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Anti-IL-12/23p40 antibodies for induction of remission in Crohn's disease (Review)

MacDonald JK, Nguyen TM, Khanna R, Timmer A

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[Intervention Review]

Anti-IL-12/23p40 antibodies for induction of remission in Crohn's disease

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ABSTRACT

Background

Ustekinumab (CNTO 1275) and briakinumab (ABT-874) are monoclonal antibodies that target the standard p40 subunit of the cytokines interleukin-12 and interleukin-23 (IL-12/23p40), which are involved in the pathogenesis of Crohn's disease.

Objectives

The objectives of this review were to assess the efficacy and safety of anti-IL-12/23p40 antibodies for induction of remission in Crohn's disease.

Search methods

We searched the following databases from inception to 12 September 2016: PubMed, MEDLINE, EMBASE, and the Cochrane Library (CENTRAL). References and conference abstracts were searched to identify additional studies.

Selection criteria

Randomized controlled trials (RCTs) trials in which monoclonal antibodies against IL-12/23p40 were compared to placebo or another active comparator in patients with active Crohn's disease were included.

Data collection and analysis

Two authors independently screened studies for inclusion and extracted data. Methodological quality was assessed using the Cochrane risk of bias tool. The primary outcome was failure to induce clinical remission, defined as a Crohn's disease activity index (CDAI) of < 150 points. Secondary outcomes included failure to induce clinical improvement, adverse events, serious adverse events, and withdrawals due to adverse events. Clinical improvement was defined as decreases of $\geq$ 70 or $\geq$ 100 points in the CDAI from baseline. We calculated the risk ratio (RR) and 95% confidence intervals (95% CI) for each outcome. Data were analyzed on an intention-to-treat basis. The overall quality of the evidence supporting the outcomes was evaluated using the GRADE criteria.

Main results

Six RCTs (n = 2324 patients) met the inclusion criteria. A low risk of bias was assigned to all studies. The two briakinumab trials were not pooled due to differences in doses and time points for analysis. In both studies there was no statistically significant difference in remission rates. One study (n = 79) compared doses of 1 mg/kg and 3 mg/kg to placebo. In the briakinumab group 70% (44/63) of patients failed to enter clinical remission at 6 or 9 weeks compared to 81% (13/16) of placebo patients (RR 0.86, 95% CI 0.65 to 1.14). Subgroup analysis revealed no significant differences by dose. The other briakinumab study (n = 230) compared intravenous doses of 200 mg, 400 mg and 700 mg with placebo. Eighty-four per cent (154/184) of briakinumab patients failed to enter clinical remission at six weeks compared to 91% (42/46) of placebo patients (RR 0.92, 95% CI 0.83 to 1.03). Subgroup analysis revealed no significant differences by dose. GRADE analyses

of the briakinumab studies rated the overall quality of the evidence for the outcome clinical remission as low. Based on the results of these two studies the manufacturers of briakinumab stopped production of this medication. The ustekinumab studies were pooled despite differences in intravenous doses (i.e. 1mg/kg, 3 mg/kg, 4.5 mg/kg, and 6 mg/kg), however the subcutaneous dose group was not included in the analysis, as it was unclear if subcutaneous was equivalent to intravenous dosing. There was a statistically significant difference in remission rates. At week six, 84% (764/914) of ustekinumab patients failed to enter remission compared to 90% (367/406) of placebo patients (RR 0.92, 95% CI 0.88 to 0.96; 3 studies; high-quality evidence). Subgroup analysis showed a statistically significant difference for the 6.0 mg/kg dose group (moderate-quality evidence). There were statistically significant differences in clinical improvement between ustekinumab and placebo-treated patients. In the ustekinumab group, 55% (502/914) of patients failed to improve clinically (i.e. 70-point decline in CDAI score), compared to 71% (287/406) of placebo patients (RR 0.78, 95% CI 0.71 to 0.85; 3 studies). Subgroup analysis revealed significant differences compared to placebo for the 1 mg/kg, 4.5 mg/kg and 6 mg/kg dosage subgroups. Similarly for a 100-point decline in CDAI, 64% (588/914) of patients in the ustekinumab group failed to improve clinically compared to 78% (318/406) of placebo patients (RR 0.82, 95% CI 0.77 to 0.88; 3 studies; high-quality evidence). Subgroup analysis showed a significant difference compared to placebo for the 4.5 mg/kg and 6.0 mg/kg (high-quality evidence) dose groups. There were no statistically significant differences in the incidence of adverse events, serious adverse events or withdrawal due to adverse events. Sixty-two per cent (860/1386) of ustekinumab patients developed at least one adverse event compared to 64% (407/637) of placebo patients (RR 0.97, 95% CI 0.90 to 1.04; 4 studies; high-quality evidence). Five per cent (75/1386) of ustekinumab patients had a serious adverse event compared to 6% (41/637) of placebo patients (RR 0.83, 95% CI 0.58 to 1.20; 4 studies; moderate-quality evidence). The most common adverse events in briakinumab patients were injection site reactions and infections. Infections were the most common adverse event in ustekinumab patients. Worsening of Crohn's disease and serious infections were the most common serious adverse events.

Authors' conclusions

High quality evidence suggests that ustekinumab is effective for induction of clinical remission and clinical improvement in patients with moderate to severe Crohn's disease. Moderate to high quality evidence suggests that the optimal dosage of ustekinumab is 6 mg/kg. Briakinumab and ustekinumab appear to be safe. Moderate quality evidence suggests no increased risk of serious adverse events. Future studies are required to determine the long-term efficacy and safety of ustekinumab in patients with moderate to severe Crohn's disease.

PLAIN LANGUAGE SUMMARY

Ustekinumab and briakinumab for the treatment of active Crohn's disease

What is Crohn's disease?
Crohn's disease is a long-term (chronic) inflammatory bowel disease that can affect any part of the gastrointestinal tract from mouth to anus. Symptoms include abdominal pain, non-bloody diarrhoea, and weight loss.

What are ustekinumab and briakinumab?
Ustekinumab and briakinumab are biologic medications. These medications can be injected under the skin using a syringe or directly infused into a vein (intravenous). Biologic therapies suppress the immune system and reduce the inflammation associated with Crohn's disease. When people with Crohn's disease are experiencing symptoms of the disease it is said to be ‘active’; periods when the symptoms stop are called ‘remission’.

What did the researchers investigate?
The researchers investigated whether ustekinumab or briakinumab produce remission in people with active Crohn's disease; and whether these medications cause any harms (side effects). The researchers searched the medical literature up to 12 September 2016.

What did the researchers find?
The researchers identified six studies that included a total of 2324 participants. Two studies compared briakinumab to placebo (a fake medicine) and four studies compared ustekinumab to placebo. All of the studies were high quality.

There was no difference in the proportion of briakinumab and placebo participants who achieved remission. An increase in side effects or severe side effects were not seen with briakinumab compared to placebo. The most common side effects in briakinumab participants were reactions at the site of injection and infections. Based on the results of these two studies the manufacturers of briakinumab stopped production of this medication.

High quality evidence suggests that ustekinumab is better than placebo for helping participants achieve remission and for reducing symptoms of active Crohn's disease. Different doses of ustekinumab were investigated and moderate to high quality suggests that 6.0 mg/kg is the most effective dose. An increase in side effects or serious side effects was not seen with ustekinumab compared to placebo. Infections were the most common adverse event in ustekinumab patients. Worsening of Crohn's disease and serious infections were the most common serious side effects in the ustekinumab studies. Ustekinumab is a promising as a therapy for inducing remission and improving symptoms in people with Crohn's disease. Further studies are required to determine the long-term effectiveness and safety of ustekinumab in patients with moderate to severe Crohn's disease. The ideal dose of ustekinumab also needs to be determined.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Briakinumab compared to placebo for induction of remission in Crohn's disease

Briakinumab compared to placebo for induction of remission in Crohn's disease

Patient or population: induction of remission in Crohn's disease
Settings:
Intervention: Briakinumab
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	placebo	Briakinumab				
Failure to induce clinical remission **(Mannon 2004)** CDAI (≤150 points) Follow-up: 9 weeks	**812 per 1000** [1]	**699 per 1000** (528 to 926)	**RR 0.86** (0.65 to 1.14)	79 (1 study)	⊕⊕⊝⊝ **low** [2,3]	
Failure to induce clinical remission **(Panaccione 2010)** CDAI (≤150 points) Follow-up: 6 weeks	**913 per 1000** [1]	**840 per 1000** (758 to 940)	**RR 0.92** (0.83 to 1.03)	230 (1 study)	⊕⊕⊝⊝ **low** [3,4]	
Failure to induce clinical response (Mannon 2004) CDAI - (≥100 point reduction) Follow-up: 9 weeks	**688 per 1000** [1]	**447 per 1000** (289 to 681)	**RR 0.65** (0.42 to 0.99)	79 (1 study)	⊕⊕⊝⊝ **low** [5]	
Failure to induce clinical response (Panaccione 2010) CDAI - (≥100 point reduction) Follow-up: 6 weeks	**783 per 1000** [1]	**642 per 1000** (525 to 775)	**RR 0.82** (0.67 to 0.99)	230 (1 study)	⊕⊕⊕⊝ **moderate** [6]	
Adverse events **(Panaccione 2010)**	**783 per 1000** [1]	**705 per 1000** (587 to 838)	**RR 0.90** (0.75 to 1.07)	230 (1 study)	⊕⊕⊕⊝ **moderate** [7]	

Follow-up: 12 weeks					
Serious adverse events **(Panaccione 2010)** Follow-up: 12 weeks	**87 per 1000** [1]	**45 per 1000** (15 to 140)	**RR 0.52** (0.17 to 1.61)	246 (1 study)	⊕⊕⊝⊝ **low** [8]
Withdrawals due to adverse event** **(Pannaccione 2010)** Follow-up: 12 weeks	**44 per 1000** [1]	**30 per 1000** (6 to 146)	**RR 0.69** (0.14 to 3.31)	246 (1 study)	⊕⊕⊝⊝ **low** [9]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**Subject numbers are higher than those reported for the efficacy analyses of the individual studies due to the 200 mg, i.v. experimental group discontinuing enrolment during the induction phase due to poor patient enrolment (Panaccione, 2010). These patients were not included in the efficacy analyses, but were included in the safety analyses.
CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Control group risk estimates come from control arm of meta-analysis, based on included trials
[2] Downgraded one level due to sparse data (57 events)
[3] Downgraded on level because the 95% CI around the effect estimate includes both benefit and no effect
[4] Downgraded one level due to sparse data (196 events)
[5] Downgraded two levels due to very sparse data (39 events)
[6] Downgraded one level due to sparse data (153 events)
[7] Downgraded one level due to sparse data (177 events)
[8] Downgraded two levels due to very sparse data (13 events)
[9] Downgraded two levels due to very sparse data (8 events)

Summary of findings 2. Ustekinumab compared to placebo for induction of remission in Crohn's disease

Ustekinumab compared to placebo for induction of remission in Crohn's disease

Patient or population: patients with induction of remission in Crohn's disease
Settings:
Intervention: Ustekinumab

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	placebo	Ustekinumab				
Failure to induce clinical remission CDAI (≤ 150) Follow-up: 6 weeks	**904 per 1000** [1]	**832 per 1000** (795 to 868)	**RR 0.92** (0.88 to 0.96)	1320 (3 studies)	⊕⊕⊕⊕ **high**	Sensitivity analysis excluding UNITI-2 trial. These patients had more severe disease at study entry
Failure to induce clinical remission (6 mg/kg subgroup) CDAI (≤ 150) Follow-up: 6 weeks	**907 per 1000** [1]	**835 per 1000** (789 to 880)	**RR 0.92** (0.87 to 0.97)	916 (2 studies)	⊕⊕⊕⊖ **moderate** [2]	
Failure to induce clinical response CDAI (≥100 point reduction) Follow-up: 6 weeks	**783 per 1000** [1]	**642 per 1000** (603 to 689)	**RR 0.82** (0.77 to 0.88)	1320 (3 studies)	⊕⊕⊕⊕ **high**	Sensitivity analysis excluding UNITI-2 trial. These patients had more severe disease at study entry
Failure to induce clinical response (6 mg/kg subgroup) CDAI (≥100 point reduction) Follow-up: 6 weeks	**780 per 1000** [1]	**647 per 1000** (601 to 710)	**RR 0.83** (0.77 to 0.91)	916 (2 studies)	⊕⊕⊕⊕ **high**	
Adverse events Follow-up: 8 weeks	**639 per 1000** [1]	**620 per 1000** (575 to 664)	**RR 0.97** (0.9 to 1.04)	2023 (4 studies)	⊕⊕⊕⊕ **high**	
Serious adverse events Follow-up: 8 weeks	**64 per 1000** [1]	**53 per 1000** (37 to 77)	**RR 0.83** (0.58 to 1.2)	2023 (4 studies)	⊕⊕⊕⊖ **moderate** [3]	
Withdrawals due to adverse event Follow-up: 8 weeks	**54 per 1000** [1]	**24 per 1000** (10 to 57)	**RR 0.44** (0.18 to 1.05)	657 (2 studies)	⊕⊕⊖⊖ **low** [4]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**Subject numbers are higher than those reported for the efficacy analyses of the individual studies due to the omission of efficacy results for subjects receiving subcutaneous placebo and 90 mg ustekinumab, as well as subjects receiving 90mg s.c. and 4.5 mg/kg of ustekinumab in the open-label arm of the study by Sandborn (2008). The results of these subjects were included in the safety analyses.
CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Control group risk estimates come from control arm of meta-analysis, based on included trials
[2] Downgraded one level due to heterogeneity detected for 6 mg/kg subgroup (I^2 = 39%)
[3] Downgraded one level due to sparse data (116 events)
[4] Downgraded two levels due to very sparse data (20 events)

BACKGROUND

Description of the condition

Crohn's disease is a chronic inflammatory disease of the gastrointestinal tract that typically presents with abdominal pain, diarrhoea, and weight loss. In North America and Northern Europe, Crohn's disease affects up to 320 people per 100,000 (Molodecky 2012). Long-term transmural inflammation can result in complications including stenoses and fistulas that require surgical management in up to a third of patients (Solberg 2007). Therapy is aimed at inducing and maintaining remission and preventing complications.

Corticosteroids were among the first available therapies for induction of remission in Crohn's disease (Summers 1979; Rutgeerts 1994). However, persistent remission (Faubion 2001) and mucosal healing (Modigliani 1990) have not been observed with corticosteroid therapy. Moreover, these drugs cause multiple adverse effects (Ford 2011; Yang 2002).

The immunosuppressives azathioprine, 6-mercaptopurine and methotrexate have been widely used as corticosteroid-sparing agents in the treatment of Crohn's disease (McDonald 2012; Chande 2013). Although azathioprine is not effective for inducing remission (Chande 2013), it is beneficial when used in combination with infliximab therapy (Colombel 2010; Chande 2013). However, azathioprine requires careful monitoring for adverse events including pancreatitis, liver toxicity, and neutropenia (Raj 2010).

Due to the limited efficacy and potential toxicities of those drugs, monoclonal antibodies directed against tumor necrosis factor alpha (TNF-α) were developed as more selective therapeutic agents. TNF-α antagonists, which include infliximab, adalimumab, and certolizumab pegol, are effective for both induction and maintenance of remission in Crohn's disease (Targan 1997; Hanauer 2002; Akobeng 2003; Hanauer 2006; Lawson 2006; Sandborn 2007; Schreiber 2007). However, concerns regarding infection (Colombel 2004; Colombel 2007; Schreiber 2007; Singh 2011) and a potentially increased risk of certain types of cancer such as non-Hodgkin's lymphoma and non-melanoma skin cancer exists (Burmester 2013; Hudesman 2013). Furthermore, primary and secondary failure of TNF-α antagonists occurs in approximately 30 and 40% of patients, respectively (Targan 1997; Hanauer 2002; Hanauer 2006; Danese 2011). These limitations provided the impetus to investigate drugs that target different inflammatory pathways.

Description of the intervention

Ustekinumab (CNTO 1275) and briakinumab (ABT-874) are fully human IgG1 monoclonal antibodies that target the common p40 subunit of the cytokines interleukin-12 and interleukin-23 (IL-12/23p40). Ustekinumab and briakinumab are effective for the treatment of psoriasis (Papp 2008; Gottlieb 2009; Reich 2011), and early Phase I and II clinical trials of ustekinumab suggest a similar benefit in Crohn's disease (Mannon 2004; Sandborn 2008; Sandborn 2012).

How the intervention might work

Crohn's disease is characterized by dysregulated T-cell activity. Interleukin-12 (IL-12) and IL-23 are released by antigen presenting cells to trigger an acquired immune response (Watanabe 2004; Peluso 2006; Benson 2011; Duvallet 2011). Specifically, IL-12 production stimulates a Th1 response, that culminates in the secretion of the pro-inflammatory cytokines IFN-γ and TNF-α (Peluso 2006; Benson 2011; Cingoz 2011). Similarly, IL-23 stimulates proliferation of Th17 lymphocytes which play a role in many chronic inflammatory conditions (Duvallet 2011). At a cellular level inhibition of IL-12/23p40 leads to apoptosis of T cells in the gut mucosa (Fuss 1999). Furthermore, blockade IL-12 and IL-23, results in disease improvement in murine models of colitis (Neurath 1995). Collectively, these data suggest a possible therapeutic role for IL-12/23p40 antibodies for the treatment of Crohn's disease.

Why it is important to do this review

Ustekinumab, a humanized monoclonal antibody directed against the p40 subunit of IL-12 and IL-23, has been more thoroughly investigated in the treatment of psoriasis where it appears to be safe and effective (Gottlieb 2014; Papp 2013). This systematic review summarizes the current evidence regarding the use of anti IL-12/23p40 antibodies for induction of remission in Crohn's disease.

OBJECTIVES

The objectives of this review were to determine the efficacy and safety of anti-IL-12/23p40 antibodies for induction of remission in Crohn's disease.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) that assessed the efficacy and safety of antibodies directed against the p40 subunit of IL-12 and IL-23 compared to placebo or other active treatments for induction of remission in Crohn's disease were considered for inclusion.

Types of participants

Participants were required to have active Crohn's disease defined by conventional clinical, radiological or endoscopic criteria. No age restrictions were applied.

Types of interventions

Interventions that involved the administration of an antibody directed against the p40 subunit of IL-12 and IL-23 were considered for inclusion. Interventions that altered IL-12 or IL-23 by another strategy, such as direct inhibition of transcription were not included (Sands 2010).

Types of outcome measures

Primary outcomes

The primary outcome measure was the proportion of patients who failed to enter clinical remission, as defined by the original studies (e.g. a Crohn's Disease Activity Index (CDAI) score of < 150)). An intention-to-treat analysis was used.

Secondary outcomes

Secondary outcome measures included:

- clinical response;
- endoscopic remission;

- steroid withdrawal;
- adverse events;
- serious adverse events; and
- withdrawal due to adverse events.

Search methods for identification of studies

Electronic searches

We searched PubMed, MEDLINE (OvidSP), EMBASE (Ovid SP), and the Cochrane Library (CENTRAL) from inception to 12 September 2016. The search strategies are listed in Appendix 1. Conference abstracts from Digestive Disease Week and the United European Gastoenterology Week were also searched to identify abstract publications.

Searching other resources

Reference lists

Manual searches of reference lists from potentially relevant papers were performed in order to identify additional studies that may have been missed using the computer-assisted search strategy.

Correspondence

Leaders in the field (W. Strober, P. Mannon, W. Sandborn) were contacted to identify other studies, which may not be published. The manufacturers of briakinumab and ustekinumab (Abbott Laboratories, Abbott Park, IL, USA and Centocor, Horsham, PA, USA) were contacted for additional data.

Trial databases

The trial databases clinicaltrials.gov, clinicaltrials.ifpma.org and the meta register of controlled trials at controlled-trials.com were searched to identify other studies that had not been reported.

Data collection and analysis

Selection of studies

All publications identified by the search strategy were assessed independently by two authors (TN and JKM), and relevant studies were selected according to the inclusion criteria. Disagreements were resolved by consensus.

Data extraction and management

Data were extracted independently by two authors (TN and JKM) using standardized extraction sheets. Information was extracted on data source; participants (age range, exclusion criteria, pre-treatment medication, co-medication, disease entity, activity); details of intervention (type of antibody, frequency and duration of treatment) and comparison treatment; outcomes studied and duration of follow up; study design features (including method of allocation, concealment, where applicable; intention-to-treat analysis); and results, including adverse events and loss to follow up. Discrepancies in the data extractions were resolved by consensus. Investigators were contacted for additional information when data were not available or unclear.

Assessment of risk of bias in included studies

We used the Cochrane risk of bias tool to assess the methodological quality of the included studies (HIggins 2011a). Two authors independently assessed the risk of bias (TN and JKM). The following study characteristics were assessed:

1. Randomization sequence generation;
2. Allocation concealment;
3. Blinding of participants, outcome assessors and investigators;
4. Incomplete outcome reporting (i.e. there was an acceptable method of dealing with attrition);
5. Selective outcome reporting (i.e. all outcomes described in the methods were included in the analysis); and
6. Other potential sources of bias.

Based on these characteristics, studies were judged to have a high, low or unclear risk of bias.

We used the GRADE approach to assess the overall quality of evidence for the primary outcome and secondary outcomes including clinical response, adverse events, serious adverse events and withdrawal due to adverse events. Outcomes from pooling of randomized trials start as high quality evidence, but may be downgraded due to: (1) risk of bias, (2) indirectness of evidence, (3) inconsistency (unexplained heterogeneity), (4) imprecision (sparse data), and (5) reporting bias (publication bias). The overall quality of evidence for each outcome was determined after considering each of these elements, and categorized as high quality (i.e. further research is very unlikely to change our confidence in the estimate of effect); moderate quality (i.e. further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate); low quality (i.e. further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate); or very low quality (i.e. we are very uncertain about the estimate) (Guyatt 2008; Schünemann 2011).

Measures of treatment effect

Data were analysed using Review Manager 5 (RevMan 5). Data were extracted from the original research articles and converted into 2×2 tables. The definitions of treatment success, remission and clinical improvement were set by the authors of each paper, and the data were combined for analysis only if these definitions were sufficiently similar (determined by consensus). All relevant outcomes in the identified studies were reported as dichotomous data so results were all pooled based on the relative risk (RR), with RR < 1.0 denoting superiority of the experimental treatment. Results were presented with 95% confidence intervals (CI). The 'Rule of Three' was used to estimate the 95% confidence interval for the frequency of rare, undetected adverse events, i.e. if no events were detected in n trial participants, the upper limit of the 95% confidence interval for the probability of the adverse event is 3/n (Loke 2007).

Unit of analysis issues

For three arm trials with a single placebo group and two treatment dose groups we split the placebo group in half to avoid a unit of analysis error (Higgins 2011b). In the case of an odd number of patients the groups were split in a way that led to a larger patient number in the placebo group for the lower dose arm in order to avoid overestimating effects in the higher dose arm, which was assumed to be more effective a priori. In order to avoid carry-over effects we only included the first part of the study (i.e. before the cross-over) for any cross-over studies (Higgins 2011b).

Dealing with missing data

Missing outcome data were presented using the conservative intention-to-treat approach (i.e. all loss to follow up were considered treatment failures).

Assessment of heterogeneity

Statistical heterogeneity was examined by calculating the I^2 statistic and the Chi^2 test. Subgroup analysis (see below) was applied to explore clinical and methodological sources of heterogeneity.

Assessment of reporting biases

For future updates of this review, if there are a sufficient number of included studies (i.e. ≥ 10), we will investigate publication bias by means of a funnel plot (Egger 1997). Publication bias was not investigated for the current version of this review due to an insufficient number of studies.

Data synthesis

Results for the different antibodies were not combined. Also studies were not combined, if subgroup analysis suggested significant heterogeneity. A fixed-effect model was applied when no heterogeneity was detected. Otherwise, a random-effects model was calculated. Data were not pooled when I^2 suggested considerable heterogeneity.

Subgroup analysis and investigation of heterogeneity

Preplanned subgroup analyses included:

- studies investigating children and studies investigating adults;
- different drug doses and/or routes of administration;
- studies investigating patients with high disease activity; and
- studies investigating only patients who failed anti-TNF-α therapy.

Due to the low number of studies identified subgroup analyses could only be performed for different drug doses.

Sensitivity analysis

Sensitivity analyses examined the impact of the following variables on the pooled effect:

- random-effects versus fixed-effect modelling;
- low risk of bias only versus unclear or high risk of bias; and
- relevant loss to follow up (> 10%): Best-case versus worst-case scenario.

Sensitivity analysis could only be performed for random-effects versus fixed-effect modelling. No publication allowed for the simulation of best-case and worst-case scenarios.

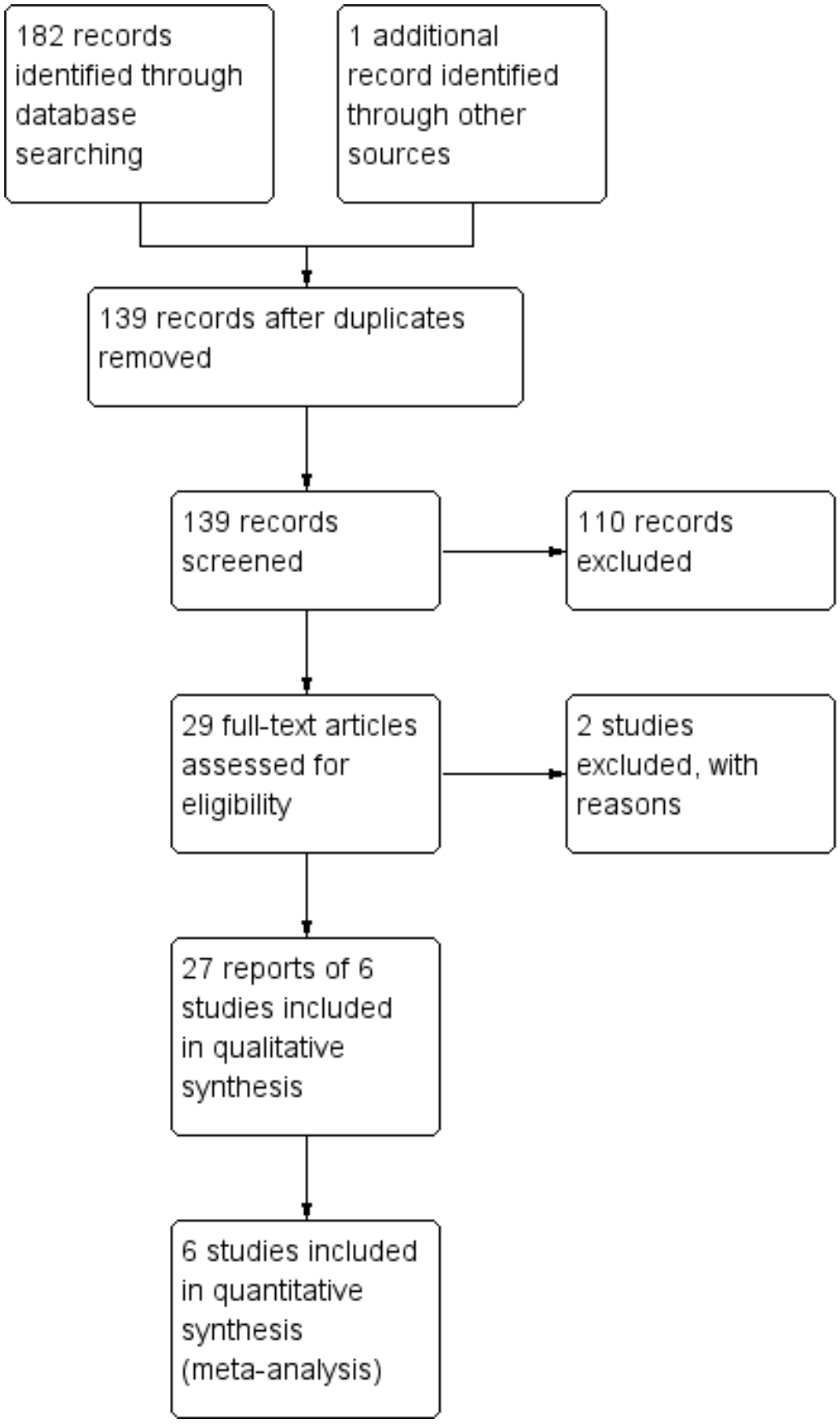
RESULTS

Description of studies

Results of the search

The literature search conducted on 12 September 2016 identified 183 records. After duplicates were removed, a total of 139 records were screened for inclusion. Of these, 16 studies were selected for full text review. Two studies were excluded leaving 27 reports of 6 trials (total 2324 patients) that met the pre-defined inclusion criteria (See Figure 1). Leaders in the field and the manufacturers of briakinumab and ustekinumab were contacted and no additional studies were identified.

Figure 1. Study flow diagram.



Included studies

All studies were multicenter randomized placebo-controlled trials investigating patients with active Crohn's disease. The six studies investigated different anti-IL12/23 antibodies. Mannon 2004 and Panaccione 2015 investigated briakinumab and four studies investigated ustekinumab (Sandborn 2008; Sandborn 2012; Feagan 2016 UNITI-1; Feagan 2016 UNITI-2). See Characteristics of included studies for further details.

Mannon 2004 investigated two different doses (1.0 mg and 3.0 mg/kg body weight) of briakinumab administered as 7 weekly subcutaneous injections against placebo. Each group was further randomized to uninterrupted therapy or a 4 week interval between the first and second doses. Follow-up in this study was between 24 and 27 weeks. As the different dosing regimens differed only slightly, the treatment arms were combined for analysis. The two doses differed markedly with respect to effectiveness and were analysed as separate studies as described in the methods section.

Sandborn 2008 was a Phase IIa study of ustekinumab that compared 4 regimens of ustekinumab to placebo in 104 patients with active CD in both TNF-α antagonist naive patients and those who had previously failed therapy with one or more of these agents. A sub-study compared intravenous to subcutaneous therapy for the induction of clinical remission, however this portion of the trial was not included as it was not placebo-controlled. Sandborn 2008 utilized a blinded cross-over design that compared four groups: subcutaneous placebo at weeks 0–3, followed by 90 mg ustekinumab at weeks 8–11; subcutaneous 90 mg ustekinumab at weeks 0–3, then placebo at weeks 8–11; intravenous placebo at week 0, followed by 4.5 mg/kg ustekinumab at week 8; or intravenous 4.5 mg/kg ustekinumab at week 0, then placebo at week 8. Cross-over to the alternate therapy occurred at week 8. The first part of the cross-over trial was eligible for inclusion in this review. The subcutaneous doses were not included in the pooled analyses, as it was not clear that this was equivalent to intravenous dosing.

Panaccione 2015 was a double-blind, placebo-controlled Phase IIb trial in which 246 patients with moderate to severe Crohn's disease were randomized (1:1:1:3) to placebo, 200 mg briakinumab, 400 mg briakinumab, or 700 mg briakinumab at weeks 0, 4, and 8 weeks. These patients were stratified by prior TNF-α antagonist use and response to anti-TNF-α therapy. Patients that achieved clinical response at week 12 in the placebo and 400 mg briakinumab groups continued these treatment regimens at weeks 12, 16, 20 in the maintenance phase. Patients with clinical response in the 700 mg briakinumab group were re-randomized (1:1:1) to placebo, 200 mg IV briakinumab, or 700 mg IV briakinumab for the maintenance phase. The maintenance data were not considered for this systematic review.

Sandborn 2012 was a double-blind, placebo-controlled Phase 2b trial of ustekinumab that randomized 526 patients, of which 524 had previously failed TNF-α antagonist treatment (99.6%), to receive a single dose of 1, 3, or 6 mg/kg of intravenous ustekinumab or placebo. Patients that responded to ustekinumab were re-randomized to receive maintenance therapy with 90 mg of subcutaneous ustekinumab or placebo at weeks 8 and 16. The maintenance data were not considered for this systematic review.

Feagan 2016 UNITI-1 was a double-blind, placebo-controlled phase III trial of ustekinumab that randomized 741 patients with moderate to severe Crohn's disease, who had failed TNF-α antagonist therapy, to a single dose of 130 mg or 6mg/kg of ustekinumab or placebo. Patients who responded to ustekinumab were randomized to receive maintenance therapy with 90 mg of subcutaneous ustekinumab (every 8 weeks or every 12 weeks) or placebo through week 40. The maintenance data were not considered for this systematic review.

Feagan 2016 UNITI-2 was a double-blind, placebo-controlled phase III trial of ustekinumab that randomized 628 patients with moderate to severe Crohn's disease, who had failed corticosteroids or immunosuppressants or both, to a single dose of 130 mg or 6 mg/kg of ustekinumab or placebo. Patients who responded to ustekinumab were randomized to receive maintenance therapy with 90 mg of subcutaneous ustekinumab (every 8 weeks or every 12 weeks) or placebo through week 40. The maintenance data were not utilized for this systematic review.

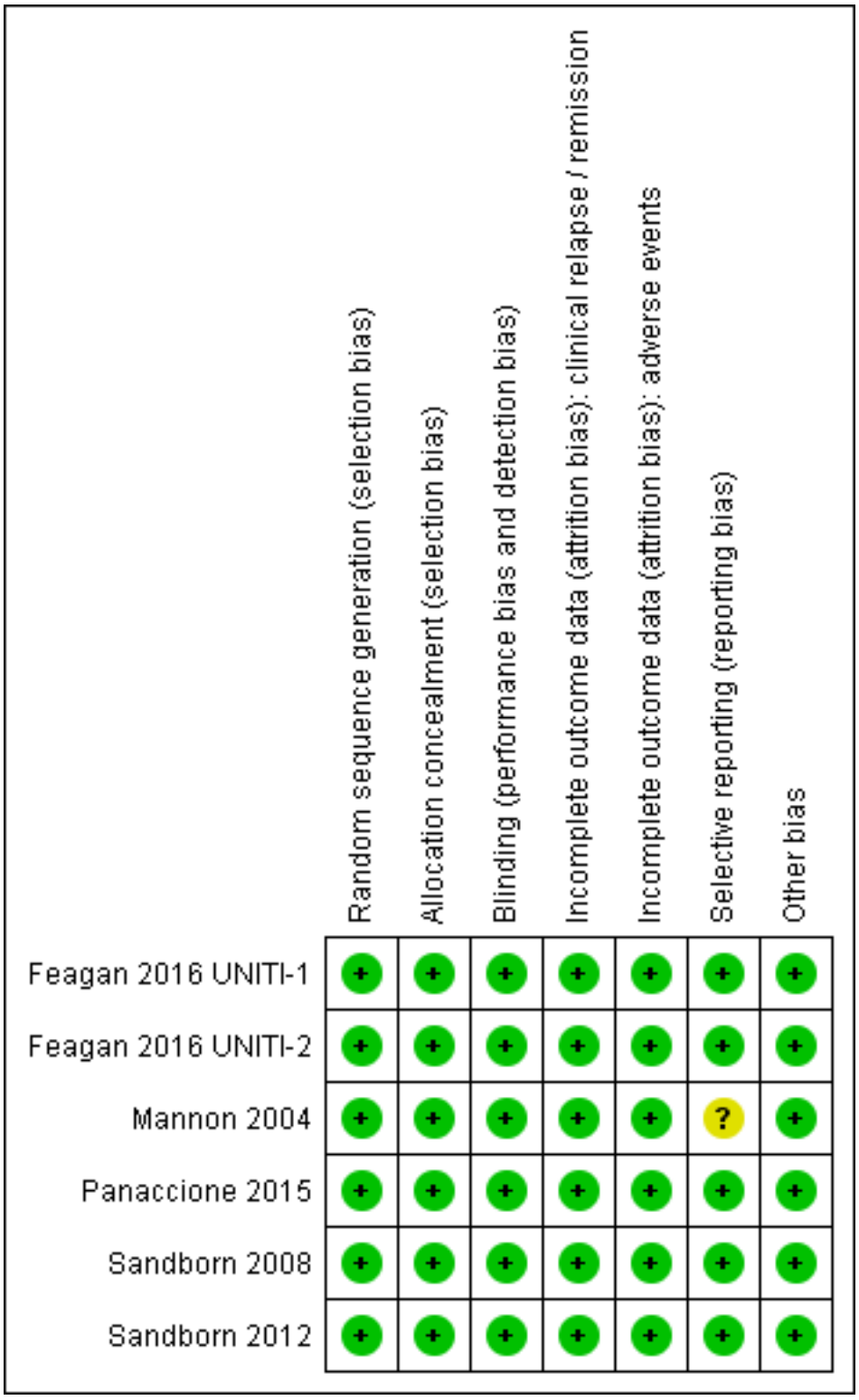
Excluded studies

We excluded two studies (See Characteristics of excluded studies). Fasanmade 2008 was a pharmacokinetics study that compared intravenous ustekinumab at a dose of 4.5 mg/kg to subcutaneously administered ustekinumab at a dose of 90 mg. The active drug assessed in the Sands 2010 study was not an antibody directed against the p40 subunit of Il-12 and IL-23 (i.e. different mechanism of action than briakinumab and ustekinumab).

Risk of bias in included studies

The risk of bias analysis is summarized in Figure 2.

Figure 2. Risk of bias summary: reviewers' judgements about each risk of bias item for each included study.



Allocation

All six studies utilized computer generated randomization and were rated as low risk of bias for random sequence generation. Five studies used a centralized randomization scheme and were rated as low risk of bias for allocation concealment (Feagan 2016 UNITI-1; Feagan 2016 UNITI-2; Panaccione 2015; Sandborn 2008; Sandborn 2012). The Mannon 2004 study allocated patients using a telephone based interactive voice response system and was rated as low risk of bias for allocation concealment.

Blinding

Five studies utilized an identical placebo and were rated as low risk of bias for blinding (Feagan 2016 UNITI-1; Feagan 2016 UNITI-2; Mannon 2004; Sandborn 2008; Sandborn 2012). Panaccione 2015 utilized a double-blind design and reported that, "The study sponsor, site personnel, and patients were unaware of the treatment assignments throughout both the induction and maintenance phases." As a result we rated this study as low risk of bias for blinding.

Incomplete outcome data

All of the studies were rated as low risk for incomplete outcome data. Drop-outs were generally balanced across treatment groups with similar reasons for withdrawal.

Selective reporting

Five studies were rated as low risk for selective reporting (Feagan 2016 UNITI-1; Feagan 2016 UNITI-2; Panaccione 2015; Sandborn 2008; Sandborn 2012). Mannon 2004 reported on pre-specified primary and secondary outcomes (safety and efficacy) but only reported on histology and laboratory scores for the treatment group. This study was rated as unclear for selective reporting.

Other potential sources of bias

All of the studies appear to be free of other sources of bias and were rated as low risk of bias for this item.

Effects of interventions

See: **Summary of findings for the main comparison** Briakinumab compared to placebo for induction of remission in Crohn's disease; **Summary of findings 2** Ustekinumab compared to placebo for induction of remission in Crohn's disease

The two trials of briakinumab were not pooled due to differences in doses and time points for analysis (Mannon 2004; Panaccione 2015). However in both trials briakinumab was not statistically different than placebo for failure to induce remission. In the Mannon 2004 (N = 79) study 70% (44/63) of briakinumab patients failed to enter clinical remission at weeks 7 or 9 compared to 81% (13/16) of placebo patients (RR 0.86, 95% CI 0.65 to 1.14). Subgroup analysis showed no statistically significant differences by briakinumab dose (1 mg/kg or 3 mg/kg). No heterogeneity was detected for the dosage subgroup comparison (I^2 = 0%). A GRADE analysis indicated that the quality of evidence supporting the primary outcome was low (See Summary of findings for the main comparison). There was a statistically significant difference in the proportion of patients who failed to have a clinical response (≥ 100 point improvement in CDAI from baseline) favouring briakinumab over placebo. Forty-four per cent (28/63) briakinumab patients failed to respond to treatment compared to 69% (11/16) of placebo patients (RR 0.65, 95% CI 0.42 to 0.99). Subgroup analysis showed no statistically significant differences by briakinumab dose (1 mg/kg or 3 mg/kg). No heterogeneity was detected for this comparison (I^2 = 0%). Sensitivity analyses utilizing a random-effects model found similar results for induction of remission and clinical response (See Table 1). A GRADE analysis indicated that the quality of evidence supporting the outcome clinical response was low (See Summary of findings for the main comparison).

In the Panaccione 2015 (N = 230) study 84% (154/184) of briakinumab patients failed to enter clinical remission compared to 91% (42/46) of placebo patients (RR 0.92, 95% CI 0.83 to 1.03). Subgroup analysis showed no differences by briakinumab dose (400 mg or 700 mg). No heterogeneity was detected for the dosage subgroup comparison (I^2 = 0%). A GRADE analysis indicated that the quality of evidence supporting the primary outcome was low (See Summary of findings for the main comparison). There was a difference in clinical response rates (≥ 100 point improvement in CDAI from baseline) between briakinumab and placebo patients at six weeks. Sixty-four per cent (117/184) of briakinumab patients failed to respond compared to 78% of placebo patients (RR 0.82 95% CI 0.67 to 0.99). Subgroup analysis showed no differences by briakinumab dose (400 mg or 700 mg). No heterogeneity was detected for this comparison (I^2 = 0%). A GRADE analysis indicated that the quality of evidence supporting this outcome was moderate (See Summary of findings for the main comparison). Although all patients completed the induction phase of this study, the sponsor ended the study during the maintenance phase because the primary endpoint was not achieved. Sensitivity analyses utilizing a random-effects model found similar results for induction of remission and clinical response (See Table 1).

The ustekinumab trials (Feagan 2016 UNITI-1; Feagan 2016 UNITI-2; Sandborn 2008; Sandborn 2012), were pooled despite differences in intravenous doses (i.e. 1mg/kg, 3 mg/kg, 4.5 mg/kg, and 6 mg/kg), however the subcutaneous dose group was not included in the analysis, as it was unclear if subcutaneous was equivalent to intravenous dosing. In the pooled analysis (4 studies, 1947 patients), ustekinumab was statistically different than placebo for failure to induce remission. At week six, 79% (1049/1332) of ustekinumab patients failed to enter remission compared to 88% (539/615) of placebo patients (RR 0.91, 95% CI 0.86 to 0.95; I^2 = 27%). Subgroup analysis showed a difference for the ustekinumab 6.0 mg/kg dose. However a moderate amount of heterogeneity was detected for this subgroup comparison (I^2 = 66%). A visual inspection of the forest plot indicated that the heterogeneity appeared to be a result of the inclusion of the Feagan 2016 UNITI-2 study in the pooled analysis. The Feagan 2016 UNITI-2 study differed from the other studies in the pooled analysis because it required objective evidence of active Crohn's disease (e.g. elevated serum C-reactive protein or fecal calprotectin concentrations or endoscopic ulcerations) for study entry whereas the other studies in the pooled analysis did not. This may be a plausible explanation for the higher response rates seen in the UNITI-2 patients compared to the other studies in the pooled analysis. To investigate if this study was the source of the heterogeneity the analysis was repeated excluding this trial. The pooled analysis now included 3 studies and 1320 participants. No heterogeneity was detected for the overall comparison (P = 0.72; I^2 = 0%) or for the 6.0 mg/kg subgroup (P 0.20; I^2 = 39%). Eighty-four per cent (764/914) of ustekinumab patients failed to enter remission at week 6 compared to 90% (367/406) of placebo patients (RR 0.92, 95% CI 0.88 to 0.96). A GRADE analysis indicated that the quality of evidence supporting the primary outcome was high (See Summary of findings 2). Subgroup analysis showed a difference in remission rates for the ustekinumab 6.0 mg/kg dose. Eighty-four per cent (523/625) of ustekinumab 6.0 mg/kg patients failed to enter remission at week 6 compared to 91% (264/291) of placebo patients (RR 0.92, 95% CI 0.88 to 0.96).

There were differences in clinical improvement between ustekinumab and placebo treated patients. In the ustekinumab

group, 50% (662/1332) of patients failed to achieve a 70-point decrease in CDAI score, compared to 68% (415/615) of placebo patients (RR 0.73, 95% CI 0.66 to 0.81; I^2 = 30%). Subgroup analysis showed differences in failure to respond for the 1mg/kg, 4.5 mg/kg, and 6 mg/kg dosage subgroups. However, moderate heterogeneity was detected for the 6.0 mg/kg subgroup (I^2 = 64%%). A visual inspection of the forest plot indicated that the heterogeneity appeared to be a result of the inclusion of the Feagan 2016 UNITI-2 study in the pooled analysis. To investigate if this study was the source of the heterogeneity the analysis was repeated excluding this trial. The pooled analysis now included 3 studies and 1320 participants. No statistically significant heterogeneity was detected for the overall comparison (P = 0.81; I^2 = 0%) or for the 6.0 mg/kg subgroup (P 0.69; I^2 = 0%). Fifty-five per cent (502/914) of ustekinumab patients failed to achieve a 70-point decrease in CDAI score at week 6 compared to 71% (287/406) of placebo patients (RR 0.78, 95% CI 0.71 to 0.85). Subgroup analysis showed differences in failure to respond for the 1 mg/kg (RR 0.78, 95% CI 0.61 to 0.98), 4.5 mg/kg (RR 0.59, 95% CI 0.37 to 0.94), and 6 mg/kg (0.78, 95% CI 0.71 to 0.87) dosage subgroups. Similarly for a 100-point decline in CDAI, 59% (782/1332) of patients in the ustekinumab group failed to have a 100-point clinical response compared to 76% (467/615) of placebo patients (RR 0.77, 95% CI 0.69 to 0.87; I^2 = 61%). Subgroup analysis showed a difference in failure to respond for the 4.5 mg/kg and 6.0 mg/kg dosage subgroups. However, a high degree of heterogeneity was detected for the 6.0 mg/kg subgroup comparison (I^2 = 80%). A visual inspection of the forest plot indicated that the Feagan 2016 UNITI-2 study could be the cause of this heterogeneity. To investigate if this study was the source of the heterogeneity the analysis was repeated excluding this trial. The pooled analysis now included 3 studies and 1320 participants. No heterogeneity was detected for the overall comparison (P = 0.57; I^2 = 0%) or for the 6.0 mg/kg subgroup (P 0.72; I^2 = 0%). Sixty-four per cent (588/914) of ustekinumab patients failed to achieve a 100-point decrease in CDAI score at week 6 compared to 78% (318/406) of placebo patients (RR 0.82, 95% CI 0.77 to 0.88). A GRADE analysis indicated that the quality of evidence supporting the outcome 100-point clinical response was high (See Summary of findings 2). Subgroup analysis showed a differences in failure to respond for the 4.5 mg/kg (RR 0.59, 95% CI 0.39 to 0.89), and 6 mg/kg (RR 0.83, 95% CI 0.77 to 0.91) dosage subgroups.

There were no differences in remission or clinical improvement rates in patients who received subcutaneous ustekinumab or placebo. Seventy-two per cent (18/25) of patients in the subcutaneous ustekinumab group failed to enter remission at six weeks compared to 77% (20/26) of placebo patients (RR 0.94, 95% CI 0.68 to 1.29). Forty-eight per cent (12/25) of patients in the subcutaneous ustekinumab group failed to achieve a 70-point decrease in CDAI at six weeks compared to 62% (16/26) of placebo patients (RR 0.78, 95% CI 0.47 to 1.30). Fifty-two per cent (13/25) of patients in the subcutaneous ustekinumab group failed to achieve a 100-point decrease in CDAI at six weeks compared to 65% of placebo patients (RR 0.80, 95% CI 0.50 to 1.27). Sensitivity analyses utilizing a random-effects model found similar results for induction of remission and clinical response.

Endoscopic remission was not assessed in any of the included studies. Steroid withdrawal following treatment was not assessed in any of the included induction studies. Sandborn 2012 evaluated corticosteroid-free remission at 22 weeks during the maintenance phase.

There was no difference in the proportion of patients who experienced at least one adverse event in the Panaccione 2015 study. Seventy-one per cent (141/200) of briakinumab patients experienced at least one adverse event compared to 78% (36/46) of placebo patients (RR 0.90, 95% CI 0.75 to 1.07). A GRADE analysis indicated that the overall quality of the evidence supporting this outcome was moderate (See Summary of findings for the main comparison). Mannon 2004 did not report on the proportion of patients who had at least one adverse event. Mannon 2004 reported that injection site reactions were the most common adverse event. Injection site reactions occurred more frequently in the briakinumab groups (77% in the 1mg/kg group and 88% in the 3 mg/kg group) than the placebo group (25%). The majority of these injection site reactions were considered mild (88%). Panaccione 2015 reported infections as the most common adverse event. Thirty-three per cent of briakinumab patients had an infection compared to 35% of placebo patients. There was no difference in either study in the proportion of patients who developed a serious adverse event or withdrew due to an adverse event. In the Mannon 2004 study, 11% (7/63) of briakinumab patients had a serious adverse event compared to 12% (2/16) of placebo patients (RR 0.89, 95% CI 0.20 to 3.88). In the Panaccione 2015 study 4% (9/200) of briakinumab patients had a serious adverse event compared to 9% (4/46) placebo patients (RR 0.52, 95% CI 0.17 to 1.61). Three per cent (2/63) of briakinumab patients in the Mannon 2004 study withdrew due to an adverse event compared to 12% (2/16) placebo patients (RR 0.25, 95% CI 0.04 to 1.67). Three per cent (6/200) of briakinumab patients in the Panaccione 2015 study withdrew due to an adverse event compared to 4% (2/46) of placebo patients (RR 0.69, 95% CI 0.14 to 3.31). GRADE analyses indicated that the overall quality of the evidence supporting the outcomes serious adverse events and withdrawal due to adverse events was low (See Summary of findings for the main comparison).

In the ustekinumab studies there was no difference in the proportion of patients who experienced at least one adverse event. Sixty-two per cent (860/1386) of ustekinumab patients experienced at least one adverse event compared to 64% (407/637) of placebo patients (RR 0.97, 95% CI 0.90 to 1.04; participants = 2023; studies = 4; I^2 = 0%). A GRADE analysis indicated that the overall quality of the evidence supporting this outcome was high (See Summary of findings 2). Infections were the most commonly reported adverse event in the ustekinumab studies. Other common adverse events included nasopharyngitis (Feagan 2016 UNITI-1; Feagan 2016 UNITI-2; Sandborn 2008; Sandborn 2012), abdominal pain (Feagan 2016 UNITI-1; Feagan 2016 UNITI-2; Sandborn 2008; Sandborn 2012), nausea (Feagan 2016 UNITI-1; Feagan 2016 UNITI-2; Sandborn 2008; Sandborn 2012), worsening Crohn's disease (Feagan 2016 UNITI-1; Feagan 2016 UNITI-2; Sandborn 2008; Sandborn 2012), arthralgia (Feagan 2016 UNITI-1; Feagan 2016 UNITI-2; Sandborn 2008; Sandborn 2012), headache (Feagan 2016 UNITI-1; Feagan 2016 UNITI-2; Sandborn 2008; Sandborn 2012), and dyspepsia (Sandborn 2008).

There was no difference in the incidence of serious adverse events. Serious adverse events occurred in 5% (75/1386) of ustekinumab patients compared to 6% (41/637) of patients in the placebo group (RR 0.83, 95% CI 0.58 to 1.20; participants = 2023; studies = 4; I^2 = 0%). A GRADE analysis indicated that the overall quality of the

evidence supporting this outcome was moderate (See Summary of findings 2). Worsening of CD and serious infections were the most common serious adverse events. Although the difference was not statistically significant, more placebo patients withdrew due to adverse events than ustekinumab patients. Five per cent (10/184) of placebo patients withdrew due to adverse events compared to 2% (10/473) of ustekinumab patients (RR 0.44, 95% CI 0.18 to 1.05; participants = 657; studies = 2; I^2 = 0%).

DISCUSSION

Summary of main results

Briakinumab (ABT-874) and ustekinumab (CNTO 1275) are monoclonal antibodies that target the shared p40 subunit of IL-12 and IL-23, that have been studied for induction of remission in CD. Neither Mannon 2004 or Panaccione 2015 found briakinumab to be superior to placebo for induction of remission in CD. Grade analyses indicated that the overall quality of the evidence supporting this outcome was low due mostly to sparse data. Both Mannon 2004 and Panaccione 2015 found briakinumab to be superior to placebo for induction of clinical improvement. Grade analyses indicated that the overall quality of the evidence supporting this outcome was low due mostly to sparse data. Subgroup analysis did not identify any significant differences by dose. The Panaccione 2015 trial was terminated during the open-label maintenance phase by the sponsor because the primary endpoint for induction of remission was not achieved, leaving to our knowledge ustekinumab as the only IL-12/23p40 antagonist currently being investigated for the treatment of CD.

Ustekinumab patients were significantly more likely than placebo patients to achieve clinical remission and clinical improvement. Subgroup analysis identified a difference for the 6.0 mg/kg dose group for induction of remission. Clinical improvement results were consistent for both a 70 and 100 point reduction in CDAI scores. Subgroup analysis identified significant differences by dose for 70 (i.e. 1mg/kg, 4.5 mg/kg, and 6 mg/kg dosage subgroups) and 100 point reduction (i.e. 4.5 mg/kg and 6.0 mg/kg subgroups) in CDAI scores. The results of the GRADE analysis indicate that overall quality of the evidence supporting the outcomes clinical remission and 100-point reduction in CDAI was high. Moderate to high quality evidence suggests that 6.0 mg/kg is the optimal dose for induction of remission and clinical response. Overall these results suggest a therapeutic benefit for ustekinumab in patients with moderate to severe CD.

With respect to safety, neither antibody led to an increase in adverse events or serious adverse events. Fewer patients that received anti-IL-12/23 monoclonal antibody treatment withdrew due to adverse events than placebo. However, these differences were not statistically significant. This may have been due to greater withdrawal of patients in the placebo group due to recurrence of CD symptoms. Although both drugs demonstrated an acceptable safety profile in these studies, the number of patients investigated did not allow for the assessment of rare adverse events. Studies with long term follow-up are required to assess the risk of rare adverse events.

Overall completeness and applicability of evidence

The results of this review are applicable to patients with moderate to severe Crohn's disease and patients with moderate to severe Crohn's disease who have failed TNF-alpha antagonists. High quality evidence suggests that ustekinumab is effective for induction of clinical remission and improvement in patients with moderate to severe Crohn's disease. Ustekinumab offers an out-of-class option for patients who fail currently available TNF-α antagonists.

Quality of the evidence

All of the included studies were judged to be at low risk of bias. GRADE analyses indicated that the overall quality of the evidence supporting the primary and secondary outcomes from the briakinumab studies was moderate to low due mostly to sparse data. GRADE analyses indicated that the overall quality of evidence supporting the primary outcome from the ustekinumab studies was rated as high quality. The secondary outcome clinical response was rated as high quality. Moderate to high quality evidence suggests that 6.0 mg/kg is the optimal dose of ustekinumab for induction of remission and clinical improvement. The outcome adverse events was rated as high quality. The outcome serious adverse events was rated as moderate quality. The outcome withdrawal due to adverse events was rated as low quality due to very sparse data.

Potential biases in the review process

To reduce potential bias in the review process we performed a comprehensive literature search to identify all eligible studies. In addition, two review authors independently assessed studies for inclusion, extracted data and assessed study quality. There are several limitations to this review. The studies that investigated briakinumab were small, thus they were only able to detect large effects and frequent adverse events.

Agreements and disagreements with other studies or reviews

The results of our review agree with other published reviews on ustekinumab and briakinumab (Khanna 2013; Niederreiter 2013; Singh 2014). Our review is the only systematic review to include a pooled analysis for the ustekinumab studies.

AUTHORS' CONCLUSIONS

Implications for practice

High quality evidence suggests that ustekinumab is effective for induction of clinical remission and improvement in patients with moderate to severe Crohn's disease. Moderate to high quality evidence suggests that the optimal dosage of ustekinumab is 6 mg/kg. Ustekinumab appears to be safe. Moderate quality evidence suggests no increased risk of serious adverse events in patients receiving ustekinumab. Production of briakinumab was stopped by the manufacturer because the primary endpoint for remission was not reached.

Implications for research

Further studies are required to determine the long-term efficacy and safety of ustekinumab in patients with moderate to severe CD.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Feagan 2016 UNITI-1

Methods	Randomized, double-blind, placebo-controlled, multicenter trial
Participants	Adult patients (≥ 18 years) with moderate to severe Crohn's disease who have failed TNF-alpha antagonist therapy (N = 741) Patients must have received TNF-alpha antagonists at approved doses and had documented primary non-response, secondary non-response or intolerance criteria
Interventions	Group 1: placebo; i.v. (n = 245) Group 2: 130 mg of ustekinumab, i.v. (n = 246) Group 3: 6 mg/kg of ustekinumab; i.v. (n = 249)
Outcomes	Primary outcome: Clinical response at week 6 (the number of patients in clinical response, as measured by a reduction in CDAI of ≥ 100 points from baseline or CDAI < 150 at week 6) The primary outcome for the maintenance study was clinical remission at week 44 Secondary outcomes: 1. Clinical remission at week 8 (the number of patients in clinical remission, defined by CDAI < 150) 2. Clinical response at week 8 3. ≥ 70 point CDAI decrease at weeks 3 and 6 4. Adverse events 5. Serious adverse events 6. Quality of Life 7. CRP
Duration of follow-up	Induction phase: 8 weeks (20 weeks for patients not entering maintenance phase) Maintenance phase: 44 weeks
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Low risk	Centralized randomization using permuted blocks

Feagan 2016 UNITI-1 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind Identical placebo
Incomplete outcome data (attrition bias) clinical relapse / remission	Low risk	Drop-outs were balanced across interventions with similar reasons for withdrawal
Incomplete outcome data (attrition bias) adverse events	Low risk	Drop-outs were balanced across interventions with similar reasons for withdrawal
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Feagan 2016 UNITI-2

Methods	Randomized, double-blind, placebo-controlled, multicenter trial
Participants	Adult patients (≥ 18 years) with moderate to severe Crohn's disease who have failed corticosteroids or immunosuppressants (azathioprine, 6-mercaptopurine or methotrexate) or both (N = 628) Patients could have received TNF-alpha antagonists without demonstration of inadequate response or intolerance
Interventions	Group 1: Placebo; i.v. 9 (n = 210) Group 2: 130 mg of Ustekinumab; i.v. (n = 209) Group 3: 6 mg/kg of body weight of Ustekinumab; i.v. (n = 209)
Outcomes	Primary outcome: Clinical response at week 6 Secondary outcomes: 1. Clinical remission at week 8 2. Clinical response through week 8 3. ≥ 70 point CDAI decrease at weeks 3 and 6 4. Adverse events 5. Serious adverse events 6. Quality of Life 7. CRP
Duration of follow-up	Induction phase: 8 weeks (20 weeks for patients not entering maintenance phase) Maintenance phase: 44 weeks
Notes	
Risk of bias	

Feagan 2016 UNITI-2 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Low risk	Centralized randomization using permuted blocks
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind Identical placebo
Incomplete outcome data (attrition bias) clinical relapse / remission	Low risk	Drop-outs were balanced across interventions with similar reasons for withdrawal
Incomplete outcome data (attrition bias) adverse events	Low risk	Drop-outs were balanced across interventions with similar reasons for withdrawal
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Mannon 2004

Methods	Randomized, double-blind, placebo-controlled, multi-center trial in the USA, Germany, and the Netherlands Patients were randomized 1:2:2 to placebo or one of the two dosages of briakinumab
Participants	Participants with clinically active Crohn's disease (N = 79) Inclusion criteria: CDAI 220-450, age ≥18 years Exclusion criteria: recently started Crohn's related medication, infections, history of malignancies, moderate to severe asthma, pregnancy/lactation, intestinal obstruction, stricture, ostomy, short bowel syndrome or probable operation in the near future
Interventions	Briakinumab was given at two different dosages: 1 mg/kg body weight subcutaneously (n = 31) or 3 mg/kg body weight subcutaneously (n = 32) Patients were enrolled into two cohorts with different dosing regimens (week 0, 4, 5, 6, 7, 8, 9 or week 0, 1, 2, 3, 4, 5, 6) with the first forty patients being enrolled in the former dosing regimen Each dosing cohort included a placebo group with 8 patients
Outcomes	Primary outcome: adverse events Secondary outcomes: clinical response (CDAI decrease ≥ 100), clinical remission (CDAI < 150), anti-drug antibodies, histologic response (subgroup, modified D'Haens score, only partially reported), cytokine secretion by lamina propria mononuclear cells (subgroup, only partially reported) Endoscopic relapse / remission and quality of life were not assessed

Mannon 2004 *(Continued)*

Duration of follow-up	~27 weeks after last injection (i.e. 5 to 6 months after randomisation)
Notes	For the purpose of this review the two different dosing regimens were combined for each dosage of briakinumab Different dosages were assessed separately The respective control groups were split evenly

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated randomization (as per investigator)
Allocation concealment (selection bias)	Low risk	Telephone interactive voice response system for treatment allocation (as per investigator)
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding of patients and investigators: The placebo was the same isotonic solution as the antibody
Incomplete outcome data (attrition bias) clinical relapse / remission	Low risk	Last observation carried forward for incomplete data Drop-outs were balanced across interventions with similar reasons for withdrawal
Incomplete outcome data (attrition bias) adverse events	Low risk	Participants who discontinued the study were included in the safety analysis unless lost to follow-up Drop-outs were balanced across interventions with similar reasons for withdrawal
Selective reporting (reporting bias)	Unclear risk	Pre-specified primary and secondary outcomes (safety and efficacy) were reported Histology and laboratory scores were only reported for the treatment group
Other bias	Low risk	The study appears to be free of other sources of bias

Panaccione 2015

Methods	Double-blind, randomized, placebo-controlled trial
Participants	Inclusion criteria: Adult patients with a diagnosis of CD for > 4 months, and a Crohn's Disease Activity Index (CDAI) score ≥ 220 and ≤ 450 (N = 246) Previous exposure to approved anti-TNF agents (including adalimumab, certolizumab, etanercept, infliximab, certain investigational drugs, and tumor necrosis factor receptor [IgG1]) was permitted if discontinued at least 8 weeks prior to baseline Secondary non responders and primary non-responders to prior anti-TNF agents were eligible Patients were allowed to continue azathioprine, 6-mercaptopurine (6-MP), or methotrexate (MTX) provided they had received these medications for at least 12 weeks with stable doses for at least 4 weeks prior to entry

Panaccione 2015 *(Continued)*

	Corticosteroids were permitted provided doses were stable (e.g. prednisolone ≤ 40 mg/day or equivalent, or budesonide ≤ 9 mg/day) for at least 2 weeks prior to entry
Interventions	I.V. infusions of briakinumab (200 mg, n = 16; 400 mg, n = 45; 700 mg, n = 139) or placebo (n = 46) administered at weeks 0, 4, and 8 and stratified at baseline (week 0) by prior TNF antagonist use (TNF antagonist naive vs TNF antagonist experienced) and TNF antagonist response (primary non-response vs secondary loss of response or secondary non responders)
Outcomes	Primary outcome: clinical remission (CDAI < 150) at week 6 Secondary outcomes: clinical remission at week 12, clinical response (CDAI decrease ≥ 100) at week 6 and 12; IBDQ
Duration of follow-up	Induction: 12 weeks Maintenance: 20 weeks (not reported in review)
Notes	200 mg group was removed from efficacy analysis due to poor enrolment (included in safety analysis) Study was stopped by sponsor during the open-label phase due to poor induction of remission results

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization
Allocation concealment (selection bias)	Low risk	Centralized allocation
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind "The study sponsor, site personnel, and patients were unaware of the treatment assignments throughout both the induction and maintenance phases"
Incomplete outcome data (attrition bias) clinical relapse / remission	Low risk	Drop-outs were balanced across interventions with similar reasons for withdrawal
Incomplete outcome data (attrition bias) adverse events	Low risk	Drop-outs were balanced across interventions with similar reasons for withdrawal
Selective reporting (reporting bias)	Low risk	Expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Sandborn 2008

Methods	Randomized, double-blind, placebo-controlled multi-center trial with a cross-over design in the USA Patients were randomized 1:1:1:1 to an intravenous or subcutaneous arm, each with a placebo group Within each arm patients crossed over to the treatment or control group after eight weeks

Sandborn 2008 *(Continued)*

Participants	Participants with clinically active Crohn's disease (N = 104) Inclusion criteria: CDAI 220-450, age ≥ 18 years. Patients had received at least one of the following in the past: 5-ASA, antibiotics, corticosteroids, azathioprine, 6-mercaptopurine, methotrexate, submaximal infliximab doses or regimens, or other anti-TNF-α-agents Exclusion criteria: > 20 mg prednisolone, recent treatment with any investigational agent or an anti-TNF-α-agents, infections, cancer, short-bowel syndrome, ostomy, obstructive symptoms with strictures
Interventions	Ustekinumab was given at 90 mg s.c. per week over four weeks (n = 25) or 4.5 mg/kg body weight i.v. once (n = 26), each compared to s.c. placebo (n = 26) or i.v. placebo (n = 27)
Outcomes	Primary outcome: Clinical response at week 8 (CDAI decrease ≥ 75 and ≥ 25%) Secondary outcomes: Clinical remission (CDAI < 150), laboratory results including CRP value, adverse events, anti-drug antibodies, adherence to therapy. Endoscopic response / remission and quality of life were not assessed.
Duration of follow-up	8 weeks until cross-over and 20 weeks thereafter
Notes	Only the first part of the cross-over design was evaluated for this review The placebo controlled study was accompanied by an unblinded study with participants who were non-responsive to infliximab The unblinded sub-study was not included in this review since it was not a placebo-controlled or active comparator study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated adaptive randomization stratified by investigative site
Allocation concealment (selection bias)	Low risk	Centralized randomization scheme
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding of patients and investigators Identical placebo
Incomplete outcome data (attrition bias) clinical relapse / remission	Low risk	Intention-to-treat analysis with worst case assumption Drop-outs were balanced across interventions with similar reasons for withdrawal
Incomplete outcome data (attrition bias) adverse events	Low risk	Drop-outs were balanced across interventions with similar reasons for withdrawal
Selective reporting (reporting bias)	Low risk	All assessed outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Sandborn 2012

Methods	Randomzed double-blind, placebo-controlled trial
Participants	Inclusion criteria: Adults (≥ 18 years) at least a 3 month history of Crohn's disease with a CDAI of 220 to 450 (N = 526) Patients had moderate to severe Crohn's disease that was resistant to TNF-α antagonists Exclusion: Previous therapy specifically targeting interleukin-12 or interleukin-23
Interventions	Intravenous ustekinumab 1 mg/kg (n = 131), 3 mg/kg (n=132), 6 mg/kg (n = 131) or placebo (n = 132)
Outcomes	The primary outcome: clinical response (≥ 100 point decrease in CDAI) at week 6 Secondary outcomes: clinical remission (CDAI score, < 150 points) at week 6, clinical response at week 4, and clinical remission at week 22 among patients with a response to ustekinumab at week 6
Duration of follow-up	Induction phase: 8 weeks Maintenance phase: 36 weeks (not included)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated adaptive randomization stratified by investigative site and the initial response to a TNFalpha antagonist
Allocation concealment (selection bias)	Low risk	Centrally generated randomization scheme
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind Identical placebo
Incomplete outcome data (attrition bias) clinical relapse / remission	Low risk	Intention-to-treat analysis and all subjects who began the study are accounted for in the results Drop-outs were balanced across interventions with similar reasons for withdrawal
Incomplete outcome data (attrition bias) adverse events	Low risk	Drop-outs were balanced across interventions with similar reasons for withdrawal
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

CDAI = Crohn's disease activity index

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Fasanmade 2008	This pharmacokinetic study compared intravenous ustekinumab at a dose of 4.5 mg/kg to subcutaneously administered ustekinumab (90 mg)
Sands 2010	Oral study drug (different route of administration) and drug is not a monoclonal antibody (different mechanism of action)

Characteristics of ongoing studies *[ordered by study ID]*

NCT01369329

Trial name or title	A phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the safety and efficacy of ustekinumab induction therapy in subjects with moderately to severely active Crohn's disease who have failed or are intolerant to TNF antagonist therapy (UNITI-1)
Methods	Double-blind, randomized, placebo-controlled study; single i.v infusion of placebo or ustekinumab; safety and efficacy assessed through 8 weeks in subjects that had previously failed TNFa therapy
Participants	~ 703 subjects **Inclusion Criteria:** • Subjects are 18 years or older and have active Crohn's disease (CDAI score of ≥ 220 ≤ 450) of at least 3 months duration confirmed radiography, histology, or endoscopy • Have received infliximab, adalimumab, or certolizumab pegol at a dose approved for the treatment of Crohn disease and did not respond initially (i.e. primary nonresponse), or responded initially but then lost response with continued therapy (i.e. secondary nonresponse), or were intolerant to the medication
Interventions	Group 1: placebo; i.v. Group 2: 130 mg of ustekinumab, i.v. Group 3: 6 mg/kg of ustekinumab; i.v.
Outcomes	Primary outcome: Clinical response at week 6 (the number of patients in clinical response, as measured by reduction in CDAI from baseline) Secondary outcomes: 1. Clinical remission at week 8 (the number of patients in clinical remission, defined by CDAI) 2. Clinical response through week 8 (the number of patients experiencing clinical response as measured by reduction in CDAI from baseline)
Starting date	July 2011
Contact information	Janssen Research & Development, LLC
Notes	This study has been completed There are no published results as of 31 March 2015

NCT01369342

Trial name or title	A phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the safety and efficacy of ustekinumab induction therapy in subjects with moderately to severely active Crohn's disease (UNITI-2)
Methods	Double-blind, randomized, placebo-controlled study; single injection of ustekinumab or placebo; safety and efficacy assessed over an 8 week period
Participants	~ 612 subjects **Inclusion Criteria:** • Subjects 18 years or older with active Crohn's disease (CDAI score of ≥ 220 ≤ 450) of at least 3 months duration confirmed by radiography, histology, or endoscopy • Has failed conventional therapy such as corticosteroids or immunomodulators (i.e. AZA, MTX, or 6-MP) at adequate therapeutic doses; or has a history of failure to respond to or tolerate corticosteroids or immunomodulators or is corticosteroid dependent or has had a history of corticosteroid dependency and has not previously demonstrated failure of or intolerance to 1 or more TNF-antagonist therapies (i.e. infliximab, adalimumab, or certolizumab pegol) per study criteria
Interventions	• Group 1: Placebo; i.v. • Group 2: 130 mg of Ustekinumab; i.v. • Group 3: 6 mg/kg of body weight of Ustekinumab; i.v.
Outcomes	Primary outcome: Clinical response at week 6 Secondary outcomes: 1. Clinical remission at week 8 2. Clinical response through week 8
Starting date	July 2011
Contact information	Janssen Research & Development, LLC
Notes	This study has been completed There are no published results as of 31 March 2015

NCT01369355

Trial name or title	A phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the safety and efficacy of ustekinumab maintenance therapy in subjects with moderately to severely active Crohn's disease
Methods	Double-blind, randomized, placebo-controlled, parallel-group design to assess whether additional subcutaneous (SC) ustekinumab treatment is beneficial in patients showing a clinical response to intravenous (IV) ustekinumab in the initial 2 induction studies
Participants	Estimated Enrolment is 1310 subjects **Inclusion Criteria:** Patients who received study agent at the start of study CNTO1275CRD3001 or CNTO1275CRD3002 and completed the Week 8 visit
Interventions	Group 1: Patients in response to IV ustekinumab will be randomized to receive either placebo,

NCT01369355 *(Continued)*	
	Group 2: Ustekinumab 90 mg SC every 12 weeks Group 3: Ustekinumab 90 mg SC every 8 weeks If patients in Groups 1 or 2 lose response, they will cross over to receive ustekinumab 90 mg every 8 weeks Other populations (nonresponders to prior IV ustekinumab or IV placebo) will receive ustekinumab at week 0 (either 90 mg SC or 130 mg IV, respectively) and continue SC ustekinumab if in response at week 8
Outcomes	Primary outcome: Clinical remission at week 44 Secondary outcomes: 1. Remission in patient subgroups such as those in remission at Week 0 or those who previously failed TNF-antagonists at week 44 2. Clinical response at week 44 3. Corticosteroid-free remission at week 44
Starting date	September 2011
Contact information	
Notes	The estimated completion date is September 2018

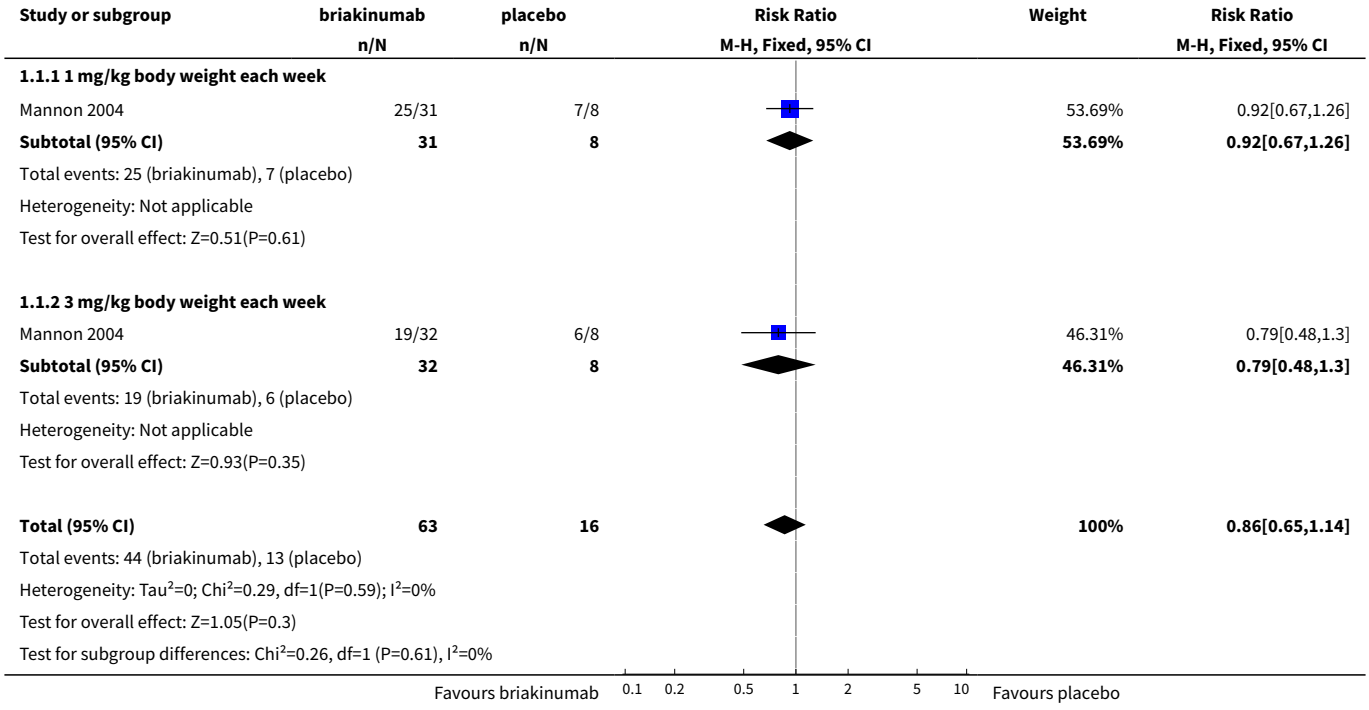
DATA AND ANALYSES

Comparison 1. Briakinumab versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Failure to induce clinical remission (7 & 9 weeks)	1	79	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.65, 1.14]
1.1 1 mg/kg body weight each week	1	39	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.67, 1.26]
1.2 3 mg/kg body weight each week	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.48, 1.30]
2 Failure to Induce clinical remission (6 weeks)	1	230	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.83, 1.03]
2.1 IV Infusion of 400 mg	1	68	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.80, 1.13]
2.2 IV Infusion of 700 mg	1	162	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.78, 1.05]
3 Failure to induce clinical response (>= 100 points; 7 & 9 weeks)	1	79	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.42, 0.99]

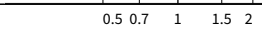
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 1 mg/kg body weight each week	1	39	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.44, 1.22]
3.2 3 mg/kg body weight each week	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.27, 1.13]
4 Failure to induce clinical response (>= 100 points; 6 weeks)	1	230	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.67, 0.99]
4.1 400 mg iv of briakinumab	1	68	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.61, 1.12]
4.2 700 mg iv of briakinumab	1	162	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.63, 1.04]
5 Adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Serious adverse events	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7 Withdrawals because of adverse events	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Briakinumab versus placebo, Outcome 1 Failure to induce clinical remission (7 & 9 weeks).



Analysis 1.2. Comparison 1 Briakinumab versus placebo, Outcome 2 Failure to Induce clinical remission (6 weeks).

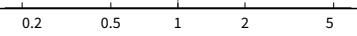
Study or subgroup	Experimental n/N	placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 IV Infusion of 400 mg					
Panaccione 2015	39/45	21/23		43.54%	0.95[0.8,1.13]
Subtotal (95% CI)	**45**	**23**		**43.54%**	**0.95[0.8,1.13]**
Total events: 39 (Experimental), 21 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.6(P=0.55)					
1.2.2 IV Infusion of 700 mg					
Panaccione 2015	115/139	21/23		56.46%	0.91[0.78,1.05]
Subtotal (95% CI)	**139**	**23**		**56.46%**	**0.91[0.78,1.05]**
Total events: 115 (Experimental), 21 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.31(P=0.19)					
Total (95% CI)	**184**	**46**		**100%**	**0.92[0.83,1.03]**
Total events: 154 (Experimental), 42 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.16, df=1(P=0.69); I^2=0%					
Test for overall effect: Z=1.37(P=0.17)					
Test for subgroup differences: Chi^2=0.16, df=1 (P=0.69), I^2=0%					



Favours briakinumab — Favours placebo

Analysis 1.3. Comparison 1 Briakinumab versus placebo, Outcome 3 Failure to induce clinical response (>= 100 points; 7 & 9 weeks).

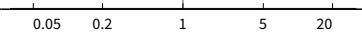
Study or subgroup	briakinumab n/N	placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 1 mg/kg body weight each week					
Mannon 2004	17/31	6/8		54.39%	0.73[0.44,1.22]
Subtotal (95% CI)	**31**	**8**		**54.39%**	**0.73[0.44,1.22]**
Total events: 17 (briakinumab), 6 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.2(P=0.23)					
1.3.2 3 mg/kg body weight each week					
Mannon 2004	11/32	5/8		45.61%	0.55[0.27,1.13]
Subtotal (95% CI)	**32**	**8**		**45.61%**	**0.55[0.27,1.13]**
Total events: 11 (briakinumab), 5 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.63(P=0.1)					
Total (95% CI)	**63**	**16**		**100%**	**0.65[0.42,0.99]**
Total events: 28 (briakinumab), 11 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.41, df=1(P=0.52); I^2=0%					
Test for overall effect: Z=2.01(P=0.04)					
Test for subgroup differences: Chi^2=0.4, df=1 (P=0.53), I^2=0%					



Favours briakinumab — Favours placebo

Analysis 1.4. Comparison 1 Briakinumab versus placebo, Outcome 4 Failure to induce clinical response (>= 100 points; 6 weeks).

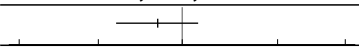
Study or subgroup	Experimental n/N	placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 400 mg iv of briakinumab					
Panaccione 2015	29/45	18/23		43.54%	0.82[0.61,1.12]
Subtotal (95% CI)	**45**	**23**		**43.54%**	**0.82[0.61,1.12]**
Total events: 29 (Experimental), 18 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.25(P=0.21)					
1.4.2 700 mg iv of briakinumab					
Panaccione 2015	88/139	18/23		56.46%	0.81[0.63,1.04]
Subtotal (95% CI)	**139**	**23**		**56.46%**	**0.81[0.63,1.04]**
Total events: 88 (Experimental), 18 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.66(P=0.1)					
Total (95% CI)	**184**	**46**		**100%**	**0.82[0.67,0.99]**
Total events: 117 (Experimental), 36 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.93); I^2=0%					
Test for overall effect: Z=2.06(P=0.04)					
Test for subgroup differences: Chi^2=0.01, df=1 (P=0.93), I^2=0%					



Favours briakinumab — Favours placebo

Analysis 1.5. Comparison 1 Briakinumab versus placebo, Outcome 5 Adverse events.

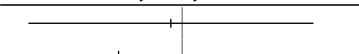
Study or subgroup	briakinumab n/N	placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Panaccione 2015	141/200	36/46		0.9[0.75,1.07]



Favours briakinumab — Favours placebo

Analysis 1.6. Comparison 1 Briakinumab versus placebo, Outcome 6 Serious adverse events.

Study or subgroup	briakinumab n/N	placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Mannon 2004	7/63	2/16		0.89[0.2,3.88]
Panaccione 2015	9/200	4/46		0.52[0.17,1.61]



Favours briakinumab — Favours placebo

Analysis 1.7. Comparison 1 Briakinumab versus placebo, Outcome 7 Withdrawals because of adverse events.

Study or subgroup	briakinumab n/N	placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Mannon 2004	2/63	2/16		0.25[0.04,1.67]
Panaccione 2015	6/200	2/46		0.69[0.14,3.31]

Favours briakinumab — Favours placebo

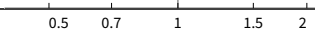
Comparison 2. Ustekinumab versus placebo

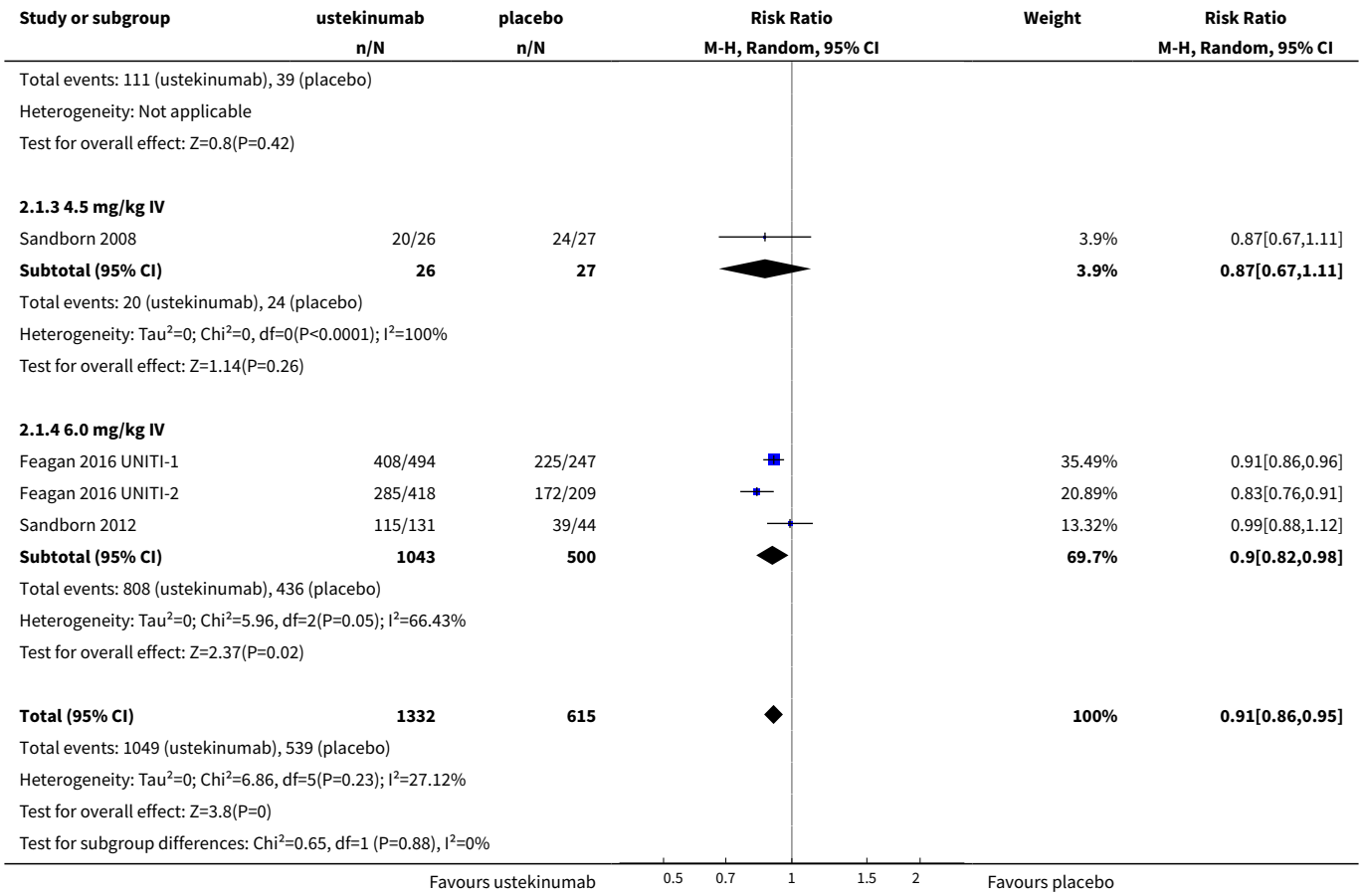
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Failure to induce clinical remission (6 weeks)	4	1947	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.86, 0.95]
1.1 1.0 mg/kg IV	1	175	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.82, 1.04]
1.2 3.0 mg/kg IV	1	176	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.83, 1.08]
1.3 4.5 mg/kg IV	1	53	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.67, 1.11]
1.4 6.0 mg/kg IV	3	1543	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.82, 0.98]
2 Failure to induce clinical remission (6 weeks; sensitivity analysis)	3	1320	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.88, 0.96]
2.1 1.0 mg/kg IV	1	175	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.82, 1.04]
2.2 3.0 mg/kg IV	1	176	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.83, 1.08]
2.3 4.5 mg/kg IV	1	53	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.67, 1.11]
2.4 6.0 mg/kg IV	2	916	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.87, 0.97]
3 Failure to induce clinical response (>= 70 points; 6 weeks)	4	1947	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.66, 0.81]
3.1 1 mg/kg IV	1	175	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.61, 0.98]
3.2 3 mg/kg IV	1	176	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.63, 1.03]
3.3 4.5 mg/kg IV	1	53	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.37, 0.94]
3.4 6 mg/kg IV	3	1543	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.61, 0.85]
4 Failure to induce clinical response (>= 70 points; 6 weeks; sensitivity analysis)	3	1320	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.71, 0.85]
4.1 1 mg/kg IV	1	175	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.61, 0.98]
4.2 3 mg/kg IV	1	176	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.63, 1.03]
4.3 4.5 mg/kg IV	1	53	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.37, 0.94]
4.4 6 mg/kg IV	2	916	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.71, 0.87]
5 Failure to Induce clinical response (>=100 points; 6 weeks)	4	1947	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.69, 0.87]
5.1 1.0 mg/kg IV	1	175	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.67, 1.01]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.2 3.0 mg/kg IV	1	176	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.70, 1.04]
5.3 4.5 mg/kg IV	1	53	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.39, 0.89]
5.4 6.0 mg/kg IV	3	1543	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.63, 0.91]
6 Failure to Induce clinical response (>=100 points; 6 weeks; sensitivity analysis)	3	1320	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.77, 0.88]
6.1 1.0 mg/kg IV	1	175	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.67, 1.01]
6.2 3.0 mg/kg IV	1	176	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.70, 1.04]
6.3 4.5 mg/kg IV	1	53	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.39, 0.89]
6.4 6.0 mg/kg IV	2	916	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.77, 0.91]
7 Failure to induce clinical remission - 90 mg, s.c. (6 weeks)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8 Failure to induce clinical response 90 mg s.c. (>= 70 points; 6 weeks)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9 Failure to induce clinical response 90 mg s.c. (>=100 points; 6 weeks)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
10 Adverse events	4	2023	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.90, 1.04]
11 Serious adverse events	4	2023	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.58, 1.20]
12 Withdrawals because of adverse events	2	657	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.18, 1.05]

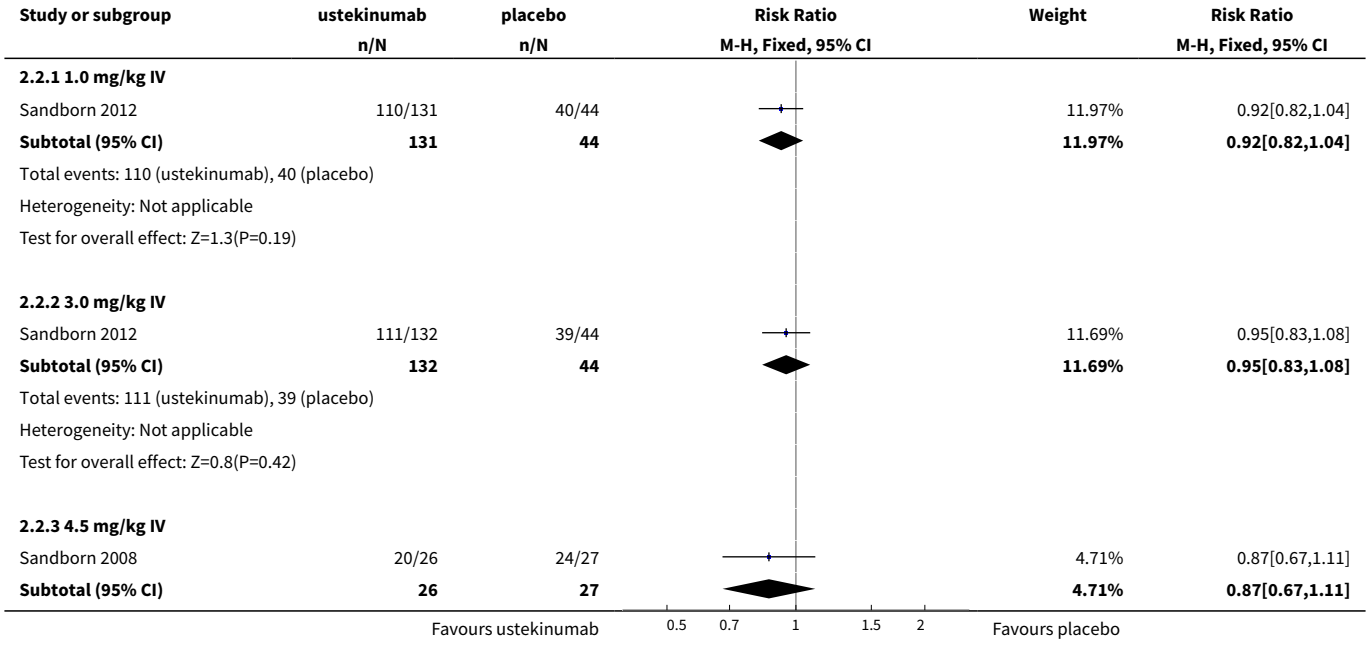
Analysis 2.1. Comparison 2 Ustekinumab versus placebo, Outcome 1 Failure to induce clinical remission (6 weeks).

Study or subgroup	ustekinumab n/N	placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 1.0 mg/kg IV					
Sandborn 2012	110/131	40/44		14%	0.92[0.82,1.04]
Subtotal (95% CI)	**131**	**44**		**14%**	**0.92[0.82,1.04]**
Total events: 110 (ustekinumab), 40 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.3(P=0.19)					
2.1.2 3.0 mg/kg IV					
Sandborn 2012	111/132	39/44		12.41%	0.95[0.83,1.08]
Subtotal (95% CI)	**132**	**44**		**12.41%**	**0.95[0.83,1.08]**

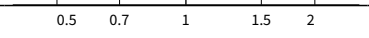




Analysis 2.2. Comparison 2 Ustekinumab versus placebo, Outcome 2 Failure to induce clinical remission (6 weeks; sensitivity analysis).



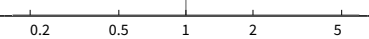
Study or subgroup	ustekinumab n/N	placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Total events: 20 (ustekinumab), 24 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=1.14(P=0.26)					
2.2.4 6.0 mg/kg IV					
Feagan 2016 UNITI-1	408/494	225/247		59.96%	0.91[0.86,0.96]
Sandborn 2012	115/131	39/44		11.67%	0.99[0.88,1.12]
Subtotal (95% CI)	**625**	**291**		**71.63%**	**0.92[0.87,0.97]**
Total events: 523 (ustekinumab), 264 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.63, df=1(P=0.2); I^2=38.52%					
Test for overall effect: Z=3.18(P=0)					
Total (95% CI)	**914**	**406**		**100%**	**0.92[0.88,0.96]**
Total events: 764 (ustekinumab), 367 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.07, df=4(P=0.72); I^2=0%					
Test for overall effect: Z=3.67(P=0)					
Test for subgroup differences: Chi^2=0.44, df=1 (P=0.93), I^2=0%					



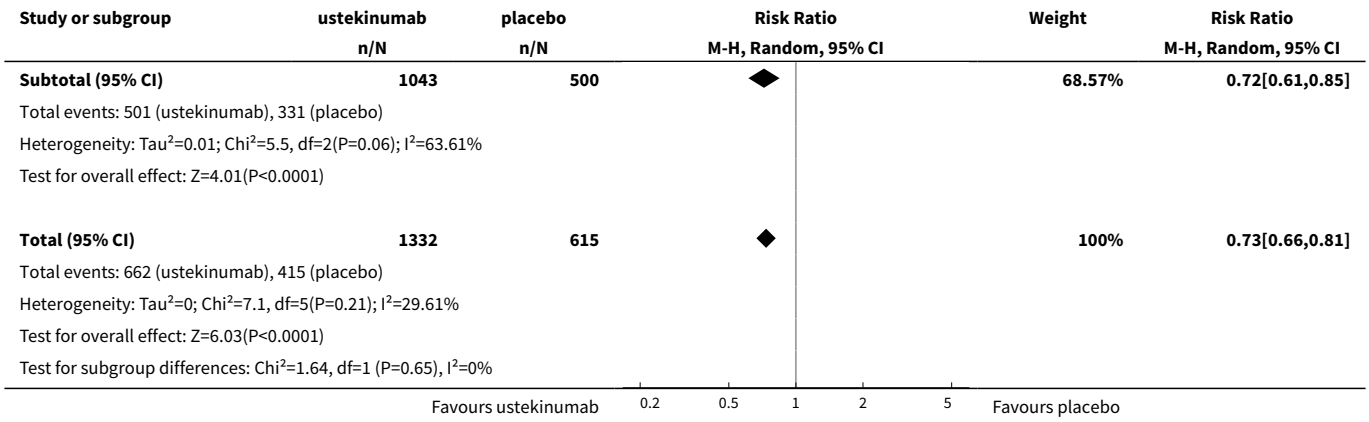
Favours ustekinumab — Favours placebo

Analysis 2.3. Comparison 2 Ustekinumab versus placebo, Outcome 3 Failure to induce clinical response (>= 70 points; 6 weeks).

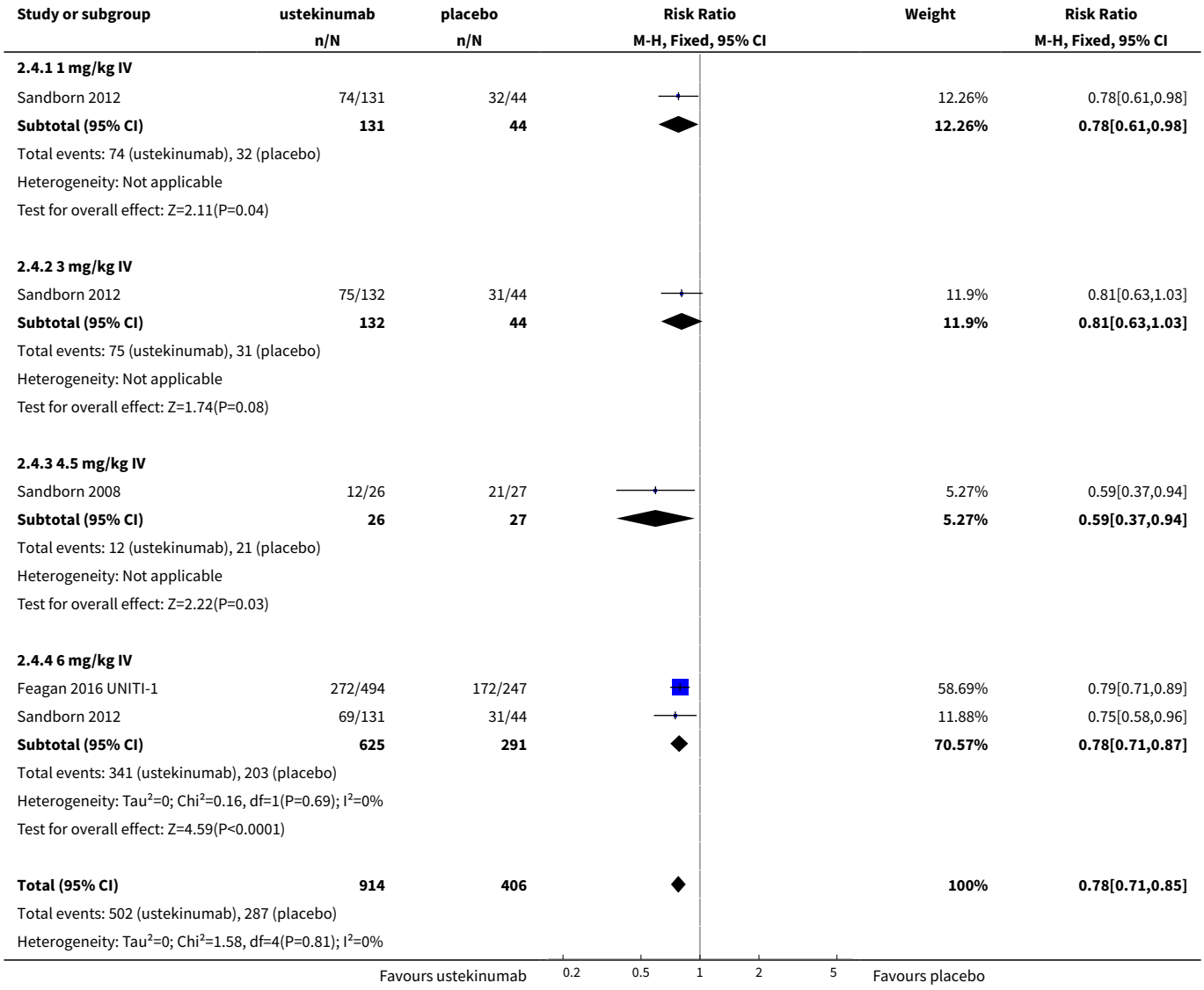
Study or subgroup	ustekinumab n/N	placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 1 mg/kg IV					
Sandborn 2012	74/131	32/44		13.84%	0.78[0.61,0.98]
Subtotal (95% CI)	**131**	**44**		**13.84%**	**0.78[0.61,0.98]**
Total events: 74 (ustekinumab), 32 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.11(P=0.04)					
2.3.2 3 mg/kg IV					
Sandborn 2012	75/132	31/44		13.22%	0.81[0.63,1.03]
Subtotal (95% CI)	**132**	**44**		**13.22%**	**0.81[0.63,1.03]**
Total events: 75 (ustekinumab), 31 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.74(P=0.08)					
2.3.3 4.5 mg/kg IV					
Sandborn 2008	12/26	21/27		4.36%	0.59[0.37,0.94]
Subtotal (95% CI)	**26**	**27**		**4.36%**	**0.59[0.37,0.94]**
Total events: 12 (ustekinumab), 21 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.22(P=0.03)					
2.3.4 6 mg/kg IV					
Feagan 2016 UNITI-1	272/494	172/247		33.06%	0.79[0.71,0.89]
Feagan 2016 UNITI-2	160/418	128/209		22.99%	0.63[0.53,0.74]
Sandborn 2012	69/131	31/44		12.53%	0.75[0.58,0.96]

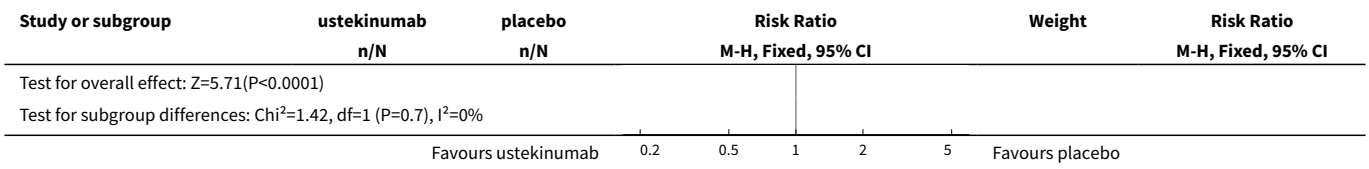


Favours ustekinumab — Favours placebo

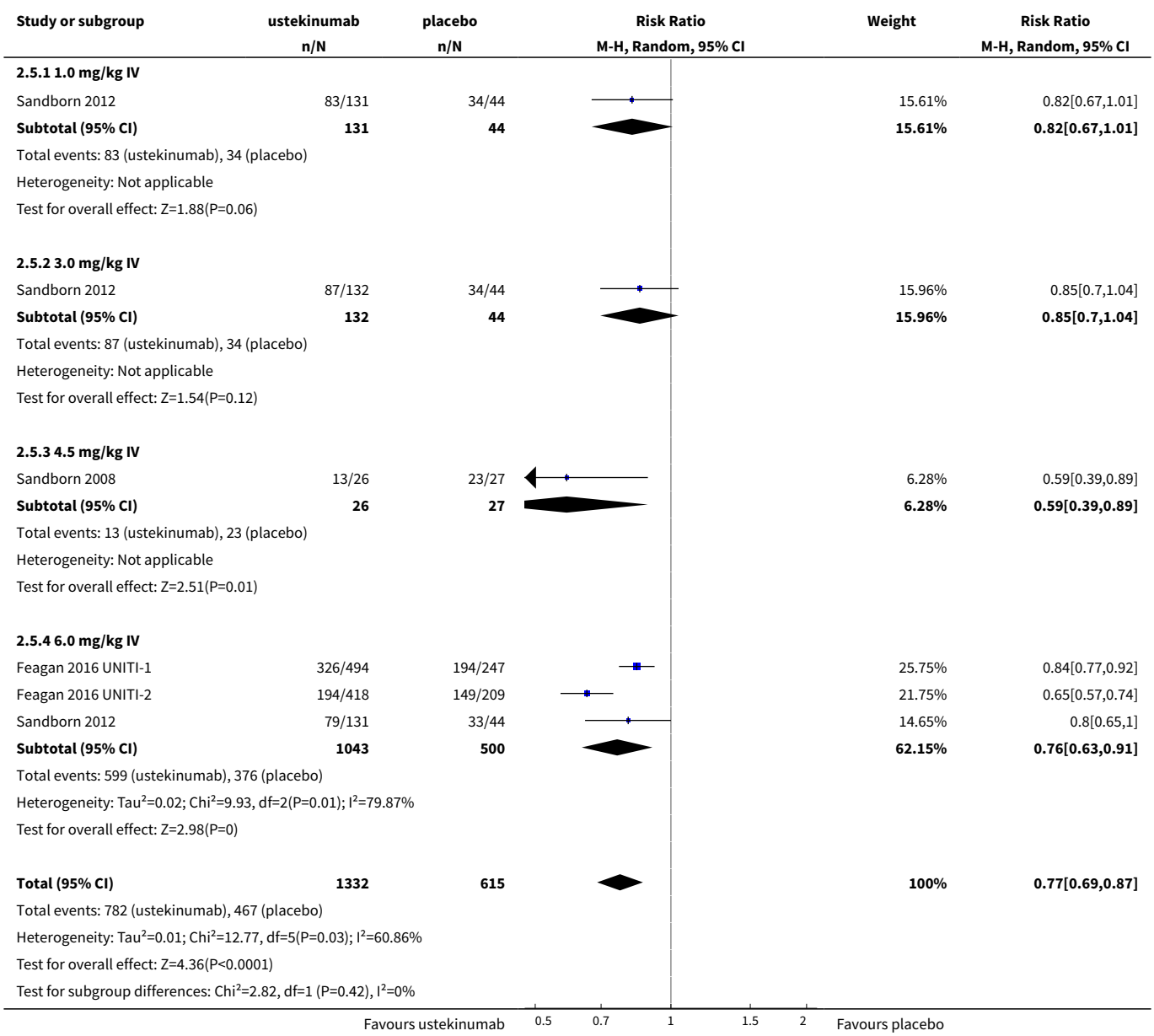


Analysis 2.4. Comparison 2 Ustekinumab versus placebo, Outcome 4 Failure to induce clinical response (>= 70 points; 6 weeks; sensitivity analysis).

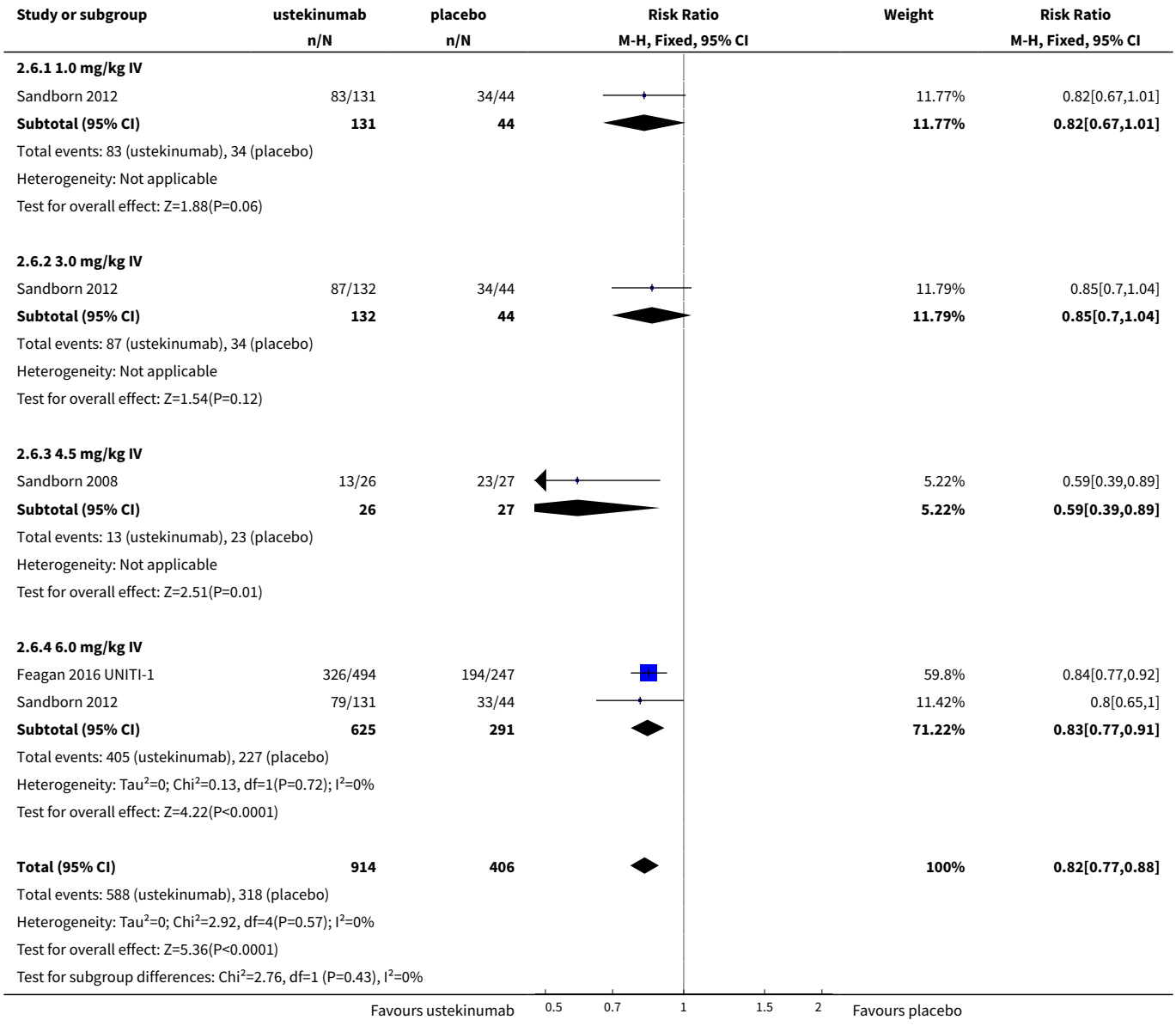




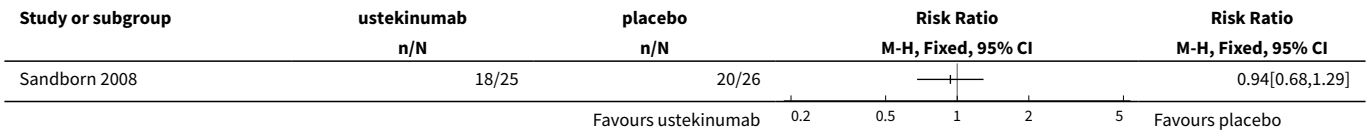
Analysis 2.5. Comparison 2 Ustekinumab versus placebo, Outcome 5 Failure to Induce clinical response (>=100 points; 6 weeks).



Analysis 2.6. Comparison 2 Ustekinumab versus placebo, Outcome 6 Failure to Induce clinical response (>=100 points; 6 weeks; sensitivity analysis).

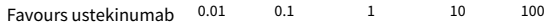


Analysis 2.7. Comparison 2 Ustekinumab versus placebo, Outcome 7 Failure to induce clinical remission - 90 mg, s.c. (6 weeks).



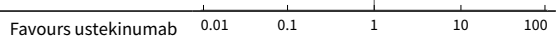
Analysis 2.8. Comparison 2 Ustekinumab versus placebo, Outcome 8 Failure to induce clinical response 90 mg s.c. (>= 70 points; 6 weeks).

Study or subgroup	ustekinumab n/N	placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Sandborn 2008	12/25	16/26		0.78[0.47,1.3]



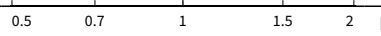
Analysis 2.9. Comparison 2 Ustekinumab versus placebo, Outcome 9 Failure to induce clinical response 90 mg s.c. (>=100 points; 6 weeks).

Study or subgroup	ustekinumab n/N	placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Sandborn 2008	13/25	17/26		0.8[0.5,1.27]



Analysis 2.10. Comparison 2 Ustekinumab versus placebo, Outcome 10 Adverse events.

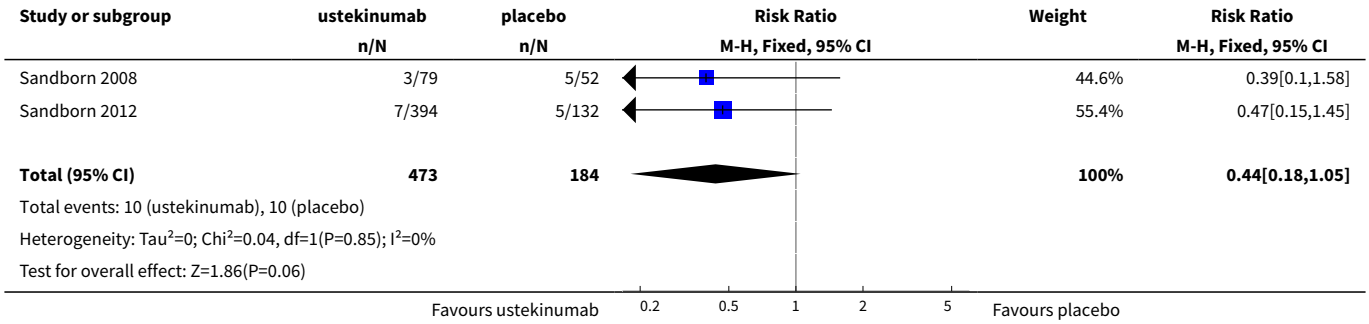
Study or subgroup	ustekinumab n/N	placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Feagan 2016 UNITI-1	323/494	159/245		38.38%	1.01[0.9,1.13]
Feagan 2016 UNITI-2	221/419	113/208		27.27%	0.97[0.83,1.13]
Sandborn 2008	59/79	41/52		8.93%	0.95[0.78,1.15]
Sandborn 2012	257/394	94/132		25.42%	0.92[0.8,1.04]
Total (95% CI)	**1386**	**637**		**100%**	**0.97[0.9,1.04]**
Total events: 860 (ustekinumab), 407 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.23, df=3(P=0.74); I^2=0%					
Test for overall effect: Z=0.88(P=0.38)					



Analysis 2.11. Comparison 2 Ustekinumab versus placebo, Outcome 11 Serious adverse events.

Study or subgroup	ustekinumab n/N	placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Feagan 2016 UNITI-1	30/494	15/245		35.69%	0.99[0.54,1.81]
Feagan 2016 UNITI-2	16/419	12/208		28.54%	0.66[0.32,1.37]
Sandborn 2008	6/79	3/52		6.44%	1.32[0.34,5.03]
Sandborn 2012	23/394	11/132		29.33%	0.7[0.35,1.4]
Total (95% CI)	**1386**	**637**		**100%**	**0.83[0.58,1.2]**
Total events: 75 (ustekinumab), 41 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.39, df=3(P=0.71); I^2=0%					
Test for overall effect: Z=0.97(P=0.33)					

Analysis 2.12. Comparison 2 Ustekinumab versus placebo, Outcome 12 Withdrawals because of adverse events.



ADDITIONAL TABLES

Table 1. Sensitivity Analysis: Fixed Effects vs. Random Effects Modelling

Outcome	Fixed Effects Modelling	Random Effects Modelling
Briakinumab /Remission (Mannon 2004)	RR 0.86 [0.65, 1.14]	RR 0.88 [0.68, 1.15]
Briakinumab /Remission (Panaccione 2015)	RR 1.05 [0.90, 1.22]	RR 0.92 [0.83, 1.03]
Ustekinumab /Remission	RR 0.94 [0.88, 1.01]	RR 0.95 [0.89, 1.02]
Briakinumab /Response (Mannon 2004)	RR 0.65 [0.42, 0.99]	RR 0.66 [0.44, 1.01]
Briakinumab /Response (Panaccione 2015)	RR 0.82 [0,67, 0.99]	RR 0.81 [0.67, 0.99]
Ustekinumab /Response	RR 0.79 [0.71, 0.89]	RR 0.80 [0.72, 0.90]

APPENDICES

Appendix 1. Search strategies

PubMed

8 Search (#6 AND #7)

7 Search (singl* OR doubl* OR tripl* OR trebl* OR blind* OR mask* OR placebo* OR single-blind* OR double-blind* OR triple-blind* OR random* OR controlled clinical)

6 Search (#1 AND #5)

5 Search (#2 OR #3 OR #4)

4 Search anti-IL-12/23p40

3 Search ((IL-12 OR interleukin 12 OR IL-23 OR interleukin 23 OR p40) AND (antibod* OR anti-IL*))

2 Search (abt-874 OR ustekinumab OR "cnto 1275" OR briakinumab)

1 Search crohn* OR IBD OR "inflammatory bowel disease*"

EMBASE

1 random$.tw.

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 crossover procedure/

14 double blind procedure/

15 single blind procedure/

16 triple blind procedure/

17 randomized controlled trial/

18 or/1-17

19 (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)

20 18 not 19

21 exp Crohn disease/ or crohn*.mp. or exp colon Crohn disease/

22 (inflammatory bowel disease* or IBD).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

23 21 or 22

24 ustekinumab.mp. or exp ustekinumab/

25 briakinumab.mp. or exp briakinumab/

26 (abt-874 or "cnto 1275").mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

27 24 or 25 or 26

28 "interleukin 12".mp. or exp interleukin 12/

29 "interleukin 23".mp. or exp interleukin 23/

30 (IL-12 or IL-23 or p40).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

31 28 or 29 or 30

32 exp monoclonal antibody/ or exp antibody/ or antibod*.mp.

33 31 and 32

34 anti-IL-12 23p40.mp.

35 27 or 33 or 34

36 20 and 23 and 35

MEDLINE

1 random$.tw.

2 factorial$.tw.

3 (crossover$ or cross over$ or cross-over$).tw.

4 placebo$.tw.

5 placebo$.tw.

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 crossover procedure/

14 double blind procedure/

15 single blind procedure/

16 triple blind procedure/

17 randomized controlled trial/

18 or/1-17

19 (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)

20 18 not 19

21 exp Crohn Disease Activity Index/ or exp Crohn disease/ or crohn*.mp.

22 ("inflammatory bowel disease*" or IBD).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

23 21 or 22

24 (ustekinumab or briakinumab or "CNTO 1275" or ABT-874).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

25 interleukin 12.mp. or exp Interleukin-12/

26 interleukin 23.mp. or exp Interleukin-23/

27 (IL-12 or IL-23 or p40).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

28 25 or 26 or 27

29 antibod*.mp. or exp Antibodies/ or exp Antibodies, Monoclonal/

30 28 and 29

31 IL-12 23p40.mp.

32 24 or 30 or 31

33 20 and 23 and 32

Cochrane Library (CENTRAL)

1 ustekinumab or briakinumab or ABT-874 or CNTO 1275

2 interleukin 12 or interleukin 23 or IL-12 or il-23 or p40

3 antibod*

4 #2 and #3 442

5 anti-il-12/23p40

6 #1 or #4 or #5

7 #6 and (Crohn* or IBD or "inflammatory bowel disease*")

Electronic databases of abstracts from Digestive Disease Week (DDW) (1994 to 2012)

- (interleukin 12, interleukin-12, IL-12, interleukin 23, interleukin-23, IL-23, p40, ustekinumab, CNTO 1275, briakinumab and ABT-874) were all searched with the search term: crohn*

WHAT'S NEW

Date	Event	Description
12 September 2016	New citation required and conclusions have changed	Updated review with one new author. Conclusions changed.
12 September 2016	New search has been performed	New literature search performed on 12 September 2016. Two new studies were added.

CONTRIBUTIONS OF AUTHORS

All authors contributed to planning the study, identification of relevant studies, assessment of methodological quality, data extraction, and manuscript preparation.

DECLARATIONS OF INTEREST

John MacDonald: None known.

Tran Nguyen: None known

Reena Khanna has received honoraria from AbbVie, Jansen, Pfizer, Shire, and Takeda for consultancy. All of these activities are outside the submitted work.

Antje Timmer received grants (paid to institution) from Sanofi-Aventis, Bayer, Takeda, Celgene, and Novartis for pharmacoepidemiological studies; and payment for lectures from The Falk Foundation, and MSD Sharp. All of these activities are outside the submitted work.

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Internal sources

- Charité - Universitätsmedizin Berlin, Germany.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We would like to acknowledge some differences between the protocol and review:

- Primary and secondary outcomes: The primary and secondary outcomes were not well defined in the protocol. The primary outcome should have been defined as the proportion of patients who failed to enter clinical remission as defined by the included studies. The secondary efficacy outcomes should have been defined in a similar manner. The secondary outcome 'adverse events' was added after the protocol was published.
- GRADE was added to the methods section. Please see MECIR C76.
- We added a section on 'Unit of analysis issues' to the Methods section to explain how we would deal with these issues. This was not predefined in the protocol.
- We added a section on 'Assessment of reporting biases' to the Methods section to explain how we would deal with issue for future updates of this review.This was not predefined in the protocol.

INDEX TERMS

Medical Subject Headings (MeSH)

Antibodies, Monoclonal [administration & dosage] [*therapeutic use]; Antibodies, Monoclonal, Humanized [administration & dosage] [*therapeutic use]; Crohn Disease [*therapy]; Injections, Intravenous; Interleukin-12 [*antagonists & inhibitors] [immunology]; Interleukin-23 [*antagonists & inhibitors] [immunology]; Randomized Controlled Trials as Topic; Remission Induction [methods]; Ustekinumab [administration & dosage] [*therapeutic use]

MeSH check words

Humans