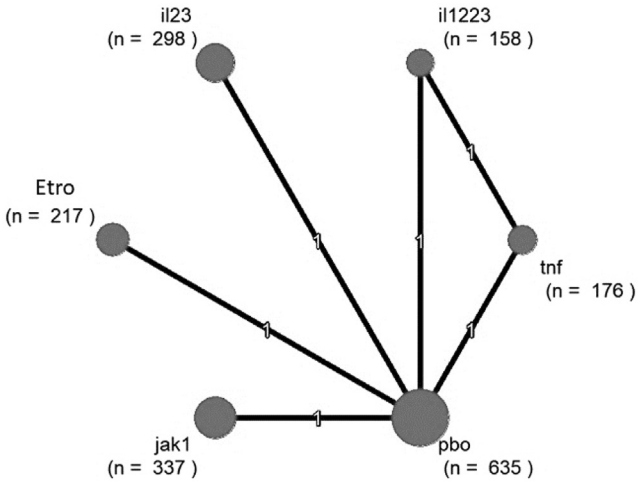
Supplementary Figure 1. (*continued*).



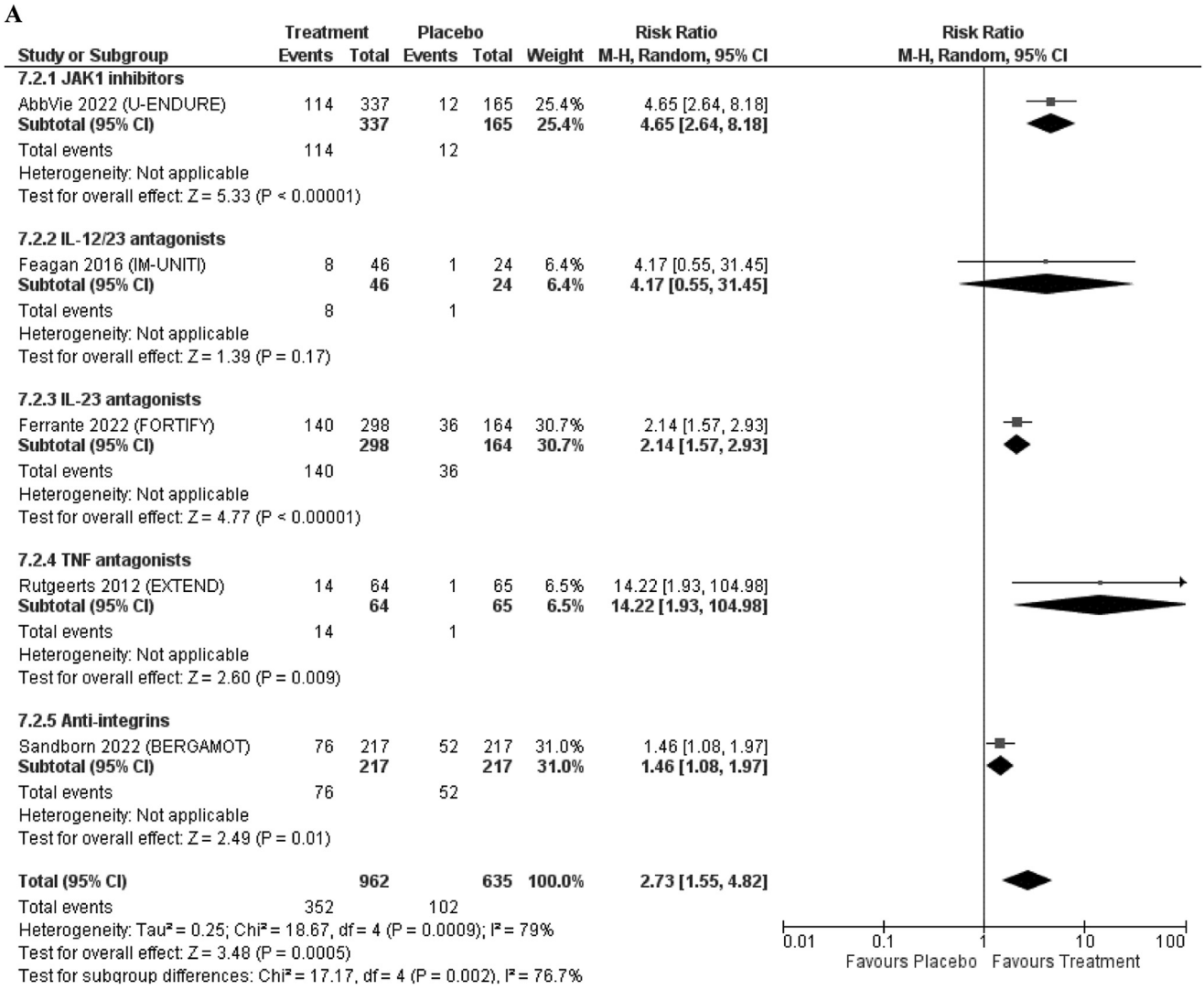
Supplementary Figure 2. Forest plot showing the efficacy of different classes of advanced therapies for the induction of endoscopic response, based on network meta-analysis with corresponding *P* scores (probability of each intervention being ranked as best in the network).



Supplementary Figure 3. Forest plot showing the efficacy of different classes of advanced therapies for the induction of endoscopic remission, based on network meta-analysis with corresponding *P* scores (probability of each intervention being ranked as best in the network).

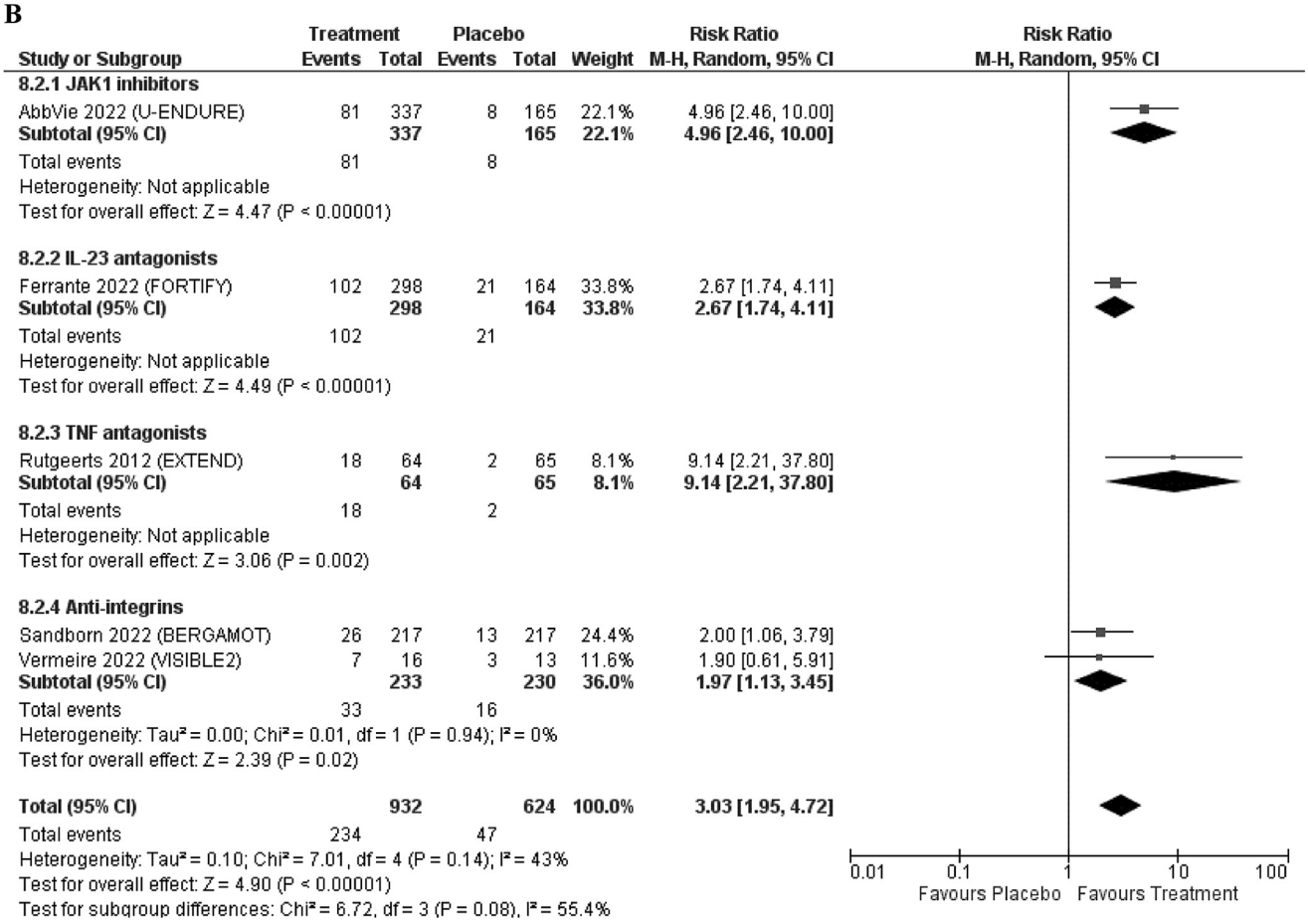


Supplementary Figure 4. Network plot showing included studies assessing efficacy of different advanced therapies for maintaining endoscopic response.



Supplementary Figure 5. Pairwise comparison showing efficacy of different advanced therapies for the maintenance of (*A*) endoscopic response, (*B*) endoscopic remission, and (*C*) ulcer-free endoscopic healing.

B



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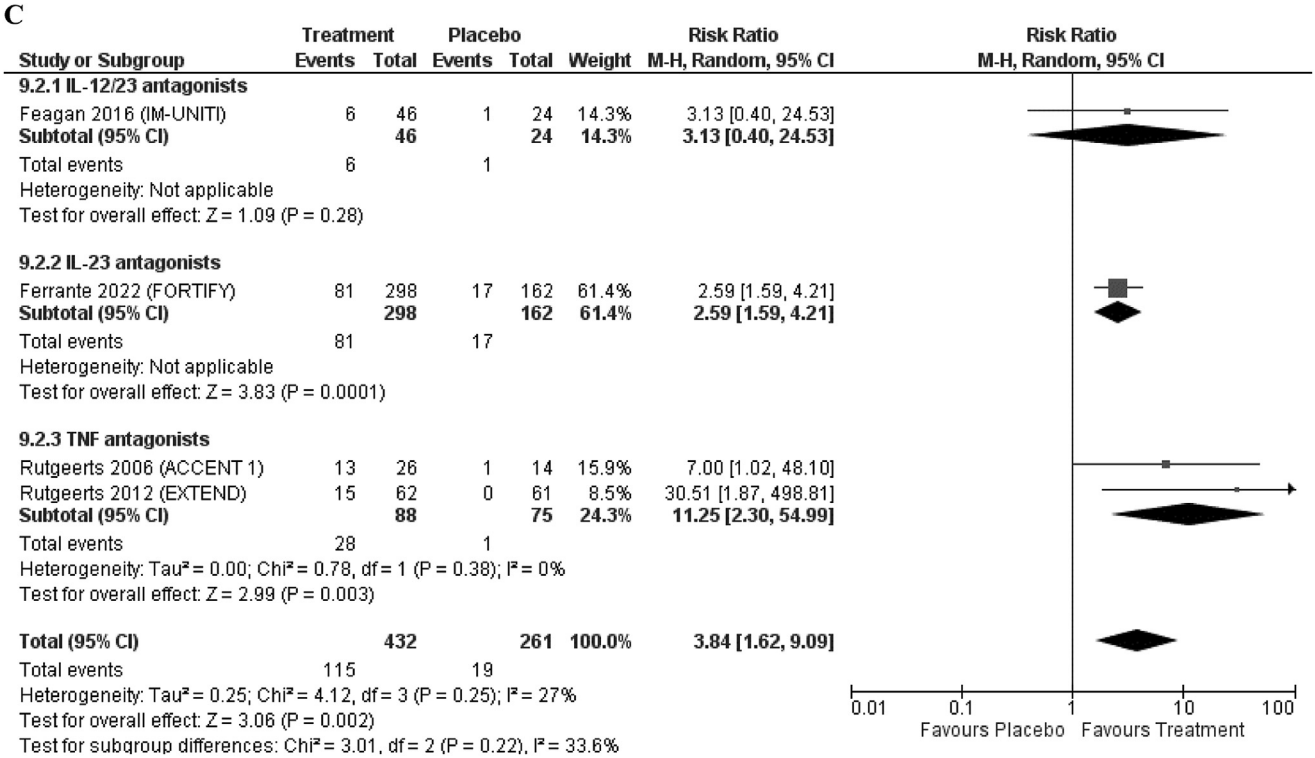

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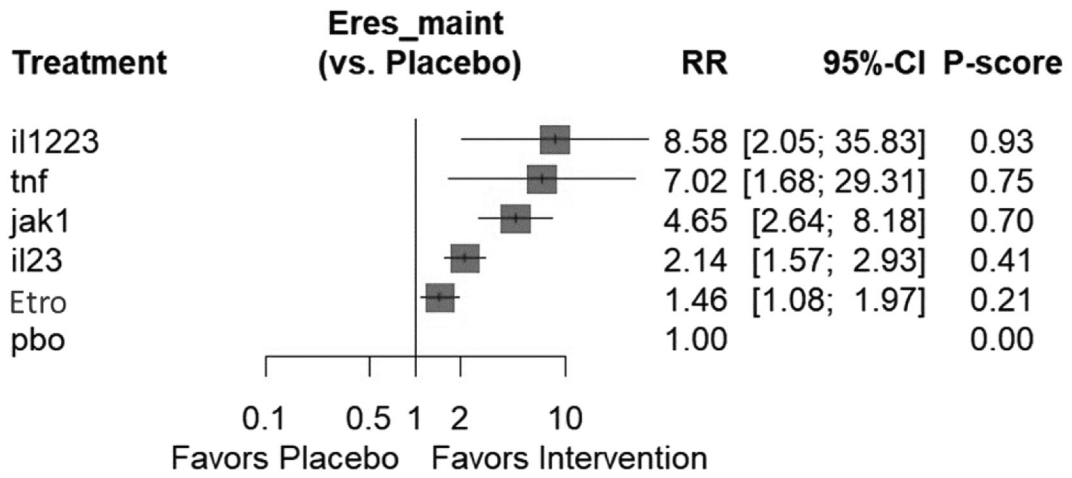
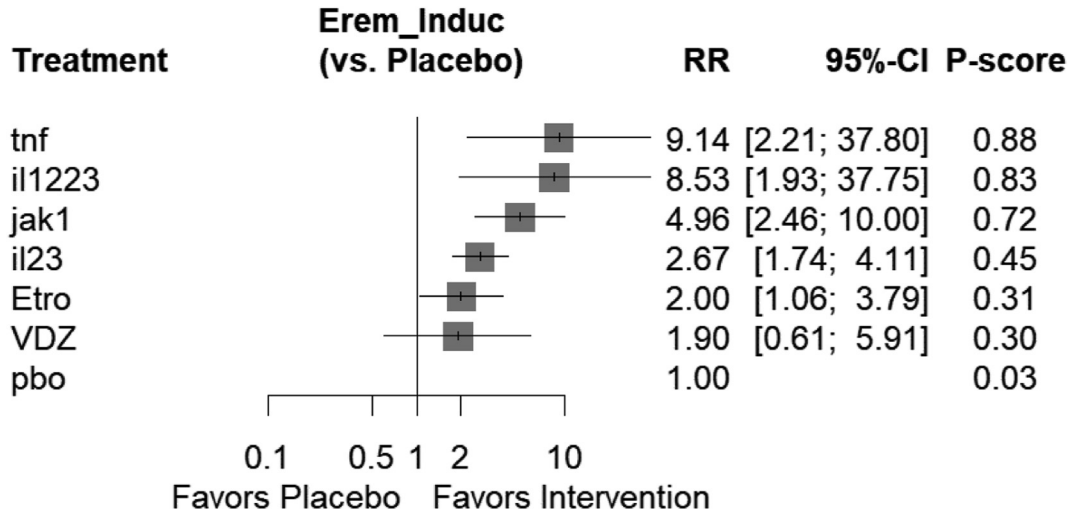


Supplementary Figure 6. Forest plot showing the efficacy of different classes of advanced therapies for the maintenance of endoscopic response, based on network meta-analysis with corresponding *P* scores (probability of each intervention being ranked as best in the network).



Supplementary Figure 7. Forest plot showing the efficacy of different advanced therapies for the maintenance of endoscopic remission based on network meta-analysis, with corresponding *P* scores (probability of each intervention being ranked as best in the network).

Supplementary Table 1. Definitions of Endoscopic Outcomes Used in Included Studies

Trial	Setting	Study drug	Total number of participants in the clinical trial	Number of participants analyzed for endoscopic outcomes	Endoscopic response definition	Endoscopic remission definition	Mucosal healing definition
Sandborn 2012 CERTIFI	Multicenter multinational	Ustekinumab	526	50	—	—	Absence of mucosal ulcers
Rutgeerts 2012 EXTEND	Multicenter multinational	Adalimumab	135	129	CDEIS score reduction by >75%	CDEIS score of ≤4	Absence of mucosal ulcers
Feagan 2016 UNITI-1	Multicenter multinational	Ustekinumab	741	107	SES-CD reduction ≥50%	SES-CD ≤2	Absence of any mucosal ulcerations in patients who had ulcers in at least 1 segment
Feagan 2016 UNITI-2	Multicenter multinational	Ustekinumab	628	145	SES-CD reduction ≥50%	SES-CD ≤2	Absence of any mucosal ulcerations in patients who had ulcers in at least 1 segment
Feagan 2016 IM-UNITI	Multicenter multinational	Ustekinumab	397	58	SES-CD reduction ≥50%	SES-CD ≤2	Absence of any mucosal ulcerations in patients who had ulcers in at least 1 segment
Feagan 2017	Multicenter multinational	Risankizumab	121	121	CEDIS >50% reduction	CDEIS ≤4 (≤2 for patients with initial isolated ileitis)	Absence of mucosal ulcers
D'Haens 2021 ADVANCE	Multicenter multinational	Risankizumab	850	850	SES-CD reduction >50%	SES-CD score ≤4 and at least 2-point reduction and no subscore greater than 1	SES-CD ulcerated surface subscore of 0, with baseline score ≥1
D'Haens 2021 MOTIVATE	Multicenter multinational	Risankizumab	569	569	SES-CD reduction >50%	SES-CD score ≤4 and at least 2-point reduction and no subscore greater than 1	SES-CD ulcerated surface subscore of 0, with baseline score ≥1
Sandborn 2022 GALAXI 1	Multicenter multinational	Guselkumab	309	309	SES-CD reduction by at least 50% or SES-CD score ≤2	SES-CD score ≤2	Absence of mucosal ulceration

Supplementary Table 1. Continued

Trial	Setting	Study drug	Total number of participants in the clinical trial	Number of participants analyzed for endoscopic outcomes	Endoscopic response definition	Endoscopic remission definition	Mucosal healing definition
Sands 2022 SERENITY	Multicenter multinational	Mirikizumab	191	191	50% reduction from baseline in SES-CD score	SES-CD score of <4 for ileal-colonic disease or <2 for isolated ileal disease, and no subscore >1	—
Sandborn 2022 BERGAMOT (cohort 3)	Multicenter multinational	Etrolizumab	385	384	50% reduction from baseline in SES-CD score	SES-CD ≤ 4 (≤ 2 for patients with ileal Crohn's disease only) with no segment having a subcategory score of >1	—
Vermeire 2017 FITZROY	Multicenter multinational	Filgotinib	172	172	SES-CD reduction by $\geq 50\%$	SES-CD ≤ 4 and ulcerated surface subscore ≤ 1in all 5 segments	SES-CD $= 0$
Rutgeerts 2006 ACCENT1	Multicenter multinational	Infliximab	573	49	—	—	Absence of all mucosal ulcerations
Ferrante 2022 FORTIFY	Multicenter multinational	Risankizumab	542	462	SES-CD reduction $>50\%$ from baseline	SES-CD ≤ 4 and at least 2-point reduction versus baseline, and no subscore >1 in any individual component	SES-CD ulcerated surface subscore of 0, with baseline score ≥ 1
Vermeire 2021 VISIBLE 2	Multicenter multinational	Vedolizumab	410	29	—	SES-CD ≤ 2	—
Sandborn 2020 CELEST	Multicenter multinational	Upadacitinib	220	220	SES-CD reduction by 50%	SES-CD ≤ 4 and ≥ 2-point reduction from baseline and no subscore >1	
U-EXCEL	Multicenter multinational	Upadacitinib	526	526	SES-CD reduction by 50% 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	SES-CD ≤ 4 and at least 2-point reduction from baseline and no subscore >1 in any individual variable	—

Supplementary Table 1. Continued

Trial	Setting	Study drug	Total number of participants in the clinical trial	Number of participants analyzed for endoscopic outcomes	Endoscopic response definition	Endoscopic remission definition	Mucosal healing definition
U-EXCEED	Multicenter multinational	Upadacitinib	495	495	SES-CD reduction by 50% 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	SES-CD $\leq$4 and at least 2-point reduction from baseline and no subscore $>$1 in any individual variable	—
U-ENDURE	Multicenter multinational	Upadacitinib	502	502	SES-CD reduction by 50 % 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	SES-CD $\leq$4 and at least 2-point reduction from baseline and no subscore $>$1 in any individual variable	—
Sands 2022 SEAVUE	Multicenter Multinational	Ustekinumab vs adalimumab	286	224	$\geq$50% reduction in SES-CD score from baseline or SES-CD score $\leq$3 or 0 in patients with baseline SES-CD score of 3	SES-CD $\leq$3, or SES-CD 0 for patients with baseline SES-CD 3	—

Supplementary Table 2. Certainty of Evidence Based on GRADE for the Network Meta-analysis

	Induction of endoscopic response		Maintenance of endoscopic remission	
	Direct	NMA	Direct	NMA
Compared with placebo				
TNF antagonists	Low[a]	Low	Moderate[b]	Moderate
IL12/23 antagonists	Moderate[b]	Moderate	—	Low
IL23 antagonists	High	High	Moderate[b]	Moderate
JAK1 inhibitors	High	High	Moderate[b]	Moderate
Etrolizumab	Low[a]	Low	Moderate[b]	Moderate
Vedolizumab	—	—	Very low[a,c]	Very low[a,c]
Compared with TNF antagonists				
IL12/23 antagonists	Low[a]	Low	Low[a]	Low
IL23 antagonists	—	Low	—	Low
JAK1 inhibitors	—	Low	—	Low
Etrolizumab	—	Low	—	Moderate
Vedolizumab	—	—	—	Low
Compared with IL12/23 antagonists				
IL23 antagonists	Low[a]	Low	—	Low
JAK1 inhibitors	—	Moderate	—	Low
Etrolizumab		Low		Low
Vedolizumab		—	—	Low
Compared with IL23 antagonists				
JAK1 inhibitors	—	Low	—	Low
Etrolizumab		Moderate	—	Low
Vedolizumab	—	—	—	Low
Compared with JAK1 inhibitors				
Etrolizumab	—	Moderate	—	Low
Vedolizumab	—	—	—	Low
Compared with etrolizumab				
Vedolizumab	—	—	—	Low

IL, interleukin; JAK1 inhibitors, Janus kinase 1 inhibitors; NMA, network meta-analysis; TNF, tumor necrosis factor.
[a]Very serious imprecision.
[b]Serious imprecision.
[c]Risk of bias because only a nonrandomly selected group of patients underwent ileocolonoscopy.

Supplementary Table 3. Comparative Efficacy of Biologic Agents and Oral Small Molecules for the Induction of Endoscopic Response and Endoscopic Remission in Biologic-Naive Patients With Moderate-to-Severe Crohn's Disease Using Network Meta-Analysis, Expressed as RR With 95% Confidence Intervals

	Induction of endoscopic response: biologic-naive patients						
Induction of endoscopic remission: biologic-naive patients	JAK1 inhibitors	0·39 (0·12–1·29)	0·35 (0·10–1·26)	—	—	—	1·50 (0·50–4·50)
	1·11 (0·14–8·69)	IL23 antagonists	0·90 (0·55–1·46)	—	—	—	**3·87 (2·38–6·30)**
	—	—	IL12/23 antagonists	—	—	—	**4·31 (2·21–8·41)**
	—	—	—	TNF antagonists	—	—	—
	—	—	—	—	Etrolizumab	—	—
	—	—	—	—	—	Vedolizumab	—
	2·81 (0·39–20·32)	**2·53 (1·44–4·43)**	—	—	—	—	Placebo

NOTE. Comparisons read from left-to-right; RR for comparisons in the cell in common between column- and row-defining treatment. RR >1 favors row-defining treatment. For the induction of endoscopic remission, RR >1 favors row-defining treatment. For the induction of endoscopic response, RR >1 favors column-defining treatment.
IL, interleukin; JAK1 inhibitors, Janus kinase 1 inhibitors; RR, risk ratio; TNF, tumor necrosis factor. Values highlighted in bold are statistically significant.

Supplementary Table 4. Comparative Efficacy of Biologic Agents and Oral Small Molecules for the Induction of Endoscopic Response and Endoscopic Remission in Biologic-Exposed Patients With Moderate-to-Severe Crohn's Disease Using Network Meta-Analysis, Expressed as RR With 95% Confidence Intervals

	Induction of endoscopic response: biologic-exposed patients						
Induction of endoscopic remission: biologic-exposed patients	JAK1 inhibitors	**2·38 (1·25–4·51)**	**3·91 (1·46–10·47)**	—	—	—	**6.43 (3·64–11·37)**
	0·97 (0·35–2·66)	IL23 antagonists	1·64 (0·76–3·54)	—	—	—	**2·71 (2·01–3·64)**
	0·68 (0·18–2·61)	0·70 (0·21–2·35)	IL12/23 antagonists	—	—	—	1·65 (0·74–3·68)
	—	—	—	TNF antagonists	—	—	—
	—	—	—	—	Etrolizumab	—	—
	—	—	—	—	—	Vedolizumab	—
	5·58 (2·43–12·77)	5·76 (3·23–10·29)	8·18 (2·85–23·50)	—	—	—	Placebo

NOTE. Comparisons read from left-to-right; RR for comparisons in the cell in common between column- and row-defining treatment. RR >1 favors row-defining treatment. For the induction of endoscopic remission, RR >1 favors row-defining treatment. For the induction of endoscopic response, RR >1 favors column-defining treatment. Values highlighted in bold are statistically significant.
IL, interleukin; JAK1 inhibitors, Janus kinase 1 inhibitors; RR, risk ratio; TNF, tumor necrosis factor.

Supplementary Table 5. Comparative Efficacy of Biologic Agents and Oral Small Molecules for the Induction and Maintenance of Ulcer-Free Endoscopic Healing in Biologic-Naive Patients With Moderate-to-Severe Crohn's Disease Using Network Meta-Analysis, Expressed as RR With 95% Confidence Intervals

		Induction of ulcer-free endoscopic healing: all patients					
Maintenance of ulcer-free endoscopic healing: all patients	JAK1 inhibitors	0·63 (0·07–5·45)	0·67 (0·07–6·09)	0·73 (0·08–6·88)	—	—	1·72 (0·21–14·31)
	—	IL23 antagonists	1·07 (0·61–1·88)	1·16 (0·50–2·65)	—	—	**2·72 (1·85–4·01)**
	—	0·83 (0·10–6·86)	IL12/23 antagonists	1·08 (0·42–2·78)	—	—	**2·55 (1·41–4·60)**
	—	0·23 (0·04–1·21)	0·28 (0·02–3·74)	TNF antagonists	—	—	**2·35 (1·13–4·91)**
	—	—	—	—	Etrolizumab	—	—
	—	—	—	—	—	Vedolizumab	—
	—	**2·59 (1·59–4·21)**	3·13 (0·40–25·53)	**11·25 (2·30–54·98)**	—	—	Placebo

NOTE. Comparisons read from left-to-right; RR for comparisons in the cell in common between column- and row-defining treatment. RR >1 favors row-defining treatment. For the induction of endoscopic remission, RR >1 favors row-defining treatment. For the induction of endoscopic response, RR >1 favors column-defining treatment. Values highlighted in bold are statistically significant.
IL, interleukin; JAK1 inhibitors, Janus kinase 1 inhibitors; RR, risk ratio; TNF, tumor necrosis factor.

Supplementary Table 6. Risk of Bias of Assessment

	Study	Random sequence allocation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective Reporting	Other sources of bias
1	Rutgeerts 2006 (ACCENT-1)	Low risk	Low risk	Low risk	Low risk	Unclear risk	Unclear risk	Unclear risk
2	Sandborn 2012 (CERTIFI)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
3	Rutgeerts 2012 (EXTEND)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
4	Feagan 2016 (UNITI-1)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
5	Feagan 2016 (UNITI-2)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
6	Feagan 2016 (IM-UNITI)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
7	Feagan 2017	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
8	Vermeire 2017 (FITZROY)	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Unclear risk
9	Sandborn 2020 (CELEST)	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
10	Reinisch 2021 (BERGAMOT)	Low risk	Low risk	Low risk	Low risk	Unclear risk	Unclear risk	Unclear risk
11	Vermeire 2021 (VISIBLE-2)	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
12	Sands 2022 (SERENITY)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
13	Sandborn 2022 (GALAXI-1)	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
14	D'Haens 2022 (ADVANCE)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
15	D'Haens 2022 (MOTIVATE)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
16	Ferrante 2022 (FORTIFY)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear risk
17	U-EXCEL (NCT03345849)	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
18	U-EXEED (NCT03345836)	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
19	U-ENDURE (NCT03345823)	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
20	Sands 2022 SEAVUE	Low risk	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk