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Efficacy and Safety of IL-12/23 and IL-23 Inhibitors for Crohn's Disease: Systematic Review and Meta-Analysis

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Declarations

Conflict of interest SKV and VS: None. MH, JKM, AZ, and CEP are employees of Alimentiv Inc. NN has received honoraria from Janssen, Abbvie, Takeda, Pfizer, Merck, Sandoz, Novartis, and Ferring. SS has received grant/research support from Pfizer and AbbVie and consulting fees from Pfizer. BES has received consulting and/or speaking from AbbVie; Abivax, Adiso Therapeutics, Alimentiv Inc., Amgen; Arena Pharmaceuticals, Artizan Biosciences, Artugen Therapeutics, AstraZeneca, Bacainn Therapeutics, Boehringer-Ingelheim, Boston Pharmaceuticals, Bristol Myers Squibb, Calibr, Celltrion Healthcare, ClostraBio, Cytoki Pharma, Connect Biopharma, Entera, Evommune, Fresenius Kabi, Galapagos, Genentech, Gilead Sciences, GlaxoSmith-Kline, Gossamer Bio, Imhotex, Immunic, Index Pharmaceuticals, Inotrem, Innovation Therapeutics, Ironwood Pharmaceuticals, Janssen, Kaleido, Kallyope, Lilly Pfizer, MiroBio, Morphic Therapeutics, MRM Health, OSE Immunotherapeutics, Progenity, Prometheus Biosciences, Protagonist Therapeutics, Q32 Bio, Redhill Biopharma, Sun Pharma, Surrozen, Synlogic, Takeda, Target RWE, Teva, Theravance Biopharma, TLL Pharmaceutical, USWM Enterprises, VielaBio, and VTA Labs; and consulting fees and stock options from Ventyx Biosciences. RP has received consulting fees from Abbott, AbbVie, Alimentiv Inc., Amgen, Arena Pharmaceuticals, AstraZeneca, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Celltrion, Cosmos Pharmaceuticals, Eisai, Elan, Eli Lilly, Ferring, Galapagos, Fresenius Kabi, Genentech, Gilead Sciences, Glaxo-Smith Kline, JAMP Bio, Janssen, Merck, Mylan, Novartis, Oppilan Pharma, Organon, Pandion Pharma, Pendopharm, Pfizer, Progenity, Protagonist Therapeutics, Roche, Sandoz, Satisfai Health, Shire, Sublimity Therapeutics, Takeda Pharmaceuticals, Theravance Biopharma, Trellus, Viatris, and UCB. BGF has received grant/research support from Millennium Pharmaceuticals, Merck, Tillotts Pharma AG, AbbVie, Novartis Pharmaceuticals, Centocor Inc., Elan/Biogen, UCB Pharma, Bristol-Myers Squibb, Genentech, ActoGenix, and Wyeth Pharmaceuticals Inc.; consulting fees from Millennium Pharmaceuticals, Merck, Centocor Inc., Elan/Biogen, Janssen-Ortho, Teva Pharmaceuticals, Bristol Myers Squibb, Celgene, UCB Pharma, AbbVie, Astra Zeneca, Serono, Genentech, Tillotts Pharma AG, Unity Pharmaceuticals, Albireo Pharma, Given Imaging Inc., Salix Pharmaceuticals, Novonordisk, GSK, Actogenix, Prometheus Therapeutics and Diagnostics, Athersys, Axcan, Gilead, Pfizer, Shire, Wyeth, Zealand Pharma, Zyngenia, Gi-Care Pharma Inc., and Sigmoid Pharma; and speaker's fees from UCB, AbbVie, and J&J/Janssen. VJ 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. CM has received consulting fees from AbbVie, Alimentiv Inc., Amgen, AVIR Pharma Inc., Bio-JAMP, Bristol Myers Squibb, Celltrion, Ferring, Fresenius Kabi, Janssen, McKesson, Mylan, Takeda, Pendopharm, Pfizer, Roche; speaker's fees from AbbVie, Amgen, AVIR Pharma Inc., Alimentiv Inc., Bristol Myers Squibb, Ferring, Fresenius Kabi, Janssen, Takeda, Pendopharm, and Pfizer; royalties from Springer Publishing; and research support from Ferring and Pfizer. Alimentiv Inc. is an academic gastrointestinal contract research organization, operating under the Alimentiv Health Trust. CM, BGF, and VJ are consultants to Alimentiv Inc. and have a primary academic appointment; they are not employees of Alimentiv and do not hold equity positions or shares in Alimentiv Inc.

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Abstract

Background—Targeting interleukin-23 (IL-23) is an important therapeutic strategy for Crohn's disease (CD).

Aims—This systematic review and meta-analysis assessed the efficacy and safety of selective IL-23p19 and IL-12/23p40 inhibitors in patients with moderate-to-severe CD.

Methods—MEDLINE, Embase, and the Cochrane library (CENTRAL) were searched from inception to May 24, 2023, for randomized, placebo- or active comparator-controlled induction and/or maintenance trials of selective IL-23p19 and IL-12/23p40 inhibitors in pediatric and adult patients with CD. The primary outcome was the proportion of patients in clinical remission. Secondary outcomes were clinical response, endoscopic remission, endoscopic response, and safety. Data were pooled using a random-effects model. Risk of bias and certainty of evidence were assessed using the Cochrane risk of bias tool and the GRADE criteria, respectively.

Results—Eighteen trials (n = 5561) were included. Most studies were rated as low risk of bias. Targeting IL-23 was significantly superior to placebo for inducing clinical (risk ratio [RR] = 1.87, 95% confidence interval [CI] 1.58–2.21) and endoscopic (RR = 3.20, 95%CI 2.17–4.70) remission and maintaining clinical remission (RR = 1.39, 95%CI 1.10–1.77) (GRADE high certainty evidence for all outcomes). Subgroup analysis showed that targeting IL-23 was superior to placebo for inducing clinical remission in biologic-naïve (RR = 2.20, 95%CI 1.46–3.32, I^2 = 0%, p = 0.39) and biologic-experienced patients (RR = 1.82, 95%CI 1.27–2.60, I^2 = 56.5%, p = 0.01). Targeting IL-23 was associated with a decreased risk of serious adverse events in induction (RR = 0.55, 95%CI 0.44–0.73) and maintenance (RR = 0.72, 95%CI 0.53–0.98) trials compared to placebo (high certainty evidence).

Conclusion—Targeting IL-23 is effective and safe for inducing and maintaining clinical and endoscopic remission in patients with moderate-to-severe CD.

Keywords

Interleukin-23 inhibitors; Ustekinumab; Biologic therapy; Crohn's disease; Inflammatory bowel disease; Risankizumab

Introduction

Crohn's disease (CD) is a chronic immune-mediated inflammatory disease (IMID) resulting from complex environmental interactions in genetically susceptible individuals. The introduction of infliximab as the first tumor necrosis factor alpha (TNF-α) antagonist nearly 25 years ago revolutionized the management of moderate-to-severely active CD [1]. While TNF-α antagonists are highly effective, approximately one-third of patients are primary non-responders to induction therapy, half of patients who have an initial response may lose response over time, and most patients do not achieve the guideline-recommended therapeutic target of endoscopic remission with anti-TNF therapy [1–3]. Thus, new approaches are needed.

Interleukin (IL)-23 is a critical inflammatory mediator, responsible for differentiation and expansion of the proinflammatory Th17 subset of CD4 + T-cells. In genome-wide association studies, IL-23 receptor (IL-23R) variants are strongly associated with the development of CD [4] and a recent study showed that patients refractory to TNF-α antagonists demonstrate immunological escape through increased expression of IL-23R on mucosal TNFR2 expressing CD4 + cells, indicating a potential therapeutic role for targeting IL-23 in this population [5]. IL-23 has 2 subunits (p40 and p19). Monoclonal antibodies targeting the shared p40 subunit block both IL-12 and IL-23 [6]. Ustekinumab was the first biologic targeting IL-12/23p40 approved for CD treatment, after pivotal phase III trials demonstrated superiority of ustekinumab over placebo for achieving and maintaining clinical remission (UNITI I and II and IM-UNITI) [7]. A subsequent head-to-head randomized controlled trial (RCT) of ustekinumab compared with adalimumab showed no difference in clinical remission rates at week 52 in patients with biologic-naïve CD [8]. However, in other IMIDs, such as psoriasis, targeting IL-23 specifically via the p19 subunit has resulted in significantly higher response rates compared to either TNF-α antagonists or ustekinumab [9, 10]. Accordingly, there has been substantial interest in developing IL-23p19 antagonists for CD, several RCTs investigating these agents have been reported, and the first agent in this class has recently been approved for CD (risankizumab) [11].

Given the expanding therapeutic armamentarium in CD and to better understand the efficacy and safety of IL-12/23p40 and IL-23p19 antagonists, we conducted a systematic review and meta-analysis of all RCTs evaluating these agents in moderate-to-severe CD.

Methods

This systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [12].

Selection Criteria

We included phase II and III RCTs of pediatric and adult patients with moderate-to-severe CD that compared anti-IL-12/23p40 (e.g., ustekinumab, briakinumab, apilimod mesylate) or anti-IL-23p19 (e.g., brazikumab, risankizumab, guselkumab, mirikizumab) to placebo or an active comparator. Clinical, endoscopic, biomarker, quality of life, and safety outcome data were collected for both induction and maintenance studies.

Data Sources, Search Strategy, and Study Selection

MEDLINE, Embase, and the Cochrane CENTRAL Register of Controlled Trials were searched to May 24, 2023 (Supplementary Appendix 1). Two authors (SKV and AZ) independently performed title and abstract review to identify relevant studies. Full-text review determined eligibility according to pre-specified criteria. Discrepancies were resolved through discussion with a third author (JKM). The bibliographies of included studies, relevant review articles, and abstracts from conference proceedings (2010–2023) were manually searched for additional studies.

Data Abstraction and Quality Assessment

Data pertaining to study characteristics, participants, interventions, comparators, and outcomes were extracted by 2 independent investigators (SKV and AZ). Discrepancies were resolved through discussion with a third author (JKM). Risk of bias was assessed using the Cochrane risk of bias tool [13]. The GRADE approach was used to assess the certainty of evidence for primary and secondary outcomes [14]. Results from RCTs were initially considered high quality, but potentially downgraded due to risk of bias, indirectness of evidence, unexplained heterogeneity, publication bias, or sparse data/imprecision.

Outcomes

The primary outcome was the proportion of patients achieving or maintaining clinical remission at study endpoint, as defined by the original studies. If data from multiple time points were reported, data were extracted at 8 weeks for induction (range: week 6–16) and 52 weeks for maintenance (range: week 24–52) trials. Secondary outcomes included the proportion of patients achieving or maintaining clinical response, patient-reported outcome (PRO)-defined response or remission, endoscopic response, endoscopic remission, and ulcer-free endoscopy (i.e., mucosal healing), as defined by the original trial. Quality of life, adverse events (AEs), serious adverse events (SAEs), and withdrawal due to adverse events were also secondary outcomes. Subgroup analyses based on IL-12/23p40 vs. IL-23p19 inhibitors and prior exposure to biologics were performed.

Statistical Analysis

Pooled risk ratios (RRs) and corresponding 95% confidence intervals (CIs) were calculated using a random-effects model to account for between- and within-study heterogeneity, given differences in trial design and patient populations. Effect sizes were only pooled if there were 3 or more studies available per outcome. Data were analyzed on an intention-to-treat basis; patients lost to follow-up or excluded for other reasons were deemed treatment

failures. Between-study heterogeneity was assessed using the I^2 statistic [15]. All analyses were performed using the '*metafor*' package R (version 4.0.1).

Results

Search Results and Included Studies

After removing duplicates, 5082 records were screened and 294 citations were selected for full-text review. A total of 29 records reporting data from 18 RCTs (n = 5561) were included (Fig. 1).

Study Characteristics and Outcomes

Characteristics of the included studies are reported in Table 1. Ten of the included studies evaluated IL-12/23p40 inhibitors (ustekinumab, briakinumab, and apilimod mesylate) and 8 studies evaluated IL-23p19 inhibitors (brazikumab, risankizumab, guselkumab, and mirikizumab). Two trials were not placebo controlled and thus, were not included in the quantitative analysis [8, 16]. Of the remaining 16 RCTs, 8 were induction studies [7, 17–21], 2 were induction responder re-randomization maintenance studies [7, 22], and 6 studies included both induction and maintenance phases [23–28]. In the maintenance phase of the SERENITY study, all patients received both placebo and the study drug in a double-dummy design to maintain study blinding; hence, the maintenance data were not included in the quantitative analysis. Of the 18 trials, 7 recruited pre-dominantly biologic-experienced patients (proportion of biologic-experienced patients: 91–100%) [7, 16, 19, 21, 25, 27], 10 recruited both biologic-experienced and biologic-naïve patients (29–76%) [7, 17, 18, 20, 21, 24, 26, 28], and 1 trial recruited exclusively biologic-naïve patients [8]. Nine studies permitted previous exposure to TNF-α antagonists and 5 studies permitted previous exposure to either TNF-α antagonists or anti-integrin agents. Only the phase III risankizumab trials allowed previous exposure to ustekinumab [21, 22].

Clinical remission (CDAI score < 150) was assessed at weeks 6 to 16 in the induction studies and at weeks 24 to 52 in the maintenance studies. Among the 7 induction studies that reported on endoscopic outcomes, all except 1 used SES-CD-based definitions. Most commonly, an SES-CD score ≤ 2 was used to define endoscopic remission and a ≥ 50% reduction from baseline was used to define endoscopic response.

Risk of Bias and Overall Quality of Evidence

All the studies were rated as having low or unclear risk of bias, except for NCT02574637 [23], which was rated as high risk of bias for "other sources of bias" (study was terminated early and only descriptive efficacy endpoints were reported, Supplementary Table 2). The results of the GRADE analyses are reported in Supplementary Tables 3 and 4.

Efficacy of IL-12/23p40 and IL-23p19 Antagonists as Induction Therapy

Clinical Outcomes—A total of 31.5% (1057/3349) of patients receiving an IL-12/23p40 or IL-23p19 inhibitor achieved clinical remission compared to 15.7% (224/1427) of patients assigned to placebo (RR 1.91, 95% CI 1.62–2.26, 15 studies, I^2 = 27.5%, high certainty evidence; Fig. 2a). On subgroup analysis, there was no significant difference in the

proportion of participants treated with an IL-12/23p40 antagonist achieved clinical remission (23.9%, 434/1815) compared to participants receiving an IL-23p19 inhibitor (37.6%, 1057/3349) (RR 0.87, 95% CI 0.61–1.24, $p = 0.43$; Supplementary Fig. 1; Supplementary Table 5).

Forty-nine percent (1636/3348) of patients treated with an IL-12/23p40 or IL-23p19 antagonist had a clinical response (> 100-point reduction in CDAI score from baseline or a CDAI score < 150) compared with 27% of patients receiving placebo (381/1427). This difference was statistically significant (RR 1.77, 95% CI 1.49–2.11, 14 studies, I^2 = 54.3%, moderate certainty of evidence; Fig. 2b). On subgroup analysis, clinical response was achieved by 40.5% (735/1814) and 48.8% (1636/3348) of patients treated with an IL-12/23p40 and IL-23p19 antagonist, respectively (RR 0.87, 95% CI 0.62–1.21, $p = 0.41$; Supplementary Fig. 2; Supplementary Table 5).

In subgroup analysis based on prior exposure to biologics, IL-12/23p40 and IL-23p19 antagonists were superior to placebo for inducing clinical remission (RR 2.20, 95% CI 1.46–3.32, $I^2 = 0\%$, $p = 0.39$; high certainty evidence; Supplementary Fig. 3) and clinical response (RR 1.39, 95% CI 1.05–1.83, $I^2 = 45.6\%$; high certainty evidence; Supplementary Fig. 4) in biologic-naïve patients. Similarly, IL-12/23p40 and IL-23p19 agents were superior to placebo for inducing clinical remission (RR 1.82, 95% CI 1.27–2.60, $I^2 = 56.5\%$; moderate certainty evidence; Supplementary Fig. 5) and response (RR 1.85, 95% CI 1.64–2.09, I^2 = 41.1%; moderate certainty evidence; Supplementary Fig. 6) in biologic-experienced patients.

The UNISTAR study was the only pediatric RCT identified. This was a phase I pharmacokinetic study evaluating 2 doses of ustekinumab. At 16 weeks, 22% of patients in the low-dose arm (3 mg/kg or 130 mg) and 29% of patients in the high-dose arm (9 mg/kg or 390 mg) achieved clinical remission.

Endoscopic Outcomes—Overall, 19.2% (312/1620) of patients receiving an IL-12/23p40 or IL-23p19 inhibitor achieved endoscopic remission compared to 5.1% (34/664) patients receiving placebo (RR 3.20, 95% CI 2.24–4.57, 7 studies, $I^2 = 0\%$, high certainty evidence; Fig. 3a). The pooled analysis showed 33.2% (554/1669) and 15.8% (242/1534) had endoscopic response (RR 2.55, 95% CI 1.90–3.42, $I^2 = 32.8\%$, high certainty evidence; Fig. 3b) and ulcer-free endoscopy, respectively (RR 2.77, 95% CI 1.93–3.98, $I^2 = 0\%$, moderate certainty evidence; Supplementary Fig. 7) compared to 11.8% (81/684) and 5.1% (31/609) in patients receiving placebo.

Treatment with IL-12/23p40 antagonists was not superior to placebo for inducing endoscopic remission or response, whereas treatment with IL-23p19 antagonists was significantly better than placebo for inducing all endoscopic outcomes. However, there was no significant difference between IL-12/23p40 and IL-23p19 antagonists for inducing endoscopic remission (RR 0.60, 95% CI 0.23–1.59, $p = 0.30$; Supplementary Table 5).

Efficacy of IL-12/23p40 and IL-23p19 Antagonists as Maintenance Therapy

Clinical Outcomes—Forty-nine percent (369/758) of participants treated with IL-12/23p40 or IL-23p19 antagonists maintained remission compared with 34.2% (148/433)

of patients randomized to placebo (RR 1.40, 95% CI 1.17–1.69, 6 studies, I^2 = 34.2%, high certainty evidence; Fig. 4a). Clinical response was maintained in 61.1% (425/695) of patients treated with IL-12/23p40 or IL-23p19 agents compared with 45.8 (182/397) of participants receiving placebo (RR 1.35, 95% CI 1.20–1.53, 5 studies, I^2 = 25.6%, Fig. 4b).

Data on clinical remission stratified by prior biologic exposure were available for brazikumab, risankizumab, and ustekinumab. Pooled analysis demonstrated overall superiority in biologic-experienced patients (RR 1.39, 95% CI 1.1–1.77, 3 studies, I^2 = 28%; Supplementary Fig. 8). Two studies reported maintenance of clinical remission in biologic-naïve patients [7, 22]. There was a numerically higher clinical remission rate among patients receiving active treatment compared to placebo in the IM-UNITI (60.9% vs 49%) and FORTIFY (68.7% vs 58.5%) studies.

Endoscopic Outcomes—Three maintenance studies reported endoscopic outcomes [7, 22, 23]. Pooled analyses showed that IL-12/23p40 and IL-23p19 agents were superior to placebo for maintaining endoscopic remission (RR 2.61, 95% CI 1.72–3.96, I^2 = 0%, moderate certainty evidence; Supplementary Fig. 9) and response (RR 2.17, 95% CI 1.60–2.95, I^2 = 0%, moderate certainty evidence; Supplementary Fig. 10). Among the individual agents, ustekinumab and brazikumab were not associated with better endoscopic outcomes compared to placebo. Risankizumab was superior to placebo for maintaining endoscopic response, remission, and ulcer-free endoscopy.

Patient-Reported Outcomes

Patients treated with IL-12/23p40 or IL-23p19 antagonists achieved statistically superior induction of Inflammatory Bowel Disease Questionnaire (IBDQ remission (29.7% vs 14.2%, RR 2.01, 95% CI 1.57–2.58, 6 studies, I^2 = 33.1%; Supplementary Fig. 11), IBDQ improvement (RR 1.49, 95% CI 1.39–1.61, 7 studies, I^2 = 0%; Supplementary Fig. 12), and PRO2 remission compared to placebo (RR 2.06, 95% CI 1.72–2.47, 6 studies, I^2 = 0%; Supplementary Fig. 13) with high certainty evidence for all the 3 outcomes. In addition, treatment with IL-12/23p40 and IL-23p19 antagonists was superior to placebo for maintenance of IBDQ improvement (RR 1.36, 95% CI 1.20–1.53, 3 studies, I^2 = 0%, high certainty evidence; Supplementary Fig. 14).

Safety Outcomes

Fifty-nine percent (2031/3418) of patients treated with an IL-12/23p40 or IL-23p19 antagonist experienced any AE compared to 65.1% (932/1431) of patients receiving placebo (RR 0.91, 95% CI 0.87–0.96, I^2 = 0%; high certainty evidence Supplementary Fig. 15). Similar results were observed for SAEs (RR 0.55, 95% CI 0.44–0.73, I^2 = 0%, high certainty evidence Supplementary Fig. 16). For maintenance trials, there was no statistically significant difference in AEs (RR 0.94, 95% CI 0.89–1.00, 6 studies, I^2 = 0%, high certainty evidence; Supplementary Fig. 17) and a significantly lower risk of serious AEs (RR 0.72, 95% CI: 0.53–0.98, I^2 = 0%, moderate certainty evidence; Supplementary Fig. 18) in patients treated with anti-IL-12/23p40 or anti-IL-23p19 agents compared to placebo. Patients receiving treatment were also less likely to withdraw due to AEs compared to patients receiving placebo during induction (RR 0.44, 95% CI 0.30–0.67, I^2 = 11.3%;

Supplementary Fig. 19), and this trend persisted but was not statistically significant during maintenance therapy (RR 0.53, 95% CI 0.23–1.19, I^2 = 35.4%; Supplementary Fig. 20).

Discussion

IL-12 and IL-23 play important roles in both homeostasis and the inflammatory process. IL-12 mediates Th1 CD4 + T-cell differentiation [29, 30], whereas IL-23 is the primary pathogenic driver of Th17-dominant inflammatory pathways [31]. Key findings of our analysis include moderate-to-high certainty evidence supporting the superiority of IL-12/23p40 and IL-23p19 antagonists compared to placebo for inducing and maintaining clinical, endoscopic, PRO, and quality of life outcomes in biologic-naïve and biologic-experienced patients. Furthermore, we show that treatment with agents blocking IL-23 in RCT settings is associated with fewer SAEs and AEs requiring treatment discontinuation compared to placebo. Taken together, these findings can help clinicians place IL-23-targeted agents in treatment algorithms for CD.

We found similar clinical efficacy with ustekinumab and IL-23p19 antagonists, relative to placebo. However, in other IMIDs, targeting p19 compared to p40 has shown superior efficacy. Although both classes inhibit pathogenic IL-23, targeting p19 is generally associated with more specific and higher affinity binding [32]. For example, in the phase III UltIMMa-1 and UltIMMa-2 RCTs, approximately 30% more patients treated with risankizumab achieved 90% improvement in the Psoriasis Area Severity Index at week 16 compared to patients treated with ustekinumab (adjusted treatment differences 27.6–33.5%, $p < 0.0001$ in both trials) [9, 33]. In patients with CD the relative efficacy of IL-23p19 antagonists and ustekinumab have been indirectly compared. First, in the GALAXI-I trial, similar clinical remission (53.0% pooled guselkumab doses vs. 46.0% ustekinumab), PRO2 remission (42.7% vs. 39.7%), endoscopic response (35.7% vs. 28.6%), and clinical biomarker response (47.0% vs. 46.0%) rates were observed between the guselkumab and ustekinumab reference arm at week 12 [20]. Similar results for clinical and PRO2 remission between guselkumab and ustekinumab at week 48 have been reported [34]. Second, 2 independently conducted network meta-analyses found that treatment with risankizumab may be more likely to induce clinical remission in patients with moderate-to-severe CD compared to ustekinumab, although this difference was not statistically significant [3, 35].

While the relative risk of achieving clinical remission compared to placebo was similar between ustekinumab and anti-IL-23-p19 agents in our analysis, we observed numerically higher rates of remission and achievement of endoscopic outcomes with anti-IL-23p19 treatment. Specific targeting of IL-23 may achieve better endoscopic outcomes. In a sub-study from the UNITI trials, there was no statistically significant difference between ustekinumab and placebo for achieving week 8 endoscopic response (20.6% vs. 13.4%, $p = 0.14$), endoscopic remission (7.7% vs. 4.1%, $p = 0.25$), or ulcer-free mucosal healing (9.0% vs. 4.1%, $p = 0.14$) [36]. In contrast, phase III trials of risankizumab showed that treatment with either 600 mg or 1200 mg was associated with significantly higher rates of endoscopic response (29–40% vs. 11–12%), endoscopic remission (19–24% vs. 4–9%), and ulcer-free endoscopy (14–21% vs. 4–8%) at week 12 ($p < 0.001$ for all comparisons in both trials), and these differences were maintained at week 52 in the FORTIFY study

[22]. These trials also enrolled difficult-to-treat patients with CD who failed multiple prior biologic therapies. However, it should be noted that comparing endoscopic outcomes across CD trials is challenging and definitions of endoscopic remission vary [37]. The head-to-head SEQUENCE trial (NCT04524611) comparing risankizumab to ustekinumab using a primary endoscopic outcome at 1 year will provide more definitive answers for whether targeting IL-23p19 is a superior treatment strategy to targeting IL-12/23p40 in CD.

Our analysis confirms that IL-12/23p40 and IL-23p19 antagonists are effective in biologic-naïve and biologic-exposed populations. We found a lower risk of SAEs and AEs requiring treatment withdrawal compared to placebo in patients treated with anti-IL-12/23p40 or anti-IL-23p19 agents, which likely relates to fewer AEs from worsening CD [38]. Although RCTs are generally underpowered for detecting rare AEs, five-year safety data in CD support the favorable safety profile of long-term ustekinumab [39]. Furthermore, a recent meta-analysis of head-to-head cohort studies suggests that ustekinumab is associated with approximately half the risk of serious infections compared to TNF-α antagonists [40]. Although long-term real world and registry-based data for IL-23p19 antagonists in CD is still required, integrated safety analyses in psoriasis and psoriatic arthritis have not identified any new or concerning safety signals [41, 42].

For patients with prior biologic failure, a network meta-analysis by Barberio et al. [35] has suggested that anti-IL-23 therapy may be the most effective strategy. It should be acknowledged that overall, patients enrolled in more recent IL-23p19 trials had more refractory disease, failed more prior biologics, and often demonstrated failure to multiple mechanisms of action beyond TNF-α antagonists alone. Therapeutic options in this difficult-to-treat population are relatively limited: although some patients with prior TNF-α antagonist failure may benefit from trialing a different anti-TNF-α agent, response rates are generally low [43] and in the GEMINI-3 trial, vedolizumab was not more effective than placebo for inducing clinical remission at week 6 in patients with CD and prior TNF-α antagonist failure [44].

Our study has some important strengths. We summarize all the phase II and III clinical trial data for targeting IL-23 in adult patients and generate estimates of treatment efficacy and safety across different disease populations by biologic exposure. These data will help inform the relative positioning of IL-23 antagonists in clinical care. However, we also acknowledge some limitations. First, although there was low statistical heterogeneity for most outcomes, there were differences in trial design, inclusion criteria, and outcome definitions. Therefore, we generated conservative effect size estimates using random-effects rather than fixed-effects models. Nevertheless, we recognize that differences in baseline populations are likely to persist. For example, even though recent trials enrolled patients using endoscopy, the baseline endoscopic requirements varied from an SES-CD ≥ 3 to ≥ 7 for ileocolonic disease. Additionally, PROs have been recently introduced for enrollment and outcome assessment, although our analyses of clinical remission defined by CDAI and PROs were consistent. Second, there were insufficient data on biomarkers, such as fecal calprotectin and C-reactive protein. Third, except for risankizumab, most data for anti-IL-23p19 agents were from phase II trials.

In conclusion, biologics targeting IL-23 are effective and safe for inducing and maintaining clinical and endoscopic remission and for improving patient quality of life. These therapies have an important role in the management of biologic-naïve and biologic-experienced patients with CD, but future head-to-head controlled studies are required to better inform the relative positioning of these drugs for the management of CD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Data availability

All relevant data are included within the article and/ or its supplementary materials.

Abbreviations

ADA	Adalimumab
AM	Apilimod mesylate
BRA	Brazikumab
BRI	Briakinumab
CD	Crohn’s disease
CDAI	Crohn’s Disease Activity Index CDEIS Crohn’s Disease Endoscopic Index of Severity
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
GUS	Guselkumab
IBD	Inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
IL-23	Interleukin-23
IL-23R	IL-23 receptor
MD	Mean difference
MIR	Mirikizumab
PASI	Psoriasis Area Severity Index
PBO	Placebo
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PRO2	Patient-reported outcome-2
RCT	Randomized controlled trial
RIS	Risankizumab
RR	Risk ratio
SES-CD	Simple endoscopic score for Crohn's disease SF Stool frequency
TNF	Tumor necrosis factor
UST	Ustekinumab

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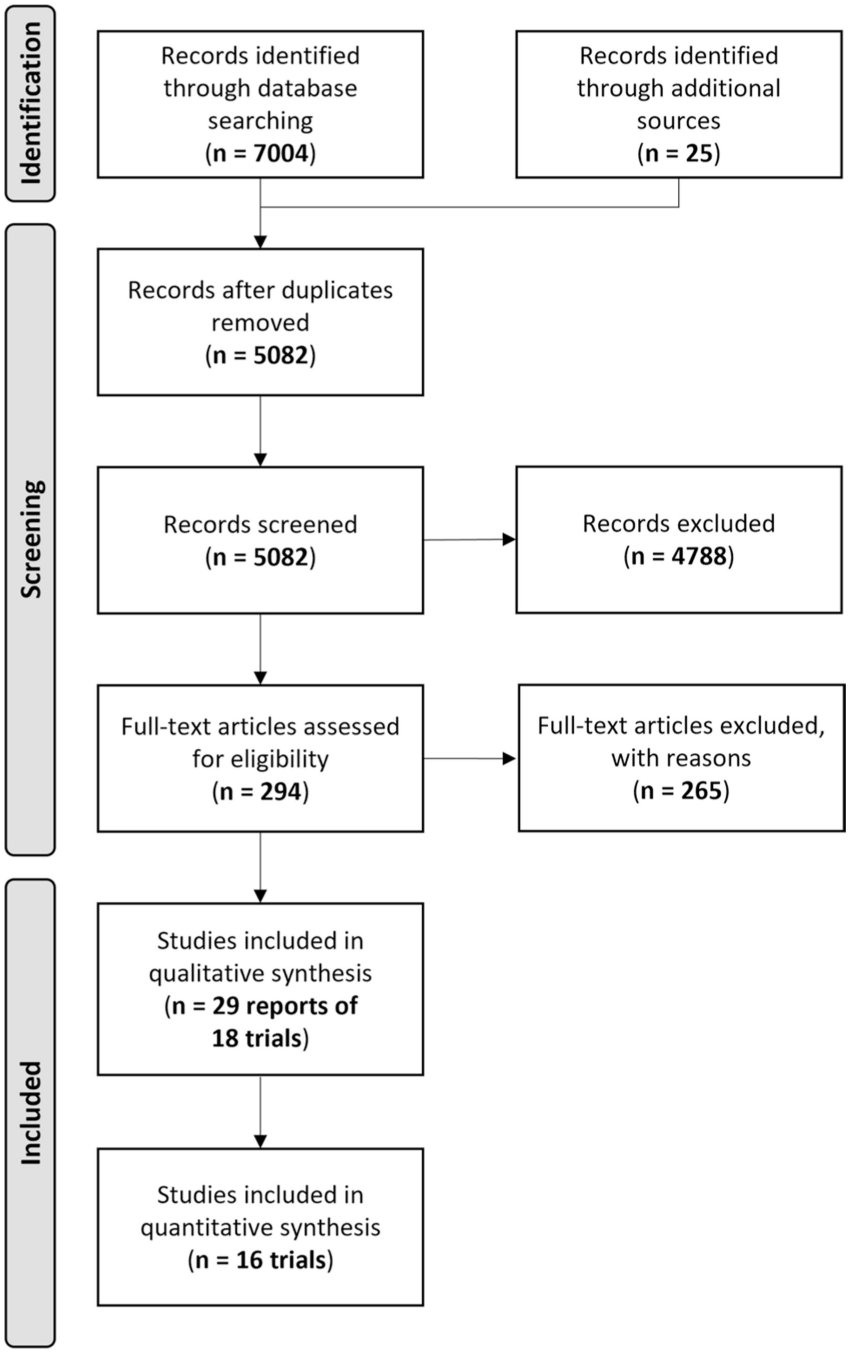

Fig. 1.
PRISMA flow diagram

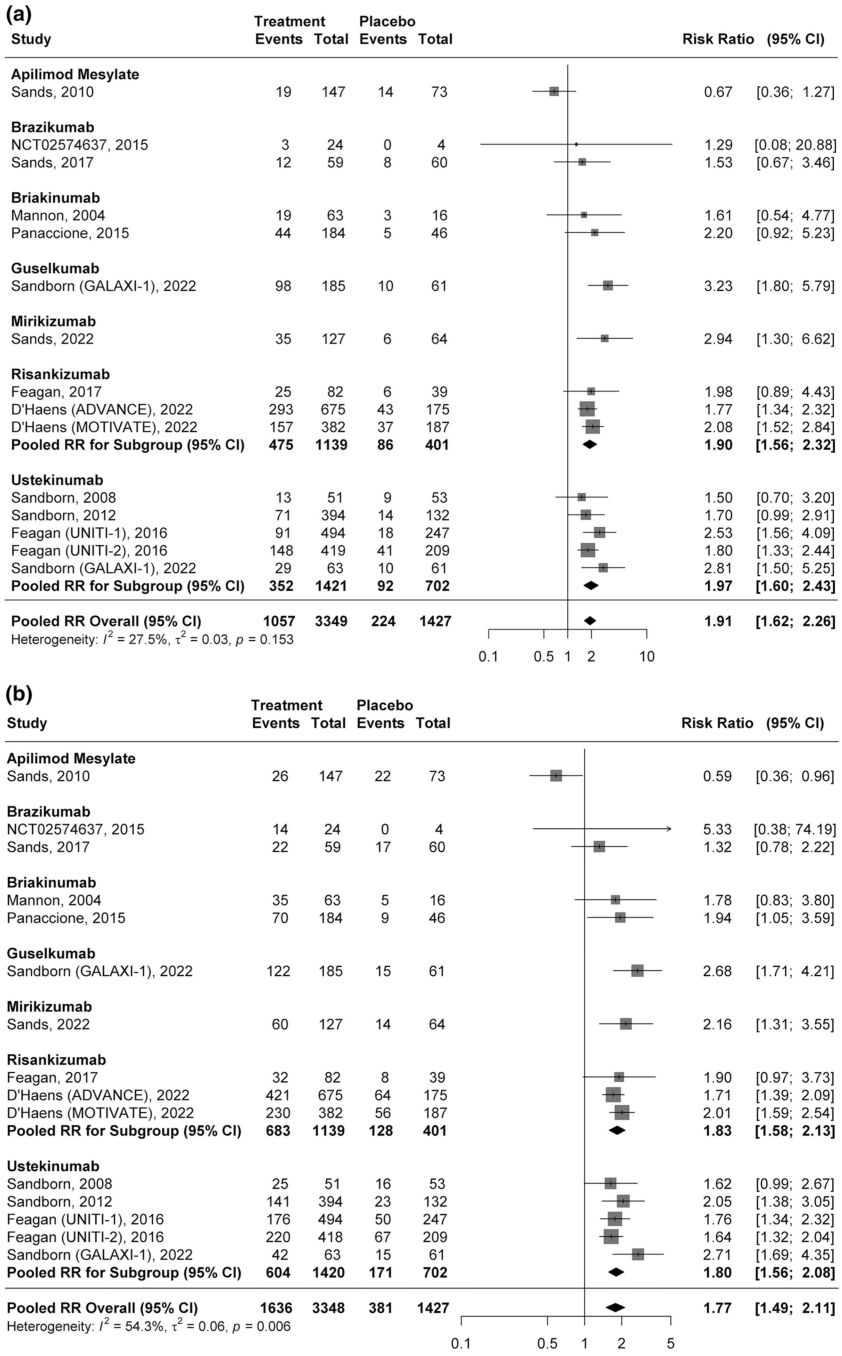

Fig. 2.

a Pooled efficacy of IL-12/23p40 and IL-23p19 antagonists for inducing clinical remission.

b Pooled efficacy of IL-12/23p40 and IL-23p19 antagonists for inducing clinical response

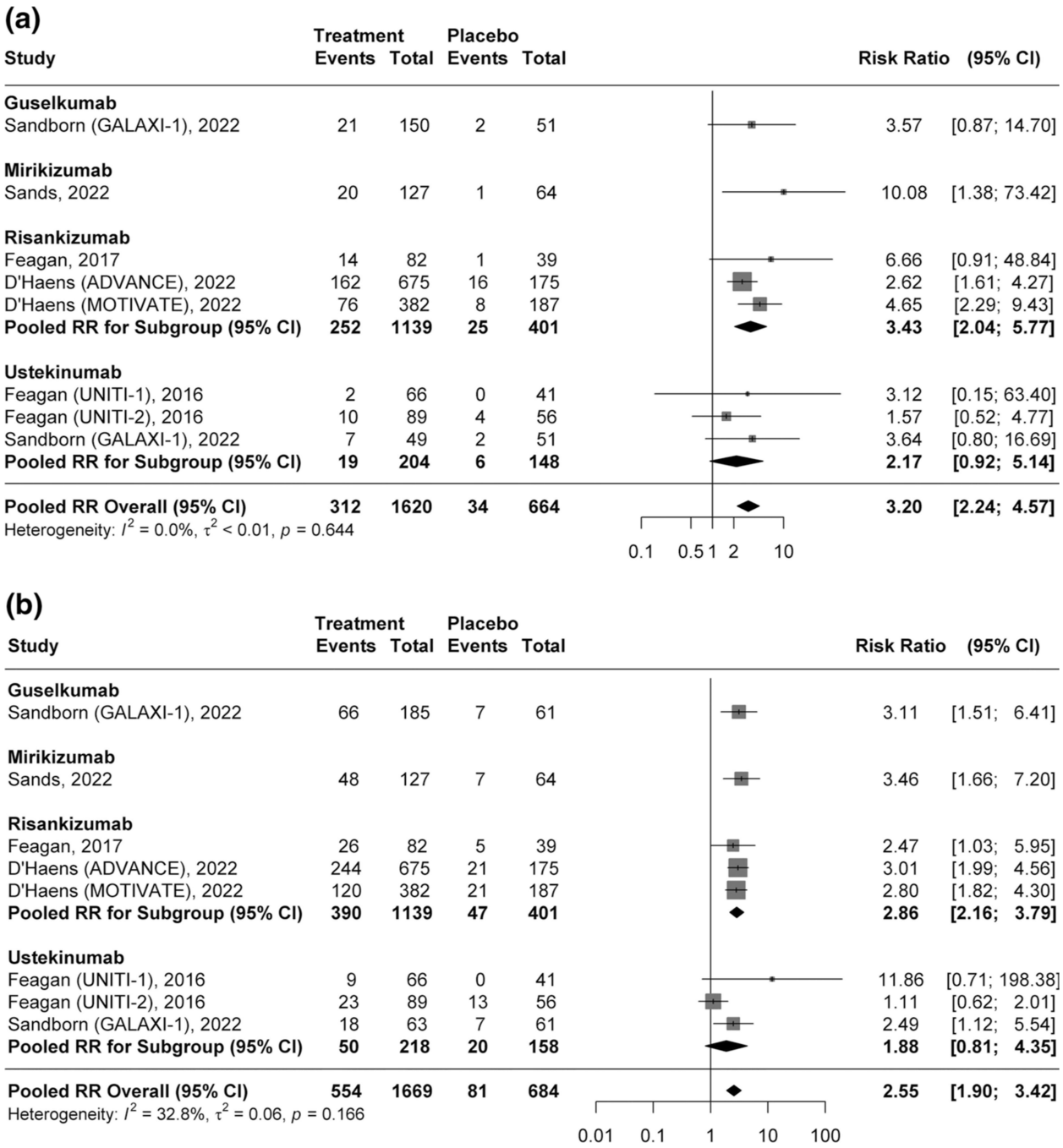

Fig. 3.

a Pooled efficacy of IL-12/23p40 and IL-23p19 antagonists for inducing endoscopic remission. **b** Pooled efficacy of IL-12/23p40 and IL-23p19 antagonists for inducing endoscopic response

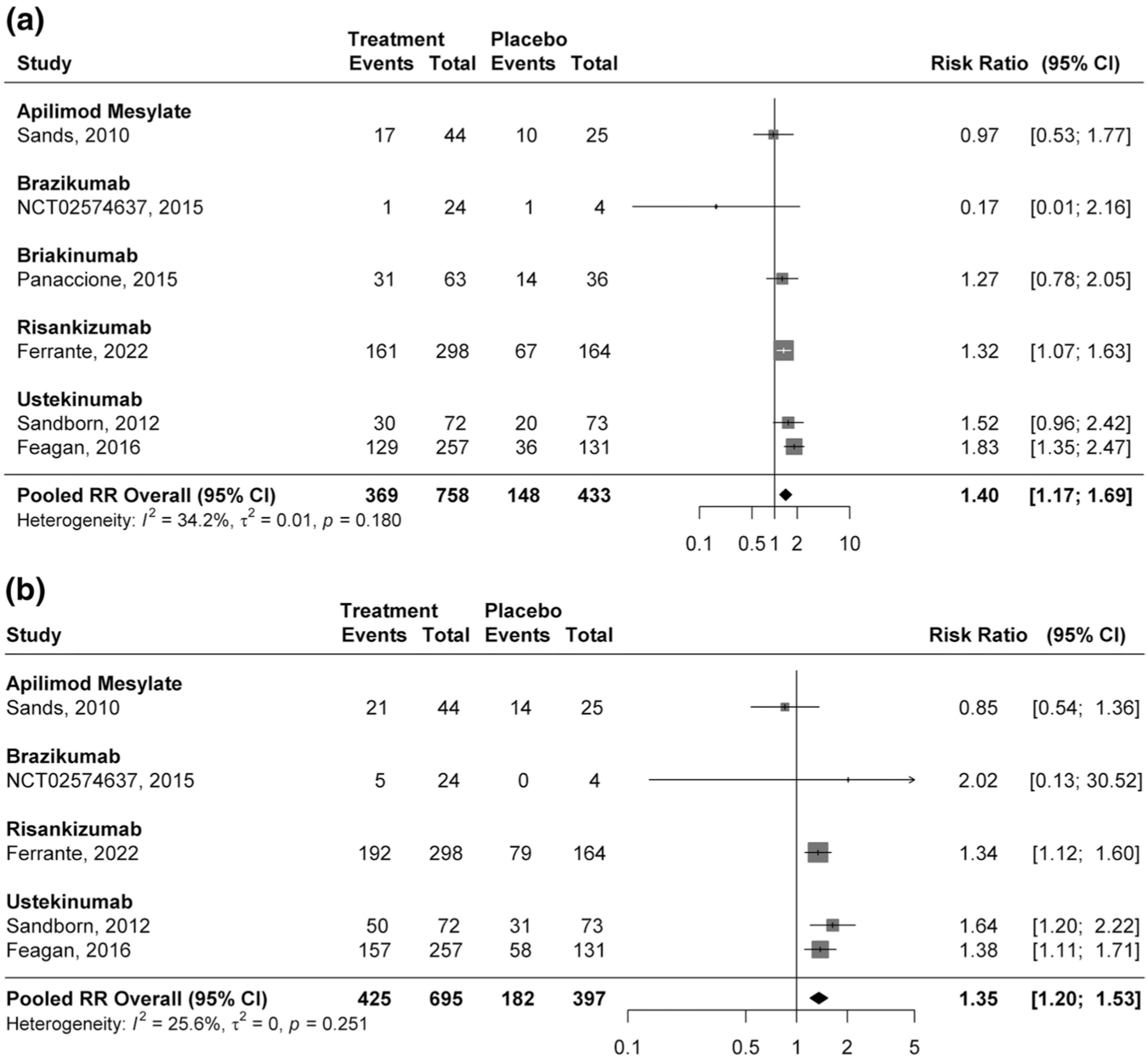

Fig. 4.

a Pooled efficacy of IL-12/23p40 and IL-23p19 antagonists for maintaining clinical remission. **b** Pooled efficacy of IL-12/23p40 and IL-23p19 antagonists for maintaining clinical response

Table 1

Baseline characteristics of the included studies

Study ID	Number of participants	Intervention (n) comparator (n)	Trial phase	Induction/ maintenance	Sex	Disease location Ileum/ colon/ ileocolonic	Concomitant steroids	Concomitant immunosuppressants	Prior biologic exposure
Mannon 2004 [17]	Total = 79 BRA:63 PBO:16	Briakinumab Placebo	II	Induction	M:33% F: 67%	BRI: 22%/32%/46% PBO: 50%/25%/25%	BRI: 25% PBO: 37.5%	BRI: 38% PBO: 12.5%	BRI: NA PBO: NA
Sandborn 2008 [18]	Total = 104 UST:51 PBO:53	Ustekinumab Placebo	II	Induction	M:55% F:45%	UST: 78.4%/55%/ PBO:75.4%/64%/-	UST:33.3% PBO:30.2%	UST:29.4% PBO:37.7%	UST:41% PBO:51%
Sands 2010 [24]	Total = 220 AM:137 PBO:73	Apilimod mesylate Placebo	II	Induction Maintenance	M:39.5% F:60.5%	AM:NA PBO:NA	AM:11.5% PBO:19%	AM:4.0% PBO:1.0%	AM:62.5% PBO:52%
Sandborn 2012 [25] (CERTIFI)	Total = 526 UST:394 PBO:132	Ustekinumab Placebo	II	Induction Maintenance	M:41.3% F:58.8%	UST:NA PBO:NA	UST:48% PBO:55.3%	UST:24.4% PBO:22.7%	UST:100% PBO:100%
Panaccione 2015 [26]	Total = 246 BRI:200 PBO:46	Briakinumab Placebo	II	Induction maintenance	M:33.7% F:66.3%	BRI:71.7%/63%/- PBO:67.4%/58.7%/-	BRI:46.2% PBO:47.8%	BRI:20% PBO:21.7%	BRI:73.9% PBO:75.5%
NCT02574637 [23]	Total = 29 BRA:24 PBO:5	Brazikumab Placebo	II	Induction maintenance	M:42.8% F:57.2%	BRA:NA PBO:NA	BRA:NA PBO:NA	BRA:NA PBO:NA	BRA:100% PBO:100%
Feagan 2016 [7] (UNITI-1)	Total = 741 UST: 494 PBO:247	Ustekinumab Placebo	III	Induction maintenance	M: 42.8% F:57.2%	UST:15.2%/15.4%/ 69.2% PBO: 11.4%/19.5%/ 67.5%	UST:46.3% PBO:44.9%	UST:30.7% PBO:32.8%	UST:99.0% PBO:99.6%
Feagan 2016 [7] (UNITI-2)	Total = 628 UST:418 PBO:210	Ustekinumab Placebo	III	Induction maintenance	M:46.6% F:53.4%	UST:24.5%/20.8%/ 54.2% PBO:21%/17.6%/ 61.4%	UST:41.2% PBO:35.7%	UST:35% PBO:34.8%	UST:29.2% PBO:37.6%
Feagan 2016 [7] (IM-UNITI)	Total = 397 UST:264 PBO:133	Ustekinumab Placebo	III	Maintenance	M:43.5% F:56.5%	UST:17%/19.7%/ 63.2% PBO:14.3%/21.1%/ 64.6%	UST:46.2% PBO:44.4%	UST:36.3% PBO:35.3%	UST:60.2% PBO:60.9%
Feagan 2017 [19]	Total = 121 RIS:82 PBO:39	Risankizumab Placebo	II	Induction	M:38.8% F:61.2%	RIS:20%/50%/29% PBO:13%/41%/46%	RIS:20% PBO:15%	RIS:15% PBO:21%	RIS:92.7% PBO:95%
Sands 2017 [27]	Total = 121 BRA:60 PBO:61	Brazikumab Placebo	II	Induction maintenance	M:37.8% F:62.2%	BRA:23.7%/27.1%/ 47.5% PBO:30%/30%/40%	BRA:40.7% PBO:40%	BRA:30.5% PBO:23.3%	BRA:100% PBO:100%

Study ID	Number of participants	Intervention (n) comparator (n)	Trial phase	Induction/ maintenance	Sex	Disease location Ileum/ colon/ ileocolonic	Concomitant steroids	Concomitant immunosuppressants	Prior biologic exposure
Sands 2022 [28] (SERENITY)	Total = 191 MIR:127 PBO:64	Mirikizumab Placebo	II	Induction maintenance	M:48.7% F:51.3%	MIR:16%/39.4%/ 43.3% PBO:17.2%/39.1%/ 43.8%	MIR:28.3% PBO:32.8%	MIR:33.8% PBO:29.7%	MIR:60.6% PBO:67.2%
Sandborn 2022 [20] (GALAXI-1)	Total = 309 GUS:185 PBO:61 UST:63	Guselkumab Placebo	II	Induction	M:59.2% F:40.8%	GUS:32.4%/41.1%/ 26.5% PBO:26.2%/42.6%/ 69.9%	GUS:34.1% PBO:39.3%	GUS:31.4% PBO:42.6%	GUS:60% PBO:68.9%
D'Haens 2022 [21] (ADVANCE)	Total = 850 RIS:675 PBO:175	Risankizumab Placebo	III	Induction	M:54% F:46%	RIS:15%/36%/50% PBO:11%/40%/49%	RIS:30% PBO:29%	RIS:24% PBO:24%	RIS:58% PBO:55%
D'Haens 2022 [21] (MOTIVATE)	Total = 569 RIS:382 PBO:187	Risankizumab Placebo	III	Induction	M:51% F:49%	RIS:14%/39%/47% PBO:14%/39%/47%	RIS:34% PBO:36%	RIS:23% PBO:21%	RIS:100% PBO:100%
Rosh 2021 [16] (UNISTAR)	Total = 44 UST (3 mg/ kg): UST (9 mg/ kg):	Ustekinumab (3 mg/kg) Ustekinumab (9 mg/kg)	I	Induction maintenance	M:41% F:59%	UST (3 mg/ kg):17%/35%/48% UST (9 mg/ kg):5%/30%/65%	UST (3 mg/ kg):30% UST (9 mg/ kg):33%	UST (3 mg/ kg):30% UST (9 mg/ kg):48%	UST (3 mg/ kg):91% UST (9 mg/ kg):91%
Sands 2022 [8] (SEAVUE)	Total = 386 UST:191 ADA:195	Ustekinumab Adalimumab	III	Induction maintenance	M:48% F:52%	UST:32%/14%/54% ADA:28%/17%/53%	UST:22% ADA:24%	UST:NA ADA:NA	UST:0% ADA:0%
Ferrante 2022 [22] (FORTIFY)	Total = 462 RIS:292 PBO:164	Risankizumab Placebo	III	Maintenance	M:51.5% F:48.5%	RIS:10%/43.2%/ 46.6% PBO:14%/38%/48%	RIS:31.2% PBO:31%	RIS:21.2% PBO:24%	RIS:72.2% PBO:75%

ADA adalimumab, *AM* apilimod mesylate, *BRA* brazikumab, *BRI* briakinumab; *GUS* guselkumab, *MIR* mirikizumab, *NA* not applicable, *PBO* placebo, *RIS* risankizumab, *UST* ustekinumab