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Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis (Review)

Murray A, Nguyen TM, Parker CE, Feagan BG, MacDonald JK

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[Intervention Review]

Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis

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ABSTRACT

Background

Oral 5-aminosalicylic acid (5-ASA) preparations were intended to avoid the adverse effects of sulfasalazine (SASP) while maintaining its therapeutic benefits. It was previously found that 5-ASA drugs in doses of at least 2 g/day were more effective than placebo but no more effective than SASP for inducing remission in ulcerative colitis (UC). This review is an update of a previously published Cochrane Review.

Objectives

To assess the efficacy, dose-responsiveness and safety of oral 5-ASA compared to placebo, SASP, or 5-ASA comparators (i.e. other formulations of 5-ASA) for induction of remission in active UC. A secondary objective was to compare the efficacy and safety of once-daily dosing of oral 5-ASA versus conventional dosing regimens (two or three times daily).

Search methods

We searched MEDLINE, Embase and the Cochrane Library on 11 June 2019. We also searched references, conference proceedings and study registers to identify additional studies.

Selection criteria

We considered randomized controlled trials (RCTs) including adults (aged 18 years or more) with active UC for inclusion. We included studies that compared oral 5-ASA therapy with placebo, SASP, or other 5-ASA formulations. We also included studies that compared once-daily to conventional dosing as well as dose-ranging studies.

Data collection and analysis

Outcomes include failure to induce global/clinical remission, global/clinical improvement, endoscopic remission, endoscopic improvement, adherence, adverse events (AEs), serious adverse events (SAEs), withdrawals due to AEs, and withdrawals or exclusions after entry. We analyzed five comparisons: 5-ASA versus placebo, 5-ASA versus sulfasalazine, once-daily dosing versus conventional dosing, 5-ASA (e.g. MMX mesalamine, Ipocol, Balsalazide, Pentasa, Olsalazine and 5-ASA micropellets) versus comparator 5-ASA (e.g. Asacol, Claversal, Salofalk), and 5-ASA dose-ranging. We calculated the risk ratio (RR) and 95% confidence interval (95% CI) for each outcome. We analyzed data on an intention-to-treat basis, and used GRADE to assess the overall certainty of the evidence.

Main results

We include 54 studies (9612 participants). We rated most studies at low risk of bias.

Seventy-one per cent (1107/1550) of 5-ASA participants failed to enter clinical remission compared to 83% (695/837) of placebo participants (RR 0.86, 95% CI 0.82 to 0.89; 2387 participants, 11 studies; high-certainty evidence). We also observed a dose-response trend for 5-ASA.

There was no difference in clinical remission rates between 5-ASA and SASP. Fifty-four per cent (150/279) of 5-ASA participants failed to enter remission compared to 58% (144/247) of SASP participants (RR 0.90, 95% CI 0.77 to 1.04; 526 participants, 8 studies; moderate-certainty evidence).

There was no difference in remission rates between once-daily dosing and conventional dosing. Sixty per cent (533/881) of once-daily participants failed to enter clinical remission compared to 61% (538/880) of conventionally-dosed participants (RR 0.99, 95% CI 0.93 to 1.06; 1761 participants, 5 studies; high-certainty evidence). Eight per cent (15/179) of participants dosed once daily failed to adhere to their medication regimen compared to 6% (11/179) of conventionally-dosed participants (RR 1.36, 95% CI 0.64 to 2.86; 358 participants, 2 studies; low-certainty evidence).

There does not appear to be any difference in efficacy among the various 5-ASA formulations. Fifty per cent (507/1022) of participants in the 5-ASA group failed to enter remission compared to 52% (491/946) of participants in the 5-ASA comparator group (RR 0.94, 95% CI 0.86 to 1.02; 1968 participants, 11 studies; moderate-certainty evidence).

There was no evidence of a difference in the incidence of adverse events and serious adverse events between 5-ASA and placebo, once-daily and conventionally-dosed 5-ASA, and 5-ASA and comparator 5-ASA formulation studies. Common adverse events included flatulence, abdominal pain, nausea, diarrhea, headache and worsening UC. SASP was not as well tolerated as 5-ASA. Twenty-nine per cent (118/411) of SASP participants experienced an AE compared to 15% (72/498) of 5-ASA participants (RR 0.48, 95% CI 0.36 to 0.63; 909 participants, 12 studies; moderate-certainty evidence).

Authors' conclusions

There is high-certainty evidence that 5-ASA is superior to placebo, and moderate-certainty evidence that 5-ASA is not more effective than SASP. Considering relative costs, a clinical advantage to using oral 5-ASA in place of SASP appears unlikely. High-certainty evidence suggests 5-ASA dosed once daily appears to be as efficacious as conventionally-dosed 5-ASA. There may be little or no difference in efficacy or safety among the various 5-ASA formulations.

PLAIN LANGUAGE SUMMARY

Oral 5-aminosalicylic acid for the treatment of active ulcerative colitis

What is ulcerative colitis?

Ulcerative colitis (UC) is a condition that causes inflammation of your large intestine (colon). Some of the symptoms associated with UC include diarrhea, abdominal pain, rectal pain, rectal bleeding, weight loss, fatigue and fever.

What is 5-aminosalicylic acid (5-ASA)?

Sulfasalazine (SASP) has been used for treating UC for decades. SASP is made up of 5-aminosalicylic acid (5-ASA) linked to a sulfur molecule. Up to a third of people treated with SASP have reported side effects, which are thought to be related to the sulfur part of the molecule. Common side effects associated with SASP include nausea, indigestion, headache, vomiting and abdominal pain. 5-ASA drugs were developed to avoid the side effects associated with SASP. 5-ASA is commonly taken by mouth.

What did the researchers investigate?

The researchers examined whether oral 5-ASA helps to cause remission in people with UC. The researchers investigated whether oral 5-ASA was better than placebo (a fake medication) or a different 5-ASA formulation.

Key results

This review includes 54 randomized trials with a total of 9612 people taking part. The review includes studies published up to June 2019. Oral 5-ASA was found to be more effective than placebo (fake drug). Although oral 5-ASA drugs are effective for treating active UC, they are no more effective than SASP therapy. People taking 5-ASA are less likely to experience side effects than those taking SASP. Side effects associated with 5-ASA are generally mild in nature, and common side effects include digestive tract symptoms (e.g. flatulence, abdominal pain, nausea, and diarrhea), headache and worsening UC. 5-ASA compounds are more expensive than SASP, so SASP may be the preferred option where cost is an important factor. 5-ASA given once daily appears to be as effective as 5-ASA given in the usual way (two or three times daily). There do not appear to be any differences in effectiveness or safety among the various 5-ASA formulations.

Conclusions

High-certainty evidence suggests that 5-ASA is superior to placebo and that 5-ASA once-daily dose has the same effectiveness and safety as the conventional 5-ASA dose. Moderate-certainty evidence also suggests that 5-ASA is not superior to SASP. Sticking to the medication does not appear to improve with once-daily dosing compared to conventional dosing. Lastly, there may be little or no difference in effectiveness or safety among the various 5-ASA formulations.

SUMMARY OF FINDINGS

Summary of findings 1. Oral 5-ASA versus placebo for induction of remission in ulcerative colitis

Oral 5-ASA versus placebo for induction of remission in ulcerative colitis

Patient or population: People with active mild-to-moderate ulcerative colitis
Settings: Outpatient
Intervention: Oral 5-ASA

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	Oral 5-ASA				
Failure to induce complete global or clinical remission Follow-up: 6 - 12 weeks	**830 per 1000** [a]	**714 per 1000** (681 to 739)	**RR 0.86** (0.82 to 0.89)	2387 (11 studies)	⊕⊕⊕⊕ HIGH	Global or clinical remission was defined as a score of 0 points for stool frequency and rectal bleeding
Failure to induce global or clinical improvement Follow-up: 6 - 12 weeks	**651 per 1000** [a]	**443 per 1000** (397 to 488)	**RR 0.68** (0.61 to 0.75)	2256 (14 studies)	⊕⊕⊕⊖ MODERATE[b]	Clinical improvement was defined as a decrease of 3 points from baseline in the overall modified UC-DAI score
Failure to induce endoscopic remission Follow-up: 6 - 14 weeks	**639 per 1000**	**492 per 1000** (428 to 569)	**RR 0.77** (0.67 to 0.89)	1154 (4 studies)	⊕⊕⊕⊖ MODERATE[c]	Endoscopic improvement was defined as endoscopy/sigmoidoscopy score of ≤ 1
Failure to adhere to medication regimen	This outcome is not reported					Not reported
Adverse events Follow-up: 6 - 12 weeks	**486 per 1000** [a]	**462 per 1000** (413 to 520)	**RR 0.95** (0.85 to 1.07)	1218 (8 studies)	⊕⊕⊕⊕ HIGH	Adverse events included headache, nausea, abdominal pain or cramps, nasopharyngitis or symptoms of upper respiratory infection, rash. anorexia or loss of appetite, flatulence or gas, gastrointestinal disorders and fever

Serious adverse events Follow-up: 6 - 12 weeks	**21 per 1,000** [a]	**11 per 1000** (4 to 33)	**RR 0.53** (0.18 to 1.56)	746 (4 studies)	⊕⊕⊝⊝ LOW[d]	Serious adverse events included aggravation of UC, malaise, abdominal abscess, pancreatitis and an inguinal hernia
Withdrawal due to adverse events Follow-up: 6 - 12 weeks	**88 per 1000** [a]	**63 per 1000** (47 to 85)	**RR 0.72** (0.54 to 0.97)	2372 (13 studies)	⊕⊕⊕⊝ MODERATE[e]	Common adverse events leading to withdrawal were not reported

*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).
CI: Confidence interval; **RR:** risk ratio **UC:** ulcerative colitis; **UC-DAI: ulcerative colitis - disease activity index**

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.

[a]Control group risk estimates come from control arm of meta-analysis, based on included trials.
[b]Downgraded one level due to heterogeneity I^2 = 47%.
[c]Downgrade one level due to heterogeneity I^2 = 42%.
[d]Downgraded two levels due to very sparse data (13 events).
[e]Downgraded one level due to sparse data (164 events).

Summary of findings 2. Oral 5-ASA versus SASP for induction of remission in ulcerative colitis

Oral 5-ASA versus SASP for induction of remission in ulcerative colitis

Patient or population: People with active mild-to-moderate ulcerative colitis
Settings: Outpatient
Intervention: Oral 5-ASA

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	SASP	Oral 5-ASA				

Failure to induce global or clinical remission Follow-up: 4 - 8 weeks	**583 per 1000** [a]	**525 per 1000** (449 to 606)	**RR 0.90** (0.77 to 1.04)	526 (8 studies)	⊕⊕⊕⊖ MODERATE[b]	Global or clinical remission was defined as the return to stool frequency (2 - 3 stools or fewer a day) without the presence of blood
Failure to induce global or clinical improvement Follow-up: 4 - 8 weeks	**467 per 1000** [a]	**411 per 1000** (355 to 472)	**RR 0.88** (0.76 to 1.01)	1053 (14 studies)	⊕⊕⊕⊕ HIGH	Clinical improvement was defined as reduction in their clinical activity index
Failure to induce endoscopic remission	See comment					2 studies reported this outcome but meta-analysis not performed as they used different measurement indices. Neither study showed significant differences in complete endoscopic remission between 5-ASA and SASP
Failure to adhere to medication regimen	See comment					Outcome not reported
Adverse events Follow-up: 4 - 8 weeks	**287 per 1000** [a]	**138 per 1000** (103 to 181)	**RR 0.48** (0.36 to 0.63)	909 (12 studies)	⊕⊕⊕⊖ MODERATE[c]	Adverse events included nausea, headache, dyspepsia, vomiting, abdominal pain and rash
Serious adverse events Follow-up: 4 - 8 weeks	**38 per 1000**	**51 per 1000** (11 to 246)	**RR 1.36** (0.28 to 6.52)	107 (2 studies)	⊕⊕⊖⊖ LOW[d]	Serious adverse events included erythematous rash, venous thrombosis, carcinoma, acute pancreatitis, rheumatoid arthritis and erythema nodosum
Withdrawal due to adverse events Follow-up: 4 - 8 weeks	**129 per 1000** [a]	**52 per 1000** (31 to 88)	**RR 0.40** (0.24 to 0.68)	640 (10 studies)	⊕⊕⊕⊖ MODERATE[e]	Common adverse events leading to withdrawal included nausea, headaches and rashes

*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).
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.

[a]Control group risk estimates come from control arm of meta-analysis, based on included trials.
[b]Downgraded one level due to sparse data (294 events).
[c]Downgraded one level due to sparse data (190 events).
[d]Downgraded two levels due to very sparse data (5 events).
[e]Downgraded one level due to sparse data (54 events).

Summary of findings 3. Once daily dosing versus conventional dosing for induction of remission in ulcerative colitis

Once-daily dosing versus conventional dosing for induction of remission in ulcerative colitis

Patient or population: People with active mild-to-moderate ulcerative colitis
Settings: Outpatient
Intervention: Once-daily dosing

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Conventional dosing	Once daily dosing				
Failure to induce global or clinical remission Follow-up: 8 weeks	**611 per 1000** [a]	**605 per 1000** (569 to 648)	**RR 0.99** (0.93 to 1.06)	1761 (5 studies)	⊕⊕⊕⊕ HIGH	Global or clinical remission was defined as UC-DAI score of ≤ 1
Failure to induce global or clinical improvement Follow-up: 8 weeks	**367 per 1000** [a]	**272 per 1000** (180 to 404)	**RR 0.74** (0.49 to 1.10)	564 (3 studies)	⊕⊕⊕⊖ MODERATE[b]	Clinical improvement was defined as decrease of ≤ 3 points from baseline in the total modified UC-DAI score
Failure to induce endoscopic remission	**892 per 1000** [a]	**910 per 1000** (180 to 404)	**RR 1.02** (0.98 to 1.07)	817 (1 study)	⊕⊕⊕⊕ HIGH	Endoscopic remission was defined as Mayo Clinic Endoscopic Subscale subscore of 0
Failure to adhere to medication regimen Follow-up: 8 weeks	**61 per 1000** [a]	**84 per 1000** (39 to 176)	**RR 1.36** (0.64 to 2.86)	358 (2 studies)	⊕⊕⊖⊖ LOW[c]	Adherence to medication regimen was defined as compliance with taking medications
Adverse events	**318 per 1000** [a]	**324 per 1000** (283 to 375)	**RR 1.02** (0.89 to 1.18)	1586 (4 studies)	⊕⊕⊕⊖ MODERATE[d]	Adverse events included flatulence, abdominal pain, nausea, diarrhea, nasopharyngitis, dys-

Follow-up: 8 weeks						pepsia, headache and worsening of ulcerative colitis
Serious adverse events Follow-up: 8 weeks	**18 per 1000** [a]	**24 per 1000** (12 to 47)	**RR 1.34** (0.68 to 2.66)	1586 (4 studies)	⊕⊕⊖⊖ LOW[e]	Serious adverse events included pancreatitis, hepatitis, polyuria, chromaturia, upper respiratory tract infection and measles
Withdrawal due to adverse events Follow-up: 8 weeks	**33 per 1000** [a]	**29 per 1000** (18 to 49)	**RR 0.89** (0.54 to 1.49)	1757 (5 studies)	⊕⊕⊖⊖ LOW[f]	Common adverse events leading to withdrawal were not reported

*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).
CI: Confidence interval; **RR:** risk ratio; **UC:** ulcerative colitis; **UC-DAI: ulcerative colitis - disease activity index**

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.

[a]Control group risk estimates come from control arm of meta-analysis, based on included trials.
[b]Downgraded one level due to sparse data (153 events).
[c]Downgraded two levels due to very sparse data (26 events).
[d]Downgraded one level due to sparse data (271 events).
[e]Downgraded two levels due to very sparse data (33 events).
[f]Downgraded two levels due to very sparse data (9 events).

Summary of findings 4. Oral 5-ASA versus comparator 5-ASA for induction of remission in ulcerative colitis

Oral 5-ASA versus comparator 5-ASA for induction of remission in ulcerative colitis

Patient or population: People with active mild-to-moderate ulcerative colitis
Settings: Outpatient
Intervention: Oral 5-ASA (MMX mesalamine, Ipocol, Balsalazide, Pentasa, Olsalazine and 5-ASA micropellets)

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				

	Comparator 5-ASA	Oral 5-ASA				
Failure to induce global or clinical remission Follow-up: 8 - 12 weeks	**519 per 1000** [a]	**488 per 1000** (446 to 529)	**RR 0.94** (0.86 to 1.02)	1968 (11 studies)	⊕⊕⊕⊖ MODERATE[b]	Global or clinical remission was defined as CAI ≤ 4 for patient functional assessment ratings or normal bowel movements and absence of rectal bleeding
Failure to induce global or clinical improvement Follow-up: 8 - 12 weeks	**346 per 1000** [a]	**308 per 1000** (267 to 350)	**RR 0.89** (0.77 to 1.01)	1647 (8 studies)	⊕⊕⊕⊖ MODERATE[c]	Clinical improvement was defined as improved CAI by ≤ 3 from baseline
Failure to induce endoscopic remission	See comment					Outcome not reported
Failure to adhere to medication regimen	See comment					Outcome not reported
Adverse events Follow-up: 8 - 12 weeks	**457 per 1000** [a]	**461 per 1000** (420 to 511)	**RR 1.01** (0.92 to 1.12)	1576 (9 studies)	⊕⊕⊕⊖ MODERATE[d]	Adverse events included headache, abdominal pain, nausea, flatulence, diarrhea, nasopharyngitis, dyspepsia and vomiting
Serious adverse events Follow-up: 8 - 12 weeks	**30 per 1,000** [a]	**18 per 1000** (7 to 47)	**RR 0.59** (0.22 to 1.56)	677 (4 studies)	⊕⊕⊖⊖ LOW[e]	Serious adverse events included aggravation of UC and a colonic polyp
Withdrawal due to adverse events Follow-up: 8 - 12 weeks	**39 per 1000** [a]	**37 per 1000** (22 to 60)	**RR 0.94** (0.57 to 1.54)	1489 (9 studies)	⊕⊕⊕⊖ MODERATE[f]	Common adverse events leading to withdrawal include abdominal pain, rashes and cephalea

*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).
CAI: clinical activity index; **CI:** Confidence interval; **RR:** risk ratio; **UC:** ulcerative colitis

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.

[a]Control group risk estimates come from control arm of meta-analysis, based on included trials.

[b]Downgraded one level due to high risk of bias in two studies in the pooled analysis (both due to lack of blinding).
[c]Downgraded one level due to high risk of bias in one study in the pooled analysis (lack of blinding).
[d] Downgraded one level due to high risk of bias in one study in the pooled analysis (lack of blinding).
[e]Downgraded two levels due to very sparse data (12 events).
[f]Downgraded one level due to sparse data (57 events).

BACKGROUND

Description of the condition

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) characterized by the inflammation of the colon. The pathogenesis of UC is still unknown, but there are genetic and environmental factors that have been correlated with the increased risk. Common symptoms for UC include abdominal pain, diarrhea, rectal pain, rectal bleeding, weight loss, fatigue and fever (Conrad 2014; Feuerstein 2014). Approximately 6% to 47% of patients experience extra-intestinal manifestations affecting the eyes, joints, liver and skin. Some of these extra-intestinal manifestations include arthritis, uveitis, oral ulcers, and primary sclerosing cholangitis (Rothfuss 2006). UC is more common in the industrialized world, especially in North America and Western Europe. The overall worldwide incidence is 1.2 to 20.3 cases per 100,000 persons a year, with a prevalence of 7.6 to 245 cases per 100,000 a year (Danese 2011; Loftus 2004). In North America, the prevalence of UC ranges from 120 to 250 cases per 100,000 people and the incidence ranges from 8 to 20 cases per 100,000 people (Loftus 2004).

UC occurs equally in both men and women and the diagnosis of UC may occur at any age; the disease has two peaks in incidence, at 15 to 30 years and at 50 to 70 years (Ordás 2012; Ponder 2013).

Treatments for UC are based on the severity of the symptoms and may include biological therapies (Adalimumab, Infliximab, Vedolizumab, Golimumab, Ustekinumab), corticosteroids, azathioprine or 6-mercaptopurine and 5-aminosalicylates (5-ASAs). For people with mild-to-moderate UC, 5-ASAs and corticosteroids are the conventional treatment for induction of remission. This is followed by thiopurines, anti-TNFs or adhesion molecule inhibitors for moderate-to-severe UC (Feuerstein 2014).

Description of the intervention

The successful management of UC was greatly facilitated after the introduction of sulfasalazine (SASP) by Svartz (Svartz 1942). SASP is composed of 5-ASA linked to sulfapyridine by a diazo bond. This bond is readily cleaved by bacterial azoreductases in the colon (Peppercorn 1972), to yield the two components. Of these, 5-ASA has been found to be the therapeutically active component, while sulfapyridine, which is primarily absorbed into systemic circulation, is assumed to function solely as a carrier molecule (Azad Khan 1977; Klotz 1980; Van Hees 1980).

How the intervention might work

Administration of unbound or uncoated 5-ASA revealed that it was readily absorbed in the upper jejunum and was unable to reach the colon in therapeutic concentrations (Myers 1987; Nielsen 1983; Schroeder 1972). Ingested SASP largely resists such premature absorption and thus is able to serve as a delivery system that transports the 5-ASA to the affected regions of the lower intestinal tract (Schroeder 1972). While corticosteroid therapy is more effective for the treatment of severe UC (Truelove 1955; Truelove 1959) the use of SASP in maintaining remission has been well established (Misiewitz 1965; Sutherland 2006a).

Despite its benefits, up to 30% of patients receiving SASP have reported adverse events (AEs) (Nielsen 1982). It was concluded that many were due to the sulfapyridine moiety, especially those effects found to be dose-dependent (Das 1973; Myers 1987). This discovery spawned more than a decade of research aimed at finding alternative 5-ASA delivery systems.

Asacol® (Proctor and Gamble) consists of a pellet of 5-ASA destined for release in the terminal ileum or colon due to a coating known as Eudragit-S, a resin that dissolves at a pH greater than 7 (Dew 1982). Claversal®/Mesasal® (Smith, Kline and French), Salofalk® (Axcan Pharma, Falk Foundation), and Rowasa® (Reid-Rowell) are similar delayed-release preparations of 5-ASA pellets coated with Eudragit L, a resin that dissolves at a pH greater than 6 (the approximate pH of the ileum/colon) (Hardy 1987; Myers 1987). Pentasa® (Marion-Merrell-Dow) is a microsphere formulation that consists of 5-ASA microgranules enclosed within a semi-permeable membrane of ethylcellulose. It is designed for controlled release that begins in the duodenum and continues into the affected regions of the lower bowel (Rasmussen 1982). Olsalazine/Dipentum® (Pharmacia & Upjohn) consists of two 5-ASA molecules linked by a diazo bond (Staerk Laursen 1990; Willoughby 1982). Other formulations, such as benzalazine, Balsalazide/Colazide® (Astra Zeneca), and Balsalazide disodium/Colazal® (Salix Pharmaceuticals) are composed of 5-ASA molecules azo-bonded to various benzoic acid derivatives (Chan 1983; Fleig 1988). Like SASP, these compounds are poorly absorbed in the upper digestive tract

but are readily metabolized by the intestinal flora in the lower bowel. MMX mesalamine (Lialdaa® or Mezavant®) uses MMX Multi Matrix System (MMX) technology to delay and extend delivery of active drug throughout the colon (Kamm 2007; Lichtenstein 2007). The newer 5-ASA preparations were intended to avoid the adverse effects of SASP while maintaining its therapeutic benefits; however, they are more expensive and have also been shown to cause adverse effects in some people (Rao 1987). The efficacy and safety of 5-ASA preparations have been evaluated in numerous clinical trials that have often lacked sufficient statistical power to arrive at definitive conclusions.

Many patients are non-adherent to conventional multi-dose treatment regimens (two or three times daily), which may result in reduced efficacy and can lead to an increased risk of relapse in patients with quiescent disease (Kane 2001; Kane 2003a), a poorer long-term prognosis (Kane 2008; Kruis 2009) and increased healthcare costs (Beaulieu 2009; Kane 2008). Poor adherence may be particularly problematic in quiescent disease (Kane 2001; Kane 2003a), since patients lack continuing symptoms that incentivize them to take medication. Although multiple factors have been shown to influence medication adherence in people with UC, it is commonly believed that a high pill burden and multi-dose regimens are major determinants (Ediger 2007; Kane 2008). Other factors affecting adherence in people with UC include disease extent and duration, medication costs, fear of side effects, individual psychosocial characteristics and the patient-physician relationship (Kane 2008). Mesalamine formulations that involve once-daily dosing may improve adherence and outcomes.

Previous systematic reviews (Feagan 2012; Sutherland 1993; Sutherland 1997; Sutherland 2006b) found that oral 5-ASA, in doses of at least 2 g/day, was more effective than placebo, but no more effective than SASP for induction of remission in UC. We proceeded with this updated review in order to include more recent studies as well as to evaluate the efficacy, dose-responsiveness (including dose-ranging studies of various 5-ASA formulations), and safety of oral 5-ASA preparations compared to placebo or SASP. We also

aimed to investigate any differences in efficacy and safety between various formulations of oral 5-ASA.

Why it is important to do this review

We conducted this review to assess the evidence supporting the use of oral 5-ASA for the treatment of UC. A secondary objective of this systematic review was to investigate the efficacy and safety of once-daily dosing of mesalamine compared to conventional dosing for the treatment of active UC. This systematic review is an update of a previously-published Cochrane Review (Feagan 2012; Sutherland 1993; Sutherland 1997; Sutherland 2006b; Wang 2016).

OBJECTIVES

To assess the efficacy, dose-responsiveness, and safety of oral 5-aminosalicylic acid (5-ASA) compared to placebo, sulfasalazine (SASP), or 5-ASA comparators (i.e. other formulations of 5-ASA) for induction of remission in active UC. A secondary objective was to compare the efficacy and safety of once-daily dosing of oral 5-ASA with conventional dosing regimens (two or three times daily) .

METHODS

Criteria for considering studies for this review

Types of studies

We considered prospective, randomized controlled clinical trials of parallel design for inclusion, with a minimum treatment duration of four weeks.

Types of participants

Adult participants (aged 18 years or more) with active mild-to-moderate UC as defined by Truelove 1955.

Types of interventions

Studies of oral 5-ASA therapy for treatment of participants with active UC compared with placebo, SASP or other formulations of 5-ASA. We also considered studies that compared once-daily 5-ASA treatment with conventional dosing of 5-ASA (two or three times daily), and 5-ASA dose-ranging studies for inclusion.

Types of outcome measures

Outcome measures included endoscopic, global or clinical measures of improvement or complete remission, as defined by the authors of each study.

Primary outcomes

The primary outcome was the proportion of participants who failed to enter complete global or clinical remission, as defined by the authors of each study and expressed as a percentage of total participants randomized (intention-to-treat (ITT) analysis).

Secondary outcomes

Secondary outcomes included:

1. proportion of participants who failed to improve clinically;
2. proportion of participants who failed to enter endoscopic remission;
3. proportion of participants who failed to improve endoscopically;
4. proportion of participants who failed to adhere to their medication regimen;
5. proportion of participants who experienced at least one adverse event (AE);
6. proportion of participants who experienced at least one serious adverse event (SAE);
7. proportion of participants who withdrew due to AEs; and
8. proportion of participants excluded or withdrawn after entry.

Search methods for identification of studies

Electronic searches

We searched the following databases from inception to 11 June 2019:

1. The Cochrane IBD group Specialized Register;
2. MEDLINE (Ovid);
3. Embase (Ovid):
4. The Cochrane Library; and
5. Clinicaltrials.gov.

We applied no language or document type restrictions. The search strategies are listed in Appendix 1.

Searching other resources

We also searched review articles and conference proceedings to identify additional studies.

Data collection and analysis

Selection of studies

Two review authors (AM and TN) independently selected relevant studies for analysis on the basis of the inclusion criteria described above. When necessary, we contacted the original investigators to clarify points about trial methodology. Disagreement between review authors were discussed and agreement was reached by consensus.

Data extraction and management

Two review authors (AM and TN) independently extracted data using a standard data extraction form. We recorded results on an ITT basis, regardless of whether or not the original authors had done so. We settled any discrepancies between review authors by consensus. We extracted the following data:

1. Baseline characteristics of the participants (age, sex, disease severity, disease duration)
2. Intervention type (dose, mode of administration)
3. Control type (placebo, no control, other intervention)
4. Prespecified primary and secondary outcomes

Assessment of risk of bias in included studies

Two review authors (AM and TN) independently assessed the risks of bias in the included studies using the Cochrane 'Risk of bias' tool (Higgins 2011). Factors assessed included:

1. Random sequence generation;
2. Allocation concealment;
3. Blinding;

4. Incomplete outcome data;
5. Selective outcome reporting; and
6. Other potential sources of bias.

Based on these criteria, studies were judged to have a low, high or unclear risk of bias for each category. Disagreements resolved by consensus. We contacted study authors when insufficient information was provided to determine risks of bias.

Measures of treatment effect

For dichotomous outcomes, we calculated the risk ratio (RR) and corresponding 95% confidence interval (95% CI). We pooled the results for each comparison group to determine the RR and 95% CI for each outcome resulting from 5-ASA therapy relative to either placebo, SASP or 5-ASA comparator, and for once-daily 5-ASA therapy relative to conventional dosing. We used a fixed-effect model. We pooled studies for analysis if participants, outcomes and interventions were similar (determined by consensus among review authors). We pooled studies comparing 5-ASA formulations for analysis if they compared equimolar doses of oral 5-ASA.

Unit of analysis issues

In trials consisting of multiple arms (i.e. different dose groups), we divided the placebo group across treatment groups. For trials with an odd number of participants, we divided the groups to ensure the group for the lower dose had the larger number of participants, to avoid overestimating the effects of the higher-dose arm. For recurring events such as AEs and SAEs, we used the primary endpoint defined by the study. Lastly, we assessed the fixed intervals for follow-up for outcomes that are measured at different time points.

Dealing with missing data

We analyzed missing dichotomous outcomes according to the ITT principle. Participants with missing data were assumed to be treatment failures. For continuous outcomes we used the number of participants who completed the trial and did not impute any missing variables.

Assessment of heterogeneity

We assessed the presence of heterogeneity among studies using the Chi^2 test (with a P value of 0.10 regarded as statistically significant) and the I^2 statistic (Higgins 2003). If we found statistically significant heterogeneity, we calculated the RR and 95% CI using a random-effects model. We did not pool data for meta-analysis if we identified a high degree of heterogeneity (e.g. $I^2 > 75\%$).

Assessment of reporting biases

We compared the outcomes listed in the protocol to the outcomes listed in the final study report. However, if we could not located the protocol we compared the outcomes listed in the Methods section to the outcomes in the Results section. If there were a sufficient number of studies included (i.e. 10 or more) in the pooled analyses, we planned to use a funnel plot to investigate a potential publication bias.

Data synthesis

We separated the trials into five comparison groups: 5-ASA versus placebo; 5-ASA versus sulfasalazine; once-daily dosing versus conventional dosing; 5-ASA versus comparator 5-ASA; and 5-ASA dose-ranging. We pooled data from studies where the intervention, participant groups and outcomes were similar. The RR and 95% CI were pooled for dichotomous outcomes and the MD and corresponding 95% CI were pooled for continuous outcomes. We used the standardized mean difference (SMD) and a 95% CI when different scales were used to measure the same outcome (e.g. different quality-of-life instruments).

Subgroup analysis and investigation of heterogeneity

We subgrouped once-daily versus conventional-dosing studies by formulation. We subgrouped the tables for 5-ASA-controlled trials by common 5-ASA comparators (e.g. Asacol, Claversal, Salofalk and Pentasa). We subgrouped the tables for dose-ranging studies by 5-ASA formulation. Trials were also subgrouped according to the specific 5-ASA preparation for those outcomes for which there were two or more studies that used a similar drug.

Sensitivity analysis

We conducted sensitivity analyses as appropriate, to investigate heterogeneity. We also conducted sensitivity analyses excluding studies with a high risk of bias. We conducted all statistical analyses using Cochrane Review Manager 5 software.

Summary of findings and assessment of the certainty of the evidence

We used the GRADE approach for rating the overall certainty of evidence for the primary outcomes and selected secondary outcomes of interest. Randomized trials start as high-certainty evidence, but may be downgraded due to: (1) limitations in design and implementation (risk of bias), (2) indirectness of evidence, (3) inconsistency (unexplained heterogeneity), (4) imprecision (sparse data), and (5) reporting bias (publication bias). The overall certainty of evidence for each outcome is determined after considering each of these elements, and categorized as high certainty (i.e. further research is very unlikely to change our confidence in the estimate of effect); moderate certainty (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 certainty (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); and very low certainty (i.e. we are very uncertain about the estimate) (Guyatt 2008; Schünemann 2019).

RESULTS

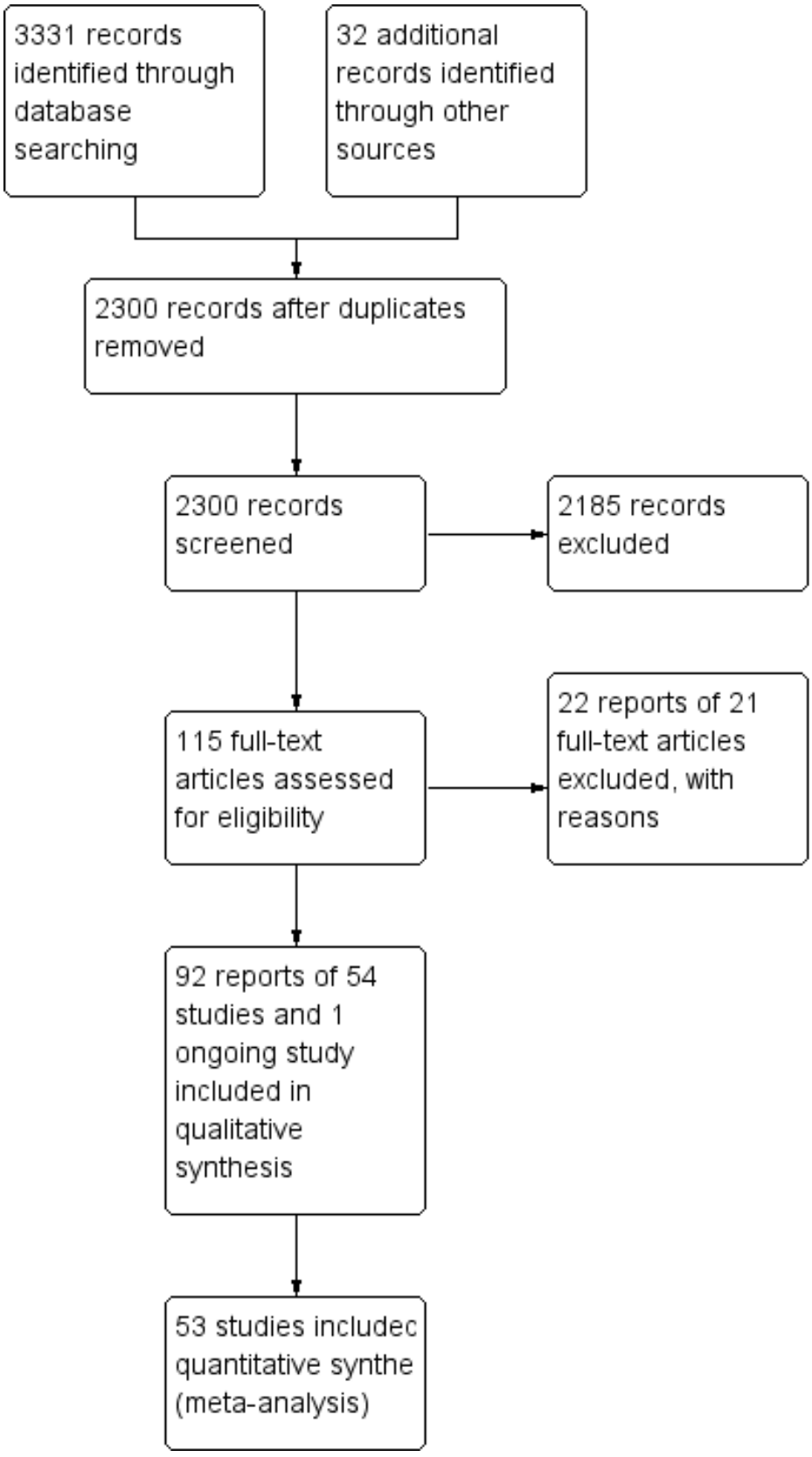
Description of studies

Results of the search

A literature search conducted on 11 June 2019 identified 3331 studies. We found 32 additional studies through searching of references. After duplicates were removed, 2300 reports remained for review of titles and abstracts. Two review authors (AM and TMN) independently reviewed the titles and abstracts of these studies and selected 115 reports of oral 5-ASA for treatment of active UC for full-text review (See Figure 1). We excluded 22 reports of 21 of these studies (see Characteristics of excluded studies), leaving 92

reports of 54 included studies (Andreoli 1987; Bresci 1990; Cai 2001; D'Haens 2006; D'Haens 2017; Ewe 1988; Farup 2001; Feagan 2013; Feurle 1989;Fleig 1988; Flourié 2013; Forbes 2005; Gibson 2006; Good 1992; Green 1998;Green 2002; Hanauer 1993; Hanauer 1996; Hanauer 2005; Hanauer 2007; Hetzel 1986; Hiwatashi 2011; Ito 2010; Jiang 2004; Kamm 2007; Kruis 1998; Kruis 2003; Kruis 2009; Levine 2002; Lichtenstein 2007; Maier 1985; Mansfield 2002; Marakhouski 2005; Miglioli 1990; Mihas 1988; Munakata 1995; Pontes 2014; Pruitt 2002; Qian 2004; Rachmilewitz 1989; Raedler 2004; Rao 1989; Rijk 1991; Riley 1988; Robinson 1994; Sandborn 2009; Sandborn 2012; Scherl 2009; Schroeder 1987; Sninsky 1991; Sutherland 1990; Tursi 2004; Willoughby 1988; Zinberg 1990) (See Characteristics of included studies). There was one ongoing study identified from clinicaltrials.gov (NCT02522767).

Figure 1. Study flow diagram.



Included studies

Of the 54 included studies, 16 were placebo-controlled (Feagan 2013; Feurle 1989; Hanauer 1993; Hanauer 1996; Hetzel 1986; Ito 2010; Kamm 2007; Lichtenstein 2007; Pontes 2014; Robinson 1994; Sandborn 2012; Scherl 2009; Schroeder 1987; Sninsky 1991;Sutherland 1990; Zinberg 1990). Eighteen studies compared 5-ASA to SASP (Andreoli 1987; Bresci 1990; Cai 2001; Ewe 1988; Fleig 1988; Good 1992; Green 2002; Jiang 2004; Maier 1985; Mansfield 2002; Mihas 1988; Munakata 1995; Qian 2004; Rachmilewitz 1989; Rao 1989; Rijk 1991;Riley 1988; Willoughby 1988). Five studies compared once-daily dosing of mesalamine with conventional dosing (D'Haens 2017; Flourié 2013; Kamm 2007; Kruis 2009; Lichtenstein 2007). Twelve trials compared the efficacy and safety of various formulations of oral 5-ASA (e.g. MMX mesalamine, Ipocol, Balsalazide, Pentasa, Olsalazine and 5-ASA micropellets) to other formulations of oral 5-ASA (e.g. Asacol, Claversal, Salofalk, Pentasa) (Farup 2001; Forbes 2005; Gibson 2006; Green 1998; Ito 2010; Kamm 2007; Kruis 1998; Levine 2002; Marakhouski 2005; Pruitt 2002; Raedler 2004; Tursi 2004). Eleven trials were dose-ranging studies of oral 5-ASA (D'Haens 2006; Hanauer 2007; Hanauer 2005; Hiwatashi 2011; Ito 2010; Kamm 2007; Kruis 2003; Miglioli 1990; Sandborn 2009; Schroeder 1987; Sninsky 1991).

Excluded studies

Twenty-two reports of 21 of these studies were excluded (See Characteristics of excluded studies). Four studies were excluded because they were not classified as RCTs (Ahluwalia 1992; Irvine 2008; Kamm 2009; Pruitt 1991), seven studies were excluded because they did not have a control group (Behrens 2013; Dignass 2018; Paoluzi 2002; Rubin 2017; Vernia 2000; Ye 2018; Yoshimura 2018), two studies because they had an ineligible comparator group (Adrizzone 2006; Gross 2011), four studies because they did not include an oral 5-ASA formulation (Levine 2017; Mahmood 2005; Safdi 1997; Vecchi 2001), two studies were not induction studies (Park 2018; Suzuki 2017), one study was a pediatric study (Turner 2017) and one study because the study drug included a combination of 5-ASA and sodium hyaluronate (Fiorino 2019).

Risk of bias in included studies

We provide a summary of the 'Risk of bias' assessment in Figure 2. Most of the included studies were of high methodological quality. We rated five studies at high risk of bias due to incomplete outcome data and lack of blinding. Thirty-two of 54 included studies did not describe the method used for randomization and we rated them as unclear for this domain. Twenty-six studies did not describe methods used for allocation concealment and we rated them as unclear for this domain. The methods used for blinding were not described in five studies, and these studies were rated as unclear. We judged 20 studies to be at unclear risk for incomplete outcome data because reasons for withdrawal were either not described or were not attributed to intervention groups. We rated six studies as unclear for selective reporting.

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

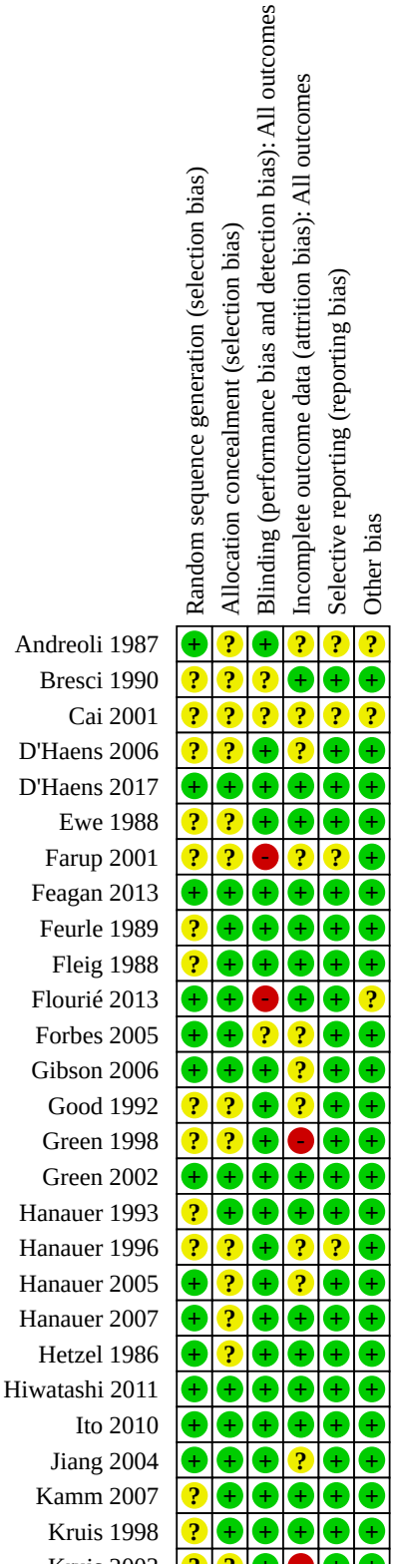
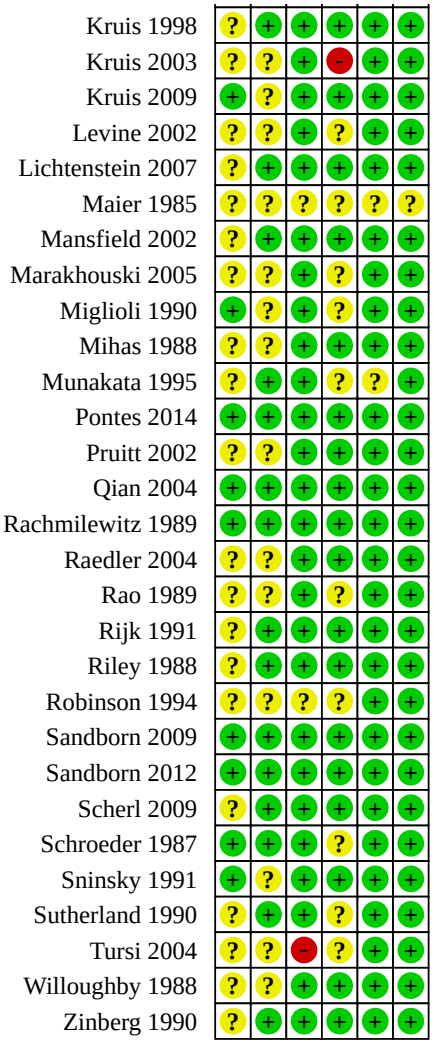


Figure 2. (Continued)



Effects of interventions

See: **Summary of findings 1** Oral 5-ASA versus placebo for induction of remission in ulcerative colitis; **Summary of findings 2** Oral 5-ASA versus SASP for induction of remission in ulcerative colitis; **Summary of findings 3** Once daily dosing versus conventional dosing for induction of remission in ulcerative colitis; **Summary of findings 4** Oral 5-ASA versus comparator 5-ASA for induction of remission in ulcerative colitis

1. 5-ASA versus placebo

Failure to induce complete global or clinical remission

Eleven studies (2387 participants) reported treatment outcomes as failure to induce complete global or clinical remission (Feagan 2013; Hanauer 1993; Hanauer 1996; Ito 2010; Kamm 2007; Lichtenstein 2007; Pontes 2014; Sandborn 2012; Schroeder 1987; Sninsky 1991; Scherl 2009). Seventy-one per cent (1107/1550) of 5-ASA participants failed to enter remission compared to 83% (695/837) of placebo participants (risk ratio (RR) 0.86, 95% confidence interval (CI) 0.82 to 0.89; I^2 = 25%; high-certainty evidence; Analysis 1.1) . There was a trend towards greater efficacy with higher doses of 5-ASA for the 2 to 2.9 g/day (RR 0.88, 95% CI 0.82 to 0.94; I^2 = 27%; 956 participants, 8 studies) and the ≥ 3 g/day subgroups (RR 0.83, 95% CI 0.77 to 0.88; I^2 = 25%; 1200 participants, 8 studies). The five trials that involved Asacol (Feagan 2013; Ito 2010; Kamm 2007; Schroeder 1987; Sninsky 1991) had a pooled RR of 0.84 (95% CI 0.79 to 0.90). Two trials using MMX mesalazine (Kamm 2007; Lichtenstein 2007) had a pooled RR of 0.81 (95% CI 0.73 to 0.89).

Failure to induce global or clinical improvement

Fourteen studies (Feagan 2013; Feurle 1989; Hanauer 1993; Hetzel 1986; Ito 2010; Kamm 2007; Lichtenstein 2007; Pontes 2014; Schroeder 1987; Robinson 1994; Sutherland 1990; Scherl 2009; Sninsky 1991; Zinberg 1990) (2256 participants) provided data on the failure to induce global or clinical improvement (including remission). Forty-one per cent (605/1459) of 5-ASA participants failed to improve clinically compared to 65% (519/797) of placebo participants (RR 0.68, 95% CI 0.61 to 0.75, I^2 = 47%; moderate-certainty evidence; Analysis 1.2).There was a trend towards greater efficacy with higher doses of 5-ASA for all dosage subgroups: < 2 g/day (RR 0.79, 95% CI 0.64 to 0.97; I^2 = 0%); 2 to 2.9 g/day (RR 0.77, 95% CI 0.67 to 0.88; I^2 = 32%); ≥ 3 g/day (RR 0.57, 95% CI 0.51 to

0.65; I^2 = 5%). Five trials involving Asacol (Feagan 2013; Ito 2010; Kamm 2007; Schroeder 1987; Sninsky 1991) had a pooled RR of 0.68 (95% CI 0.58 to 0.80). Four studies involved Olsalazine (Feurle 1989; Hetzel 1986; Robinson 1994; Zinberg 1990), and resulted in a pooled RR of 0.80 (95% CI 0.65 to 0.97). Two trials using MMX mesalazine (Kamm 2007; Lichtenstein 2007) had a pooled RR of 0.64 (95% CI 0.55 to 0.75).

Failure to induce endoscopic remission

Four studies (Hanauer 1993; Hanauer 1996; Kamm 2007; Scherl 2009) (1154 participants) reported on failure to induce complete endoscopic remission. Fifty per cent (399/805) of 5-ASA participants failed to enter endoscopic remission compared to 64% (223/349) of placebo participants (RR 0.77, 95% CI 0.67 to 0.89; I^2 = 42%; moderate-certainty evidence; Analysis 1.3). The doses of 3 g or more were shown to be more effective compared to the other doses (RR 0.70, 95% CI 0.56 to 0.87; I^2 = 51%).

Failure to induce endoscopic improvement

Four studies (Hanauer 1996; Hetzel 1986; Robinson 1994; Zinberg 1990) (416 participants), all involving Olsalazine, reported failure to induce endoscopic remission or improvement. Forty-four per cent (113/255) of 5-ASA participants failed to improve endoscopically compared to 63% (102/161) of placebo participants (RR 0.71, 95% CI 0.59 to 0.86; I^2 = 43%; low-certainty evidence; Analysis 1.4).

Adverse events

Eight studies (1218 participants) reported the proportion of participants who experienced at least one AE (Feurle 1989; Feagan 2013; Hetzel 1986; Ito 2010; Lichtenstein 2007; Pontes 2014; Schroeder 1987; Scherl 2009). There was no difference in the incidence of AEs between 5-ASA and placebo participants. Fifty-two per cent (386/749) of 5-ASA participants experienced at least one AE compared to 49% (228/469) of placebo participants (RR 0.95, 95% CI 0.85 to 1.07; I^2 = 0%; high-certainty evidence; Analysis 1.5). Three trials that involved Asacol (Feagan 2013; Ito 2010; Schroeder 1987) had a pooled RR of 1.03 (95% CI 0.87 to 1.21). Two studies that involved Olsalazine (Hetzel 1986; Feurle 1989) had a pooled RR of 1.09 (95% CI 0.55 to 2.15). Commonly-reported AEs included: headache, nausea, abdominal pain or cramps, nasopharyngitis or symptoms of upper respiratory infection, rash. anorexia or loss of appetite, flatulence or gas, gastrointestinal disorders and fever. Diarrhea was reported in four studies involving Olsalazine (Feurle 1989; Hanauer 1996; Robinson 1994; Zinberg 1990) and one study of Pentasa (Hanauer 1993).

Serious adverse events

Four studies (546 participants) reported on the proportion of participants who experienced at least one SAE (Feagan 2013; Ito 2010; Lichtenstein 2007; Pontes 2014). Two per cent (7/466) of participants in the 5-ASA group experienced an SAE compared to 2% (6/280) of placebo participants (RR 0.53, 95% CI 0.18 to 1.56,I^2 = 0%; low-certainty evidence; Analysis 1.6). SAEs reported include aggravation of UC, malaise, abdominal abscess, pancreatitis and an inguinal hernia.

Withdrawals due to adverse events

Thirteen studies (2372 participants) reported the proportion of participants withdrawn due to AEs (Feagan 2013; Feurle 1989; Hanauer 1993; Hanauer 1996; Hetzel 1986; Ito 2010; Kamm 2007; Lichtenstein 2007; Robinson 1994; Schroeder 1987; Scherl 2009; Sninsky 1991; Zinberg 1990). Withdrawals due to AEs were reported for 6% (91/1542) of 5-ASA participants compared to 9% (73/830) of placebo participants (RR 0.72, 95% CI 0.54 to 0.97; I^2 = 13%; moderate-certainty evidence; Analysis 1.7). The pooled analysis of five Asacol trials (Feagan 2013; Ito 2010; Kamm 2007; Schroeder 1987; Sninsky 1991) showed a higher proportion of placebo participants (9.7%) were withdrawn due to AEs compared to Asacol participants (3.5%) (RR 0.50, 95% CI 0.30 to 0.84). However, when five Olsalazine studies (Feurle 1989; Hanauer 1996; Hetzel 1986; Robinson 1994; Zinberg 1990) were pooled a higher proportion of Olsalazine participants (8.8%) were withdrawn due to AEs compared to placebo (3.3%) (RR 2.58, 95% CI 1.16 to 5.70). When two MMX mesalamine studies were pooled (Kamm 2007; Lichtenstein 2007) a higher proportion of placebo participants (7.3%) were withdrawn due to AEs compared to MMX mesalamine (2.2%) (RR 0.31, 95% CI 0.14 to 0.72). An inspection of the forest plot showed the difference in withdrawals favoring 5-ASA over placebo was driven by the large Feagan 2013 study, which reported that worsening of UC was the most common AE leading to withdrawal. Worsening of UC leading to withdrawal was reported for 10 of 12 withdrawals in the 5-ASA group compared to all 30 withdrawals in the placebo group (Feagan 2013). A sensitivity analysis excluding Feagan 2013 showed no difference in withdrawals due to AEs between 5-ASA and placebo. Withdrawals due to AEs occurred in 6% (79/1402) of 5-ASA participants compared to 6% (43/689) of placebo participants (RR 0.88, 95% CI 0.62 to 1.24; I^2 = 5%). The common AEs leading to withdrawal were not reported.

Exclusions or withdrawals after study entry

Fifteen studies (2529 participants) reported the proportion of participants excluded or withdrawn after entry (Feagan 2013; Feurle 1989; Hanauer 1993; Hanauer 1996; Hetzel 1986; Ito 2010; Kamm 2007; Lichtenstein 2007; Pontes 2014; Scherl 2009; Schroeder 1987; Sutherland 1990; Robinson 1994; Sninsky 1991; Zinberg 1990). Twenty-four per cent (388/1642) of 5-ASA participants were withdrawn or excluded after entry compared to 37% (332/887) of placebo participants (R 0.61, 95% CI 0.51 to 0.72; I^2 = 37%; See Analysis 1.8).

2. 5-ASA versus sulfasalazine

Failure to induce complete global or clinical remission

The failure to induce complete global or clinical remission was reported in eight studies (526 participants) (Andreoli 1987; Green 2002; Jiang 2004; Mansfield 2002; Maier 1985; Rachmilewitz 1989; Riley 1988; Riley 1988). Fifty-four per cent (150/279) of 5-ASA participants failed to enter remission compared to 58% (144/247) of SASP participants (RR 0.90, 95% CI 0.77 to 1.04; I^2 = 0%; moderate-certainty evidence; Analysis 2.1). Two studies involving Claversal (Andreoli 1987; Rachmilewitz 1989) had a pooled RR of 1.00 (95% CI 0.83 to 1.21). Two studies involving Balsalazide (Green 2002; Mansfield 2002) had a pooled RR of 0.93 (95% CI 0.57 to 1.51). Two studies involving Olsalazine (Jiang 2004; Rijk 1991) had a pooled 0.66 (95% CI 0.43 to 1.02).

Failure to induce global or clinical improvement

Fourteen studies (Bresci 1990; Cai 2001; Ewe 1988; Fleig 1988; Good 1992; Maier 1985; Mihas 1988; Munakata 1995; Jiang 2004; Rao 1989; Rachmilewitz 1989; Riley 1988; Qian 2004; Willoughby 1988) (1053 participants) reported failure to induce global or

clinical improvement (including remission). Thirty-seven per cent (227/608) of 5-ASA participants failed to improve compared to 47% (208/445) of SASP participants (RR 0.88, 95% CI 0.76 to 1.01; I^2 = 0%; high-certainty evidence; Analysis 2.2). Six Olsalazine trials (Cai 2001; Ewe 1988; Jiang 2004; Qian 2004; Rao 1989; Willoughby 1988) had a pooled RR of 0.76 (95% CI 0.57 to 1.00).

Failure to induce endoscopic remission

Since only two studies (Jiang 2004; Rachmilewitz 1989) reported failure to induce complete endoscopic remission, we did not conduct a meta-analysis for this outcome. We did not pool the studies, as they used different indices to measure endoscopic remission. Neither study showed significant differences in complete endoscopic remission between 5-ASA and SASP.

Failure to induce endoscopic improvement

Six studies (Fleig 1988; Munakata 1995; Rao 1989; Rijk 1991; Riley 1988; Willoughby 1988) (362 participants) provided data on failure to induce endoscopic improvement (including remission). Forty-one per cent (78/189) of 5-ASA participants failed to improve endoscopically compared to 45% (78/173) of SASP participants: RR 0.82, 95% CI 0.65 to 1.02; I^2 = 0%; moderate-certainty evidence; Analysis 2.3). Three trials involving Olsalazine (Rao 1989; Rijk 1991; Willoughby 1988) had a pooled RR of 0.93 (95% CI 0.62 to 1.39).

Failure to adhere to medication regimen

No studies reported this outcome.

Adverse events

Twelve studies (909 participants) reported the proportion of participants who experienced at last one AE (Bresci 1990; Cai 2001; Ewe 1988; Fleig 1988; Green 2002; Mansfield 2002; Mihas 1988; Munakata 1995; Qian 2004; Rachmilewitz 1989; Rao 1989; Rijk 1991). It should be noted that, with two exceptions (Mihas 1988; Rao 1989), the inclusion criteria for entry included tolerance of SASP. Nevertheless, SASP participants were significantly more likely than 5-ASA participants to experience an AE. Fourteen per cent (72/498) of 5-ASA participants experienced at least one AE compared to 29% (118/411) of SASP participants (RR 0.48, 95% CI 0.36 to 0.63; I^2 = 0%; moderate-certainty evidence; Analysis 2.4). Five Olsalazine trials (Cai 2001; Ewe 1988; Rao 1989; Rijk 1991; Qian 2004) had a combined RR of 0.48 (95% CI 0.32 to 0.71), and two Balsalazide trials (Green 2002; Mansfield 2002) had a combined RR of 0.16 (95% CI 0.05 to 0.52).Commonly-reported AEs included: nausea, headache, dyspepsia, vomiting, abdominal pain and rash. Diarrhea was reported in three studies involving Olsalazine (Ewe 1988; Jiang 2004; Willoughby 1988).

Serious adverse events

Two studies (107 participants) reported on the proportion of participants who experienced at least one SAE (Green 2002; Mansfield 2002). There was no difference between the 5-ASA and SASP groups. Six per cent of participants (3/54) in the 5-ASA group experienced an SAE compared to 4% (2/53) of SASP participants (RR 1.36, 95% CI 0.28 to 6.52; low-certainty evidence; Analysis 2.5). SAEs reported include erythematous rash, venous thrombosis, carcinoma, acute pancreatitis, rheumatoid arthritis and erythema nodosum.

Withdrawals due to adverse events

Ten studies (640 participants) reported the proportion of participants withdrawn due to AEs (Ewe 1988; Fleig 1988; Green 2002; Mansfield 2002; Mihas 1988; Qian 2004; Rachmilewitz 1989; Rao 1989; Riley 1988; Willoughby 1988). SASP resulted in a higher proportion of participants withdrawn due to AEs.Thirteen per cent (39/303) of SASP participants were withdrawn due to AEs compared to 4% (15/337) of 5-ASA participants (RR 0.40, 95% CI 0.24 to 0.68; I^2 = 0%; moderate-certainty evidence; Analysis 2.6). When four Olsalazine trials were combined (Ewe 1988; Rao 1989; Qian 2004; Willoughby 1988), the RR was 0.63 (95% CI 0.24 to 1.66). The pooling of two Balsalazide trials (Green 2002; Mansfield 2002) had a combined RR of 0.16 (95% CI 0.05 to 0.52).The common AEs leading to withdrawal include nausea, headaches and rashes.

Exclusions or withdrawals after study entry

Ten studies (701 participants) reported the proportion of participants excluded or withdrawn after entry (Andreoli 1987; Fleig 1988; Green 2002; Mansfield 2002; Munakata 1995; Rachmilewitz 1989; Rao 1989; Rijk 1991; Riley 1988; Willoughby 1988).Twenty-six per cent (86/337) of SASP participants were withdrawn or excluded after entry compared to 19% (70/364) of 5-ASA participants (RR 0.76, 95% CI 0.58 to 0.99; I^2 = 28%; Analysis 2.7).

3. Once-daily dosing versus conventional dosing

Failure to induce complete global or clinical remission

Five studies (1761 participants) reported treatment outcomes for failure to induce complete global or clinical remission (D'Haens 2017; Flourié 2013; Kamm 2007; Kruis 2009; Lichtenstein 2007). Sixty per cent (533/881) of conventionally-dosed 5-ASA participants failed to enter remission compared to 61% (538/880) of participants who were dosed once daily (RR 0.99, 95% CI 0.93 to 1.06; I^2 = 0%; high-certainty evidence; Analysis 3.1). None of the subgroup comparisons by formulation showed any differences in efficacy between once-daily dosing and conventional dosing. However, only five formulations were evaluated in this pooled analysis.

Failure to induce global or clinical improvement

Three studies (564 participants) reported treatment outcomes for failure to induce global or clinical improvement including remission (Flourié 2013; Kamm 2007; Lichtenstein 2007). Thirty-seven per cent (104/283) of conventionally-dosed 5-ASA participants failed to improve clinically compared to 28% (79/281) of participants who were dosed once daily (RR 0.74, 95% CI 0.49 to 1.10; I^2 = 59%; moderate-certainty evidence; Analysis 3.2). A visual inspection of the forest plot indicated that Flourié 2013 was the likely source of the heterogeneity. When we performed a sensitivity analysis excluding this study at high risk of bias the I^2 value dropped to 0%. Forty-six per cent (82/179) of conventionally-dosed 5-ASA participants failed to improve clinically compared to 40% (71/179) of participants who were dosed once daily (RR 0.87, 95% CI 0.68 to 1.10; I^2 = 0%; Analysis 3.3).

Failure to induce endoscopic remission

One study (D'Haens 2017) (817 participants) reported on the failure to induce endoscopic remission. Eighty-nine per cent (364/408) of conventionally-dosed participants failed to induce endoscopic remission compared to 91% (373/409) of once-daily participants (RR 1.02, 95% CI 0.98 to 1.07; high-certainty evidence; Analysis 3.4).

Failure to induce endoscopic improvement

One study (D'Haens 2017) (817 participants) reported on the failure to induce endoscopic response. Fifty-two percent (212/408) of conventionally-dosed participants failed to induce endoscopic response compared to 55% (224/409) of participants in the once-daily group (RR 1.05, 95% CI 0 0.93 to 1.20) (Analysis 3.5).

Failure to adhere to medication regimen

Two studies (358 participants) provided dichotomous data for failure to adhere to the medication regimen at study endpoint (Kamm 2007; Lichtenstein 2007). Eight per cent (15/179) of once-daily dosed participants compared to 6% (11/179) of conventionally-dosed participants failed to adhere to the medication regimen (RR 1.36, 95% CI 0.64 to 2.86; I^2 = 34%; low-certainty evidence; Analysis 3.6). Only one study (Flourié 2013) reported on a continuous outcome for compliance with medication (MD −4.00, 95% CI −17.38 to 9.38; Analysis 3.7).

Adverse events

Four studies (1586 participants) reported the proportion of participants who experienced at least one AE (D'Haens 2017; Flourié 2013; Kruis 2009; Lichtenstein 2007). Thirty-three per cent (259/796) of participants who were dosed once daily experienced at least one AE compared to 32% (251/790) of conventionally-dosed participants (RR 1.02, 95% CI 0.89 to 1.18; I^2 = 37%; moderate-certainty evidence; Analysis 3.8). Common AEs included flatulence, abdominal pain, nausea, diarrhea, nasopharyngitis, dyspepsia, headache and worsening of UC.

Serious adverse events

Four studies (1586 participants) reported on the proportion of participants who experienced at least one SAE (D'Haens 2017; Flourié 2013; Kruis 2009; Lichtenstein 2007).Two per cent (19/796) of participants in the once-daily group experienced an SAE compared to 2% (14/790) of participants in the conventional-dosing group (RR 1.34, 95% CI 0.68 to 2.66; low-certainty evidence; Analysis 3.9). SAEs reported include pancreatitis, hepatitis, polyuria, chromaturia, upper respiratory tract infection and measles.

Withdrawals due to adverse events

Five studies (1757 participants) reported the proportion of participants withdrawn due to AEs (D'Haens 2017; Flourié 2013; Kamm 2007; Kruis 2009; Lichtenstein 2007).There was no difference in the proportion of participants withdrawn due to AEs between once-daily and conventionally-dosed participants. Three per cent (29/876) of conventionally-dosed participants were withdrawn due to AEs compared to 3% (26/881) of participants dosed once daily (RR 0.89, 95% CI 0.54 to 1.49; I^2 = 0%; low-certainty evidence; Analysis 3.10). The common AEs leading to withdrawal were not reported.

Withdrawals or exclusions after study entry

Four studies (944 participants) reported on the proportion of participants excluded or withdrawn after entry (Flourié 2013; Kamm 2007; Kruis 2009; Lichtenstein 2007). There was no difference in the proportion of participants excluded or withdrawn after entry between once-daily and conventionally-dosed participants. Fourteen per cent (67/472) of participants dosed once daily were excluded or withdrawn after entry compared to 14% (66/472) of conventionally-dosed participants (RR 1.02, 95% CI 0.74 to 1.39; I^2 = 0%; Analysis 3.11).

4. 5-ASA versus comparator 5-ASA

Failure to induce complete global or clinical remission

Eleven studies (1968 participants) reported treatment outcomes for failure to induce complete global or clinical remission (Farup 2001; Forbes 2005; Gibson 2006; Ito 2010; Kamm 2007; Kruis 1998; Levine 2002; Marakhouski 2005; Pruitt 2002; Raedler 2004; Tursi 2004). 5-ASA formulations included MMX mesalamine, Ipocol, Balsalazide, Pentasa, Olsalazine and 5-ASA micropellets. Comparator 5-ASA formulations included Asacol, Claversal, Salofalk, and Pentasa.

We did not include Green 1998 in the pooled analysis because it enrolled participants with moderate-to-severe disease, whereas the other studies in the pooled analysis enrolled participants with mild to moderately-active UC. Green 1998 also allowed the use of rectal steroid foam to relieve active symptoms, which was not allowed in the other 5-ASA controlled studies. Fifty per cent (507/1022) of participants in the 5-ASA group failed to enter remission compared to 52% (491/946) of participants in the 5-ASA comparator group (RR 0.94, 95% CI 0.86 to 1.02; I^2 = 0%; moderate-certainty evidence; Analysis 4.1). However, a sensitivity analysis excluding the two studies at high risk of bias (Farup 2001; Tursi 2004) produced similar results (1681 participants, 9 studies). Forty-eight per cent (405/842) of participants in the 5-ASA group failed to enter remission compared to 50% (424/839) of participants in the 5-ASA comparator group (RR 0.95, 95% CI 0.87 to 1.04; I^2 = 0%). Green 1998 compared Balsalazide 6.75 g/day (n = 50) to Asacol 2.4 g/day (n = 49). At eight weeks 22% of participants in the Balsalazide group failed to enter remission compared to 45% of participants in the Asacol group (RR 0.49; 95% CI 0.27 to 0.90).

Failure to induce global or clinical improvement

Eight studies (1647 participants) reported treatment outcomes for failure to induce global or clinical improvement including remission (Farup 2001; Gibson 2006; Ito 2010; Kamm 2007; Kruis 1998; Levine 2002; Marakhouski 2005; Raedler 2004). Thirty per cent (260/862) of participants in the 5-ASA group failed to improve clinically compared to 35% (272/785) of participants in the 5-ASA comparator group (RR 0.89, 95% CI 0.77 to 1.01; I^2 = 0%; moderate-certainty evidence; Analysis 4.3). The various formulations of 5-ASA included Balsalazide, Pentasa, Olsalazine, MMX mesalazine, and 5-ASA micropellets; the comparator formulations of 5-ASA included Asacol, Claversal, Salofalk and Pentasa. However, a sensitivity analysis excluding the study at high risk of bias (Farup 2001) produced similar results (1420 participants, 7 studies). Thirty-two per cent (226/712) of participants in the 5-ASA group failed to improve clinically compared to 35% (247/708) of participants in the 5-ASA comparator group (RR 0.91, 95% CI 0.79 to 1.05; I^2 = 0%; Analysis 4.4).

Failure to induce endoscopic remission

No studies reported this outcome.

Failure to induce endoscopic improvement

No studies reported this outcome.

Failure to adhere to medication regimen

No studies reported this outcome.

Adverse events

Nine studies (1576 participants) reported the proportion of participants who experienced at least one AE (Forbes 2005; Gibson 2006; Ito 2010; Kruis 1998; Levine 2002; Marakhouski 2005; Pruitt 2002; Raedler 2004; Tursi 2004). The pooled risk ratio showed no difference in the incidence of AEs between various formulations of 5-ASA (including Balsalazide, Pentasa, Olsalazine, Ipocol and 5-ASA micropellets) and comparator formulations of 5-ASA (including Asacol, Claversal and Salofalk). Forty-six per cent (365/792) of participants in the 5-ASA group experienced at least one AE compared to 46% (358/784) of participants in the 5-ASA comparator group (RR 1.01, 95% CI 0.92 to 1.12; I^2 = 10%; moderate-certainty evidence; Analysis 4.5). Common AEs included headache, abdominal pain, nausea, flatulence, diarrhea, nasopharyngitis, dyspepsia, vomiting and the worsening of UC.

Serious adverse events

Four studies (677 participants) reported on the proportion of participants who experienced at least one SAE (Kruis 1998; Levine 2002; Marakhouski 2005; Pruitt 2002). Two per cent (6/343) of participants experienced an SAE in the 5-ASA group compared to 3% (10/334) of participants in the comparator 5-ASA group. There was no difference between the 5-ASA versus comparator 5-ASA group (RR 0.59, 95% CI 0.22 to 1.56; low-certainty evidence; Analysis 4.6). SAEs reported include aggravation of UC and a colonic polyp.

Withdrawals due to adverse events

Nine studies (1489 participants) reported the proportion of participants withdrawn due to AEs (Forbes 2005; Ito 2010; Kamm 2007; Kruis 1998; Levine 2002; Marakhouski 2005; Pruitt 2002; Raedler 2004; Tursi 2004). The pooled risk ratio showed no difference in withdrawals due to AEs between various formulations of 5-ASA (including Balsalazide, Pentasa, Olsalazine, MMX mesalazine; Ipocol and 5-ASA micropellets) and comparator formulations of 5-ASA (including Asacol, Claversal and Salofalk). Four per cent (28/749) of participants in the 5-ASA group were withdrawn due to AEs compared to 4% (29/740) of participants in the 5-ASA comparator group (RR 0.94, 95% CI 0.57 to 1.54; I^2 = 15%; moderate-certainty evidence; Analysis 4.7). The common AEs leading to withdrawal include abdominal pain, rashes and cephalea.

Withdrawals or exclusions following study entry

Ten studies (1574 participants) reported the proportion of participants excluded or withdrawn after entry (Forbes 2005; Gibson 2006; Ito 2010; Kamm 2007; Kruis 1998; Levine 2002; Marakhouski 2005; Pruitt 2002; Raedler 2004; Tursi 2004). The pooled risk ratio showed no difference in exclusions or withdrawals after entry between various formulations of 5-ASA (including Balsalazide, Pentasa, Olsalazine, MMX mesalazine, Ipocol and 5-ASA micropellets) and comparator formulations of 5-ASA (including Asacol, Claversal and Salofalk). Eighteen per cent (144/792) of participants in the 5-ASA group were excluded or withdrawn after entry compared to 18% (143/782) of participants in the 5-ASA comparator group (RR 0.99, 95% CI 0.80 to 1.22; I^2 = 0%; Analysis 4.8).

5. High-dose versus low-dose 5-ASA

Failure to induce complete global or clinical remission

Several randomized trials have looked at dose-ranging for various formulations of 5-ASA (e.g. Asacol, Salofalk, Pentasa, MMX mesalamine).
Two studies examined the efficacy of various doses of Salofalk or Pentasa for induction of global or clinical remission in participants with mild or moderately-active UC (Hiwatashi 2011; Kruis 2003). Kruis 2003 found no difference in efficacy between Salofalk 4.5 g/day compared to 3 g/day (RR 1.35, 95% CI 0.96 to 1.89; 213 participants; Analysis 5.1) or 1.5 g/day (RR 0.91, 95% CI 0.69 to 1.22; 212 participants; Analysis 5.1). In Kruis 2003 34% (36/107) of participants in the 3 g/day group failed to enter remission compared to 50% (51/103) of participants in the 1.5 g/day group (RR 0.68, 95% CI 0.49 to 0.95). Hiwatashi 2011 examined the efficacy of Pentasa 4 g/day compared to 2.25 g/day in participants with moderately-active UC and found 78% (47/60) in the 4 g group compared to 86% (54/63) in the 2.25 g group failed to achieve global or clinical remission (RR 0.91, 95% CI 0.77 to 1.08; Analysis 5.1).

Ito 2010 compared Asacol 3.6 g/day with Asacol 2.4 g/day. Fifty-five per cent (36/65) of participants in the 3.6 g/day Asacol group failed to enter remission compared to 70% (46/66) of participants in the 2.4 g/day dose group (RR 0.79, 95% CI 0.61 to 1.04).

D'Haens 2006 and Kamm 2007 investigated the efficacy of MMX mesalamine 2.4 g/day dosed once daily versus 4.8 g/day dosed once daily for induction of remission in active UC. Sixty-one per cent (59/96) of participants in the 4.8 g/day group failed to enter remission compared to 60% (59/98) of participants in the 2.4 g/day group (RR 1.03, 95% CI 0.82 to 1.29, I^2 = 0%).

Failure to induce global or clinical improvement

Six studies examined the efficacy of various doses of Asacol for global or clinical improvement including remission in participants with mild or moderately-active UC (Hanauer 2005; Hanauer 2007; Miglioli 1990; Sandborn 2009; Schroeder 1987; Sninsky 1991).
In Schroeder 1987 26% (10/38) in the 4.8 g/day group compared to 73% (8/11) in the 1.6 g/day group failed to induce clinical remission or improvement (RR 0.36, 95% CI 0.19 to 0.69; Analysis 5.2).
Miglioli 1990 found 29% (7/24) of the 3.6 g/day dosing group compared to 48% (12/25) of the 1.2 g/day dosing group failed to induce clinical remission or improvement (RR 0.61, 95% CI 0.29 to 1.28; Analysis 5.2).
A pooled analysis of two studies (Miglioli 1990; Sninsky 1991) found that 55% (42/77) of the 2.4 g/day group compared to 59% (46/78) of the 1.6 or 1.2 g/day group failed to induce clinical remission or improvement (RR 0.92, 95% CI 0.70 to 1.21; I^2 = 0%; 155 participants; Analysis 5.2).
A pooled analysis of two studies (Miglioli 1990; Ito 2010) found 35% (31/89) of the 3.6 g/day group failed to induce clinical remission or improvement compared with 51% (46/90) of participants in the 2.4 g/day group (RR 0.68, 95% CI 0.48 to 0.97; I^2 = 0%; 179 participants; Analysis 5.2).

A pooled analysis of the ASCEND studies (I, II and III; 1459 participants) found no difference in clinical improvement between Asacol 4.8 g/day and 2.4 g/day. Thirty-seven per cent (266/727) of participants in the 4.8 g/day group failed to improve clinically

compared to 41% (302/732) of participants in the 2.4 g/day group (RR 0.89, 95% CI 0.78 to 1.01; I^2 = 0%; Analysis 5.2).

Subgroup analyses indicated that participants with moderate disease may benefit from the higher dose of 4.8 g/day (Hanauer 2005; Hanauer 2007), particularly among participants previously treated with corticosteroids, oral 5-ASA, rectal therapies or multiple UC medications (Hanauer 2005; Hanauer 2007; Sandborn 2009).

Kamm 2007 provided data for the failure to induce global/clinical remission or improvement. Thirty-five per cent (30/85) of participants in the 4.8 g/day group failed to improve clinically compared to 39% (33/84) of participants in the 2.4 g/day group (RR 0.90, 95% CI 0.61 to 1.33; Analysis 5.2).

Hiwatashi 2011 examined the efficacy of Pentasa 4 g/day compared to 2.25 g/day in participants with moderately-active UC. Twenty-five per cent (15/60) of participants in the 4 g/day group failed to improve clinically compared to 57% (36/63) of participants in the 2.25 g/day group (RR 0.44, 95% CI 0.27 to 0.71; Analysis 5.2).

Failure to induce endoscopic remission

No studies reported this outcome.

Failure to induce endoscopic improvement

No studies reported this outcome.

Failure to adhere to medication regimen

No studies reported this outcome

Adverse events

Three dose-ranging studies (807 participants) reported the proportion of participants who experienced at least one AE (Hiwatashi 2011; Kruis 2003; Schroeder 1987). No differences in AE rates were found across any of the dosing subgroups: Asacol 4.8 g versus 1.6 g/day (RR 0.76, 95% CI 0.48 to 1.21; 49 participants); Salofalk 4.5 g versus 3 g/day (RR 0.96, 95% CI 0.78 to 1.20; 213 participants); Salofalk 4.5 g versus 1.5 g/day (RR 0.96, 95% CI 0.77 to 1.19; 209 participants); Salofalk 3 g versus 1.5 g/day (RR 1.04, 95% CI 0.84 to 1.29; 213 participants); Pentasa 4 g versus 2.25 g/day (RR 0.93, 95% CI 0.78 to 1.11; 123 participants). The most common AE reported in D'Haens 2006 was headache. Other less frequent AEs included diarrhea, nausea and abdominal pain. AEs for Kamm 2007, which included two different dose groups for once-daily MMX mesalamine (2.4 g/day and 4.8 g/day), an Asacol reference arm and a placebo group, are reported above (Analysis 5.3.

Serious adverse events

Two studies (336 participants) reported on the proportion of participants who experienced at least one SAE (Hiwatashi 2011; Kruis 2003). No differences in SAE rates were found across any of the dosing subgroups: Salofalk 4.5 g versus 3 g/day (RR 0.50, 95% CI 0.05 to 5.48; 213 participants); Pentasa 4 g versus 2.25 g/day (RR 5.25, 95% CI 0.26 to 107.07; 123 participants; Analysis 5.4). SAEs include aggravation of nasopharyngitis and UC aggravation.

Withdrawal due to adverse events

Five dose-ranging studies (1178 participants) reported the proportion of participants who were withdrawn due to AEs (Hanauer 2005; Hiwatashi 2011; Kruis 2003; Schroeder 1987; Sninsky 1991). No differences in rates of withdrawal due to AEs were found in any of the dosing subgroups: Asacol 4.8 g/day versus 2.4 g/day (RR 0.93, 95% CI 0.24 to 3.63; 268 participants); Asacol 4.8 g/day versus 1.6 g/day (RR 0.29, 95% CI 0.02 to 4.26; 49 participants); Asacol 2.4 g/day versus 1.6 g/day (RR 5.00, 95% 0.25 to 101.73; 106 participants); Salofalk 4.5 g/day versus 3 g/day (RR 1.30, 95% CI 0.50 to 3.36; 213 participants); Salofalk 4.5 g/day versus 1.5 g/day (RR 0.80, 95% 0.34 to 1.84; 209 participants); Salofalk 3 g/day versus 1.5 g/day (RR 0.61, 95% CI 0.25 to 1.52; 210 participants); and Pentasa 4 g/day versus 2.25 g/day (RR 0.21, 95% CI 0.01 to 4.28; 123 participants; Analysis 5.5). The common AEs leading to withdrawal included UC aggravation, dizziness and headaches.

Withdrawal or exclusions following study entry

Six dose-ranging studies (1442 participants) reported the proportion of participants who were excluded or withdrawn after entry (Hanauer 2005; Hiwatashi 2011; Kruis 2003; Miglioli 1990; Schroeder 1987; Sninsky 1991). We found a difference between Salofalk 3 g/day and 1.5 g/day (RR 0.61, 95% CI 0.38 to 0.99; 210 participants) and between Salofalk 4.5 g/day and 1.5 g/day (RR 0.62, 95% CI 0.38 to 0.99; 209 participants). However, no other differences were found in rates of exclusions or withdrawals after entry in other dosing subgroups: Asacol 4.8 g/day versus 2.4 g/day (RR 0.68, 95% CI 0.40 to 1.16; 386 participants); Asacol 4.8 g/day versus 1.6 g/day (RR 0.19, 95% CI 0.04 to 1.01; 49 participants); Asacol 3.6 g/day versus 2.4 g/day (RR 0.50, 95% CI 0.10 to 2.48; 48 participants); Asacol 3.6 g/day versus 1.2 g/day (RR 0.42, 95% CI 0.09 to 1.95; 49 participants); Asacol 2.4 g/day versus 1.6 or 1.2 g/day (RR 1.07, 95% CI 0.60 to 1.92; 155 participants); Salofalk 4.5 g/day versus 3 g/day (RR 1.01, 95% CI 0.59 to 1.74; 213 participants); and Pentasa 4 g/day versus 2.25 g/day (RR 0.53, 95% CI 0.24 to 1.14; 123 participants; Analysis 5.6).

DISCUSSION

Summary of main results

This systematic review largely confirms the results of previous meta-analyses (Feagan 2012; Sutherland 1993; Sutherland 1997; Sutherland 2006b; Wang 2016), but differs from the previous work in a variety of ways. This update identified one new included study (D'Haens 2017) and one ongoing study (NCT02522767), and therefore now includes 54 studies with 9612 participants. D'Haens 2017 is a dosing study and assessed 3.2 g of oral mesalazine administered as two 1600 mg tablets taken once daily or four 400 mg tablets taken twice daily. NCT02522767 is an ongoing study assessing 4 g extended-release granules of mesalamine and placebo. We have also added serious adverse events (SAEs) as a new secondary outcome in this version of this review.

The effectiveness of oral 5-ASA preparations for the treatment of mild-to-moderate active UC was confirmed. Oral 5-ASA is superior to placebo for induction of remission and clinical improvement in participants with active mild-to-moderate UC. The number needed to treat for an additional beneficial outcome from treatment is nine patients.

As we found in our previous meta-analysis, there was a trend in favor of a slight benefit for the newer 5-ASA preparations over SASP for the induction of global/clinical and endoscopic improvement (including remission). There are several points to be considered. It is possible that larger sample populations would confirm this

finding, but the clinical relevance of such a difference would be debatable. Another possible explanation for the difference may be related to our use of the ITT principle, which should benefit medications with lower dropout rates, in this case 5-ASA.

The assumption that SASP serves only as a pro-drug to deliver 5-ASA to its site of action has been questioned in light of the observation that increasing doses of 5-ASA, within the dose-response range of SASP, fail to enhance its efficacy beyond that of the standard 2 to 4 g therapeutic doses of SASP (Hayllar 1991). In active disease, a variety of 5-ASA to SASP mass ratios were studied; doses of 5-ASA corresponding to up to 10 g of SASP were commonly prescribed while just 2 to 4 g/day of SASP were used as controls. Despite this discrepancy, we could not confirm a significant superiority of 5-ASA. Furthermore, when trial arms were subdivided according to their 5-ASA/SASP mass ratios, r (r < 1/2, 1/1 > r ≥ 1/2, r ≥ 1/1), no general dose trends could be detected (data not shown). It has been suggested that if an increase in the colonic concentration of 5-ASA within the range of SASP dose-dependence does not parallel an enhanced efficacy, then 5-ASA is unlikely to be the only mediator of therapeutic activity (Hayllar 1991). Elucidation of the mechanisms of action of 5-ASA, sulfapyridine, and SASP (reviewed by Greenfield 1993), corroborated by their individual clinical effects, may explain this curious finding, as well as facilitate the determination of the currently unknown etiology of UC.

It was apparent that the newer 5-ASA preparations were not entirely free of causing adverse effects in a number of participants. However, the incidence of AEs, SAEs and withdrawals due to the 5-ASA formulations did not significantly differ from that associated with placebo. Furthermore, there were significantly more withdrawals due to AEs with SASP than with 5-ASA.

Olsalazine caused a significantly higher proportion of withdrawals due to AEs relative to placebo, but lower than the proportion caused by SASP. The most common AE attributed to Olsalazine was diarrhea, an effect previously observed in approximately 10% of participants receiving the drug (Ireland 1987). It should be noted that there may have been a bias in favor of SASP, since many of the studies involved participants who were known to have tolerated SASP in the past. It has been suggested that protocol alterations may reduce the withdrawal rates in future trials, since encouraging participants to take Olsalazine with meals appears to reduce the incidence of diarrhea to approximately 3% of participants (Jarnerot 1996); of the included Olsalazine trials, only two reported that participants were instructed to take their medication with meals (Hetzel 1986; Zinberg 1990). Mesalamine-induced interstitial nephritis is a serious but rare AE (Elseviers 2004). Although there have been case reports of interstitial nephritis in people with IBD treated with 5-ASA (Arend 2004; Frandsen 2002; Maeda 2001), there were no reports of interstitial nephritis in the studies included in this systematic review.

This meta-analysis indicates that oral 5-ASA administered once daily is as effective as conventional dosing (twice or three times daily) for induction therapy in mild to moderately-active UC. High-certainty evidence suggests no difference between once-daily and conventional dosing for induction of remission, and moderate-certainty evidence suggests no differences in clinical improvement. Furthermore, subgroup analyses by drug formulation (MMX mesalazine, Salofalk, Asacol and Pentasa) showed no differences in efficacy between once-daily and conventional dosing for induction of remission. However, the latter results should be interpreted cautiously since only five formulations were evaluated in this analysis.

We found no differences between once-daily and conventionally-dosed oral 5-ASA for safety outcomes, including the overall incidence of AEs, SAEs, withdrawal from treatment due to an AE or exclusions or withdrawals after entry. In keeping with the well-established safety profile of oral 5-ASA, most of the AEs reported in the studies were mild-to-moderate in intensity. Common AEs were gastrointestinal symptoms (e.g. flatulence, abdominal pain, nausea, and diarrhea), headache and worsening UC.

Important patient preference and adherence differences may exist between dosing regimens. In the study that measured participant preference, most preferred once-daily dosing to conventional dosing (Kruis 2009). Although it is generally believed that administration of fewer tablets and less frequent dosing improves both efficacy and adherence, we could not demonstrate the superiority of once-daily dosing for either of these outcomes. This result suggests that patient adherence may not be enhanced by once-daily dosing in the clinical trial setting. Several possible explanations exist for these observations, but the most plausible one concerns the unique aspects of the clinical trial environment. It is noteworthy that adherence was remarkably high in the studies that measured this outcome (Kamm 2007; Lichtenstein 2007). The pooled adherence rate was 92% in the once-daily dosing group compared to 94% in the conventional-dosing group. These rates likely reflect the highly supervised environment in which the studies were conducted. Adherence to medication in clinical trials is generally greater than in clinical practice, since participants are highly selected volunteers who are more likely, in general, to adhere to drug regimens (Andrade 1995; Kane 2001; Kane 2006; Kane 2008). In addition, adherence is continuously reinforced during the clinical trial process. Thus, it may be difficult to detect differences in adherence between once-daily and multiple-dose regimens in this setting. Accordingly, there is a need to compare dosing regimens in large-scale community-based studies.Reported adherence rates in community-based studies range from 40% to 60% and are especially poor among people in remission (Kane 2001; Kane 2003a; Levy 1999; Shale 2003). However, whether once-daily dosing regimens improve adherence in the community remains unknown.

Experience from other indications suggests that factors other than the dosing regimen are important for long-term compliance (Brixner 2007; Kane 2008). Long-term observations in people with UC as well as in other indications indicate that patients' and physicians' behaviors play a dominant role in adherence (Beaulieu 2009; Magowan 2006). The patient-physician relationship should reinforce adherence through education, open communication and mutual agreement about the value of treatment (Kane 2008).

Moderate-certainty evidence suggests that there may be little or no difference in efficacy or safety between the various formulations of oral 5-ASA. To further support the conclusion that there is no difference in efficacy between 5-ASA formulations, it should be noted that only one induction study reported a difference in efficacy between two different formulations of 5-ASA (Green 1998). Green 1998 reported that Balsalazide 6.75 g/day was superior to Asacol 2.4 g/day for induction of complete remission (none or mild symptoms and sigmoidoscopy score of 0 or 1 at 12 weeks). However, two similar trials did not support these findings (Levine 2002; Pruitt 2002).

Pharmacokinetic studies suggest that systemic exposure to 5-ASA is similar for all oral 5-ASA formulations and 5-ASA pro-drugs (Sandborn 2002a; Sandborn 2002b; Sandborn 2002c; Sandborn 2003). With the exception of Olsalazine-related diarrhea (Feurle 1989; Hanauer 1996; Robinson 1994; Zinberg 1990), there does not appear to be any difference in safety between the various formulations of oral 5-ASA. The overall pooled risk ratios showed no differences in the incidence of AEs, SAEs, withdrawal due to AEs or exclusions or withdrawals after entry. Thus, all of the 5-ASA formulations can be considered safe and effective for the treatment of active UC, and from a practical standpoint they can be considered therapeutically equivalent at equimolar doses (Sandborn 2002a). Treatment with sulfasalazine and Olsalazine may not be preferable due to the high frequency of AEs. When selecting among the remaining 5-ASA formulations, physicians and patients should consider dose-response data for 5-ASA doses up to 4 to 4.8 g/day of 5-ASA, adherence issues related to dose forms (size of dose form and total number of tablets or capsules per day), and price, when deciding which formulations to use (Sandborn 2002a).

The ASCEND I, ASCEND II and ASCEND III studies compared Asacol 4.8 g/day to Asacol 2.4 g/day in people with mild to moderately-active UC (Hanauer 2005; Hanauer 2007), or in people with moderately-active disease (Sandborn 2009). A pooled analysis of the three studies (1459 participants) showed no difference between the dose groups in failure to induce clinical improvement. However, subgroup analyses indicated that participants with moderate disease may benefit from the higher dose of 4.8 g/day (Hanauer 2005; Hanauer 2007), particularly among participants previously treated with corticosteroids, oral 5-ASA, rectal therapies or multiple UC medications (Hanauer 2005; Hanauer 2007; Sandborn 2009). Both doses appear to have similar efficacy in participants with mild disease, which suggests that a dose of 2.4 g/day may be preferred for people with mildly-active disease. Hiwatashi 2011 compared Pentasa 4 g/day to Pentasa 2.25 g/day in people with moderate disease and found a difference in favor of the higher-dose group for clinical improvement which appears to confirm the results of the ASCEND studies. Hiwatashi 2011 concluded that people with severe symptoms such as relapse-remitting and moderately-active disease should be treated initially with 4 g/day.

A pooled analysis of two studies (194 participants) comparing MMX mesalazine 4.8 g to 2.4 g day did not show a difference between the dose groups in failure to induce clinical remission or improvement, suggesting that both dosage groups are efficacious in people with mild to moderately-active UC (D'Haens 2006; Kamm 2007). A subgroup analysis by severity did not show any advantage for the higher dose (4.8 g/day) in participants with moderate disease (Kamm 2007). However, further research may be necessary to identify those who will benefit from varying doses of MMX mesalamine (Kamm 2007). Kruis 2003 evaluated the efficacy of three doses of Salofalk mesalamine pellets (1.5, 3.0, and 4.5 g/day) in people with active UC, and found no difference in remission rates between 4.5 g/day and 3 g/day, and a difference in remission rates between 3 g and 1.5 g/day. Kruis 2003 concluded that there was no dose response between the three dose groups and recommended the lowest effective dose (1.5 g/day) for treatment of people with mild-to-moderate UC. People failing at this dose might benefit from an increase to 3 g/day, but doses higher than this amount do not appear to provide any additional benefit (Kruis 2003).

Overall completeness and applicability of evidence

We believe the evidence from this review is applicable to most people with mild-to-moderate ulcerative colitis. The evidence assesses 5-ASA compared with placebo, sulfasalazine and comparator 5-ASA. The studies also assess 5-ASA dose-ranging studies and once-daily dosing studies compared to conventional-dosing studies. All the safety and efficacy outcomes which we aimed to report on were included in the studies, but there were a couple of outcomes that were rarely reported, including failure to adhere to the medication regimen and endoscopic remission. The review found mainly moderate-to-high-certainty evidence for the oral 5-ASA versus placebo and oral 5-ASA versus SASP studies, which might therefore imply that this area does not require additional studies. However, the evidence comparing oral 5-ASA with comparator 5-ASA is mostly of moderate certainty, and once-daily with conventional dosing is mostly low-to-moderate-certainty evidence. Additional studies for these comparisons may therefore change the overall results.

Quality of the evidence

We assessed the included studies using the Cochrane 'Risk of bias' tool and GRADE criteria. Five studies were rated at high risk of bias due to incomplete outcome data (Green 1998; Kruis 2003) and lack of blinding (Farup 2001; Flourié 2013; Tursi 2004). Thirty-two of 54 included studies did not describe the method used for randomization and were rated as unclear for this domain. Twenty-six studies did not describe methods used for allocation concealment and were rated as unclear for this domain. The methods used for blinding were not described in five studies, and we rated these studies as unclear. Twenty studies were rated as unclear for incomplete outcome data because reasons for withdrawal were either not described or were not attributed to intervention groups. Six studies were rated as unclear for selective reporting.

For the oral 5-ASA versus placebo comparison clinical remission and AEs were rated as high certainty. The outcomes clinical improvement, endoscopic remission and withdrawal due to AEs were rated as moderate, due to heterogeneity and sparse data, and SAEs were rated as low certainty due to very sparse data (Summary of findings 1). For the 5-ASA versus SASP studies the outcomes induction of remission and clinical improvement were rated as moderate certainty (due to sparse data) and high certainty respectively. The AEs and withdrawal due to AE outcomes were both rated as moderate, due to sparse data, and SAEs were low-certainty due to very sparse data (Summary of findings 2). For the once-daily compared to conventional-dosing studies, the overall certainty of the evidence using the GRADE approach was rated as high for the primary outcome (clinical remission) and moderate for the secondary outcomes of clinical improvement and AEs, due to sparse data (Summary of findings 3). The studies comparing the various formulations of 5-ASA indicated that the overall certainty of the evidence for the primary outcome (failure to induce complete global or clinical remission) was moderate, due to a high risk of bias (lack of blinding) in two studies in the pooled analysis (See Summary of findings 4).

Potential biases in the review process

A comprehensive literature search helped minimize bias in relation to study selection. In addition two review authors independently

screened the studies, extracted the data and assessed the risks of bias. There were limitations to drawing general conclusions. Almost every study used a unique clinical or endoscopic index. Unlike Crohn's disease, the lack of standard indices in UC prevented the collection of consistent treatment efficacy data and makes comparisons across clinical studies difficult. The use of endoscopic remission as an outcome would provide a more rigorous assessment of treatment efficacy in clinical trials. Clinicians should use a standardized approach to assess endoscopic appearance to allow for comparisons across trials. Most of the included studies were not of sufficient duration to permit documentation of endoscopic healing. Results were also periodically obscured in several studies that failed to specify the treatment arm to which certain excluded participants were initially randomized. Despite these and other common factors that must be considered when interpreting meta-analyses, the data provided strong evidence that pointed towards a number of conclusions.

Agreements and disagreements with other studies or reviews

We have identified two other systematic reviews that have assessed 5-ASA for the induction of remission in UC (Ford 2011; Kane 2003b). Ford 2011 is a systematic review and meta-analysis assessing the efficacy of 5-ASA in people with UC. The review included 37 RCTs with 19 induction studies (nine studies comparing 5-ASA to placebo and 10 studies comparing different doses of 5-ASA) and 18 maintenance studies. This review concluded that 5-ASAs are highly effective for both the induction of remission and prevention of relapse in UC participants.

Kane 2003b is a systematic review on the efficacy of oral 5-ASA for active UC. Thirty-one studies were identified and 19 met the inclusion criteria. This review suggested that mesalamine is superior to placebo for treating active UC and that 5-ASA products appear to be as effective as sulfasalazine, but available data do not suggest a difference in efficacy between any of the 5-ASA preparations.

AUTHORS' CONCLUSIONS

Implications for practice

5-ASA was superior to placebo and no more effective than SASP. Nonetheless, it is clear that the newer 5-ASA preparations have yet to be proven to be more clinically beneficial than SASP for the treatment of UC. The decision to use 5-ASA or SASP should consider tolerance to SASP. Oral 5-ASA administered once daily is as effective and safe as conventional dosing (twice or three times daily) for induction therapy in mild to moderately-active UC. There do not appear to be any differences in efficacy or safety between the various formulations of 5-ASA. Among people with mildly-active UC a dosage of 4 to 4.8 g/day does not appear to provide any additional benefit over a dosage of 2 to 2.4 g/day. Patients with severe symptoms and moderately-active disease may benefit from an initial dosage of 4 to 4.8 g/day.
When selecting among the various 5-ASA formulations, physicians and patients should consider dose-response data, adherence issues related to dose forms (size of dose form and total number of tablets or capsules per day) (Sandborn 2002a).

Implications for research

Future trials comparing the efficacy of oral 5-ASA with placebo or SASP do not appear to be justified. There is little evidence to suggest that there is a difference in efficacy between the oral 5-ASA drugs.

Future trials should look at enhancing patient adherence to medication. Adherence to therapy is important for treatment success and may be an important predictor of relapse (Kane 2003a; Kane 2001).

Future trials could assess whether once-daily dosing regimens improve adherence in the community. There is currently one ongoing study comparing 5-ASA to placebo. One of the trials (NCT02522767) assessed a 4 g extended-release once-daily dosing regimen, but did not assess medication adherence.
Future trials may be necessary to identify people who will benefit from varying doses of MMX mesalamine or Salofalk.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Andreoli 1987

Study characteristics		
Methods	Randomized, double-blind trial comparing 5-aminosalicylic acid and SASP	
Participants	Male and female participants, aged 19 to 63 years, with acute ulcerative colitis (N = 12)	
Interventions	1.5 g/day 5-ASA or 3 g/day SASP for 2 months	
Outcomes	Clinical endoscopic remission within 2 months of start of therapy was considered as a positive indication of remission induction	
Notes	Abstract - funding support and conflicts of interest were not reported	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Allocation of drugs was performed using a table of random numbers
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	Unclear risk	Not described

Andreoli 1987 *(Continued)*

Other bias	Unclear risk	Not described

Bresci 1990

Study characteristics	
Methods	Randomized trial comparing 5-aminosalicylic acid and SASP
Participants	Adults with ulcerative colitis of at least 2 years duration, with mild-to-moderate relapse (N = 86)
Interventions	2.4 g/day 5-ASA (n = 44) or 3 g/day SASP (n = 42) for 6 weeks
Outcomes	Clinical improvement, endoscopic and histologic appearance, indexes of phlogosis, hematic crasis, hepatic and renal functionality, and adverse events
Notes	Funding support and conflicts of interest were not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts were reported
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

Cai 2001

Study characteristics	
Methods	Randomized controlled trial
Participants	Adults (aged 18 to 65 years) with active ulcerative colitis (N = 135)
Interventions	Olsalazine 3 g/day (n = 105) or SASP 4 g/day (n = 30)
Outcomes	Clinical improvement and adverse events

Cai 2001 *(Continued)*

Notes	Funding support and conflicts of interest were not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	Unclear risk	Not described
Other bias	Unclear risk	Not described

D'Haens 2006

Study characteristics

Methods	Randomized, multicenter, double-blind, parallel-group, dose-ranging study
Participants	Adultss (aged ≥ 18 years) with histologically-confirmed, newly-diagnosed or relapsing mild to moderately-active ulcerative colitis (N = 38)
Interventions	MMX mesalazine (SPD476) 1.2 (n = 13), 2.4 (n = 14) or 4.8 g/day (n = 11), given once daily for 8 weeks
Outcomes	Primary outcome: remission defined as a UC-DAI score ≤ 1 with a score of 0 for rectal bleeding and stool frequency, and at least a 1-point reduction from baseline in sigmoidoscopy score. Secondary outcomes: change in UC-DAI score, sigmoidoscopic appearance and histology from baseline to week 8, and the change in symptoms (rectal bleeding and stool frequency) from baseline to weeks 2, 4 and 8 for the 3 dose groups
Notes	Study was funded by Shire Pharmaceuticals Inc. Conflicts of interest were not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described

D'Haens 2006 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind: MMX mesalazine and placebo tablets were identical in appearance
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The 1.2 g/day group had 6 withdrawals (6/13) compared to 3 (3/14) in the 2.4 g/day and 1 (1/11) in the 4.8 g/day groups. LOCF was used to address incomplete outcome data
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

D'Haens 2017

Study characteristics	
Methods	Randomized, active-controlled, multicenter, non-inferiority induction trial
Participants	Adults (18 years and older) diagnosed with mild-to-moderate ulcerative colitis (N = 817)
Interventions	Participants received 3.2 g of oral mesalazine administered as 2 x 1600 mg tablets each morning or 4 x 400 mg tablets taken twice daily for 8 weeks
Outcomes	Primary outcome: The proportion of participants in clinical and endoscopic remission at week 8 Secondary outcomes: Endoscopic remission, endoscopic response, clinical remission at week 8, rectal bleeding subscore of 0 at week 8, clinical and endoscopic response at week 8, clinical remission at week 12, clinical response at week 12, rectal bleeding subscore of 0 at week 12, clinical remission at weeks 8 and 10 and 12, clinical response at weeks 8 and 12
Notes	Study was funded by Tillotts Pharma, AG. Author conflicts of interest are reported in the manuscript

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomization schedule was generated by computer in permuted blocks of 6 without stratification
Allocation concealment (selection bias)	Low risk	An interactive web response system was used to manage randomization and dispense the study drug
Blinding (performance bias and detection bias) All outcomes	Low risk	All participants took the same numer of identical-looking 1600 mg or 400 mg placebo tablets. Investigators, central readers and participants were unaware of the participant assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants involved in the trial were accounted for with reasons
Selective reporting (reporting bias)	Low risk	Expected outcomes were reported in the published study

D'Haens 2017 *(Continued)*

Other bias	Low risk	The study appears to be free from other sources of bias

Ewe 1988

Study characteristics	
Methods	Randomized, double-blind trial comparing 5-aminosalicylic acid (olsalazine) and SASP
Participants	Adults with mild-to-moderate active chronic ulcerative colitis (N = 40)
Interventions	1.5 g/day 5-ASA (olsalazine) for 14 days, and followed by 3 g/day SASP for a further 14 days (n = 20), or vice versa (n = 20)
Outcomes	Clinical improvement: at each study visit a physical examination was performed and a detailed history was taken. In addition, a diary completed daily by the participant was evaluated. The diary was designed to record stool frequency and consistency, and blood staining of stools. Based on these variables investigators rated the efficacy of treatment as “improved”, ”no change” or “worse”
Notes	Cross-over trial. Data for outcomes were available before cross-over Funding support and conflicts of interest were not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data available for 40 of 41 participants entered in the study
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

Farup 2001

Study characteristics	
Methods	Randomized, open-label, non-inferiority study
Participants	Adults with confirmed diagnosis of active mild-to-moderate ulcerative colitis (N = 227). People with proctitis were excluded

Farup 2001 *(Continued)*

Interventions	Pentasa sachet prolonged-release granules 2 x 1 g packets twice daily (n = 74), 1 packet 4 times daily (n = 76) or pentasa prolonged-release 500 mg tablets - 2 tablets 4 times daily (n = 77) for 8 weeks
Outcomes	Primary outcome: mean improvement in UC-DAI Secondary outcomes: remission (UC-DAI 0 or 1), improvement (reduction in UC-DAI of ≥ 2 from baseline), satisfaction with regimen, adverse events
Notes	Study was funded by Ferring Pharmaceuticals, Denmark Conflicts of interest were not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	80 participants did not complete the study. Reasons are provided but are not attributed to individual treatment groups
Selective reporting (reporting bias)	Unclear risk	Expected outcomes were reported but reporting for withdrawals and adverse events was inadequate
Other bias	Low risk	The study appears to be free of other sources of bias

Feagan 2013

Study characteristics

Methods	Randomized, double-blind, placebo-controlled, multicenter, phase 3 study
Participants	Adults (18 years or older) with a documented diagnosis of mild-to-moderate UC, defined by a modified UC-DAI (N = 281)
Interventions	Asacol 4.8 g/day (n = 140) or placebo (n = 141)
Outcomes	Primary outcome: proportion of participants in clinical remission, defined as a score of 0 for stool frequency and rectal bleeding, and absence of fecal urgency at week 6 Secondary outcomes: clinical remission at weeks 6 and 10, endoscopic remission (defined as a sigmoidoscopic score of ≤ 1) at week 6, endoscopic remission at week 10, improvement (defined as a decrease of at least 3 points from baseline in the modified UC-DAI score) at week 6, improvement at week 10, mean changes in the modified UC-DAI and UCCS from baseline to week 10, and adverse events
Notes	Study was funded by Tillotts Pharma, AG.

Feagan 2013 *(Continued)*

	Author conflicts of interest are reported in the manuscript

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Generated in permutated blocks by computer
Allocation concealment (selection bias)	Low risk	An interactive voice/web response system managed the randomization procedure and dispensed the study drug
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and central readers were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants involved in the trial were accounted for with reasons
Selective reporting (reporting bias)	Low risk	Expected outcomes were reported in the published study
Other bias	Low risk	The study appears to be free of other sources biases

Feurle 1989

Study characteristics

Methods	Double-blinded, placebo-controlled, and centrally-randomized, with stratification in blocks of 10 for each of the 12 centres
Participants	Outpatients with mild-to-moderate ulcerative colitis recruited in West Germany between 1984 and 1986 (N = 105)
Interventions	Olsalazine 2 g/day (4 doses of 2 gelatin capsules each; n = 52) or 8 placebo capsules with identical appearance (n = 53). Participants were advised to start with fewer than 8 pills and reach complete dosage by the third or fourth day and continue for 4 weeks. Compliance was verified by laboratory tests
Outcomes	Clinical and laboratory examinations were performed at recruitment, after 2 weeks, and at the end of 4 weeks. Endoscopy and biopsy were performed on days 0 and 28. Clinical observations were made on days 0, 14, and 28 Endoscopic score was the mean of redness/hyperemia, contact bleeding, spontaneous bleeding and erosions, each graded on a 3-point scale. Clinical status was based on number of stools, presence of blood in stool, stool consistency, and mucous in stool. The clinical score was considered improved when at least 3 of the 4 parameters increased. Occurrence of withdrawals and side effects was also tabulated
Notes	Funding support and conflicts of interest were not reported

Risk of bias

Bias	Authors' judgement	Support for judgement

Feurle 1989 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Centralized randomization
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind: identical placebo capsule
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts balanced across intervention groups 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

Fleig 1988

Study characteristics	
Methods	Prospective, randomized, double-blind comparison of benzalazine (SAB) and SASP.
Participants	Consecutive patients were randomized. Participants, aged 18 to 75 years, with histologically- and endoscopically-diagnosed ulcerative colitis for 16 months with an acute episode defined as the occurrence of diarrhea with at least 5 stools daily for at least 3 days. Endoscopic appearance was graded according to a 4-point scale (N = 43)
Interventions	Equimolar, identical-appearing doses of either SASP (2 tablets, 3 times/day; 0.5 g per tablet; n = 21) or SAB (2 tablets, 3 times/day; 0.36 g per tablet; n = 22) for 6 weeks, except for the first week when dosage of either was 2 tablets, 4 times daily
Outcomes	Laboratory and clinical evaluations were performed once a week, in addition to participant diaries to record number and consistency of stools, and occurrence of rectal bleeding. Endoscopy was performed at entry and after 6 weeks to determine severity of inflammation and to obtain a biopsy which was evaluated on a 4-point scale Efficacy was evaluated in terms of positive changes in major clinical (number and consistency of stools), sigmoidoscopic, and morphological (histologic grading of inflammation) criteria. Occurrence of side effects and withdrawals were also reported
Notes	Study was funded by Henning Berlin GmbH Conflicts of interest were not reported

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described

Fleig 1988 *(Continued)*

Allocation concealment (selection bias)	Low risk	Participants received the medication assigned to their patient number according to the sequence of entry into the trial. Treatment was randdomly assigned to patient numbers
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind: tablets of identical appearance. Assignment was blind to both participants and treating physicians
Incomplete outcome data (attrition bias) All outcomes	Low risk	Two participants in 5-ASA group were lost to follow-up
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

Flourié 2013

Study characteristics	
Methods	Multicenter, controlled, randomized, investigator-blinded, comparative, non-inferiority study
Participants	Adults (18 years or older) with newly-diagnosed or relapsing mild-to-moderate ulcerative colitis, with disease extension beyond the rectum (N = 206)
Interventions	Mesalazine (4 g/day), either once daily with 2 sachets of 2 g mesalazine granules in the morning (n = 102), or twice daily with 1 x 2 g sachet in the morning and one in the evening (n = 104) for 8 weeks
Outcomes	Primary outcome: percentage of participants in clinical and endoscopic remission after 8 weeks (defined as UC-DAI score $\leq$ 1) Secondary outcomes: complete remission at week 8 (clinical and endoscopic UC-DAI = 0), clinical and endoscopic improvement at week 8 (decrease in UC-DAI by at least 2 points), clinical remission at weeks 4, 8 and 12, determined by normal stool frequency, no bloody stools and no active disease by physician's assessment, time to remission (based on participant's diary with normal stool frequency and cessation of bleeding; estimated using Kaplan–Meier methodology), mucosal healing at 8 weeks (defined as a UC-DAI endoscopic subscore of 0 or 1, or alternatively a Rachmilewitz endoscopic index of < 4), adherence, global patient's acceptability and adverse events
Notes	Study was funded by Ferring Pharmaceuticals Author conflicts of interest are reported in the manuscript

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomized centrally by a computer-generated randomization system
Allocation concealment (selection bias)	Low risk	To maintain the investigator-blind trial design, sealed treatment boxes were identical in size and weight, and contained written instruction about the dosing arm to which the participant was assigned; investigators were unaware of this information

Flourié 2013 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	High risk	Only investigators were blinded in this trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants involved with the study are accounted for
Selective reporting (reporting bias)	Low risk	Expected outcomes were reported
Other bias	Unclear risk	The study appeared to be free of other sources of biases

Forbes 2005

Study characteristics	
Methods	Randomized non-inferiority trial
Participants	Adults with ulcerative colitis with mild-to-moderate relapse (N = 88)
Interventions	Asacol 2 x 400 mg tablets 3 times/day (2.4 g/day, n = 42) or ipocol 2 x 400 mg tablets 3 times/day (2.4 g/day, n = 46) for 8 weeks
Outcomes	Outcomes included clinical remission (investigator's overall clinical assessment), modified St Mark's Colitis Activity score, macroscopic and microscopic appearance of the rectum, and adverse events. Outcomes were evaluated at entry and weeks 2, 4, and 8. Tablet counts were performed by pharmacy departments to check compliance
Notes	Lagap Pharmaceuticals Ltd provided all the drugs used for the study, and arranged the blinded packaging and the telephone randomization service. The company also monitored the conduct of the trials and appropriate documentation in the various centres to comply with Good Clinical Practice, together with providing modest running expenses. Conflicts of interest were not reported

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 telephone randomization by Lagap Pharmaceuticals Ltd
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Study drug was provided in an anonymous blister package with instructions to take 2 x 400 mg tablets 3 times a day. The tablets themselves were not identical as they are somewhat different in shape. Participants were advised that they might find that they were prescribed a tablet shaped differently from those they had received before, but not that this was or was not Asacol or ipocol. Clinical investigators took care neither to see nor to enquire about the nature of the tablets

Forbes 2005 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	During the course of the study, 11 participants withdrew from the Asacol group, and 9 withdrew from the Ipocol group: reasons for withdrawal were not provided
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

Gibson 2006

Study characteristics	
Methods	Multicenter, randomized, double-blind, double-dummy parallel-group trial
Participants	Adults (19 to 70 years) with mild to moderately-active ulcerative colitis confirmed by standard endoscopic and histopathological criteria (N = 258)
Interventions	Eudragit-L-coated mesalazine tablets (Salofalk 3 g/day, n = 131) or ethylcellulose-coated mesalazine tablets (Pentasa 3 g/day, n = 127) for 8 weeks
Outcomes	**Primary outcome:** clinical remission (CAI ≤ 4) **Secondary outcomes:** CAI; clinical improvement (clinical remission or improved CAI of > 3 from baseline), number of stools per week; number of bloody stools per week; time to first symptomatic remission; endoscopic remission (EI < 4); endoscopic improvement; histological remission; histological improvement; physician's global assessment; and adverse events
Notes	LOCF if participants withdrew early. Participants were assumed to be treatment failures if no CAI score was available. Adherence checked by tablet count The study was sponsored by Dr Falk Pharma GmbH (Freiburg, Germany) Conflicts of interest were not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated using the program "Rancode +"
Allocation concealment (selection bias)	Low risk	Sequentially-numbered, sealed, non-transparent envelopes
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	43 participants were excluded from the per protocol analysis but it is not clear which groups they came from. ITT analysis was presented for the primary outcome
Selective reporting (reporting bias)	Low risk	Expected outcomes were reported

Gibson 2006 *(Continued)*

Other bias	Low risk	The study appears to be free of other sources of bias

Good 1992

Study characteristics		
Methods	Multicenter, double-blind, randomized comparison of SASP and mesalamine. Each site was independently randomized in blocks of 6	
Participants	People with endoscopically-confirmed active ulcerative colitis (N = 117)	
Interventions	Mesalamine, 1 g/day (n = 27), 2 g/day (n = 31), or 4 g/day (n = 30) or SASP, 4 g/day (n = 29). Drugs were dispensed in blister packs according to a double-dummy technique	
Outcomes	Clinical assessments were performed at entry, 4 weeks, and at 8 weeks Efficacy was rated according to positive changes in disease activity index and a physician's overall assessment	
Notes	Abstract - funding support and conflicts of interest were not reported	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
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

Green 1998

Study characteristics	
Methods	Multicenter, randomized, double-blind, double-dummy, parallel-group study
Participants	Adults (18 to 80 years) with moderate-to-severely active ulcerative colitis confirmed by flexible sigmoidoscopy (N = 99)

Green 1998 *(Continued)*

Interventions	Balsalazide (2.25 g 3 times daily: 6.75 g/day, n = 50) or Asacol (0.8 g 3 times daily: 2.4 g/day, n = 49) for 12 weeks
Outcomes	Primary outcome: The proportion of participants achieving complete remission (based on diary card) by 12 weeks. Participants left the study at weeks 4 or 8 if they achieved complete remission. Complete remission was defined as none or mild symptoms, sigmoidoscopic grade of 0 or 1 and no use of rectal steroid foam. Other outcomes included participant and investigator satisfaction, laboratory assessments, median time to relief of symptoms, cumulative days free of symptoms, study dropouts, dropouts due to treatment failure and adverse events. Outcomes were evaluated at entry and weeks 2, 4, 8 and 12. Adherence was assessed at follow-up visits
Notes	Participants were provided with rectal steroid foam as relief medication for use as required Funding support and conflicts of interest were not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy: placebos of identical appearance to the Balsalazide capsules and mesalamine tablets were provided. Participants received 3 capsules (Balsalazide/placebo) and 2 tablets (mesalamine/placebo) 3 times daily
Incomplete outcome data (attrition bias) All outcomes	High risk	38% of the participants (38 of 101) did not complete the study (15 Balsalazide; 23 mesalamine), the main reason being treatment failure, which was more common in the mesalamine group (6 Balsalazide; 16 mesalamine; P = 0.015). Other reasons for withdrawal included noncompliance with the study protocol (6 Balsalazide, 3 mesalamine), unacceptable adverse events (1 Balsalazide, 1 mesalamine), and treatment with excluded medication (1 Balsalazide, 1 mesalamine). 3 participants (1 Balsalazide, 2 mesalamine) who were erroneously admitted into the study were also withdrawn; 1 receiving Balsalazide did not have UC, 1 receiving mesalamine was not using adequate contraception, and 1 receiving mesalamine was included into the study after the recruitment deadline had passed
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

Green 2002

Study characteristics

Methods	Double-blind and randomized
Participants	Patients with acute relapse of ulcerative colitis and newly-diagnosed patients (N = 57)

Green 2002 *(Continued)*

Interventions	Sulfasalazine, 3 g daily (n = 29), or Balsalazide, 6.75 g daily (n = 28), according to a double-dummy protocol for 12 weeks. Some participants were receiving concomitant oral or topical steroids
Outcomes	1. Remission rates at the end of the study or withdrawal 2. Treatment success or failure at the end of the study or withdrawal
Notes	This study was sponsored by Biorex Laboratories Limited Conflicts of interest were not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random-number table
Allocation concealment (selection bias)	Low risk	Centralized randomization
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant from the SASP group was lost to follow-up
Selective reporting (reporting bias)	Low risk	Expected outcome were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Hanauer 1993

Study characteristics

Methods	Multicenter, double-blind, placebo-controlled, randomized, dose-response trial conducted at 20 sites
Participants	Adults, over 18 years old, with mild-to-moderate active ulcerative colitis confirmed by clinical and colonoscopic evidence with a score ≥ 5 on a 15-point index, were selected from 06 March 1987 to 04 August 1988. Participants were stratified according to extent of disease. Therapies of steroids, SASP, or other mesalamine formulations were stopped at least 7 days before trial. Immunosuppressives were stopped at least 90-days before study (N = 374)
Interventions	Mesalamine (pentasa) 1 g (n = 92), 2 g (n = 97) or 4 g per day (n = 95), or placebo (n = 90), in 250 mg capsules in identical blister cards for 8 weeks. Loperamide (2 mg) was dispensed to participants when absolutely necessary for control of diarrhea
Outcomes	In addition to daily patient diaries, clinical assessments and sigmoidoscopy were performed at weeks 1, 4, 8 or upon withdrawal Clinical improvement was assessed using the physician's global assessment, assessment of treatment failure, sigmoidoscopic index, biopsy score, participants' perceptions, and trips to the toilet. Induction

Hanauer 1993 *(Continued)*

	of remission was assessed by more stringent criteria for physician's assessment, sigmoidoscopic index and biopsy score
Notes	Study was funded by Marion Merrell Dow Inc. Conflicts of interest were not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Sequentially-numbered drug containers of identical appearance
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind: study drug was supplied in 250 mg capsules in identical blister cards to ensure blinding of both the investigator and the participant
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 participants were lost to follow-up. More participants withdrew from the placebo group due to insufficient therapeutic effect
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

Hanauer 1996

Study characteristics

Methods	Multicenter, double-blind, placebo-controlled, randomized, dose-ranging trial
Participants	Patients from 24 centers with mild to moderately-active ulcerative colitis. No anti-diarrheals were allowed (N = 273)
Interventions	Olsalazine, 2 g (n = 92) or 3 g per day (n = 91), or placebo (n = 90) for 12 weeks. Full dosage was reached after 1 week
Outcomes	Assessments were performed at entry, 6 and 12 weeks (or upon termination) End points included induction of clinical remission (according to number of bowel movements and amount of blood in stool) and induction of endoscopic remission or endoscopic improvement (evaluated on a 5-pt scale, where 0 or 1 indicated remission)
Notes	Abstract - funding support and conflicts of interest were not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described

Hanauer 1996 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	Unclear risk	Expected outcomes were reported, Post hoc rescoring of endoscopic reports were reported for endoscopic remission
Other bias	Low risk	The study appears to be free of other sources of bias

Hanauer 2005

Study characteristics	
Methods	Multicenter, randomized, double-blind, double-dummy, parallel-group study (ASCEND II)
Participants	Adults (aged 18 to 75 years) with moderately-active ulcerative colitis confirmed by endoscopy or radiography (N = 386)
Interventions	Asacol 2.4 g/day (400 mg tablet; n = 139) or 4.8 g/day of mesalamine (Asacol 800 mg tablet; n = 129) for 6 weeks
Outcomes	Primary outcome: treatment success at 6 weeks defined as either complete remission or a clinical response to therapy. Complete remission was defined as complete resolution of: (i) stool frequency (normal stool frequency); (ii) rectal bleeding (no rectal bleeding); (iii) PFA score (generally well); (iv) endoscopy findings (normal), and a PGA score of 0. A clinical response to therapy was defined as improvement in the baseline PGA score and improvement in at least one other clinical assessment (stool frequency, rectal bleeding, PFA, endoscopy findings) and no worsening in any other clinical assessment Secondary outcomes: overall improvement at week 3, improvement from baseline in each of the clinical assessment subscores at weeks 3 and 6, overall improvement at week 6 in the subgroup of participants with ulcerative colitis limited to the left side of the colon (proctitis, proctosigmoiditis, or left-sided colitis), time to normalization of stool frequency (based on the participant's daily diary), time to resolution of rectal bleeding (based on the participant's daily diary), and change from baseline in the UC-DAI, and adverse events
Notes	The study was funded by Procter & Gamble Pharmaceuticals, Inc. (Cincinnati, OH), who also provided study drug for the investigation Conflicts of interest were not reported

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Permutated block randomization scheme

Hanauer 2005 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy: identical placebos were used. Both participants and investigative staff were blinded to treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	18.7% of participants in 2.4 g/day group withdrew (26/139) compared to 12.4% of the 4.8 g/day group (16/129). More participants withdrew from the 2.4 g/day group due to lack of treatment effect
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

Hanauer 2007

Study characteristics	
Methods	Multicenter, randomized, double-blind, double-dummy, parallel-group study (ASCEND I)
Participants	Adults (aged 18 to 75 years) with mild to moderately-active ulcerative colitis confirmed by endoscopy or radiography (N = 301)
Interventions	Asacol 2.4 g/day (400 mg tablet; n = 154) or 4.8 g/day of Asacol (800 mg tablet; n = 147) for 6 weeks
Outcomes	Primary outcome: treatment success at week 6. Secondary efficacy end points included the proportion of participants who improved from baseline at week 3 and the percentage of participants whose clinical assessment scores (stool frequency, rectal bleeding, sigmoidoscopy scores, PFA scores and PGA scores) improved from baseline scores at weeks 3 and 6, improvement in QOL from baseline to weeks 3 and 6, and time to symptom relief (stool frequency, rectal bleeding or both) and adverse events. Overall improvement or treatment success was defined as either complete remission or a clinical response to therapy. Complete remission was defined as normal stool frequency, no rectal bleeding, a PFA score of 0 (generally healthy), normal endoscopy findings and a PGA score of 0 (quiescent disease activity). A clinical response to therapy was defined as a decrease in the PGA score of at least one point from baseline, plus improvement in at least one other clinical assessment parameter (stool frequency, rectal bleeding, PFA or endoscopy findings) and no worsening in any of the other clinical assessments
Notes	This study was supported by Procter & Gamble Pharmaceuticals Author conflicts of interest are reported in the manuscript

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Permutated block randomization scheme
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias)	Low risk	Double-blind, double-dummy: identical placebos were used. Both investigators and participants were blinded to treatment assignment

Hanauer 2007 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts balanced across intervention groups 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

Hetzel 1986

Study characteristics	
Methods	Random, double-blinded allocation of placebo or ADS. Participants were seen 1 week before trial, and weekly during treatment, and 6 weeks after completion of treatment
Participants	People with mild-to-moderate exacerbation of ulcerative proctitis or left-sided colitis (N = 30). None had evidence of a severe attack of colitis (i.e. no fever, tachycardia, hemoglobin < 10 g/l or ESR > 30 mm/h). Diagnosis confirmed by sigmoidoscopy, histology of rectal biopsies, radiological or colonoscopic appearance, and negative stool samples (for salmonella, shigella, campylobacter, *Clostridium difficile*). People known to be intolerant of SASP were included to determine whether their sensitivity extended to olsalazine sodium (ADS)
Interventions	Disodium azodisalicylate (ADS, olsalazine sodium; n = 15), 2 g/day (1 g twice a day; 4 gelatin capsules; n = 15), or matching placebo with meals for 6 weeks
Outcomes	Sigmoidoscopic appearances at weeks 0 and 6 were graded according to a 4-point scale (Grade 0- normal mucosa; grade 1- mild mucosal hyperemia; grade 2 -moderately-severe proctitis with granularity of mucosa; grade 3- severe proctitis with spontaneous bleeding and/or ulceration and/or pus). Rectal biopsies (also at weeks 0 and 6) were assessed by a single experienced observer. Comparisons between samples were classified as 'much improved', 'improved', 'unchanged' or 'worse'
Notes	This study was supported by Pharmacia (Australia) Conflicts of interest were not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random-number code
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind: matching placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts balanced across intervention groups with similar reasons for withdrawal

Hetzel 1986 *(Continued)*

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

Hiwatashi 2011

Study characteristics	
Methods	Multicenter, randomized, double-blind, parallel-group study
Participants	Patients (aged 15 to 64 years) with moderately-active ulcerative colitis (modified Mayo score 6 to 8 points) (N = 123)
Interventions	2.25 g/day mesalazine (3 round 250 mg tablets, 3 times a day; n = 63) or 4.0 g/day mesalazine (4 oval 500 mg tablets, 2 times a day; n = 60)
Outcomes	Primary outcome: Mean change in UC-DAI Secondary outcomes: Mean change in each UC-DAI variable (stool frequency, rectal bleeding, mucosal appearance, and physician's overall assessment of disease), clinical remission, clinical improvement and adverse events
Notes	Funding support and conflicts of interest were not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Biased-coin minimization algorithm
Allocation concealment (selection bias)	Low risk	Centralized randomization by independent CRO
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy: Study medication consisted of a round tablet containing 250 mg of mesalazine, an oval tablet containing 500 mg of mesalazine and placebo tablets identical in size and appearance to the study drugs
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 participants dropped out from the 2.25 g/day group and 1 participant dropped out from the 4.0 g/day group
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

Ito 2010

Study characteristics

Ito 2010 *(Continued)*

Methods	Multicenter, randomized, double-blind, double-dummy, placebo-controlled trial
Participants	Patients (aged ≥ 16 to < 65 years) with mild to moderately-active ulcerative colitis. Disease activity was assessed using the UC-DAI (Sutherland 1987). Patients with mild-to-moderate active ulcerative colitis who had a score of 3 to 8 on the UC-DAI with a bloody stool score of ≥ 1 were eligible for the study (N = 229)
Interventions	The objective of the study was to demonstrate the superiority of Asacol 3.6 g/day and non-inferiority of Asacol 2.4 g/day against pentasa 2.25 g/day. Participants were randomized to Asacol 3.6 g/day (n = 65), Asacol 2.4 g/day (n = 66), pentasa 2.25 g/day (n = 65) or placebo (n = 33) for 8 weeks
Outcomes	Participants were evaluated at baseline and week 8 or at early withdrawal Primary outcome: Reduction in UC-DAI score from baseline Secondary outcomes: Reduction in each UC-DAI item score, the proportion of participants achieving remission (a UC-DAI score of ≤ 2 and zero points for bloody stool score); the proportion of participants achieving efficacy (remission or participant who did not achieve remission but whose reduction of UC-DAI score is ≥ 2)
Notes	Study was supported by ZERIA Pharmaceutical Co., Ltd., Research and Development Division Author conflicts of interest are reported in the manuscript

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Biased-coin minimization algorithm
Allocation concealment (selection bias)	Low risk	Centralized randomization: A person independent from the study was in charge of the random allocation. The randomization code was sealed and stored until the blind was removed
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy: the appearance of the medication was identical
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts balanced across intervention groups with similar reasons for withdrawal
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	The study appears to be free of other sources of bias

Jiang 2004

Study characteristics	
Methods	Randomized, double-blind, double-dummy comparison of olsalazine and SASP
Participants	Male and female patients (average age 32.6 years) with acute relapse of ulcerative colitis (N = 42)

Jiang 2004 *(Continued)*

Interventions	Olsalazine 2 g/day (n = 21) or SASP 4 g/day (n = 21) for 8 weeks. Lopermide (1 to 2 pills/day) was given to participants unable to tolerate diarrhea but not for more than 10 days
Outcomes	Clinical and laboratory examinations were performed at entry and after 1, 2, 4, 6 and 8 weeks of treatment. Colonoscopy and biopsy were performed 3 days before treatment and within 3 days of completion Outcomes included induction of complete remission (subsidence of clinical symptoms with a relatively normal mucous membrane on colonoscopy), induction of clinical remission (0 to 2 stools a day with no gross blood or red cells in stool), colonoscopic remission (evaluated on a 2- or 5-point scale) and histological remission (evaluated on a 5-point scale)
Notes	Study was supported by Youth Research Foundation of the PublicHealthBureau of Shandong Province, No. 2001CA2EFB2 Conflicts of interest were not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Allocation of drugs was performed using a table of random numbers
Allocation concealment (selection bias)	Low risk	Participant
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The number of participants who completed the trial was not reported
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

Kamm 2007

Study characteristics

Methods	Multicenter, randomized, double-blind, double-dummy, placebo-controlled trial with an Asacol reference group
Participants	Adults (aged ≥ 18 years) with mild to moderately-active ulcerative colitis (N = 341). New or relapsing cases of ulcerative colitis were included in the study. Ulcerative colitis was defined by symptomatic, radiographic and endoscopic criteria. Disease activity was assessed using a modified UC-DAI (Sutherland 1987). People with mild-to-moderate active ulcerative colitis with a score of 4 to 10 on the UC-DAI and a sigmoidoscopy score ≥ 1 and a physician's global assessment score ≤ 2 with comparable histology were eligible for the study. To increase stringency, patients showing any mucosal friability were given a sigmoidoscopy score of at least 2. During the screening period patients were permitted to continue receiving a stable dose of mesalamine (≤ 2.0 g/day) if they were receiving this treatment prior to screening. This was withdrawn at baseline if the patient was found to be eligible for inclusion

Kamm 2007 *(Continued)*

Interventions	MMX mesalamine 2.4 g/day (n = 84) or 4.8 g/day (n = 85) given once daily, Asacol 2.4 g/day (n = 86) given in 3 divided doses, or placebo (n = 86)
Outcomes	Outcomes were evaluated at entry and week 8 or at early withdrawal. Primary outcome: the proportion of participants at week 8 in clinical and endoscopic remission (modified UC-DAI of ≤ 1 with rectal bleeding and stool frequency scores of 0, no mucosal friability, and a ≥ 1 point reduction in sigmoidoscopy score from baseline) Secondary outcomes: the proportion of participants achieving clinical remission (a score of zero points for stool frequency and rectal bleeding); clinical improvement (a decrease ≥ 3 points from baseline in modified UC-DAI), changes in modified UC-DAI score (baseline to week 8); changes in sigmoidoscopic appearance (baseline to week 8); and changes in rectal bleeding and stool frequency (from baseline to any study visit). Other secondary outcomes included an analysis of treatment failure rate, a comparison of time to withdrawal and adverse events
Notes	This study was supported by Shire Pharmaceuticals Inc. Author conflicts of interest are reported in the manuscript

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Centralized randomization: Participants were randomized centrally by an interactive voice response system
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts balanced across intervention groups with similar reasons for withdrawal
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	The study appears to be free of other sources of bias

Kruis 1998

Study characteristics

Methods	Multicenter, randomized, double-blind, double-dummy, parallel-group study
Participants	Adults (18 to 75 years) with a mild-to-moderate (endoscopic score < 4) attack of ulcerative colitis (N = 168)
Interventions	Olsalazine 3 g/day (n = 88) or mesalazine (claversal) 3 g/day (n = 80) for 12 weeks
Outcomes	Primary outcome: Endoscopic remission (defined as a score of 0 or 1 on the Rachmilewitz index)

Kruis 1998 *(Continued)*

	Secondary outcomes: Clinical remission (< 1 on modified Rachmilewitz index), physician's global assessment on 4-point scale
Notes	This study was supported by a grant from Pharmacia & Upjohn AB, Uppsala, Sweden Conflicts of interest were not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Centralized randomization
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy
Incomplete outcome data (attrition bias) All outcomes	Low risk	25% dropout rate, but dropouts balanced across intervention groups 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

Kruis 2003

Study characteristics

Methods	Multicenter, randomized, double-blind trial
Participants	Adults (aged 18 to 70 years) with mild-to-moderate (CAI 6 to 12; EI $\geq$ 4) attack of UC with at least 1 previous episode or persistently bloody diarrhea at least 14 days preceding entry (N = 316)
Interventions	Mesalamine (Salofalk pellets) 1.5 g/day (0.5 g 3 times daily; n = 103); 3.0 g/day (1.0 g 3 times daily; n = 107) or 4.5 g/day (1.5 g 3 times daily; n = 106) for 8 weeks
Outcomes	Primary outcome: Clinical remission (CAI $\leq$ 4) Secondary outcomes: Endoscopic remission (EI < 4); endoscopic improvement (reduction of EI by at least 1 point); clinical improvement (CAI decreased by at least 3 points), life quality index; physician's global assessment; and adverse events
Notes	This study was supported by Dr. Falk Pharma GmbH, Freiburg, Germany Conflicts of interest were not reported

Risk of bias

Bias	Authors' judgement	Support for judgement

Kruis 2003 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	The drug was dispensed by sachets containing mesalamine pellets or a mixture of mesalamine and placebo pellets. The pellets with active drug and placebo pellets were identical in outward appearance. To ensure blindness, the sachets of the 3 different dose groups contained the same number and volume of pellets. In the sachets with the highest dose all pellets consisted of the active drug
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropout rate in 1.5 g/day group was 32.0% (33/103) compared to 19.6% (21/107) in the 3.0 g/day group and 19.8% (21/106) in the 4.5 g/day group. The most frequent reason for premature termination was inefficiency of treatment (23%, 17%, and 13%, respectively). No other reasons for withdrawal were provided
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

Kruis 2009

Study characteristics	
Methods	Randomized, double-blind, double-dummy, parallel-group, multicenter, phase III non-inferiority study assessing the efficacy and safety of mesalazine (Salofalk granules) 3.0 g once-daily dosing versus 1 g 3 times daily dosing for the treatment of active ulcerative colitis
Participants	Adults (aged 18 to 75 years) with active ulcerative colitis (CAI ≥ 6 and EI ≥ 4; Rachmilewitz criteria) were recruited from 54 centers in 13 countries for an 8-week induction trial (N = 380)
Interventions	Mesalazine 3.0 g once daily (n = 191) or 1 g three times daily (n = 189) Adherence with study medication was checked by counting the medication returned at study visits
Outcomes	Primary outcome: Clinical remission at the end of the study (defined by CAI ≤ 4) Secondary outcomes: Clinical improvement (decrease in CAI by at least 1 point baseline), disease activity index (DAI) , EI, histological index (HI, based on Riley), time to first resolution of clinical symptoms, PGA and participant preference
Notes	This study was funded in full by Dr Falk Pharma, Freiburg, Germany Author conflicts of interest are reported in the manuscript

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated

Kruis 2009 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts balanced across intervention groups with similar reasons for withdrawal
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	The study appears to be free of other sources of bias

Levine 2002

Study characteristics	
Methods	Multicenter, randomized, double-blind, double-dummy, dose-response, parallel-group study
Participants	Adults (aged 18 to 80 years) with mild to moderately-active ulcerative colitis confirmed by flexible sigmoidoscopy (N = 154)
Interventions	Balsalazide 6.75 g/day (n = 35), Balsalazide 2.25 g/day (n = 35) or Asacol 2.4 g/day (n = 36) for 8 weeks
Outcomes	Primary outcome: Difference between treatment groups in rectal bleeding and in at least one other symptom. Improvement was defined as improvement in at least one category of the disease activity scale (i.e. normal, mild, moderate, severe) Secondary outcomes: Remission status (normal stool frequency and no blood in stool for 48 hours before visit, physician's global assessment score of quiescent and a sigmoidoscopy score of mild or normal), rectal biopsy score, and IBDQ score
Notes	For the purposes of this review we used only the comparison between Balsalazide 6.75 g and Asacol 2.4 g (i.e. equimolar doses) Funding support and conflicts of interest were not reported

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy: Placebos were identical in appearance to the Balsalazide capsules and mesalamine (Asacol) tablets

Levine 2002 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	31% dropout rate. Dropouts appear to be balanced across intervention groups. More participants withdrew from the low-dose Balsalazide and mesalamine groups due to lack of therapeutic effect than the high-dose Balsalazide group
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

Lichtenstein 2007

Study characteristics	
Methods	Multicenter, randomized, double-blind, double-dummy, placebo-controlled trial
Participants	People with newly-diagnosed or relapsing (relapsed ≤ 6 weeks prior to entry) mild to moderately-active ulcerative colitis (modified UC-DAI score of 4 - 10, with a sigmoidoscopy score ≥ 1 and a PGA score ≤ 2 with compatible histology) (N = 262)
Interventions	Participants were randomized to MMX mesalamine 4.8 g/day (n = 94) given once daily, 2.4 g twice daily (n = 93), or placebo (n = 93) for 8 weeks
Outcomes	Outcomes were evaluated at the screening visit (week –1) baseline (week 0), week 2, week 4 and week 8 or at early withdrawal Primary outcome: Clinical and endoscopic remission at week 8 (modified UC-DAI of ≤ 1 with rectal bleeding and stool frequency scores of 0, no mucosal friability, and a ≥ 1 point reduction in sigmoidoscopy score from baseline) Secondary outcomes: Clinical remission (a score of zero points for stool frequency and rectal bleeding); clinical improvement (a decrease ≥ 3 points from baseline in modified UC-DAI), changes in modified UC-DAI score (baseline to week 8); changes in sigmoidoscopic appearance (baseline to week 8); and changes in rectal bleeding and stool frequency (from baseline to any study visit). Other secondary outcomes included an analysis of treatment failure rate, a comparison of time to withdrawal and adverse events
Notes	This study was supported by Shire Pharmaceuticals Inc. Author conflicts of interest are reported in the manuscript

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Participants were randomized centrally by an interactive voice response system
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy. MMX mesalamine and placebo tablets were identical in appearance

Lichtenstein 2007 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts balanced across intervention groups with similar reasons for withdrawal. There were a higher number of withdrawals in the placebo group due to lack of efficacy
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

Maier 1985

Study characteristics	
Methods	Randomized controlled trial
Participants	People with active inflammatory bowel disease (ulcerative colitis n = 30, or Crohn's disease n = 30)
Interventions	Oral 5-ASA, 0.5 g 3 times daily (n = 15) or oral SASP, 1.0 g 3 times daily (n = 15) for 8 weeks
Outcomes	Remission and clinical improvement
Notes	Study also enrolled 30 participants with Crohn's disease Funding support and conflicts of interest were not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	Unclear risk	Not described
Other bias	Unclear risk	Not described

Mansfield 2002

Study characteristics

Mansfield 2002 *(Continued)*

Methods	Randomized, multicenter, double-blind, parallel-group study. Clinical and laboratory examinations were performed at recruitment, and weeks 2, 4 and 8
Participants	Adults with newly-diagnosed or recently-relapsed ulcerative colitis confirmed by sigmoidoscopy in conjunction with a negative stool culture (N = 50)
Interventions	Sulfasalazine, 3 g daily (n = 24), or Balsalazide, 6.75 g daily (n = 26) according to a double-dummy protocol for 8 weeks
Outcomes	Clinical and sigmoidoscopic remission. Remission was defined as a stool frequency ≤ 2 a day without blood and with a sigmoidoscopic appearance of normal rectal mucosa or minimal erythema
Notes	The study was initially sponsored by Biorex Laboratories Ltd Conflicts of interest were not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Centralized randomization
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy, identical gelatine capsules
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants were lost to follow-up. More participants were withdrawn from the SASP group due to adverse events than the Balsalazide group. Othe dropouts were balanced across intervention groups 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

Marakhouski 2005

Study characteristics

Methods	Multicenter, randomized, double-blind, double-dummy, parallel-group study
Participants	Adults (18 to 70 years) with mild to moderately-active ulcerative colitis (N = 233)
Interventions	Mesalazine pellets (Salofalk; n = 115) or mesalazine tablets (n = 118) at an initial dose of 1.5 g/day. In case of inadequate response the dose could be increased up to 3 g/day after the first follow-up visit at 2 weeks. Participants were treated for 8 weeks
Outcomes	Primary outcome: Complete response (clinical remission) defined as CAI ≤ 4 at individual study end

Marakhouski 2005 *(Continued)*

	Secondary outcomes: Time to first response; endoscopic remission (defined as EI < 4) and improvement; histological improvement; and PGA
Notes	This study was supported by a grant from Dr. Falk Pharma GmbH, Freiburg, Germany Conflicts of interest were not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy: placebos of identical appearance to 5-ASA tablets and pellets were used to ensure double-blind performance of the trial
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	13.5% dropout rate. Dropouts were balanced across groups. Reasons for dropping out were summarized across both groups
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

Miglioli 1990

Study characteristics

Methods	Multicenter, randomized, double-blind, double-dummy, parallel dose-response study
Participants	Adults (aged 18 to 65 years) with clinically mild active ulcerative colitis based on Truelove and Witts criteria (Truelove 1955) (N = 73)
Interventions	Mesalazine (Asacol 400 mg tablets) at daily doses of 1.2 g (n = 25), 2.4 g (n = 24) or 3.6 g (n = 24) for 4 weeks
Outcomes	Clinical remission or improvement, endoscopic and histological improvement. Clinical remission was defined as no more than 2 bowel movements a day with no visible blood in the stool in the symptomless participant. Clinical improvement defined as a clear decrease in severity of symptoms and signs not satisfying remission criteria
Notes	The study was supported by Giuliani SpA and Bracco, SpA, Italy Conflicts of interest were not reported

Risk of bias

Bias	Authors' judgement	Support for judgement

Miglioli 1990 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy: identical placebo tablets
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	11 participants did not complete the study (5 in 1.2 g/day group; 4 in 2.4 g/day group; and 2 in 3.6 g/day group because of worsening of disease in 5, lack of improvement in 4 and loss to follow-up and intercurrent disease in 1). It is not clear which reasons apply to each group
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

Mihas 1988

Study characteristics	
Methods	A prospective, controlled, double-blind trial
Participants	Adults (18 year or older) with exacerbated ulcerative colitis (N = 19)
Interventions	Oral 5-ASA 0.8 g 3 times a day (2.4g/day, n = 7) vs sulfasalazine 1g 3 times a day (3g/day, n = 12) for 4 weeks
Outcomes	Response to treatment was based on endoscopic appearance, subjective symptoms, objective criteria and laboratory findings
Notes	Abstract publication only - funding support and conflicts of interest were not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	A prospective double-blind trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/12 participants from sulfasalazine group were unable to complete the study because of adverse events

Mihas 1988 *(Continued)*

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

Munakata 1995

Study characteristics		
Methods	Multicenter, double-blind, double-dummy comparison of SASP and mesalazine	
Participants	Patients, 16 years and older, with mild to moderately-active ulcerative colitis were enrolled from July 1992 to March 1994 (N = 109)	
Interventions	Controlled-release mesalazine, 1.5 g/day plus SASP-matched placebo (n = 52) or active SASP, 3 g/day, with mesalazine-matched placebo (n = 57), for 4 weeks	
Outcomes	Clinical and endoscopic assessment was performed at entry, and after 2 and 4 weeks Improvement was assessed as changes in clinical status based on disease activity and severity of symptoms, compared to baseline findings Improvement was also measured by endoscopic findings	
Notes	Funding support and conflicts of interest were not reported	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Centralized randomization Randomization was under the direction of a central controller
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	9 participants dropped out of the study
Selective reporting (reporting bias)	Unclear risk	Not described
Other bias	Low risk	The study appears to be free of other sources of bias

Pontes 2014

Study characteristics

Pontes 2014 *(Continued)*

Methods	Randomized, double-blind, placebo- and active-controlled proof-of-concept study
Participants	Adults (18 to 65 years) with mild-to-moderate active ulcerative colitis (Total Mayo score (TMS) ≥5 and ≤10,) confirmed by endoscopy (N = 34)
Interventions	Dersalazine 3 x 400 mg twice a day (2.4 g/day, n = 13), mesalazine 3 x 400 mg twice a day (2.4 g/day, n = 8), or placebo (n = 13) for 4 weeks
Outcomes	Primary safety outcome: Proportion of participants with AEs of severe intensity or treatment withdrawal Secondary safety outcomes: proportion of participants with AEs, AEs with suspected relationship to study medication, and with clinically relevant abnormalities in laboratory tests or physical examination Secondary efficacy outcomes: Change in TMS from baseline to week 4, change in partial Mayo score (PMS) from baseline to weeks 2 and 4, complete remission, clinical remission, TMS clinical response and mucosal healing rates by week 4, and PMS clinical response by weeks 2 and 4
Notes	Study was supported by Palau Pharma S.A. Author conflicts of interest are reported in the manuscript

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization list in blocks of 4 with a ratio of 2:1:1 (dersalazine sodium:mesalazine:placebo)
Allocation concealment (selection bias)	Low risk	Centrally randomized
Blinding (performance bias and detection bias) All outcomes	Low risk	The treatments had indistinguishable appearance and were uniquely identified with a randomization number according to a computer-generated randomization list
Incomplete outcome data (attrition bias) All outcomes	Low risk	5 participants did not complete the 4-week treatment (3 from placebo group, and 2 from dersalazine group)
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	They study appears to be free of other sources of bias

Pruitt 2002

Study characteristics

Methods	Multicenter, randomized, double-blind, double-dummy, parallel-group study
Participants	People (aged 12 to 80 years) with mild to moderately-active ulcerative colitis confirmed by flexible sigmoidoscopy (N = 173)
Interventions	Balsalazide 6.75 g/day (n = 84) or Asacol 2.4 g/day (n = 89) for 8 weeks

Pruitt 2002 *(Continued)*

Outcomes	Primary outcome: Proportion of participants in symptomatic remission (based on diary card) at the end of week 8 or at early completion of treatment. Symptomatic remission was defined as PFA rating of normal or mild and absence of rectal bleeding Secondary outcomes: Time to symptomatic remission, proportion of participants in complete remission (symptomatic remission plus sigmoidoscopic evaluation score of normal or mild), improvement in sigmoidoscopic evaluation score, change from baseline in PGA of disease activity at week 8 or early completion and adverse events
Notes	Funding support and conflicts of interest were not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy: each study drug treatment was administered 3 times daily as 3 capsules (Balsalazide active drug or placebo) and 2 tablets (Asacol active drug or placebo) to maintain blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts balanced across intervention groups 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

Qian 2004

Study characteristics

Methods	Randomized, double-blind, double-dummy, parallel-group study
Participants	Adults (aged 18 to 70 years) with active ulcerative colitis (N = 56)
Interventions	Olsalazine (250 mg capsules: 4 capsules twice daily; n = 31) or SASP (250 mg tabletss, 4 tablets 4 times daily; n = 25) for 8 weeks
Outcomes	Clinical improvement and adverse events
Notes	Funding support and conflicts of interest were not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-stratified randomization

Qian 2004 *(Continued)*

Allocation concealment (selection bias)	Low risk	Pharmaceuticals were packed and encoded according to random numbers. The encoding process was monitored by the staff from Shanghai Pharmaceutical Affairs Bureau
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 participants from SASP group were unable to complete the study
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	The study appears to be free of other sources of bias

Rachmilewitz 1989

Study characteristics	
Methods	Randomized, double-blind parallel-group comparison of mesalazine versus SASP. Drugs were centrally packaged and labelled. Entry assessment involved physical exam, history, colonoscopy, and lab tests. In addition to participant diaries, assessments, including lab test, urine analysis, blood counts and liver/kidney function tests, were performed at bi-weekly follow-ups. Mandatory repeat colonoscopy was performed after week 8
Participants	Outpatients, aged 18 to 70 years, at 46 centres in 7 countries, with active mild-to-moderate ulcerative colitis (N = 220)
Interventions	Coated mesalazine (Mesasal), 1.5 g/day (n = 115), or SASP 3 g/day (n = 105) for 8 weeks in a double-dummy manner. Compliance was monitored by pill counts
Outcomes	Clinical/endoscopic remission was defined as a clinical/endoscopic activity index score $\leq$ 4. Improvement was also assessed as changes in frequency and consistency of stools, and blood in stools The incidence of adverse effects was also tabulated
Notes	Funding support and conflicts of interest were not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated Participants were randomised in groups of 4 according to a predetermined list generated by a computer
Allocation concealment (selection bias)	Low risk	Centralized randomization
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy

Rachmilewitz 1989 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts balanced across intervention groups 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

Raedler 2004

Study characteristics	
Methods	Phase 2, multicenter, randomized, double-blind, double-dummy, parallel-group study
Participants	Adults (18 to 75 years) with recurrent mild to moderately-active ulcerative colitis (N = 362)
Interventions	3 g/day mesalazine in sachets of micropellets (1.5 g sachet taken twice daily with liquid, n = 181) or tablets (Claversal 500 mg; 2 tablets taken 3 times daily, n = 181) for 8 weeks Adherence assessed by tablet and sachet counts
Outcomes	Primary outcome: Clinical remission (sum of CAI components 1 to 4 based on Rachmilewitz was CAI $\leq$ 2) within 8 weeks of treatment Secondary outcomes: Complete clinical remission (sum of CAI components 1 to 7 was < 4), endoscopic remission (EI based on Rachmilewitz was $\leq$ 2)
Notes	This study was funded by a grant from Merckle Conflicts of interest were not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy: active drug and the matching placebo were identical in appearance, form, smell and taste. Medication labels were identical for both treatments
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts balanced across intervention groups 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

Rao 1989

Study characteristics	
Methods	Randomized, double-blind, double-dummy, multicenter comparison of Olsalazine and SASP. At entry and at 4 weeks, participants were assessed clinically, by sigmoidoscopy, rectal biopsy, blood tests, stool samples and urine analysis. Participants also kept stool diary records
Participants	Outpatients with a first attack of mild to moderately-severe ulcerative colitis, confirmed by sigmoidoscopic and histologic evidence and negative stool cultures (N = 37)
Interventions	Olsalazine, 2 g/day (n = 20), or enteric-coated SASP, 3 g/day (n = 17), provided in sealed blister packs, administered 4 times a day. Full dosage was reached after 7 days and continued for 4 weeks. Double-dummy technique required each participant to take a physically indistinguishable dummy containing mainly potato starch. Compliance was confirmed by pill counts
Outcomes	Changes in daily stool frequency and consistency, sigmoidoscopic and histological appearance, and clinical assessments were defined as 'improved' (an increase by at least 1 point), 'unchanged' or 'worsened'. Remission was defined as the lack of blood in stool, no more than 2 bowel movements a day, and no systemic disturbance. Overall improvement was defined as a positive change in at least 2 of the above criteria
Notes	Pharmacia Limited supplied the double dummy packs containing olsalazine capsules and sulphasalazine tablets Funding support and conflicts of interest were not reported

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy. Participants received Olsalazine or sulphasalazine along with physically-indistinguishable dummies. The drugs were provided in sealed blister packs
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	3 participants in the Olsalazine group did not complete the study, compared with 4 participants in the SASP group. Reasons for withdrawal were not given
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

Rijk 1991

Study characteristics

Rijk 1991 *(Continued)*

Methods	Prospective, double-blinded, multicenter trial comparing Olsalazine and Sulfasalazine. Participants were centrally randomized
Participants	People with active ulcerative colitis (N = 55)
Interventions	6 g/day SASP (n = 28) or 3 g/day Olsalazine (n = 27) in externally-indistinguishable capsules, for 6 weeks
Outcomes	Remission was assessed on the basis of clinical and endoscopic criteria. Withdrawals and occurrence of adverse events were also measured
Notes	Abstract - funding support and conflicts of interest were not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Centralized randomization
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind: externally-indistinguishable capsules
Incomplete outcome data (attrition bias) All outcomes	Low risk	6 participants from each group were withdrawn because of adverse events or increasing severity of disease
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

Riley 1988

Study characteristics

Methods	Randomized, double-blind, double-dummy comparison of mesalamine and SASP. History, physical, blood counts, urine samples, sigmoidoscopy and biopsy were performed upon entry
Participants	Adult outpatients with mild-to-moderate ulcerative colitis relapse or first attack, recruited from 3 hospitals in close geographical proximity. All were passing blood at least once a day and all had hemorrhagic rectal mucosa (N = 60)
Interventions	SASP 2 g/day (n = 20), delayed-release mesalazine (Asacol), 800 mg/day (n = 20), or Asacol 2.4 g/day (n = 21). Each participant received 3 sets of tablets (2 placebo and 1 active) in a double-dummy method
Outcomes	In addition to daily diaries, participants were assessed at 2 and 4 weeks and any other time they wished. At 4 weeks, clinical assessment, biopsy and sigmoidoscopy were repeated Stool frequency, rectal bleeding, sigmoidoscopic, and histologic measures were used for comparison of groups. Withdrawals and adverse events were also measured
Notes	Financial support for this study was provided by Tillotts Laboratories, UK

Riley 1988 *(Continued)*

	Conflicts of interest were not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Centralized randomization Medications were centrally prepackaged and randomly distributed to each centre
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant dropped out of the SASP group
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

Robinson 1994

Study characteristics

Methods	Double-blind, randomized, single-center trial.
Participants	People with acute attacks of mild-to-moderate ulcerative colitis. No concomitant medications for UC were allowed (N = 98)
Interventions	Olsalazine, 3 g/day, or placebo for 28 days
Outcomes	Participant evaluations were performed at days 14 and 28 for clinical and laboratory parameters Efficacy was based on evaluations of diarrhea, rectal bleeding, mucorrhea, sigmoidoscopic score, nausea, abdominal tenderness, stool consistency, and global disease severity rating compared to baseline status
Notes	Abstract - funding support and conflicts of interest were not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described

Robinson 1994 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
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 2009

Study characteristics	
Methods	Multicenter, randomized, double-blind, double-dummy, active-controlled trial (ASCEND III)
Participants	Adults (aged 18 to 75 years) with moderately-active ulcerative colitis that extended proximally beyond 15 cm from the anal verge, as confirmed by flexible sigmoidoscopy or colonoscopy (N = 772)
Interventions	Asacol 2.4 g/day (400 mg tablet; n = 383) or 4.8 g/day of mesalamine (Asacol 800 mg tablet; n = 389) for 6 weeks
Outcomes	Primary outcome: treatment success (overall improvement) at week 6, defined as improvement in the PGA (based on clinical assessments of rectal bleeding, stool frequency, and sigmoidoscopy), with no worsening in any individual clinical assessment Secondary outcomes: clinical remission at weeks 3 and 6; improvement in stool frequency, rectal bleeding, and PFA assessments at weeks 3 and 6; improvement in the sigmoidoscopy with CFT, PGA, and UC-DAI assessments at week 6; and treatment success in participants with left-sided disease at week 6
Notes	This study was supported by Procter & Gamble Pharmaceuticals Author conflicts of interest are reported in the manuscript

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The investigator or designated representative telephoned the Interactive Voice Response System for patient randomization and allocation of study medication once the patient was determined to be eligible for the study
Allocation concealment (selection bias)	Low risk	Interactive Telephone Voice Response System
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy, identical placebos

Sandborn 2009 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts balanced across intervention groups 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 2012

Study characteristics	
Methods	Phase 3, multicenter, randomized, double-blind, double dummy, placebo-controlled trial
Participants	Adults (18 to 75 years of age) with active, mild-to-moderate ulcerative colitis for at least 6 months, with UC-DAI score of 4 - 10 points (N = 489)
Interventions	Budesonide MMX 9 mg/day (n = 123), budesonide MMX 6 mg/day (n = 121), mesalamine (Asacol 2.4 g/day, as reference, n = 124), or placebo (n = 121) for 8 weeks
Outcomes	Primary outcome: Combined clinical and endoscopic remission at week 8. Remission was defined as combined clinical and endoscopic remission with a UC-DAI score ≤ 1 point, with subscores of 0 for both rectal bleeding and stool frequency, no mucosal friability on colonoscopy, and a ≥ 1-point reduction from baseline in the endoscopic index score Secondary outcomes: Clinical improvement (≥ 3-point reduction in UC-DAI), endoscopic improvement (≥ 1-point reduction in the UC-DAI mucosal appearance subscore), symptom resolution (score of 0 for both rectal bleeding and stool frequency subscores from the UC-DAI), histologic healing (histologic score of ≤ 1 (corresponding to a histologic activity grade of 0) according to the Saverymuttu scale, and adverse events
Notes	This study was supported by Santarus, Inc, and Cosmo Pharmaceuticals SpA Author conflicts of interest are reported in the manuscript

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization for this study was developed by an external contractor and administered centrally
Allocation concealment (selection bias)	Low risk	The interactive voice response system was used to centrally randomize participants to study drug
Blinding (performance bias and detection bias) All outcomes	Low risk	A double-dummy procedure was used to maintain blinding, with participants in each treatment group receiving their blinded study drug 3 times daily
Incomplete outcome data (attrition bias) All outcomes	Low risk	140 participants were unable to complete the study (34 from budesonide 9 mg daily, 32 from budesonide 6 mg daily, 29 from Asacol 2.4 g/day, and 45 from placebo group)
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported in the published study

Sandborn 2012 *(Continued)*

Other bias	Low risk	The study appears to be free of other sources of bias

Scherl 2009

Study characteristics	
Methods	Multicenter, randomized, double-blind, placebo-controlled trial
Participants	Acute are of mild-to-moderate active UC; baseline Modified Mayo Disease Activity Index (MMDAI) score between 6 and 10 (Table 1), inclusive (e.g., mild to moderately-active UC) with an individual subscale score = 2 for rectal bleeding and mucosal appearance; disease extending at least 20 cm from the rectum on screening endoscopy /sigmoidoscopy; had not taken = 6.75 g / day of Balsalazide, or greater than 2.4 g / day of mesalamine or equivalent daily dose of any other 5-ASA product during the 14 days before the initiation of study medication (n = 250) Participants assessment included MMDAI (deletion of friability from endoscopy score equal to 1), and physical exam, laboratory tests and participant diary cards
Interventions	Balsalazide 3.3 g/day (n = 167) or matching placebo (n = 83)
Outcomes	Participants were assessed at screening visit, baseline, day 7, day 14, day 28 and day 56 and follow-up Primary outcome: Clinical improvement (≥ 3-point improvement in MMDAI) and improvement in the rectal bleeding (≥ 1 point improvement) at week 8 or end of treatment. Clinical improvement was defined as a ≥ 3 point improvement from baseline in the total MMDAI score and a ≥ 1 point improvement from baseline in the rectal bleeding subscale of the MMDAI Secondary outcomes: Clinical remission, defined as a score of 0 for rectal bleeding and a combined score of ≤ 2 for bowel frequency and physician's assessment using the MMDAI subscales, at week 8 or end of treatment; proportion of participants who experienced mucosal healing, defined as an endoscopy or sigmoidoscopy score of 0 or 1 at week 8 or end of treatment; proportion of participants with improvement (≥ 1 point improvement) from baseline to week 8 or end of treatment in the MMDAI subscale of mucosal appearance, bowel frequency, rectal bleeding, and physician's assessment; proportion of participants achieving complete remission, defined as a MMDAI score of ≤ 1, at week 8 or end of treatment; and mean change from baseline to week 8 or end of treatment for the MMDAI score
Notes	The study was funded by Salix Pharmaceuticals Author conflicts of interest are reported in the manuscript

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Centralized, automated, validated interactive voice response system
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind: All tablets were identical in appearance. Both the investigator and participant were blinded to assigned treatment throughout the study
Incomplete outcome data (attrition bias)	Low risk	3 participants lost to follow-up

Scherl 2009 *(Continued)*
All outcomes

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

Schroeder 1987

Study characteristics	
Methods	Placebo-controlled, double-blinded, and randomized
Participants	People, age 15 to 70 years, with mild-to-moderate ulcerative colitis seen at the Mayo Clinic (Rochester, Minn.) from 01 September 1984 to 28 February 1986 (N = 87). UC was defined by symptomatic, radiographic, endoscopic criteria. Colonic involvement was determined by flexible proctosigmoidoscopy with double-contrast x-ray films of colon or complete colonoscopy, or both. Newly- or previously-diagnosed cases were included. Participants receiving corticosteroids or SASP were required to stop such therapy at least 1 week prior to start of study. Pre-entry evaluations included history, physical, blood count, chemistry screening, urinalysis, stool sample (had to be negative for ova, parasites, enteric pathogens) Participant population was stratified into 4 strata: 1- previous treatment, left-sided disease; 2- previous treatment, universal disease; 3- no previous treatment, left-sided disease; 4- no previous treatment, universal disease
Interventions	Asacol tablets (400 mg of 5-ASA, coated with pH-sensitive polymer Eudragit-S which dissolves at pH 7 or higher) or matching placebo (500 mg microcellulose with identical pH-sensitive coating, n = 38) 4.8 g/day (n = 38) or 1.6 g/day (latter dose only used in stratum 1, n = 11), 12 tablets daily for 6 weeks. No pill count, but participants were asked about compliance
Outcomes	Evaluation occurred at 3 weeks and 6 weeks Clinical response, described as 'complete', 'partial', or 'no response', was determined on the basis of stool frequency, amount of rectal bleeding, and PGA (which included sigmoidoscopic appearance) on 4-point scales, compared to baseline data. 'Complete response' indicated resolution of all symptoms. Occurences of adverse reactions was also tabulated
Notes	Early termination of treatment for any reason was deemed to constitute treatment failure This study was supported by Tillotts Laboratories, UK Conflicts of interest were not reported

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization sequence was developed by the Section of Medical Research Statistics, Rochester Methodist Hospital
Allocation concealment (selection bias)	Low risk	Centralized randomization according to a sequence used by the dispensing pharmacist
Blinding (performance bias and detection bias)	Low risk	Double-blind: matching placebo

Schroeder 1987 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More placebo participants (n = 16) did not complete the study than 5-ASA participants (n = 5). Placebo participants were more likely to drop out due to flare of UC or no improvement
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

Sninsky 1991

Study characteristics

Methods	Multicenter, double-blind, placebo-controlled, computer-randomized trial involving 5 university-based medical centers, 1 IBD center, and 3 private-practice sites.
Participants	Adults, ages 18 to 75 years, with mildly- to moderately-active ulcerative colitis were enrolled from November 1988 to June 1989 (N = 158). Diagnosis by symptomatic, radiographic, and endoscopic criteria had to have been confirmed by colonoscopy, proctosigmoidoscopy or barium enema within 24 months of start of study. Cases of both newly- and previously-diagnosed disease showing continued active signs, despite SASP therapy were included. Steroid therapy had to be stopped at least 1 month before start of study; SASP and topical rectal therapies were discontinued at least 1 week before start. Concomitant use of corticosteroids, aspirin, NSAIDs, metronidazole, 6-mercaptopurine, azathioprine, cyclosporine, or other investigational drugs was not permitted Participants were not stratified according to clinical characteristics. Initial participant evaluation and follow-up exams consisted of lab tests, flexible proctosigmoidoscopy and radiographic films or colonoscopy at entry, followed by sigmoidoscopy at 3 and 6 weeks
Interventions	1.6 g/day (n = 53) or 2.4 g/day (n = 53) oral mesalamine (Asacol) in 400 mg tablets coated with pH-sensitive polymer (Eudragit-S) or matching placebo tablets (n = 52) containing microcellulose. Compliance was checked by pill count at each visit and by review of participant diaries
Outcomes	Clinical grading was based on stool frequency, rectal bleeding, sigmoidoscopic findings, and PFA, each on 4-point scale, which together gave the PGA, also on a 4-point scale. The change in this clinical grade was indicated by classifying each participant as being 'in remission', 'improved', 'maintained', or 'worsened'. Withdrawals and adverse events were also reported
Notes	This study was supported by a clinical grant from Norwich Eaton Pharmaceuticals Inc., Norwich, New York Conflicts of interest were not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Unclear risk	Not described

Sninsky 1991 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind: matching placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts balanced across intervention groups 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

Sutherland 1990

Study characteristics	
Methods	Double-blind, placebo-controlled, multicenter, parallel trial with random allocation of placebo or drug
Participants	Patients were initially screened with a baseline history, physical exam, and flexible sigmoidoscopy or colonoscopy in order to calculate the activity index Men and non-pregnant women, at least 18 years of age, with ulcerative colitis of variable extent, from 5 American and 2 Canadian centers and all enrolled between July 1985 and September 1986 (n = 136). Ulceration had to extend at least 20 cm proximal to the anus. Participants had to have a minimum score of 4 measured by DAI (4 subgroups for each of bowel frequency, presence of blood, sigmoidoscopic appearance, and physician's assessment of severity for a maximum score of 12)
Interventions	Random allocation of Rowasa (250 mg tablets) taken as 4 tablets, 4 times a day, for a total of either 4 g/day (n = 47) or 2 g/day (n = 45), and an identical-appearing placebo (n = 44) for 6 weeks. Compliance was measured by pill counts
Outcomes	Follow-up was assessed by telephone contact at end of week 1, 2, 4 and 5 and by clinical exam at the ends of weeks 3 and 6. Each clinic visit included flexible sigmoidoscopy and a PGA Efficacy was assessed by changes in the DAI and PGA. The change in PGA was described as 'much or somewhat improved', 'unchanged', or 'somewhat worse or much worse'. The change in the DAI score was evaluated by end-of-study score minus 'baseline'
Notes	Funding support and conflicts of interest were not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	All assignments to treatment and subsequent assessments of response to treatment were under double-blind conditions
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind: identical placebo
Incomplete outcome data (attrition bias)	Unclear risk	34% dropout rate, but dropouts appear to be balanced across intervention groups with similar reasons for withdrawal

Sutherland 1990 *(Continued)*

All outcomes		
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

Tursi 2004

Study characteristics	
Methods	Multicenter, randomized trial
Participants	Adults (19 to 69 years) with mild-to-moderate active ulcerative colitis confirmed by endoscopic evaluation (N = 90)
Interventions	Balsalazide 4.5 g/day (n = 30) or Balsalazide 2.25 g/day + VSL#3 (n = 30) or Asacol 2.4 g/day (n = 30) for 8 weeks
Outcomes	Primary outcome: Symptomatic remission based on clinical evaluation and diary card at 2, 4 and 8 weeks. Symptomatic remission was defined as PFA ratings of normal bowel movements and absence of rectal bleeding Secondary outcomes: Time to symptomatic remission, the proportion of participants achieving improvement in endoscopic evaluation score at 8 weeks, change in CAI from baseline at 8 weeks, improvement in histology at 8 weeks, and adverse events
Notes	For the purposes of this review we used only the comparison between Balsalazide 4.5 g/day and Asacol 2.4 g/day (n = 60) This study was supported by departmental sources Conflicts of interest were not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label. Physicians and participants were not blinded. Histological specimens were examined and graded for inflammation by 1 histopathologist blind to the treatment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	4 participants withdrew from the Balsalazide group (13%) compared to 8 from the Asacol group (26%). Reasons for withdrawal are similar, except that 2 participants from the Asacol group withdrew for adverse events
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

Willoughby 1988

Study characteristics	
Methods	Randomized, double-dummy, multicenter comparison of SASP and Olsalazine
Participants	Out-patients with mild to moderately-active ulcerative colitis, either first attack or relapse (N = 56)
Interventions	Oral sulphasalazine, 3 g/day (n = 30), or oral olsalazine, 3 g/day (n = 26), each in divided doses. Dose escalation schedule was used for first week of treatment after which full-dose therapy continued for further 4 weeks. Tablets were counted to monitor compliance
Outcomes	As well as diary cards, participants were clinically assessed upon entry, after 2 weeks, and after 5 weeks. Biopsy, sigmoidoscopy, and lab tests were performed at entry and after week 5 Clinical response was evaluated as changes in stool frequency and loss of blood and mucus from stools. Sigmoidoscopic and histological assessments were considered to have improved if score on a standard scale increased by at least 1 point (Dick 1964). Withdrawals and adverse effects were also tabulated
Notes	Prarmacia UK Ltd. supplied the active and placebo drugs used in this study Funding support and conflicts of interest were not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomization was not described Randomization was restricted in blocks of four to ensure approximately equal numbers of patients allocated to each form of treatment
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts appear to be balanced across intervention groups 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

Zinberg 1990

Study characteristics	
Methods	Double-blind, placebo-controlled trial
Participants	Men and women, 18 to 75 years of age, with mild-to-moderate ulcerative colitis - visible blood in the stool and disease involvement of 15 cm or more above the anal verge as defined by flexible sigmoi-

Zinberg 1990 *(Continued)*

	doscopy or colonoscopy (N = 15). The exacerbation could be a first instance or relapse of established disease. At least 3 days prior to participation, SASP, antidiarrheal agents, antispasmodics, and anticholinergics were discontinued. Oral or rectal steroids were not permitted within 1 week of study entry and other immunosuppressants were not permitted within 1 month of study. Concomitant medications not permitted during the study included NSAIDs, salicylates, digitalis derivatives, tranquilizers, and anti-depressants At initial patient interview, history and physical exam were performed including baseline laboratory studies. Urine analysis for enteric pathogens was also performed
Interventions	Olsalazine (Pharmacia) in opaque gelatin capsules, each of 250 mg (n = 7) or indistinguishable placebo capsules (n = 8) in identical containers, 12 capsules/day (3 with each meal and 3 at bedtime) for 28 days Compliance was assessed by interview as well as by pill count
Outcomes	Evaluations were performed at the end of the 2nd and 4th weeks. Endoscopic evaluation was performed at entry and after 4 weeks Clinical evaluation included participant recordings of number of daily bowel movements, stool consistency, presence of blood and mucus, urgency, and incontinence. Endoscopic evaluation assessed the severity of ulceration, friability, erythema, and exudate, each on a 3-point scale. The sum of these 3 scores gave a total endoscopic score. Improvement was assessed in terms of the changes in both clinical and endoscopic evaluations
Notes	Funding support and conflicts of interest were not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Centralized randomization Randomization was on an alternate basis between drug and placebo and allocated by pharmaceutical manufacturer
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind: physically-indistinguishable placebo capsules were provided in identical containers
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts balanced across intervention groups 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

AE: adverse event; CAI: clinical activity index; CFT: contact friability test; EI: endoscopy index; ESR: erythrocyte sedimentation rate; IBD: inflammatory bowel disease; LOCF: last observation carried forward; MMDAI: modified Mayo disease activity index; PFA: patient functional assessment; PGA: physician global assessment; QOL: quality of life; SASP: sulfasalazine; UCCS: ulcerative colitis clinical score; UC-DAI: ulcerative colitis disease activity index;

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

Study	Reason for exclusion
Adrizzone 2006	Ineligible comparator group (AZA)
Ahluwalia 1992	Not a randomized control trial
Behrens 2013	No control group
Dignass 2018	No control group (both groups received 1000 mg mesalamine a day)
Fiorino 2019	The study drug was not pure 5-ASA, but also contained sodium hyaluronate
Gross 2011	Ineligible comparator group (Budesonide)
Irvine 2008	Not a randomized control trial
Kamm 2009	Not a randomized control trial
Levine 2017	Not an oral 5-ASA formulation
Mahmood 2005	Not an oral 5-ASA formulation
Paoluzi 2002	No control group
Park 2018	Maintenance study
Pruitt 1991	Not a randomized control trial
Rubin 2017	Compares once-daily budesonide to placebo in people who are refractory to 5-ASA treatment
Safdi 1997	Not an oral 5-ASA formulation
Suzuki 2017	Not an induction trial
Turner 2017	A pediatric study
Vecchi 2001	Not an oral 5-ASA formulation
Vernia 2000	No control group
Ye 2018	No control group (both groups received same oral regimen)
Yoshimura 2018	No control group

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

NCT02522767

Study name	A randomized, double-blind, placebo-controlled, multicenter study investigating the efficacy and safety of mesalamine 4 g extended release granules (sachet) for the induction of clinical and endoscopic remission in active, mild to moderate ulcerative Colitis
Methods	Participants were randomized to 1 of 2 groups: 1. Mesalamine (4g extended release granules) 2. Placebo comparator

NCT02522767 *(Continued)*

Participants	Inclusion criteria: 1. Men or women aged 18 to 75 years 2. Mild to moderate ulcerative colitis Exclusion criteria: 1. Disease limited to proctitis < 15 cm 2. Short bowel syndrome 3. Prior colon resection surgery 4. History of severe/fulminant ulcerative colitis 5. Evidence of other forms of inflammatory bowel disease 6. Infectious disease (including human immunodeficiency virus [HIV], hepatitis B virus [HBV], or hepatitis C virus [HCV]) 7. Intolerant or allergic to aspirin or salicylate derivatives 8. Use of rectal formulations (5-aminosalicylic acid [5-ASA], steroids) within ≤ 7 days 9. Women who are pregnant or nursing 10. History or known malignancy 11. History of bleeding disorders, active gastric or active duodenal ulcers, autoimmune diseases, or mental/emotional disorders, that would interfere with their participation in the trial
Interventions	4g extended release granules of Mesalamine and placebo
Outcomes	Primary outcomes: 1. Proportion of participants with remission (time frame: at week 8); defined by the Clinical and Endoscopic Response Score based on a modified 9-point Mayo score Secondary outcomes: 1. Proportion of participants with remission in the primary endpoint and the Physician's Global Assessment (PGA) (time frame: at week 8) 2. Time to cessation of rectal bleeding (time frame: up to week 8) 3. Severity of adverse events (time frame: up to week 16) 4. Incidence of adverse events (time frame: up to week 16)
Starting date	October 2015
Contact information	Clinical Development Support: DK0-Disclosure@ferring.com
Notes	This study is currently recruiting participants The estimated completion date is 28 February 2018

DATA AND ANALYSES

Comparison 1. 5-ASA versus placebo

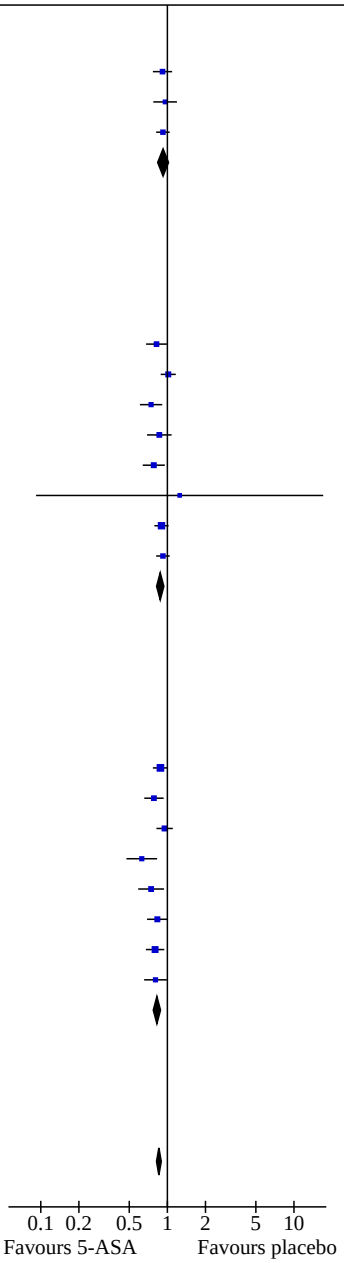
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Failure to induce global/clinical remission	11	2387	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.82, 0.89]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1.1 Dose of 5-ASA: < 2 g	3	231	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.84, 1.02]
1.1.2 Dose of 5-ASA: 2 - 2.9 g	8	956	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.82, 0.94]
1.1.3 Dose of 5-ASA: ≥ 3 g	8	1200	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.77, 0.88]
1.2 Failure to induce global/clinical improvement (including remission)	14	2256	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.61, 0.75]
1.2.1 Dose of 5-ASA: < 2 g	3	231	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.64, 0.97]
1.2.2 Dose of 5-ASA: 2 - 2.9 g	10	877	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.67, 0.88]
1.2.3 Dose of 5-ASA: ≥ 3 g	9	1148	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.51, 0.65]
1.3 Failure to induce endoscopic remission	4	1154	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.67, 0.89]
1.3.1 Dose of 5-ASA: < 2 g	1	122	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.64, 1.14]
1.3.2 Dose of 5-ASA: 2 - 2.9 g	3	393	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.70, 1.05]
1.3.3 Dose of 5-ASA: ≥ 3 g	4	639	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.56, 0.87]
1.4 Failure to induce endoscopic improvement (including remission)	4	416	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.59, 0.86]
1.4.1 Dose of 5-ASA: 2 - 2.9 g	3	265	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.58, 0.92]
1.4.2 Dose of 5-ASA: ≥ 3 g	2	151	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.49, 0.96]
1.5 Adverse events	8	1218	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.85, 1.07]
1.5.1 Dose of 5-ASA: < 2 g	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.74, 2.13]
1.5.2 Dose of 5-ASA: 2 - 2.9 g	5	377	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.82, 1.33]
1.5.3 Dose of 5-ASA: ≥ 3 g	5	811	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.80, 1.05]
1.6 Serious adverse events	4	746	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.18, 1.56]
1.6.1 Dose of 5-ASA: 2 - 2.9 g	3	243	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.14, 3.33]
1.6.2 Dose of 5-ASA: ≥ 3 g	3	503	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.10, 1.92]
1.7 Withdrawals due to adverse events	13	2372	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.54, 0.97]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.7.1 Dose of 5-ASA: < 2 g	3	231	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.19, 1.63]
1.7.2 Dose of 5-ASA: 2 - 2.9 g	9	926	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.65, 1.94]
1.7.3 Dose of 5-ASA: ≥ 3 g	9	1215	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.41, 0.87]
1.8 Exclusions and withdrawals after study entry	15	2529	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.51, 0.72]
1.8.1 Dose of 5-ASA: < 2 g	3	231	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.42, 0.98]
1.8.2 Dose of 5-ASA: 2 - 2.9 g	11	1014	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.53, 0.92]
1.8.3 Dose of 5-ASA: ≥ 3 g	10	1284	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.41, 0.66]

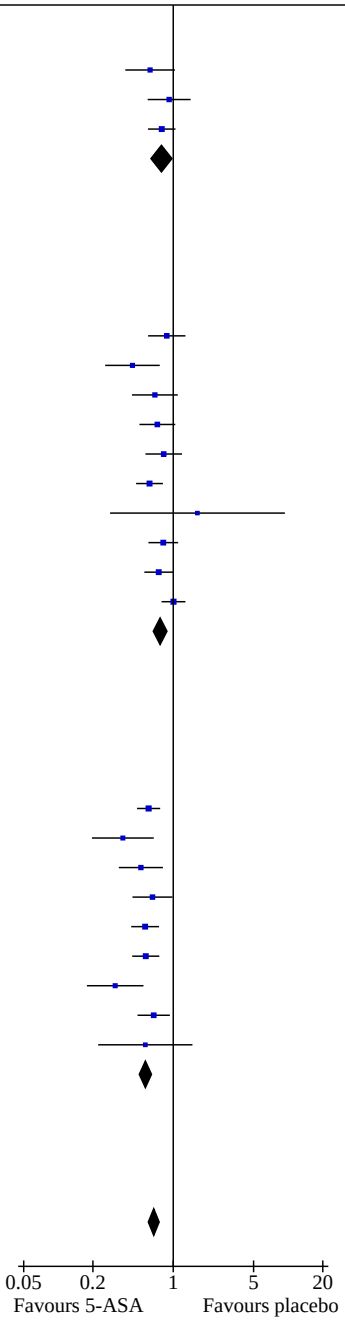
Analysis 1.1. Comparison 1: 5-ASA versus placebo, Outcome 1: Failure to induce global/clinical remission

Study or Subgroup	5-ASA Events	5-ASA Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Dose of 5-ASA: < 2 g						
Hanauer 1993	73	92	26	30	4.5%	0.92 [0.77 , 1.09]
Schroeder 1987	10	11	18	19	1.5%	0.96 [0.77 , 1.19]
Sninsky 1991	47	53	25	26	3.9%	0.92 [0.82 , 1.04]
Subtotal (95% CI)		**156**		**75**	**9.9%**	**0.92 [0.84 , 1.02]**
Total events:	130		69			
Heterogeneity: Chi² = 0.13, df = 2 (P = 0.94); I² = 0%						
Test for overall effect: Z = 1.55 (P = 0.12)						
1.1.2 Dose of 5-ASA : 2 - 2.9 g						
Hanauer 1993	69	97	26	30	4.6%	0.82 [0.68 , 0.99]
Hanauer 1996	81	92	39	45	6.0%	1.02 [0.89 , 1.17]
Ito 2010	46	66	15	16	2.8%	0.74 [0.61 , 0.91]
Kamm 2007	57	86	33	43	5.1%	0.86 [0.69 , 1.08]
Lichtenstein 2007	60	93	38	46	5.9%	0.78 [0.64 , 0.95]
Pontes 2014	1	8	1	10	0.1%	1.25 [0.09 , 17.02]
Sandborn 2012	93	124	101	121	11.8%	0.90 [0.79 , 1.02]
Sninsky 1991	47	53	25	26	3.9%	0.92 [0.82 , 1.04]
Subtotal (95% CI)		**619**		**337**	**40.0%**	**0.88 [0.82 , 0.94]**
Total events:	454		278			
Heterogeneity: Chi² = 9.54, df = 7 (P = 0.22); I² = 27%						
Test for overall effect: Z = 3.87 (P = 0.0001)						
1.1.3 Dose of 5-ASA: ≥ 3 g						
Feagan 2013	98	140	112	141	12.8%	0.88 [0.77 , 1.01]
Hanauer 1993	67	95	27	30	4.7%	0.78 [0.66 , 0.93]
Hanauer 1996	75	91	39	45	6.0%	0.95 [0.82 , 1.10]
Ito 2010	36	65	15	17	2.7%	0.63 [0.47 , 0.83]
Kamm 2007	50	85	34	43	5.2%	0.74 [0.59 , 0.94]
Lichtenstein 2007	65	94	39	47	6.0%	0.83 [0.69 , 1.00]
Scherl 2009	103	167	64	83	9.8%	0.80 [0.68 , 0.95]
Schroeder 1987	29	38	18	19	2.8%	0.81 [0.66 , 0.99]
Subtotal (95% CI)		**775**		**425**	**50.1%**	**0.83 [0.77 , 0.88]**
Total events:	523		348			
Heterogeneity: Chi² = 9.33, df = 7 (P = 0.23); I² = 25%						
Test for overall effect: Z = 5.67 (P < 0.00001)						
Total (95% CI)		**1550**		**837**	**100.0%**	**0.86 [0.82 , 0.89]**
Total events:	1107		695			
Heterogeneity: Chi² = 24.06, df = 18 (P = 0.15); I² = 25%						
Test for overall effect: Z = 7.02 (P < 0.00001)						
Test for subgroup differences: Chi² = 3.82, df = 2 (P = 0.15), I² = 47.6%						

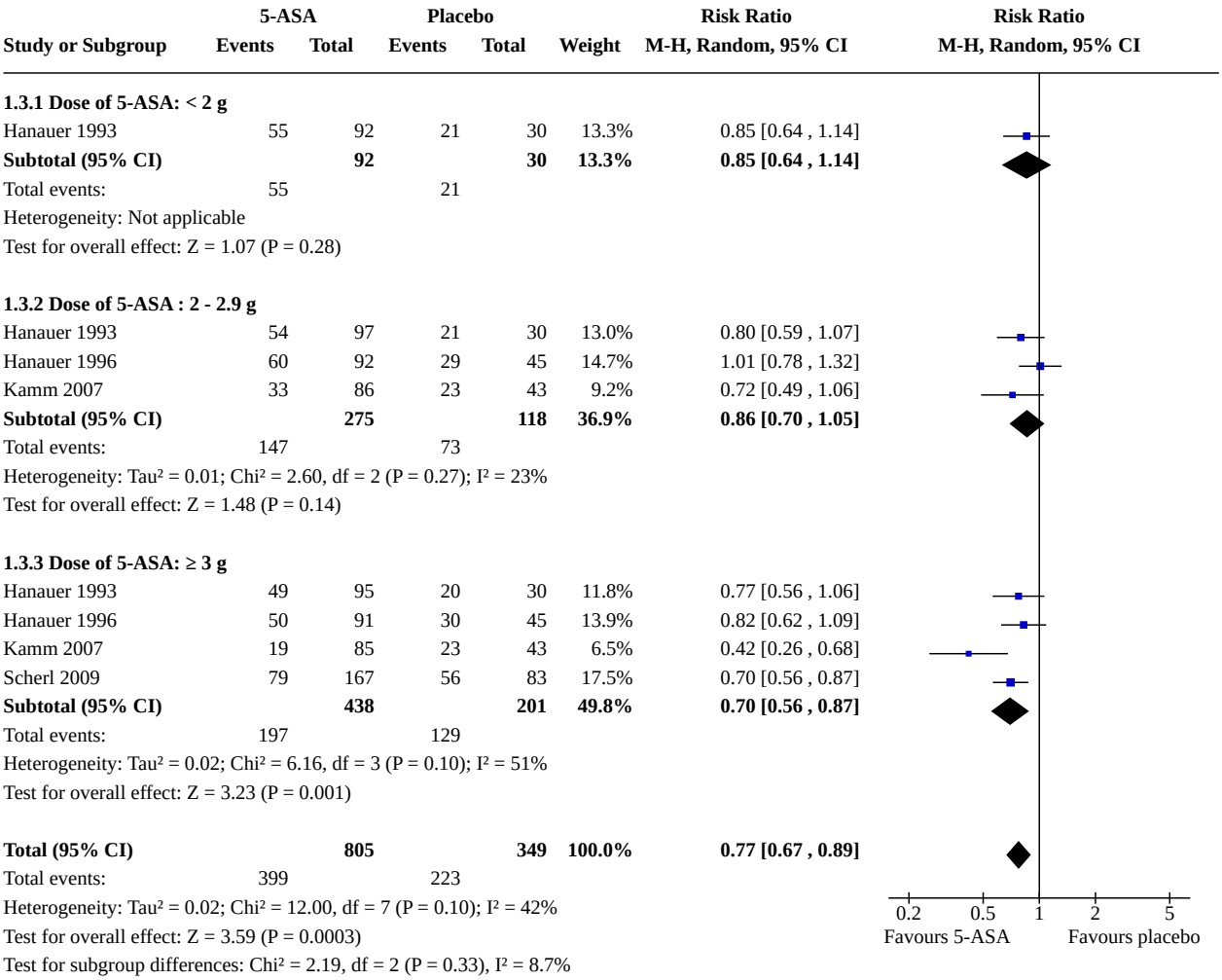


Analysis 1.2. Comparison 1: 5-ASA versus placebo, Outcome 2: Failure to induce global/clinical improvement (including remission)

Study or Subgroup	5-ASA Events	5-ASA Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Dose of 5-ASA: < 2 g						
Hanauer 1993	27	92	14	30	3.3%	0.63 [0.38 , 1.03]
Schroeder 1987	8	11	15	19	4.0%	0.92 [0.60 , 1.42]
Sninsky 1991	34	53	21	26	6.3%	0.79 [0.60 , 1.05]
Subtotal (95% CI)		**156**		**75**	**13.6%**	**0.79 [0.64 , 0.97]**
Total events:	69		50			
Heterogeneity: Tau² = 0.00; Chi² = 1.43, df = 2 (P = 0.49); I² = 0%						
Test for overall effect: Z = 2.21 (P = 0.03)						
1.2.2 Dose of 5-ASA: 2 - 2.9 g						
Feurle 1989	25	52	29	53	4.7%	0.88 [0.60 , 1.28]
Hanauer 1993	20	97	14	30	2.9%	0.44 [0.26 , 0.76]
Hetzel 1986	9	15	13	15	3.7%	0.69 [0.44 , 1.09]
Ito 2010	36	66	12	16	4.9%	0.73 [0.51 , 1.04]
Kamm 2007	38	86	23	43	4.8%	0.83 [0.57 , 1.19]
Lichtenstein 2007	44	93	35	46	6.4%	0.62 [0.48 , 0.81]
Pontes 2014	2	8	2	13	0.4%	1.63 [0.28 , 9.36]
Robinson 1994	29	50	34	48	5.9%	0.82 [0.61 , 1.10]
Sninsky 1991	32	53	21	26	6.1%	0.75 [0.56 , 1.00]
Sutherland 1990	37	45	18	22	7.0%	1.00 [0.79 , 1.28]
Subtotal (95% CI)		**565**		**312**	**46.7%**	**0.77 [0.67 , 0.88]**
Total events:	272		201			
Heterogeneity: Tau² = 0.01; Chi² = 13.17, df = 9 (P = 0.16); I² = 32%						
Test for overall effect: Z = 3.77 (P = 0.0002)						
1.2.3 Dose of 5-ASA: ≥ 3 g						
Feagan 2013	57	140	94	141	7.2%	0.61 [0.48 , 0.77]
Hanauer 1993	15	95	13	30	2.4%	0.36 [0.20 , 0.68]
Ito 2010	24	65	12	17	3.8%	0.52 [0.34 , 0.81]
Kamm 2007	30	85	23	43	4.3%	0.66 [0.44 , 0.99]
Lichtenstein 2007	41	94	36	47	6.2%	0.57 [0.43 , 0.75]
Scherl 2009	58	167	50	83	6.4%	0.58 [0.44 , 0.76]
Schroeder 1987	10	38	16	19	2.7%	0.31 [0.18 , 0.55]
Sutherland 1990	26	47	18	22	5.5%	0.68 [0.49 , 0.93]
Zinberg 1990	3	7	6	8	1.2%	0.57 [0.22 , 1.47]
Subtotal (95% CI)		**738**		**410**	**39.7%**	**0.57 [0.51 , 0.65]**
Total events:	264		268			
Heterogeneity: Tau² = 0.00; Chi² = 8.43, df = 8 (P = 0.39); I² = 5%						
Test for overall effect: Z = 8.97 (P < 0.00001)						
Total (95% CI)		**1459**		**797**	**100.0%**	**0.68 [0.61 , 0.75]**
Total events:	605		519			
Heterogeneity: Tau² = 0.03; Chi² = 39.85, df = 21 (P = 0.008); I² = 47%						
Test for overall effect: Z = 7.06 (P < 0.00001)						
Test for subgroup differences: Chi² = 12.62, df = 2 (P = 0.002), I² = 84.1%						

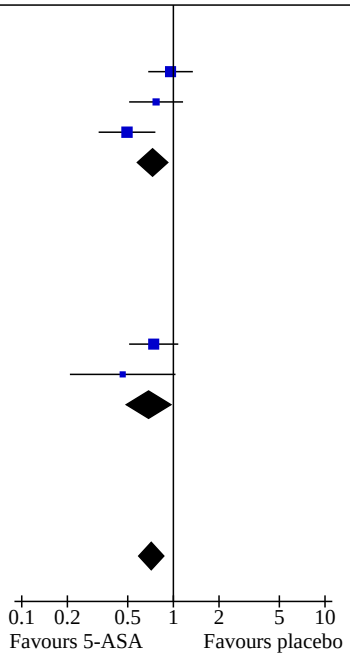


Analysis 1.3. Comparison 1: 5-ASA versus placebo, Outcome 3: Failure to induce endoscopic remission



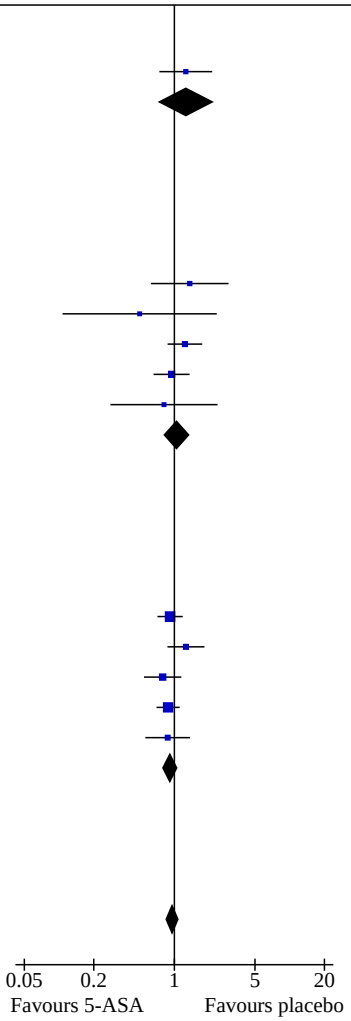
Analysis 1.4. Comparison 1: 5-ASA versus placebo, Outcome 4: Failure to induce endoscopic improvement (including remission)

Study or Subgroup	5-ASA Events	5-ASA Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 Dose of 5-ASA : 2 - 2.9 g						
Hanauer 1996	47	92	24	45	27.1%	0.96 [0.68 , 1.34]
Hetzel 1986	10	15	13	15	10.9%	0.77 [0.51 , 1.16]
Robinson 1994	17	50	33	48	28.3%	0.49 [0.32 , 0.76]
Subtotal (95% CI)		**157**		**108**	**66.3%**	**0.73 [0.58 , 0.92]**
Total events:	74		70			
Heterogeneity: Chi² = 5.68, df = 2 (P = 0.06); I² = 65%						
Test for overall effect: Z = 2.69 (P = 0.007)						
1.4.2 Dose of 5-ASA: ≥ 3 g						
Hanauer 1996	36	91	24	45	27.0%	0.74 [0.51 , 1.08]
Zinberg 1990	3	7	8	8	6.7%	0.46 [0.21 , 1.03]
Subtotal (95% CI)		**98**		**53**	**33.7%**	**0.69 [0.49 , 0.96]**
Total events:	39		32			
Heterogeneity: Chi² = 1.09, df = 1 (P = 0.30); I² = 8%						
Test for overall effect: Z = 2.19 (P = 0.03)						
Total (95% CI)		**255**		**161**	**100.0%**	**0.71 [0.59 , 0.86]**
Total events:	113		102			
Heterogeneity: Chi² = 6.97, df = 4 (P = 0.14); I² = 43%						
Test for overall effect: Z = 3.47 (P = 0.0005)						
Test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.77), I² = 0%						



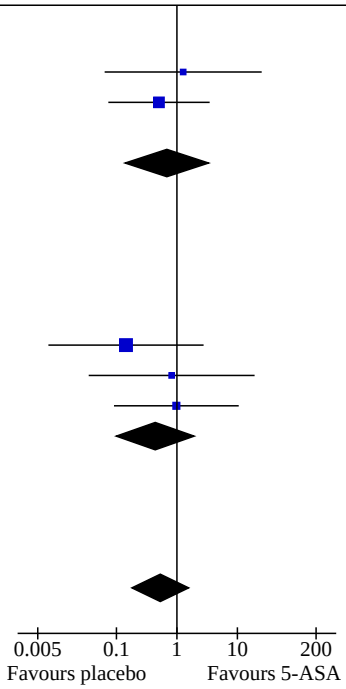
Analysis 1.5. Comparison 1: 5-ASA versus placebo, Outcome 5: Adverse events

Study or Subgroup	5-ASA Events	5-ASA Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.5.1 Dose of 5-ASA: < 2 g						
Schroeder 1987	8	11	11	19	3.0%	1.26 [0.74 , 2.13]
Subtotal (95% CI)		**11**		**19**	**3.0%**	**1.26 [0.74 , 2.13]**
Total events:	8		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.85 (P = 0.40)						
1.5.2 Dose of 5-ASA : 2 - 2.9 g						
Feurle 1989	12	52	9	53	3.3%	1.36 [0.63 , 2.95]
Hetzel 1986	2	15	4	15	1.5%	0.50 [0.11 , 2.33]
Ito 2010	56	66	11	16	6.5%	1.23 [0.87 , 1.74]
Lichtenstein 2007	44	93	23	46	11.3%	0.95 [0.66 , 1.36]
Pontes 2014	3	8	6	13	1.7%	0.81 [0.28 , 2.37]
Subtotal (95% CI)		**234**		**143**	**24.2%**	**1.04 [0.82 , 1.33]**
Total events:	117		53			
Heterogeneity: Chi² = 2.73, df = 4 (P = 0.60); I² = 0%						
Test for overall effect: Z = 0.34 (P = 0.73)						
1.5.3 Dose of 5-ASA: ≥ 3 g						
Feagan 2013	62	140	68	141	24.8%	0.92 [0.71 , 1.18]
Ito 2010	53	65	11	17	6.4%	1.26 [0.87 , 1.82]
Lichtenstein 2007	38	94	24	47	11.7%	0.79 [0.55 , 1.15]
Scherl 2009	87	167	49	83	24.0%	0.88 [0.70 , 1.11]
Schroeder 1987	21	38	12	19	5.9%	0.88 [0.56 , 1.37]
Subtotal (95% CI)		**504**		**307**	**72.9%**	**0.91 [0.80 , 1.05]**
Total events:	261		164			
Heterogeneity: Chi² = 3.61, df = 4 (P = 0.46); I² = 0%						
Test for overall effect: Z = 1.30 (P = 0.19)						
Total (95% CI)		**749**		**469**	**100.0%**	**0.95 [0.85 , 1.07]**
Total events:	386		228			
Heterogeneity: Chi² = 8.55, df = 10 (P = 0.58); I² = 0%						
Test for overall effect: Z = 0.78 (P = 0.43)						
Test for subgroup differences: Chi² = 1.97, df = 2 (P = 0.37), I² = 0%						



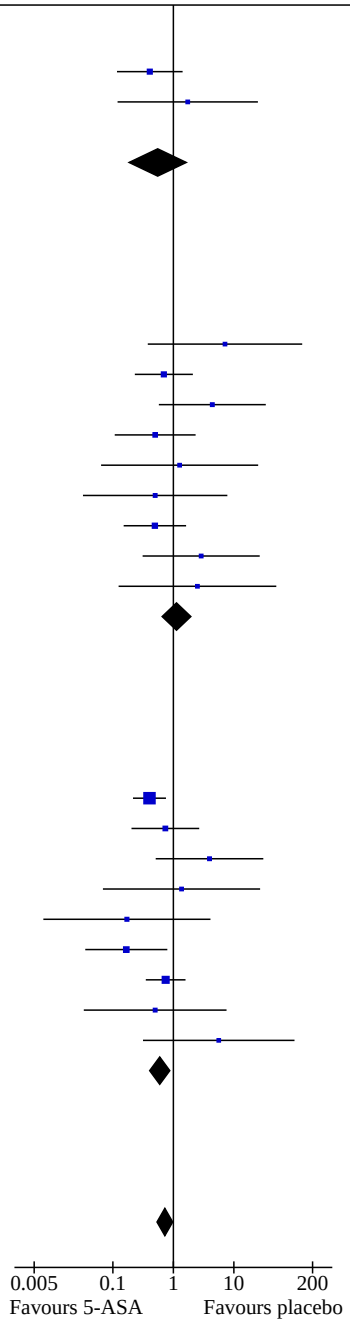
Analysis 1.6. Comparison 1: 5-ASA versus placebo, Outcome 6: Serious adverse events

Study or Subgroup	5-ASA Events	5-ASA Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.6.1 Dose of 5-ASA: 2 - 2.9 g						
Ito 2010	2	66	0	16	8.8%	1.27 [0.06 , 25.21]
Lichtenstein 2007	2	93	2	47	29.3%	0.51 [0.07 , 3.48]
Pontes 2014	0	8	0	13		Not estimable
Subtotal (95% CI)		**167**		**76**	**38.1%**	**0.68 [0.14 , 3.33]**
Total events:	4		2			
Heterogeneity: Chi² = 0.26, df = 1 (P = 0.61); I² = 0%						
Test for overall effect: Z = 0.47 (P = 0.64)						
1.6.2 Dose of 5-ASA: ≥ 3 g						
Feagan 2013	0	140	3	141	38.4%	0.14 [0.01 , 2.76]
Ito 2010	1	65	0	17	8.7%	0.82 [0.03 , 19.24]
Lichtenstein 2007	2	94	1	46	14.8%	0.98 [0.09 , 10.52]
Subtotal (95% CI)		**299**		**204**	**61.9%**	**0.44 [0.10 , 1.92]**
Total events:	3		4			
Heterogeneity: Chi² = 1.14, df = 2 (P = 0.57); I² = 0%						
Test for overall effect: Z = 1.09 (P = 0.27)						
Total (95% CI)		**466**		**280**	**100.0%**	**0.53 [0.18 , 1.56]**
Total events:	7		6			
Heterogeneity: Chi² = 1.41, df = 4 (P = 0.84); I² = 0%						
Test for overall effect: Z = 1.15 (P = 0.25)						
Test for subgroup differences: Chi² = 0.16, df = 1 (P = 0.69), I² = 0%						



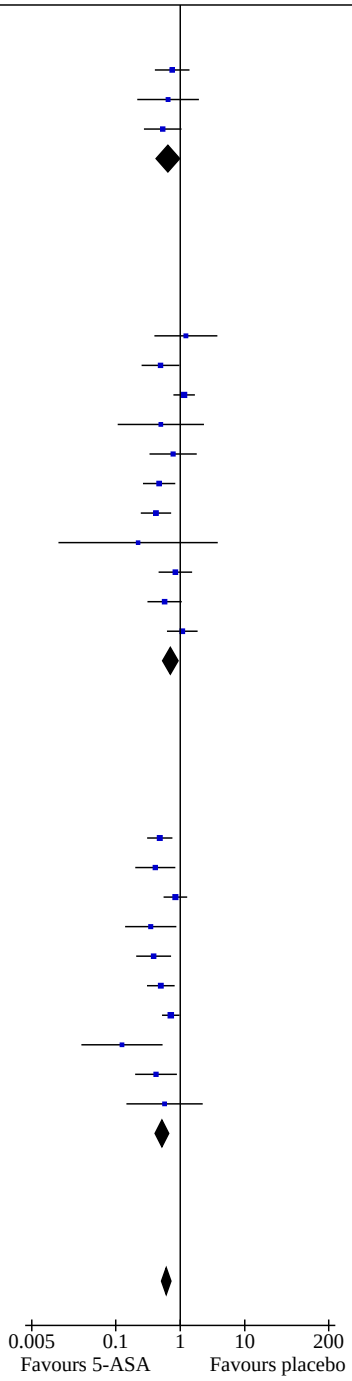
Analysis 1.7. Comparison 1: 5-ASA versus placebo, Outcome 7: Withdrawals due to adverse events

Study or Subgroup	5-ASA Events	5-ASA Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.7.1 Dose of 5-ASA: < 2 g						
Hanauer 1993	5	92	4	30	6.6%	0.41 [0.12 , 1.42]
Schroeder 1987	1	11	1	19	0.8%	1.73 [0.12 , 24.95]
Sninsky 1991	0	53	0	26		Not estimable
Subtotal (95% CI)		**156**		**75**	**7.4%**	**0.55 [0.19 , 1.63]**
Total events:	6		5			
Heterogeneity: Chi² = 0.93, df = 1 (P = 0.34); I² = 0%						
Test for overall effect: Z = 1.08 (P = 0.28)						
1.7.2 Dose of 5-ASA : 2 - 2.9 g						
Feurle 1989	3	52	0	53	0.5%	7.13 [0.38 , 134.75]
Hanauer 1993	9	97	4	30	6.7%	0.70 [0.23 , 2.10]
Hanauer 1996	9	92	1	45	1.5%	4.40 [0.58 , 33.69]
Hetzel 1986	2	15	4	15	4.4%	0.50 [0.11 , 2.33]
Ito 2010	2	66	0	16	0.9%	1.27 [0.06 , 25.21]
Kamm 2007	1	86	1	43	1.5%	0.50 [0.03 , 7.80]
Lichtenstein 2007	5	93	5	46	7.4%	0.49 [0.15 , 1.62]
Robinson 1994	3	50	1	48	1.1%	2.88 [0.31 , 26.74]
Sninsky 1991	2	53	0	26	0.7%	2.50 [0.12 , 50.26]
Subtotal (95% CI)		**604**		**322**	**24.7%**	**1.13 [0.65 , 1.94]**
Total events:	36		16			
Heterogeneity: Chi² = 8.18, df = 8 (P = 0.42); I² = 2%						
Test for overall effect: Z = 0.43 (P = 0.67)						
1.7.3 Dose of 5-ASA: ≥ 3 g						
Feagan 2013	12	140	30	141	32.9%	0.40 [0.22 , 0.75]
Hanauer 1993	7	95	3	30	5.0%	0.74 [0.20 , 2.67]
Hanauer 1996	8	91	1	45	1.5%	3.96 [0.51 , 30.67]
Ito 2010	2	65	0	17	0.9%	1.36 [0.07 , 27.15]
Kamm 2007	0	85	1	43	2.2%	0.17 [0.01 , 4.10]
Lichtenstein 2007	2	94	6	47	8.8%	0.17 [0.03 , 0.79]
Scherl 2009	15	167	10	83	14.7%	0.75 [0.35 , 1.59]
Schroeder 1987	1	38	1	19	1.5%	0.50 [0.03 , 7.56]
Zinberg 1990	2	7	0	8	0.5%	5.63 [0.31 , 100.52]
Subtotal (95% CI)		**782**		**433**	**67.9%**	**0.59 [0.41 , 0.87]**
Total events:	49		52			
Heterogeneity: Chi² = 11.01, df = 8 (P = 0.20); I² = 27%						
Test for overall effect: Z = 2.67 (P = 0.008)						
Total (95% CI)		**1542**		**830**	**100.0%**	**0.72 [0.54 , 0.97]**
Total events:	91		73			
Heterogeneity: Chi² = 21.89, df = 19 (P = 0.29); I² = 13%						
Test for overall effect: Z = 2.14 (P = 0.03)						
Test for subgroup differences: Chi² = 3.78, df = 2 (P = 0.15), I² = 47.1%						



Analysis 1.8. Comparison 1: 5-ASA versus placebo, Outcome 8: Exclusions and withdrawals after study entry

Study or Subgroup	5-ASA Events	5-ASA Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.8.1 Dose of 5-ASA: < 2 g						
Hanauer 1993	23	92	10	30	4.7%	0.75 [0.40 , 1.39]
Schroeder 1987	3	11	8	19	2.0%	0.65 [0.22 , 1.95]
Sninsky 1991	12	53	11	26	4.2%	0.54 [0.27 , 1.05]
Subtotal (95% CI)		**156**		**75**	**10.8%**	**0.64 [0.42 , 0.98]**
Total events:	38		29			
Heterogeneity: Tau² = 0.00; Chi² = 0.53, df = 2 (P = 0.77); I² = 0%						
Test for overall effect: Z = 2.06 (P = 0.04)						
1.8.2 Dose of 5-ASA : 2 - 2.9 g						
Feurle 1989	6	52	5	53	1.9%	1.22 [0.40 , 3.76]
Hanauer 1993	16	97	10	30	4.1%	0.49 [0.25 , 0.97]
Hanauer 1996	47	92	20	45	7.6%	1.15 [0.78 , 1.69]
Hetzel 1986	2	15	4	15	1.1%	0.50 [0.11 , 2.33]
Ito 2010	16	66	5	16	3.0%	0.78 [0.33 , 1.80]
Kamm 2007	16	86	17	43	5.1%	0.47 [0.26 , 0.84]
Lichtenstein 2007	17	93	20	46	5.4%	0.42 [0.24 , 0.72]
Pontes 2014	0	8	3	13	0.3%	0.22 [0.01 , 3.81]
Robinson 1994	14	50	16	48	4.8%	0.84 [0.46 , 1.53]
Sninsky 1991	14	53	12	26	4.7%	0.57 [0.31 , 1.06]
Sutherland 1990	22	45	10	22	5.4%	1.08 [0.62 , 1.86]
Subtotal (95% CI)		**657**		**357**	**43.5%**	**0.70 [0.53 , 0.92]**
Total events:	170		122			
Heterogeneity: Tau² = 0.08; Chi² = 17.45, df = 10 (P = 0.07); I² = 43%						
Test for overall effect: Z = 2.52 (P = 0.01)						
1.8.3 Dose of 5-ASA: ≥ 3 g						
Feagan 2013	22	140	46	141	6.6%	0.48 [0.31 , 0.76]
Hanauer 1993	13	95	10	30	3.8%	0.41 [0.20 , 0.84]
Hanauer 1996	34	91	20	45	7.0%	0.84 [0.55 , 1.28]
Ito 2010	8	65	6	17	2.7%	0.35 [0.14 , 0.87]
Kamm 2007	13	85	17	43	4.6%	0.39 [0.21 , 0.72]
Lichtenstein 2007	21	94	21	47	6.0%	0.50 [0.31 , 0.82]
Scherl 2009	56	167	39	83	8.8%	0.71 [0.52 , 0.98]
Schroeder 1987	2	38	8	19	1.2%	0.13 [0.03 , 0.53]
Sutherland 1990	9	47	10	22	3.6%	0.42 [0.20 , 0.89]
Zinberg 1990	2	7	4	8	1.4%	0.57 [0.15 , 2.23]
Subtotal (95% CI)		**829**		**455**	**45.7%**	**0.52 [0.41 , 0.66]**
Total events:	180		181			
Heterogeneity: Tau² = 0.05; Chi² = 14.53, df = 9 (P = 0.10); I² = 38%						
Test for overall effect: Z = 5.30 (P < 0.00001)						
Total (95% CI)		**1642**		**887**	**100.0%**	**0.61 [0.51 , 0.72]**
Total events:	388		332			
Heterogeneity: Tau² = 0.06; Chi² = 36.62, df = 23 (P = 0.04); I² = 37%						
Test for overall effect: Z = 5.86 (P < 0.00001)						
Test for subgroup differences: Chi² = 2.72, df = 2 (P = 0.26), I² = 26.5%						



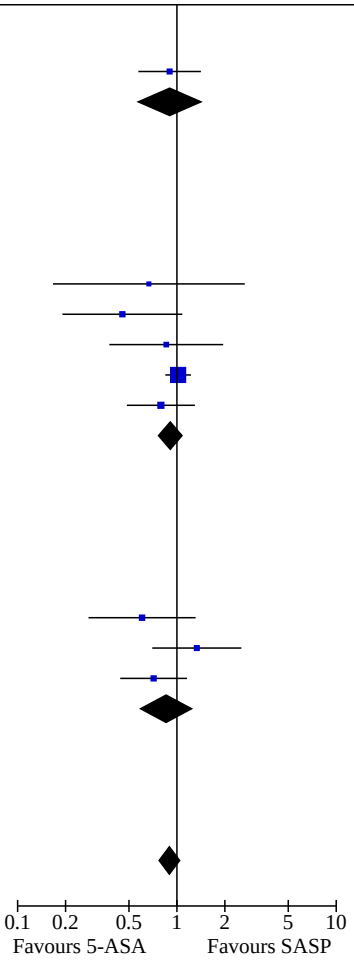
Comparison 2. 5-ASA versus sulfasalazine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Failure to induce global/clinical remission	8	526	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.77, 1.04]
2.1.1 5-ASA / SASP < 1/2	1	29	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.57, 1.41]
2.1.2 1/1 > 5-ASA / SASP ≥ 1/2	5	359	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.77, 1.08]
2.1.3 5-ASA / SASP ≥ 1/1	3	138	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.59, 1.23]
2.2 Failure to induce global/clinical improvement (including remission)	14	1053	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.76, 1.01]
2.2.1 5-ASA / SASP < 1/2	3	123	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.47, 1.27]
2.2.2 1/1 > 5-ASA / SASP ≥ 1/2	11	804	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.77, 1.05]
2.2.3 5-ASA / SASP ≥ 1/1	3	126	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.54, 1.22]
2.3 Failure to induce endoscopic improvement (including remission)	6	362	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.65, 1.02]
2.3.1 5-ASA / SASP < 1/2	1	29	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.58, 1.04]
2.3.2 1/1 > 5-ASA / SASP ≥ 1/2	4	246	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.53, 1.02]
2.3.3 5-ASA / SASP ≥ 1/1	2	87	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.72, 1.57]
2.4 Adverse events	12	909	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.36, 0.63]
2.4.1 5-ASA / SASP < 1/2	1	56	Risk Ratio (M-H, Fixed, 95% CI)	0.35 [0.10, 1.20]
2.4.2 1/1 > 5-ASA / SASP ≥ 1/2	9	746	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.41, 0.73]
2.4.3 5-ASA / SASP ≥ 1/1	2	107	Risk Ratio (M-H, Fixed, 95% CI)	0.16 [0.05, 0.52]
2.5 Serious adverse events	2	107	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.28, 6.52]
2.6 Withdrawals due to adverse events	10	640	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.24, 0.68]
2.6.1 5-ASA / SASP < 1/2	2	85	Risk Ratio (M-H, Fixed, 95% CI)	0.16 [0.02, 1.41]
2.6.2 1/1 > 5-ASA / SASP ≥ 1/2	5	361	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.32, 1.39]
2.6.3 5-ASA / SASP ≥ 1/1	4	194	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.10, 0.60]
2.7 Exclusions and withdrawals after study entry	10	701	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.58, 0.99]
2.7.1 5-ASA / SASP < 1/2	1	29	Risk Ratio (M-H, Fixed, 95% CI)	0.10 [0.01, 1.80]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.7.2 1/1 > 5-ASA / SASP ≥ 1/2	6	478	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.71, 1.34]
2.7.3 5-ASA / SASP ≥ 1/1	4	194	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.25, 0.77]

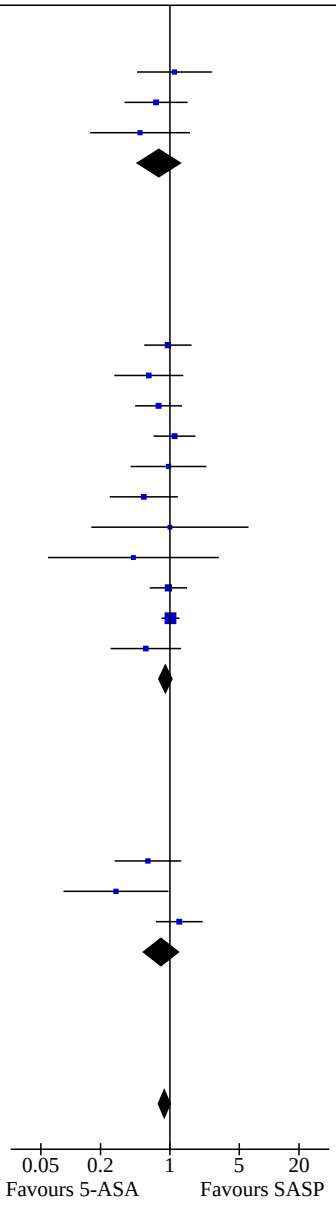
Analysis 2.1. Comparison 2: 5-ASA versus sulfasalazine, Outcome 1: Failure to induce global/clinical remission

Study or Subgroup	5-ASA Events	5-ASA Total	SASP Events	SASP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 5-ASA / SASP < 1/2						
Riley 1988	14	20	7	9	6.3%	0.90 [0.57 , 1.41]
Subtotal (95% CI)		**20**		**9**	**6.3%**	**0.90 [0.57 , 1.41]**
Total events:	14		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.46 (P = 0.65)						
2.1.2 1/1 > 5-ASA / SASP ≥ 1/2						
Andreoli 1987	2	6	3	6	2.0%	0.67 [0.17 , 2.67]
Jiang 2004	5	21	11	21	7.2%	0.45 [0.19 , 1.08]
Maier 1985	6	15	7	15	4.6%	0.86 [0.38 , 1.95]
Rachmilewitz 1989	78	115	70	105	48.0%	1.02 [0.85 , 1.22]
Rijk 1991	13	27	17	28	10.9%	0.79 [0.48 , 1.30]
Subtotal (95% CI)		**184**		**175**	**72.7%**	**0.91 [0.77 , 1.08]**
Total events:	104		108			
Heterogeneity: Chi² = 4.40, df = 4 (P = 0.35); I² = 9%						
Test for overall effect: Z = 1.11 (P = 0.27)						
2.1.3 5-ASA / SASP ≥ 1/1						
Green 2002	7	28	12	29	7.7%	0.60 [0.28 , 1.31]
Mansfield 2002	13	26	9	24	6.1%	1.33 [0.70 , 2.54]
Riley 1988	12	21	8	10	7.1%	0.71 [0.44 , 1.16]
Subtotal (95% CI)		**75**		**63**	**21.0%**	**0.85 [0.59 , 1.23]**
Total events:	32		29			
Heterogeneity: Chi² = 3.13, df = 2 (P = 0.21); I² = 36%						
Test for overall effect: Z = 0.84 (P = 0.40)						
Total (95% CI)		**279**		**247**	**100.0%**	**0.90 [0.77 , 1.04]**
Total events:	150		144			
Heterogeneity: Chi² = 7.89, df = 8 (P = 0.44); I² = 0%						
Test for overall effect: Z = 1.45 (P = 0.15)						
Test for subgroup differences: Chi² = 0.09, df = 2 (P = 0.96), I² = 0%						



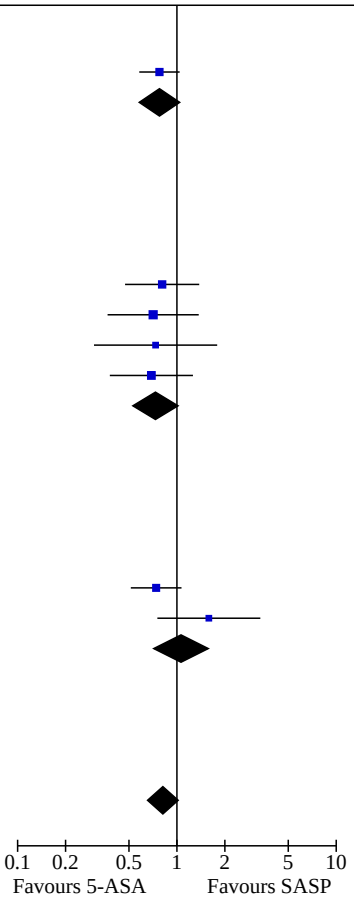
Analysis 2.2. Comparison 2: 5-ASA versus sulfasalazine, Outcome 2: Failure to induce global/clinical improvement (including remission)

Study or Subgroup	5-ASA Events	5-ASA Total	SASP Events	SASP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.2.1 5-ASA / SASP < 1/2						
Good 1992	12	27	4	10	2.6%	1.11 [0.47 , 2.65]
Qian 2004	9	31	10	25	4.9%	0.73 [0.35 , 1.51]
Riley 1988	4	20	4	10	2.4%	0.50 [0.16 , 1.59]
Subtotal (95% CI)		**78**		**45**	**9.9%**	**0.77 [0.47 , 1.27]**
Total events:	25		18			
Heterogeneity: Chi² = 1.24, df = 2 (P = 0.54); I² = 0%						
Test for overall effect: Z = 1.01 (P = 0.31)						
2.2.2 1/1 > 5-ASA / SASP ≥ 1/2						
Bresci 1990	16	44	16	42	7.3%	0.95 [0.55 , 1.65]
Cai 2001	15	105	7	30	4.9%	0.61 [0.28 , 1.36]
Ewe 1988	10	20	13	20	5.8%	0.77 [0.45 , 1.32]
Fleig 1988	14	22	12	21	5.5%	1.11 [0.68 , 1.81]
Good 1992	12	31	4	10	2.7%	0.97 [0.40 , 2.33]
Jiang 2004	6	21	11	21	4.9%	0.55 [0.25 , 1.20]
Maier 1985	2	15	2	15	0.9%	1.00 [0.16 , 6.20]
Mihas 1988	1	7	4	12	1.3%	0.43 [0.06 , 3.11]
Munakata 1995	22	52	25	57	10.7%	0.96 [0.63 , 1.49]
Rachmilewitz 1989	71	115	64	105	29.9%	1.01 [0.82 , 1.25]
Rao 1989	6	21	9	18	4.3%	0.57 [0.25 , 1.30]
Subtotal (95% CI)		**453**		**351**	**78.2%**	**0.90 [0.77 , 1.05]**
Total events:	175		167			
Heterogeneity: Chi² = 6.61, df = 10 (P = 0.76); I² = 0%						
Test for overall effect: Z = 1.36 (P = 0.17)						
2.2.3 5-ASA / SASP ≥ 1/1						
Good 1992	10	30	5	9	3.4%	0.60 [0.28 , 1.30]
Riley 1988	3	21	5	10	3.0%	0.29 [0.08 , 0.97]
Willoughby 1988	14	26	13	30	5.4%	1.24 [0.72 , 2.14]
Subtotal (95% CI)		**77**		**49**	**11.9%**	**0.81 [0.54 , 1.22]**
Total events:	27		23			
Heterogeneity: Chi² = 5.78, df = 2 (P = 0.06); I² = 65%						
Test for overall effect: Z = 1.01 (P = 0.31)						
Total (95% CI)		**608**		**445**	**100.0%**	**0.88 [0.76 , 1.01]**
Total events:	227		208			
Heterogeneity: Chi² = 14.24, df = 16 (P = 0.58); I² = 0%						
Test for overall effect: Z = 1.88 (P = 0.06)						
Test for subgroup differences: Chi² = 0.49, df = 2 (P = 0.78), I² = 0%						



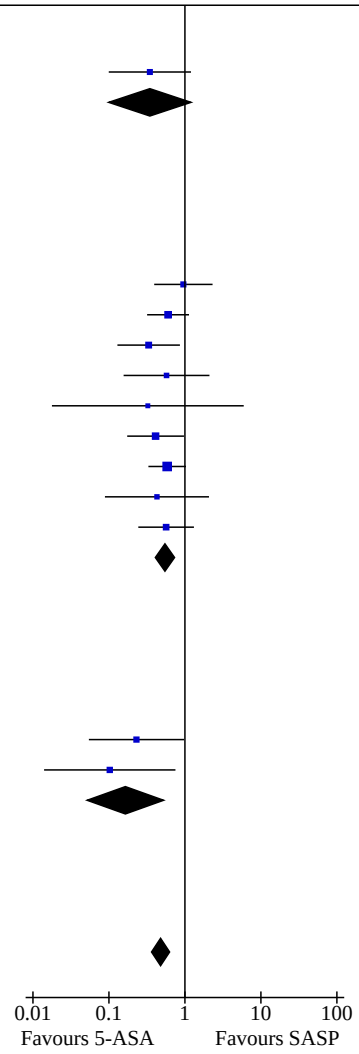
Analysis 2.3. Comparison 2: 5-ASA versus sulfasalazine, Outcome 3: Failure to induce endoscopic improvement (including remission)

Study or Subgroup	5-ASA Events	5-ASA Total	SASP Events	SASP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.3.1 5-ASA / SASP < 1/2						
Riley 1988	15	20	9	9	15.3%	0.78 [0.58 , 1.04]
Subtotal (95% CI)		**20**		**9**	**15.3%**	**0.78 [0.58 , 1.04]**
Total events:	15		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.70 (P = 0.09)						
2.3.2 1/1 > 5-ASA / SASP ≥ 1/2						
Fleig 1988	11	22	13	21	15.8%	0.81 [0.47 , 1.38]
Munakata 1995	11	52	17	57	19.2%	0.71 [0.37 , 1.37]
Rao 1989	6	21	7	18	8.9%	0.73 [0.30 , 1.79]
Rijk 1991	10	27	15	28	17.5%	0.69 [0.38 , 1.26]
Subtotal (95% CI)		**122**		**124**	**61.4%**	**0.73 [0.53 , 1.02]**
Total events:	38		52			
Heterogeneity: Chi² = 0.17, df = 3 (P = 0.98); I² = 0%						
Test for overall effect: Z = 1.87 (P = 0.06)						
2.3.3 5-ASA / SASP ≥ 1/1						
Riley 1988	14	21	9	10	14.5%	0.74 [0.51 , 1.07]
Willoughby 1988	11	26	8	30	8.8%	1.59 [0.75 , 3.34]
Subtotal (95% CI)		**47**		**40**	**23.3%**	**1.06 [0.72 , 1.57]**
Total events:	25		17			
Heterogeneity: Chi² = 4.82, df = 1 (P = 0.03); I² = 79%						
Test for overall effect: Z = 0.29 (P = 0.77)						
Total (95% CI)		**189**		**173**	**100.0%**	**0.82 [0.65 , 1.02]**
Total events:	78		78			
Heterogeneity: Chi² = 3.97, df = 6 (P = 0.68); I² = 0%						
Test for overall effect: Z = 1.80 (P = 0.07)						
Test for subgroup differences: Chi² = 2.23, df = 2 (P = 0.33), I² = 10.3%						



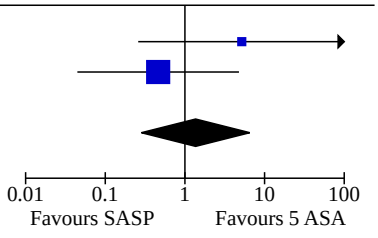
Analysis 2.4. Comparison 2: 5-ASA versus sulfasalazine, Outcome 4: Adverse events

Study or Subgroup	5-ASA Events	5-ASA Total	SASP Events	SASP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.4.1 5-ASA / SASP < 1/2						
Qian 2004	3	31	7	25	6.2%	0.35 [0.10 , 1.20]
Subtotal (95% CI)		**31**		**25**	**6.2%**	**0.35 [0.10 , 1.20]**
Total events:	3		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.67 (P = 0.09)						
2.4.2 1/1 > 5-ASA / SASP ≥ 1/2						
Bresci 1990	8	44	8	42	6.5%	0.95 [0.39 , 2.31]
Cai 2001	21	105	10	30	12.4%	0.60 [0.32 , 1.13]
Ewe 1988	4	20	12	20	9.6%	0.33 [0.13 , 0.86]
Fleig 1988	3	22	5	21	4.1%	0.57 [0.16 , 2.10]
Mihas 1988	0	7	2	12	1.5%	0.33 [0.02 , 5.94]
Munakata 1995	6	52	16	57	12.2%	0.41 [0.17 , 0.97]
Rachmilewitz 1989	16	115	25	105	20.9%	0.58 [0.33 , 1.03]
Rao 1989	2	21	4	18	3.4%	0.43 [0.09 , 2.07]
Rijk 1991	6	27	11	28	8.6%	0.57 [0.24 , 1.31]
Subtotal (95% CI)		**413**		**333**	**79.3%**	**0.55 [0.41 , 0.73]**
Total events:	66		93			
Heterogeneity: Chi² = 3.36, df = 8 (P = 0.91); I² = 0%						
Test for overall effect: Z = 4.09 (P < 0.0001)						
2.4.3 5-ASA / SASP ≥ 1/1						
Green 2002	2	28	9	29	7.1%	0.23 [0.05 , 0.97]
Mansfield 2002	1	26	9	24	7.5%	0.10 [0.01 , 0.75]
Subtotal (95% CI)		**54**		**53**	**14.5%**	**0.16 [0.05 , 0.52]**
Total events:	3		18			
Heterogeneity: Chi² = 0.42, df = 1 (P = 0.51); I² = 0%						
Test for overall effect: Z = 3.06 (P = 0.002)						
Total (95% CI)		**498**		**411**	**100.0%**	**0.48 [0.36 , 0.63]**
Total events:	72		118			
Heterogeneity: Chi² = 7.86, df = 11 (P = 0.73); I² = 0%						
Test for overall effect: Z = 5.30 (P < 0.00001)						
Test for subgroup differences: Chi² = 4.23, df = 2 (P = 0.12), I² = 52.8%						



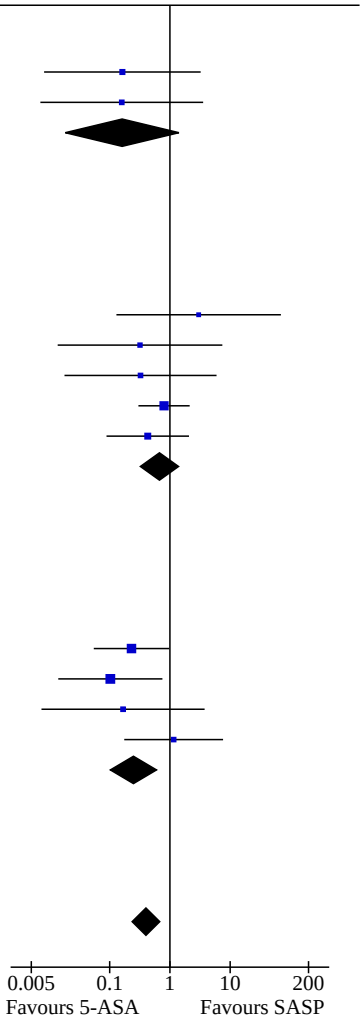
Analysis 2.5. Comparison 2: 5-ASA versus sulfasalazine, Outcome 5: Serious adverse events

Study or Subgroup	5-ASA Events	5-ASA Total	SASP Events	SASP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Green 2002	2	28	0	29	19.1%	5.17 [0.26 , 103.18]
Mansfield 2002	1	26	2	24	80.9%	0.46 [0.04 , 4.77]
Total (95% CI)		**54**		**53**	**100.0%**	**1.36 [0.28 , 6.52]**
Total events:	3		2			
Heterogeneity: Chi² = 1.59, df = 1 (P = 0.21); I² = 37%						
Test for overall effect: Z = 0.39 (P = 0.70)						
Test for subgroup differences: Not applicable						

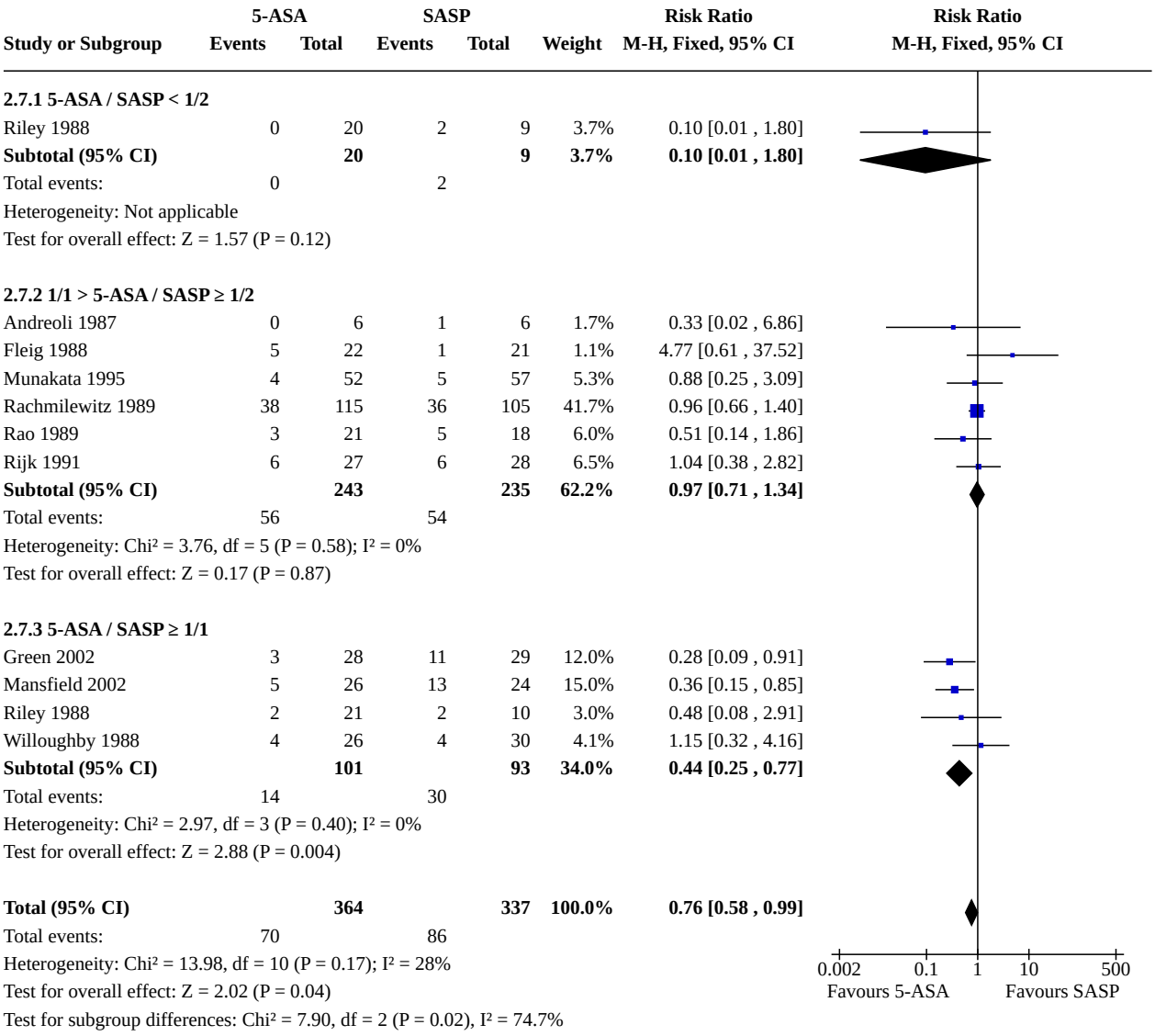


Analysis 2.6. Comparison 2: 5-ASA versus sulfasalazine, Outcome 6: Withdrawals due to adverse events

Study or Subgroup	5-ASA Events	5-ASA Total	SASP Events	SASP Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.6.1 5-ASA / SASP < 1/2						
Qian 2004	0	31	2	25	6.3%	0.16 [0.01 , 3.24]
Riley 1988	0	20	1	9	4.7%	0.16 [0.01 , 3.56]
Subtotal (95% CI)		**51**		**34**	**11.0%**	**0.16 [0.02 , 1.41]**
Total events:	0		3			
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.99); I² = 0%						
Test for overall effect: Z = 1.65 (P = 0.10)						
2.6.2 1/1 > 5-ASA / SASP ≥ 1/2						
Ewe 1988	1	20	0	20	1.2%	3.00 [0.13 , 69.52]
Fleig 1988	0	22	1	21	3.5%	0.32 [0.01 , 7.42]
Mihas 1988	0	7	2	12	4.4%	0.33 [0.02 , 5.94]
Rachmilewitz 1989	7	115	8	105	19.2%	0.80 [0.30 , 2.13]
Rao 1989	2	21	4	18	9.9%	0.43 [0.09 , 2.07]
Subtotal (95% CI)		**185**		**176**	**38.2%**	**0.67 [0.32 , 1.39]**
Total events:	10		15			
Heterogeneity: Chi² = 1.76, df = 4 (P = 0.78); I² = 0%						
Test for overall effect: Z = 1.08 (P = 0.28)						
2.6.3 5-ASA / SASP ≥ 1/1						
Green 2002	2	28	9	29	20.3%	0.23 [0.05 , 0.97]
Mansfield 2002	1	26	9	24	21.5%	0.10 [0.01 , 0.75]
Riley 1988	0	21	1	10	4.6%	0.17 [0.01 , 3.77]
Willoughby 1988	2	26	2	30	4.3%	1.15 [0.17 , 7.62]
Subtotal (95% CI)		**101**		**93**	**50.8%**	**0.25 [0.10 , 0.60]**
Total events:	5		21			
Heterogeneity: Chi² = 3.38, df = 3 (P = 0.34); I² = 11%						
Test for overall effect: Z = 3.10 (P = 0.002)						
Total (95% CI)		**337**		**303**	**100.0%**	**0.40 [0.24 , 0.68]**
Total events:	15		39			
Heterogeneity: Chi² = 8.10, df = 10 (P = 0.62); I² = 0%						
Test for overall effect: Z = 3.41 (P = 0.0006)						
Test for subgroup differences: Chi² = 3.71, df = 2 (P = 0.16), I² = 46.1%						



Analysis 2.7. Comparison 2: 5-ASA versus sulfasalazine, Outcome 7: Exclusions and withdrawals after study entry

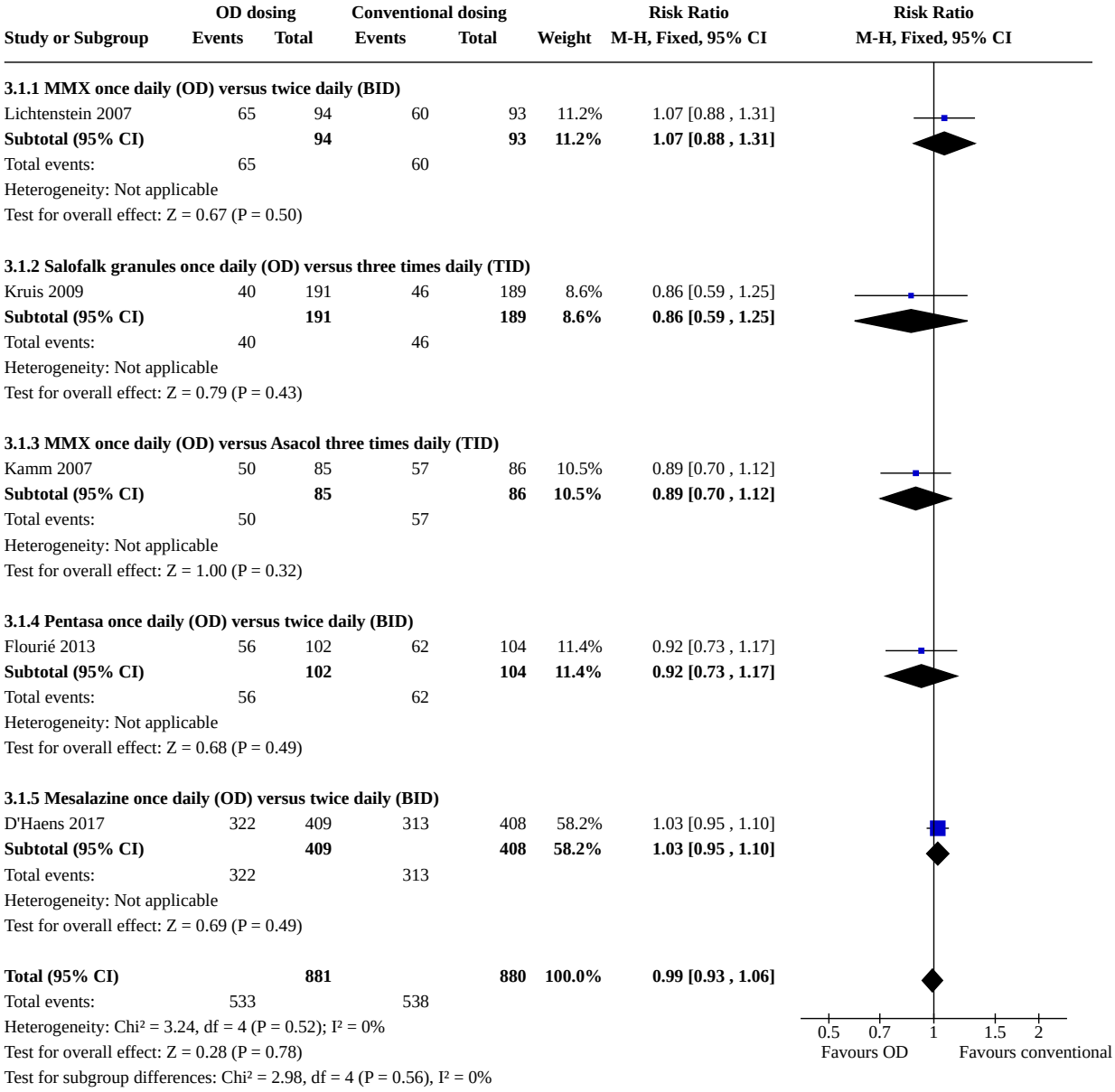


Comparison 3. Once daily dosing versus conventional dosing

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Failure to induce global/clinical remission	5	1761	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.93, 1.06]
3.1.1 MMX once daily (OD) versus twice daily (BID)	1	187	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.88, 1.31]
3.1.2 Salofalk granules once daily (OD) versus three times daily (TID)	1	380	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.59, 1.25]
3.1.3 MMX once daily (OD) versus Asacol three times daily (TID)	1	171	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.70, 1.12]

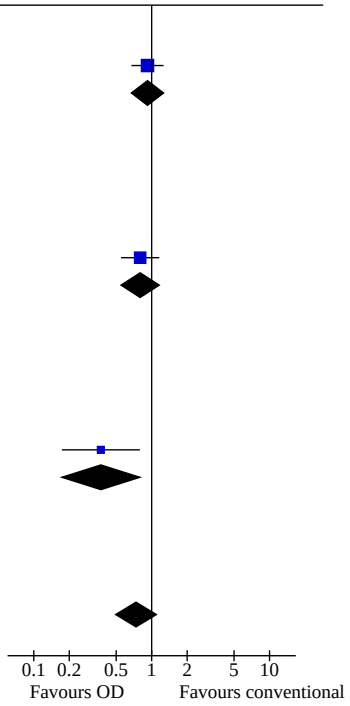
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1.4 Pentasa once daily (OD) versus twice daily (BID)	1	206	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.73, 1.17]
3.1.5 Mesalazine once daily (OD) versus twice daily (BID)	1	817	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.95, 1.10]
3.2 Failure to induce global/clinical improvement (including remission)	3	564	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.49, 1.10]
3.2.1 MMX (OD versus BID)	1	187	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.67, 1.26]
3.2.2 MMX (OD) versus Asacol (TID)	1	171	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.55, 1.16]
3.2.3 Pentasa (OD versus BID)	1	206	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.17, 0.79]
3.3 Failure to induce global/clinical improvement (sensitivity analysis)	2	358	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.68, 1.10]
3.3.1 MMX (OD versus BID)	1	187	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.67, 1.26]
3.3.2 MMX (OD) versus Asacol (TID)	1	171	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.55, 1.16]
3.4 Failure to induce endoscopic remission	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.5 Failure to induce endoscopic improvement (including remission)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.6 Failure to adhere to medication regimen	2	358	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.64, 2.86]
3.7 Compliance	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.8 Adverse events	4	1586	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.89, 1.18]
3.9 Serious adverse events	4	1586	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [0.68, 2.66]
3.10 Withdrawals due to adverse events	5	1757	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.54, 1.49]
3.11 Exclusions and withdrawals after study entry	4	944	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.74, 1.39]

Analysis 3.1. Comparison 3: Once daily dosing versus conventional dosing, Outcome 1: Failure to induce global/clinical remission



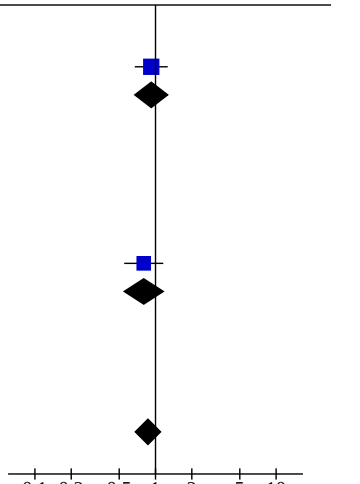
Analysis 3.2. Comparison 3: Once daily dosing versus conventional dosing, Outcome 2: Failure to induce global/clinical improvement (including remission)

Study or Subgroup	OD dosing Events	OD dosing Total	Conventional dosing Events	Conventional dosing Total	Weight	Risk Ratio M-H, Random, 95% CI
3.2.1 MMX (OD versus BID)						
Lichtenstein 2007	41	94	44	93	42.8%	0.92 [0.67 , 1.26]
Subtotal (95% CI)		**94**		**93**	**42.8%**	**0.92 [0.67 , 1.26]**
Total events:	41		44			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.51 (P = 0.61)						
3.2.2 MMX (OD) versus Asacol (TID)						
Kamm 2007	30	85	38	86	38.6%	0.80 [0.55 , 1.16]
Subtotal (95% CI)		**85**		**86**	**38.6%**	**0.80 [0.55 , 1.16]**
Total events:	30		38			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.18 (P = 0.24)						
3.2.3 Pentasa (OD versus BID)						
Flourié 2013	8	102	22	104	18.6%	0.37 [0.17 , 0.79]
Subtotal (95% CI)		**102**		**104**	**18.6%**	**0.37 [0.17 , 0.79]**
Total events:	8		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.55 (P = 0.01)						
Total (95% CI)		**281**		**283**	**100.0%**	**0.74 [0.49 , 1.10]**
Total events:	79		104			
Heterogeneity: Tau² = 0.07; Chi² = 4.91, df = 2 (P = 0.09); I² = 59%						
Test for overall effect: Z = 1.51 (P = 0.13)						
Test for subgroup differences: Chi² = 4.70, df = 2 (P = 0.10), I² = 57.4%						



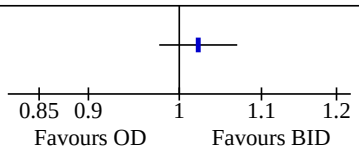
Analysis 3.3. Comparison 3: Once daily dosing versus conventional dosing, Outcome 3: Failure to induce global/clinical improvement (sensitivity analysis)

Study or Subgroup	OD dosing Events	OD dosing Total	Conventional dosing Events	Conventional dosing Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.3.1 MMX (OD versus BID)						
Lichtenstein 2007	41	94	44	93	53.9%	0.92 [0.67 , 1.26]
Subtotal (95% CI)		**94**		**93**	**53.9%**	**0.92 [0.67 , 1.26]**
Total events:	41		44			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.51 (P = 0.61)						
3.3.2 MMX (OD) versus Asacol (TID)						
Kamm 2007	30	85	38	86	46.1%	0.80 [0.55 , 1.16]
Subtotal (95% CI)		**85**		**86**	**46.1%**	**0.80 [0.55 , 1.16]**
Total events:	30		38			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.18 (P = 0.24)						
Total (95% CI)		**179**		**179**	**100.0%**	**0.87 [0.68 , 1.10]**
Total events:	71		82			
Heterogeneity: Chi² = 0.33, df = 1 (P = 0.56); I² = 0%						
Test for overall effect: Z = 1.18 (P = 0.24)						
Test for subgroup differences: Chi² = 0.33, df = 1 (P = 0.56), I² = 0%						



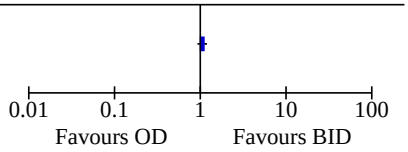
Analysis 3.4. Comparison 3: Once daily dosing versus conventional dosing, Outcome 4: Failure to induce endoscopic remission

Study or Subgroup	OD dosing Events	OD dosing Total	BID dosing Events	BID dosing Total	Risk Ratio M-H, Fixed, 95% CI
D'Haens 2017	373	409	364	408	1.02 [0.98 , 1.07]



Analysis 3.5. Comparison 3: Once daily dosing versus conventional dosing, Outcome 5: Failure to induce endoscopic improvement (including remission)

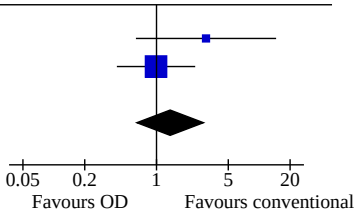
Study or Subgroup	OD Events	OD Total	BID Events	BID Total	Risk Ratio M-H, Fixed, 95% CI
D'Haens 2017	224	409	212	408	1.05 [0.93 , 1.20]



Analysis 3.6. Comparison 3: Once daily dosing versus conventional dosing, Outcome 6: Failure to adhere to medication regimen

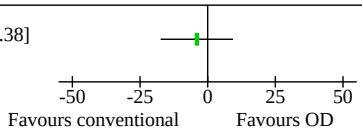
Study or Subgroup	OD dosing Events	OD dosing Total	Conventional dosing Events	Conventional dosing Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kamm 2007	6	85	2	86	18.0%	3.04 [0.63 , 14.62]
Lichtenstein 2007	9	94	9	93	82.0%	0.99 [0.41 , 2.38]
Total (95% CI)		**179**		**179**	**100.0%**	**1.36 [0.64 , 2.86]**
Total events:	15		11			

Heterogeneity: Chi² = 1.51, df = 1 (P = 0.22); I² = 34%
Test for overall effect: Z = 0.80 (P = 0.42)
Test for subgroup differences: Not applicable



Analysis 3.7. Comparison 3: Once daily dosing versus conventional dosing, Outcome 7: Compliance

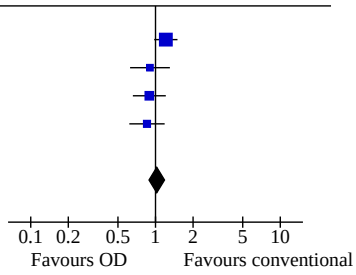
Study or Subgroup	OD dosing Mean	OD dosing SD	OD dosing Total	Conventional dosing Mean	Conventional dosing SD	Conventional dosing Total	Mean Difference IV, Fixed, 95% CI
Flourié 2013	104	23.7	102	108	65.4	104	-4.00 [-17.38 , 9.38]



Analysis 3.8. Comparison 3: Once daily dosing versus conventional dosing, Outcome 8: Adverse events

Study or Subgroup	OD dosing Events	OD dosing Total	Conventional dosing Events	Conventional dosing Total	Weight	Risk Ratio M-H, Fixed, 95% CI
D'Haens 2017	131	409	108	408	42.9%	1.21 [0.98 , 1.50]
Flourié 2013	35	102	38	100	15.2%	0.90 [0.63 , 1.30]
Kruis 2009	55	191	61	189	24.3%	0.89 [0.66 , 1.21]
Lichtenstein 2007	38	94	44	93	17.5%	0.85 [0.62 , 1.18]
Total (95% CI)		**796**		**790**	**100.0%**	**1.02 [0.89 , 1.18]**
Total events:	259		251			

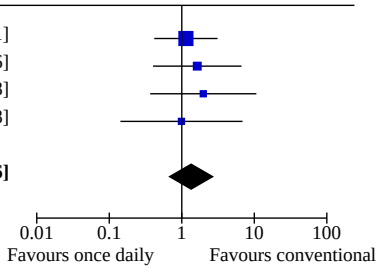
Heterogeneity: Chi² = 4.75, df = 3 (P = 0.19); I² = 37%
Test for overall effect: Z = 0.32 (P = 0.75)
Test for subgroup differences: Not applicable



Analysis 3.9. Comparison 3: Once daily dosing versus conventional dosing, Outcome 9: Serious adverse events

Study or Subgroup	Once daily dosing Events	Once daily dosing Total	Conventional dosing Events	Conventional dosing Total	Weight	Risk Ratio M-H, Fixed, 95% CI
D'Haens 2017	8	409	7	408	49.8%	1.14 [0.42 , 3.11]
Flourié 2013	5	102	3	100	21.5%	1.63 [0.40 , 6.66]
Kruis 2009	4	191	2	189	14.3%	1.98 [0.37 , 10.68]
Lichtenstein 2007	2	94	2	93	14.3%	0.99 [0.14 , 6.88]
Total (95% CI)		**796**		**790**	**100.0%**	**1.34 [0.68 , 2.66]**
Total events:	19		14			

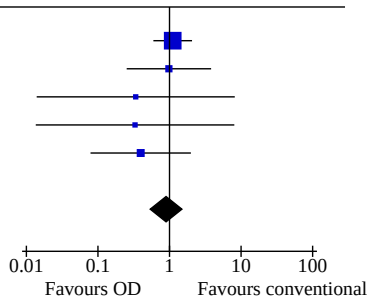
Heterogeneity: Chi² = 0.48, df = 3 (P = 0.92); I² = 0%
Test for overall effect: Z = 0.85 (P = 0.39)
Test for subgroup differences: Not applicable



Analysis 3.10. Comparison 3: Once daily dosing versus conventional dosing, Outcome 10: Withdrawals due to adverse events

Study or Subgroup	OD dosing Events	OD dosing Total	Conventional dosing Events	Conventional dosing Total	Weight	Risk Ratio M-H, Fixed, 95% CI
D'Haens 2017	20	409	18	408	59.9%	1.11 [0.60 , 2.06]
Flourié 2013	4	102	4	100	13.4%	0.98 [0.25 , 3.81]
Kamm 2007	0	85	1	86	5.0%	0.34 [0.01 , 8.16]
Kruis 2009	0	191	1	189	5.0%	0.33 [0.01 , 8.05]
Lichtenstein 2007	2	94	5	93	16.7%	0.40 [0.08 , 1.99]
Total (95% CI)		**881**		**876**	**100.0%**	**0.89 [0.54 , 1.49]**
Total events:	26		29			

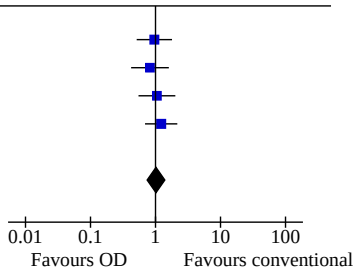
Heterogeneity: Chi² = 2.19, df = 4 (P = 0.70); I² = 0%
Test for overall effect: Z = 0.43 (P = 0.67)
Test for subgroup differences: Not applicable



Analysis 3.11. Comparison 3: Once daily dosing versus conventional dosing, Outcome 11: Exclusions and withdrawals after study entry

Study or Subgroup	OD dosing Events	OD dosing Total	Conventional dosing Events	Conventional dosing Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Flourié 2013	16	102	17	104	25.5%	0.96 [0.51 , 1.79]
Kamm 2007	13	85	16	86	24.1%	0.82 [0.42 , 1.60]
Kruis 2009	17	191	16	189	24.4%	1.05 [0.55 , 2.02]
Lichtenstein 2007	21	94	17	93	25.9%	1.22 [0.69 , 2.16]
Total (95% CI)		**472**		**472**	**100.0%**	**1.02 [0.74 , 1.39]**
Total events:	67		66			

Heterogeneity: Chi² = 0.83, df = 3 (P = 0.84); I² = 0%
Test for overall effect: Z = 0.11 (P = 0.92)
Test for subgroup differences: Not applicable



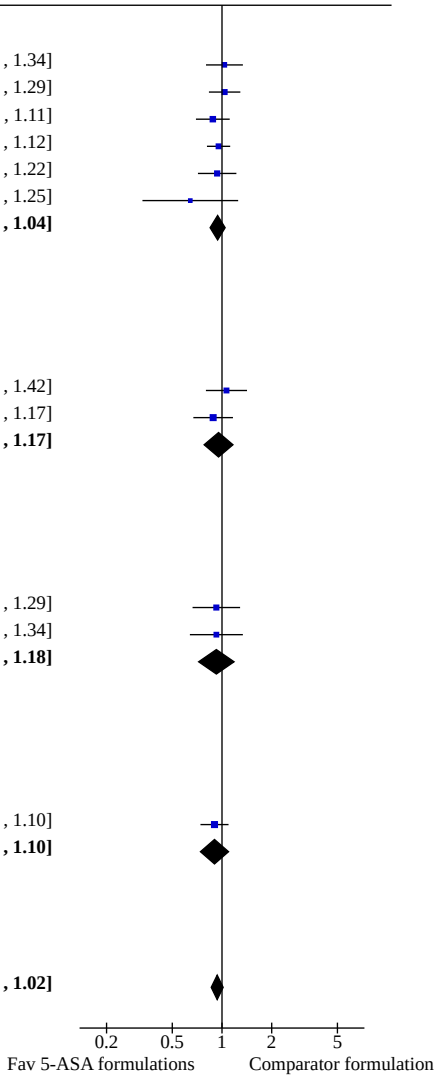
Comparison 4. 5-ASA versus comparator 5-ASA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Failure to induce global/clinical remission	11	1968	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.86, 1.02]
4.1.1 Asacol comparator	6	720	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.85, 1.04]
4.1.2 Claversal comparator	2	530	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.78, 1.17]
4.1.3 Salofalk comparator	2	491	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.72, 1.18]
4.1.4 Pentasa comparator	1	227	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.74, 1.10]
4.2 Failure to induce global/clinical remission (sensitivity analysis)	9	1681	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.87, 1.04]
4.2.1 Asacol comparator	5	660	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.86, 1.07]
4.2.2 Claversal comparator	2	530	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.78, 1.17]
4.2.3 Salofalk comparator	2	491	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.72, 1.18]
4.3 Failure to induce global/clinical improvement (including remission)	8	1647	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.77, 1.01]
4.3.1 Asacol comparator	3	399	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.73, 1.11]
4.3.2 Claversal comparator	2	530	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.67, 1.10]
4.3.3 Salofalk comparator	2	491	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.74, 1.36]
4.3.4 Pentasa comparator	1	227	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.45, 1.08]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.4 Failure to induce global/clinical improvement (sensitivity analysis)	7	1420	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.79, 1.05]
4.4.1 Asacol comparator	3	399	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.73, 1.11]
4.4.2 Claversal comparator	2	530	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.67, 1.10]
4.4.3 Salofalk comparator	2	491	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.74, 1.36]
4.5 Adverse events	9	1576	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.92, 1.12]
4.5.1 Asacol comparator	5	556	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.80, 1.03]
4.5.2 Claversal comparator	2	530	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [1.01, 1.66]
4.5.3 Salofalk comparator	2	490	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.81, 1.20]
4.6 Serious adverse events	4	677	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.22, 1.56]
4.6.1 Asacol comparator	2	277	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.05, 2.11]
4.6.2 Claversal comparator	1	168	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.16, 2.95]
4.6.3 Salofalk comparator	1	232	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.14, 6.74]
4.7 Withdrawals due to adverse events	9	1489	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.57, 1.54]
4.7.1 Asacol comparator	6	726	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.22, 1.04]
4.7.2 Claversal comparator	2	530	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [0.70, 3.14]
4.7.3 Salofalk comparator	1	233	Risk Ratio (M-H, Fixed, 95% CI)	3.90 [0.44, 34.35]
4.8 Exclusions and withdrawals after study entry	9	1574	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.80, 1.22]
4.8.1 Asacol comparator	5	553	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.67, 1.24]
4.8.2 Claversal comparator	2	530	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.74, 1.63]
4.8.3 Salofalk comparator	2	491	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.67, 1.51]

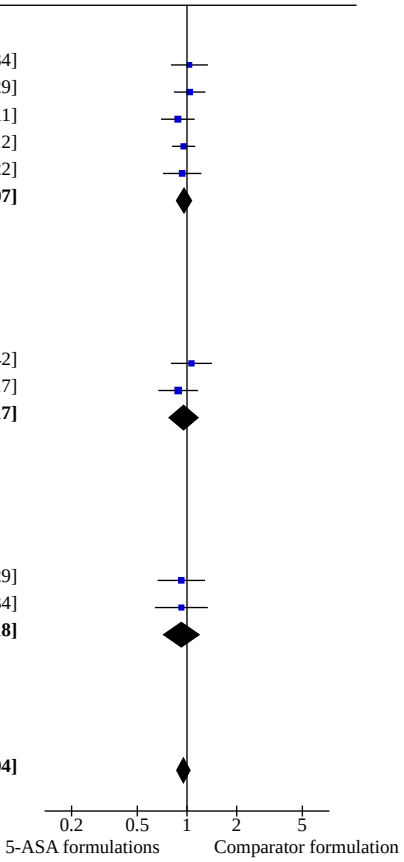
Analysis 4.1. Comparison 4: 5-ASA versus comparator 5-ASA, Outcome 1: Failure to induce global/clinical remission

Study or Subgroup	5-ASA formulations Events	Total	5-ASA comparator Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.1.1 Asacol comparator						
Forbes 2005	34	46	30	42	6.2%	1.03 [0.80 , 1.34]
Ito 2010	47	65	46	66	9.0%	1.04 [0.83 , 1.29]
Kamm 2007	49	84	57	86	11.1%	0.88 [0.70 , 1.11]
Levine 2002	41	49	43	49	8.5%	0.95 [0.81 , 1.12]
Pruitt 2002	45	84	51	89	9.7%	0.93 [0.72 , 1.22]
Tursi 2004	9	30	14	30	2.8%	0.64 [0.33 , 1.25]
Subtotal (95% CI)		**358**		**362**	**47.2%**	**0.94 [0.85 , 1.04]**
Total events:	225		241			
Heterogeneity: Chi² = 2.88, df = 5 (P = 0.72); I² = 0%						
Test for overall effect: Z = 1.14 (P = 0.25)						
4.1.2 Claversal comparator						
Kruis 1998	48	88	41	80	8.4%	1.06 [0.80 , 1.42]
Raedler 2004	61	181	69	181	13.6%	0.88 [0.67 , 1.17]
Subtotal (95% CI)		**269**		**261**	**22.0%**	**0.95 [0.78 , 1.17]**
Total events:	109		110			
Heterogeneity: Chi² = 0.85, df = 1 (P = 0.36); I² = 0%						
Test for overall effect: Z = 0.47 (P = 0.64)						
4.1.3 Salofalk comparator						
Gibson 2006	43	127	48	131	9.3%	0.92 [0.66 , 1.29]
Marakhouski 2005	37	118	39	115	7.8%	0.92 [0.64 , 1.34]
Subtotal (95% CI)		**245**		**246**	**17.1%**	**0.92 [0.72 , 1.18]**
Total events:	80		87			
Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%						
Test for overall effect: Z = 0.63 (P = 0.53)						
4.1.4 Pentasa comparator						
Farup 2001	93	150	53	77	13.8%	0.90 [0.74 , 1.10]
Subtotal (95% CI)		**150**		**77**	**13.8%**	**0.90 [0.74 , 1.10]**
Total events:	93		53			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.05 (P = 0.30)						
Total (95% CI)		**1022**		**946**	**100.0%**	**0.94 [0.86 , 1.02]**
Total events:	507		491			
Heterogeneity: Chi² = 4.07, df = 10 (P = 0.94); I² = 0%						
Test for overall effect: Z = 1.58 (P = 0.11)						
Test for subgroup differences: Chi² = 0.20, df = 3 (P = 0.98), I² = 0%						



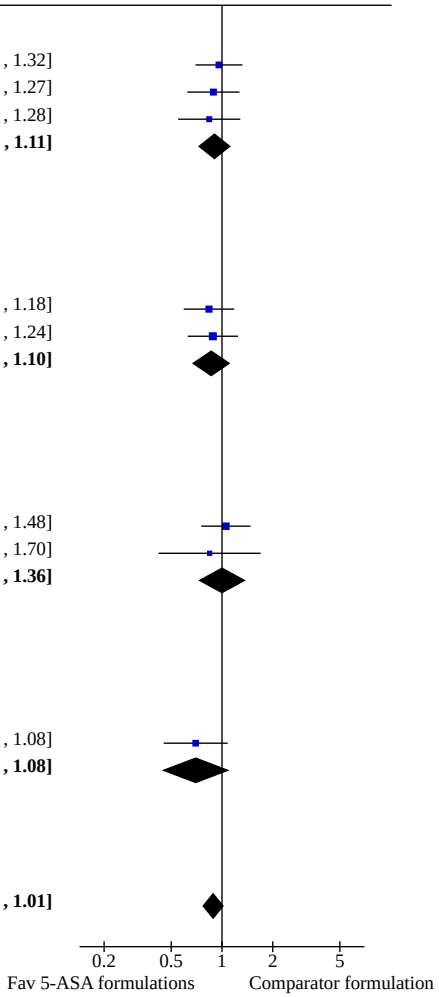
Analysis 4.2. Comparison 4: 5-ASA versus comparator 5-ASA, Outcome 2: Failure to induce global/clinical remission (sensitivity analysis)

Study or Subgroup	5-ASA formulations Events	Total	5-ASA comparator Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.2.1 Asacol comparator						
Forbes 2005	34	46	30	42	7.4%	1.03 [0.80 , 1.34]
Ito 2010	47	65	46	66	10.8%	1.04 [0.83 , 1.29]
Kamm 2007	49	84	57	86	13.3%	0.88 [0.70 , 1.11]
Levine 2002	41	49	43	49	10.1%	0.95 [0.81 , 1.12]
Pruitt 2002	45	84	51	89	11.7%	0.93 [0.72 , 1.22]
Subtotal (95% CI)		**328**		**332**	**53.2%**	**0.96 [0.86 , 1.07]**
Total events:	216		227			
Heterogeneity: Chi² = 1.38, df = 4 (P = 0.85); I² = 0%						
Test for overall effect: Z = 0.78 (P = 0.44)						
4.2.2 Claversal comparator						
Kruis 1998	48	88	41	80	10.1%	1.06 [0.80 , 1.42]
Raedler 2004	61	181	69	181	16.3%	0.88 [0.67 , 1.17]
Subtotal (95% CI)		**269**		**261**	**26.4%**	**0.95 [0.78 , 1.17]**
Total events:	109		110			
Heterogeneity: Chi² = 0.85, df = 1 (P = 0.36); I² = 0%						
Test for overall effect: Z = 0.47 (P = 0.64)						
4.2.3 Salofalk comparator						
Gibson 2006	43	127	48	131	11.1%	0.92 [0.66 , 1.29]
Marakhouski 2005	37	118	39	115	9.3%	0.92 [0.64 , 1.34]
Subtotal (95% CI)		**245**		**246**	**20.4%**	**0.92 [0.72 , 1.18]**
Total events:	80		87			
Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%						
Test for overall effect: Z = 0.63 (P = 0.53)						
Total (95% CI)		**842**		**839**	**100.0%**	**0.95 [0.87 , 1.04]**
Total events:	405		424			
Heterogeneity: Chi² = 2.37, df = 8 (P = 0.97); I² = 0%						
Test for overall effect: Z = 1.08 (P = 0.28)						
Test for subgroup differences: Chi² = 0.07, df = 2 (P = 0.96), I² = 0%						



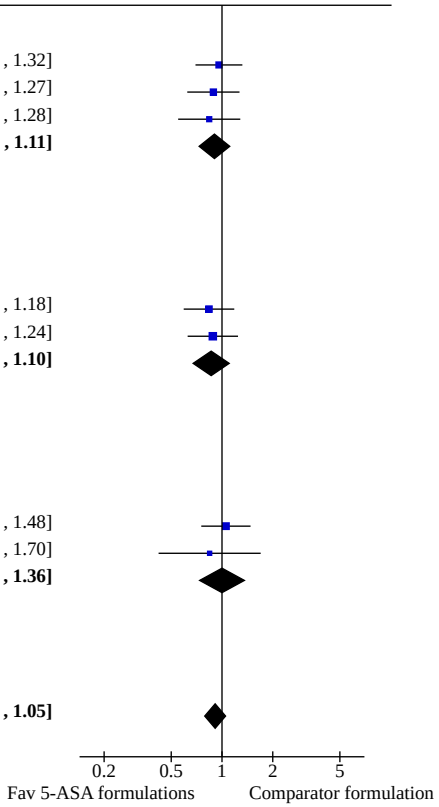
Analysis 4.3. Comparison 4: 5-ASA versus comparator 5-ASA, Outcome 3: Failure to induce global/clinical improvement (including remission)

Study or Subgroup	5-ASA formulations Events	Total	5-ASA comparator Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.3.1 Asacol comparator						
Ito 2010	34	65	36	66	12.7%	0.96 [0.70 , 1.32]
Kamm 2007	33	84	38	86	13.4%	0.89 [0.62 , 1.27]
Levine 2002	21	49	25	49	8.9%	0.84 [0.55 , 1.28]
Subtotal (95% CI)		**198**		**201**	**35.0%**	**0.90 [0.73 , 1.11]**
Total events:	88		99			
Heterogeneity: Chi² = 0.26, df = 2 (P = 0.88); I² = 0%						
Test for overall effect: Z = 0.97 (P = 0.33)						
4.3.2 Claversal comparator						
Kruis 1998	35	88	38	80	14.2%	0.84 [0.59 , 1.18]
Raedler 2004	45	181	51	181	18.2%	0.88 [0.63 , 1.24]
Subtotal (95% CI)		**269**		**261**	**32.4%**	**0.86 [0.67 , 1.10]**
Total events:	80		89			
Heterogeneity: Chi² = 0.05, df = 1 (P = 0.83); I² = 0%						
Test for overall effect: Z = 1.18 (P = 0.24)						
4.3.3 Salofalk comparator						
Gibson 2006	45	127	44	131	15.4%	1.05 [0.75 , 1.48]
Marakhouski 2005	13	118	15	115	5.4%	0.84 [0.42 , 1.70]
Subtotal (95% CI)		**245**		**246**	**20.8%**	**1.00 [0.74 , 1.36]**
Total events:	58		59			
Heterogeneity: Chi² = 0.32, df = 1 (P = 0.57); I² = 0%						
Test for overall effect: Z = 0.00 (P = 1.00)						
4.3.4 Pentasa comparator						
Farup 2001	34	150	25	77	11.8%	0.70 [0.45 , 1.08]
Subtotal (95% CI)		**150**		**77**	**11.8%**	**0.70 [0.45 , 1.08]**
Total events:	34		25			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.61 (P = 0.11)						
Total (95% CI)		**862**		**785**	**100.0%**	**0.89 [0.77 , 1.01]**
Total events:	260		272			
Heterogeneity: Chi² = 2.59, df = 7 (P = 0.92); I² = 0%						
Test for overall effect: Z = 1.76 (P = 0.08)						
Test for subgroup differences: Chi² = 1.82, df = 3 (P = 0.61), I² = 0%						



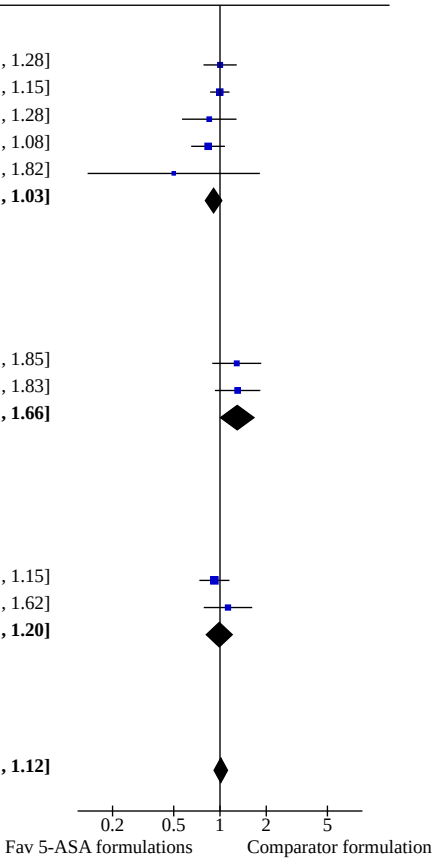
Analysis 4.4. Comparison 4: 5-ASA versus comparator 5-ASA, Outcome 4: Failure to induce global/clinical improvement (sensitivity analysis)

Study or Subgroup	5-ASA formulations Events	Total	5-ASA comparator Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.4.1 Asacol comparator						
Ito 2010	34	65	36	66	14.4%	0.96 [0.70 , 1.32]
Kamm 2007	33	84	38	86	15.2%	0.89 [0.62 , 1.27]
Levine 2002	21	49	25	49	10.1%	0.84 [0.55 , 1.28]
Subtotal (95% CI)		**198**		**201**	**39.7%**	**0.90 [0.73 , 1.11]**
Total events:	88		99			
Heterogeneity: Chi² = 0.26, df = 2 (P = 0.88); I² = 0%						
Test for overall effect: Z = 0.97 (P = 0.33)						
4.4.2 Claversal comparator						
Kruis 1998	35	88	38	80	16.1%	0.84 [0.59 , 1.18]
Raedler 2004	45	181	51	181	20.6%	0.88 [0.63 , 1.24]
Subtotal (95% CI)		**269**		**261**	**36.7%**	**0.86 [0.67 , 1.10]**
Total events:	80		89			
Heterogeneity: Chi² = 0.05, df = 1 (P = 0.83); I² = 0%						
Test for overall effect: Z = 1.18 (P = 0.24)						
4.4.3 Salofalk comparator						
Gibson 2006	45	127	44	131	17.5%	1.05 [0.75 , 1.48]
Marakhouski 2005	13	118	15	115	6.1%	0.84 [0.42 , 1.70]
Subtotal (95% CI)		**245**		**246**	**23.6%**	**1.00 [0.74 , 1.36]**
Total events:	58		59			
Heterogeneity: Chi² = 0.32, df = 1 (P = 0.57); I² = 0%						
Test for overall effect: Z = 0.00 (P = 1.00)						
Total (95% CI)		**712**		**708**	**100.0%**	**0.91 [0.79 , 1.05]**
Total events:	226		247			
Heterogeneity: Chi² = 1.30, df = 6 (P = 0.97); I² = 0%						
Test for overall effect: Z = 1.29 (P = 0.20)						
Test for subgroup differences: Chi² = 0.56, df = 2 (P = 0.76), I² = 0%						



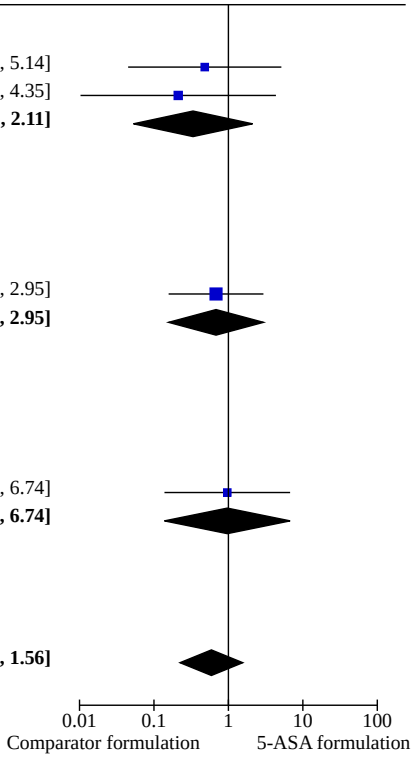
Analysis 4.5. Comparison 4: 5-ASA versus comparator 5-ASA, Outcome 5: Adverse events

Study or Subgroup	5-ASA formulations Events	Total	5-ASA comparator Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.5.1 Asacol comparator						
Forbes 2005	34	46	31	42	9.0%	1.00 [0.78 , 1.28]
Ito 2010	55	65	56	66	15.5%	1.00 [0.86 , 1.15]
Levine 2002	23	53	26	51	7.4%	0.85 [0.57 , 1.28]
Pruitt 2002	45	84	57	89	15.4%	0.84 [0.65 , 1.08]
Tursi 2004	3	30	6	30	1.7%	0.50 [0.14 , 1.82]
Subtotal (95% CI)		**278**		**278**	**49.0%**	**0.91 [0.80 , 1.03]**
Total events:	160		176			
Heterogeneity: Chi² = 3.50, df = 4 (P = 0.48); I² = 0%						
Test for overall effect: Z = 1.53 (P = 0.13)						
4.5.2 Claversal comparator						
Kruis 1998	41	88	29	80	8.5%	1.29 [0.89 , 1.85]
Raedler 2004	56	181	43	181	12.0%	1.30 [0.93 , 1.83]
Subtotal (95% CI)		**269**		**261**	**20.5%**	**1.30 [1.01 , 1.66]**
Total events:	97		72			
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.96); I² = 0%						
Test for overall effect: Z = 2.02 (P = 0.04)						
4.5.3 Salofalk comparator						
Gibson 2006	66	127	74	131	20.3%	0.92 [0.73 , 1.15]
Marakhouski 2005	42	118	36	114	10.2%	1.13 [0.78 , 1.62]
Subtotal (95% CI)		**245**		**245**	**30.5%**	**0.99 [0.81 , 1.20]**
Total events:	108		110			
Heterogeneity: Chi² = 0.90, df = 1 (P = 0.34); I² = 0%						
Test for overall effect: Z = 0.11 (P = 0.91)						
Total (95% CI)		**792**		**784**	**100.0%**	**1.01 [0.92 , 1.12]**
Total events:	365		358			
Heterogeneity: Chi² = 8.85, df = 8 (P = 0.36); I² = 10%						
Test for overall effect: Z = 0.24 (P = 0.81)						
Test for subgroup differences: Chi² = 6.23, df = 2 (P = 0.04), I² = 67.9%						



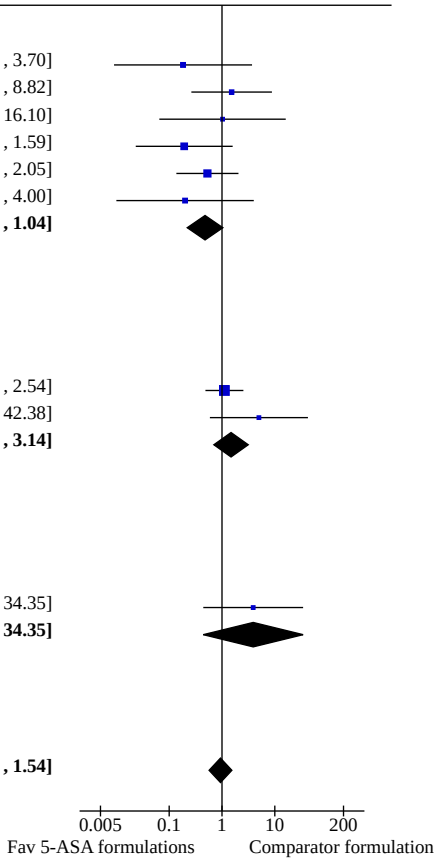
Analysis 4.6. Comparison 4: 5-ASA versus comparator 5-ASA, Outcome 6: Serious adverse events

Study or Subgroup	5-ASA formulations Events	Total	5-ASA comparator Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.6.1 Asacol comparator						
Levine 2002	1	53	2	51	19.1%	0.48 [0.05 , 5.14]
Pruitt 2002	0	84	2	89	22.7%	0.21 [0.01 , 4.35]
Subtotal (95% CI)		**137**		**140**	**41.8%**	**0.33 [0.05 , 2.11]**
Total events:	1		4			
Heterogeneity: Chi² = 0.18, df = 1 (P = 0.67); I² = 0%						
Test for overall effect: Z = 1.17 (P = 0.24)						
4.6.2 Claversal comparator						
Kruis 1998	3	88	4	80	39.2%	0.68 [0.16 , 2.95]
Subtotal (95% CI)		**88**		**80**	**39.2%**	**0.68 [0.16 , 2.95]**
Total events:	3		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.51 (P = 0.61)						
4.6.3 Salofalk comparator						
Marakhouski 2005	2	118	2	114	19.0%	0.97 [0.14 , 6.74]
Subtotal (95% CI)		**118**		**114**	**19.0%**	**0.97 [0.14 , 6.74]**
Total events:	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.03 (P = 0.97)						
Total (95% CI)		**343**		**334**	**100.0%**	**0.59 [0.22 , 1.56]**
Total events:	6		10			
Heterogeneity: Chi² = 0.75, df = 3 (P = 0.86); I² = 0%						
Test for overall effect: Z = 1.06 (P = 0.29)						
Test for subgroup differences: Chi² = 0.65, df = 2 (P = 0.72), I² = 0%						



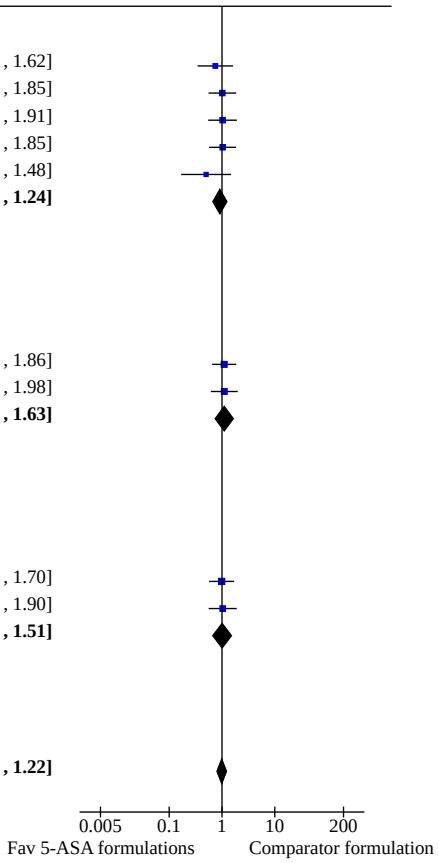
Analysis 4.7. Comparison 4: 5-ASA versus comparator 5-ASA, Outcome 7: Withdrawals due to adverse events

Study or Subgroup	5-ASA formulations Events	Total	5-ASA comparator Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.7.1 Asacol comparator						
Forbes 2005	0	46	2	42	8.6%	0.18 [0.01 , 3.70]
Ito 2010	3	65	2	66	6.5%	1.52 [0.26 , 8.82]
Kamm 2007	1	84	1	86	3.2%	1.02 [0.07 , 16.10]
Levine 2002	1	53	5	51	16.7%	0.19 [0.02 , 1.59]
Pruitt 2002	3	84	6	89	19.1%	0.53 [0.14 , 2.05]
Tursi 2004	0	30	2	30	8.2%	0.20 [0.01 , 4.00]
Subtotal (95% CI)		**362**		**364**	**62.4%**	**0.48 [0.22 , 1.04]**
Total events:	8		18			
Heterogeneity: Chi² = 3.42, df = 5 (P = 0.64); I² = 0%						
Test for overall effect: Z = 1.87 (P = 0.06)						
4.7.2 Claversal comparator						
Kruis 1998	11	88	9	80	31.0%	1.11 [0.49 , 2.54]
Raedler 2004	5	181	1	181	3.3%	5.00 [0.59 , 42.38]
Subtotal (95% CI)		**269**		**261**	**34.3%**	**1.48 [0.70 , 3.14]**
Total events:	16		10			
Heterogeneity: Chi² = 1.71, df = 1 (P = 0.19); I² = 42%						
Test for overall effect: Z = 1.03 (P = 0.30)						
4.7.3 Salofalk comparator						
Marakhouski 2005	4	118	1	115	3.3%	3.90 [0.44 , 34.35]
Subtotal (95% CI)		**118**		**115**	**3.3%**	**3.90 [0.44 , 34.35]**
Total events:	4		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.23 (P = 0.22)						
Total (95% CI)		**749**		**740**	**100.0%**	**0.94 [0.57 , 1.54]**
Total events:	28		29			
Heterogeneity: Chi² = 9.46, df = 8 (P = 0.30); I² = 15%						
Test for overall effect: Z = 0.26 (P = 0.79)						
Test for subgroup differences: Chi² = 6.00, df = 2 (P = 0.05), I² = 66.6%						



Analysis 4.8. Comparison 4: 5-ASA versus comparator 5-ASA, Outcome 8: Exclusions and withdrawals after study entry

Study or Subgroup	5-ASA formulations Events	Total	5-ASA comparator Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.8.1 Asacol comparator						
Forbes 2005	9	46	11	42	8.0%	0.75 [0.34 , 1.62]
Ito 2010	16	65	16	66	11.0%	1.02 [0.56 , 1.85]
Kamm 2007	16	84	16	86	11.0%	1.02 [0.55 , 1.91]
Levine 2002	16	53	15	51	10.6%	1.03 [0.57 , 1.85]
Tursi 2004	4	30	8	30	5.5%	0.50 [0.17 , 1.48]
Subtotal (95% CI)		**278**		**275**	**46.1%**	**0.91 [0.67 , 1.24]**
Total events:	61		66			
Heterogeneity: Chi² = 1.83, df = 4 (P = 0.77); I² = 0%						
Test for overall effect: Z = 0.60 (P = 0.55)						
4.8.2 Claversal comparator						
Kruis 1998	23	88	19	80	13.8%	1.10 [0.65 , 1.86]
Raedler 2004	21	181	19	181	13.2%	1.11 [0.62 , 1.98]
Subtotal (95% CI)		**269**		**261**	**27.0%**	**1.10 [0.74 , 1.63]**
Total events:	44		38			
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.99); I² = 0%						
Test for overall effect: Z = 0.49 (P = 0.63)						
4.8.3 Salofalk comparator						
Gibson 2006	21	127	22	131	15.0%	0.98 [0.57 , 1.70]
Marakhouski 2005	18	118	17	115	11.9%	1.03 [0.56 , 1.90]
Subtotal (95% CI)		**245**		**246**	**26.9%**	**1.01 [0.67 , 1.51]**
Total events:	39		39			
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.91); I² = 0%						
Test for overall effect: Z = 0.03 (P = 0.98)						
Total (95% CI)		**792**		**782**	**100.0%**	**0.99 [0.80 , 1.22]**
Total events:	144		143			
Heterogeneity: Chi² = 2.36, df = 8 (P = 0.97); I² = 0%						
Test for overall effect: Z = 0.11 (P = 0.91)						
Test for subgroup differences: Chi² = 0.58, df = 2 (P = 0.75), I² = 0%						



Comparison 5. 5-ASA dose ranging

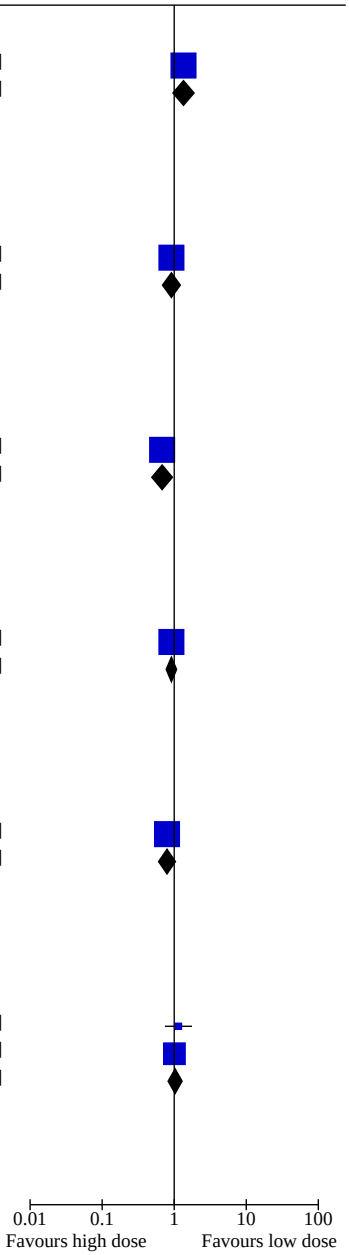
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Failure to Induce Global/Clinical Remission	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1.1 Salofalk 4.5 g versus 3 g/day	1	213	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.96, 1.89]
5.1.2 Salofalk 4.5 g versus 1.5 g/day	1	209	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.69, 1.22]
5.1.3 Salofalk 3 g versus 1.5 g/day	1	210	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.49, 0.95]
5.1.4 Pentasa 4 g versus 2.25 g/day	1	123	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.77, 1.08]
5.1.5 Asacol 3.6 g versus 2.4 g/day	1	131	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.61, 1.04]
5.1.6 MMX mesalazine 4.8 g versus 2.4 g/day	2	194	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.82, 1.29]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.2 Failure to Induce Global/Clinical Remission or Improvement	9		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.2.1 Asacol 4.8 g versus 1.6 g/day	1	49	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.19, 0.69]
5.2.2 Asacol 3.6 g versus 1.2 g/day	1	49	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.29, 1.28]
5.2.3 Asacol 2.4 g versus 1.6 or 1.2 g/day	2	155	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.70, 1.21]
5.2.4 Asacol 3.6 g versus 2.4 g/day	2	179	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.48, 0.97]
5.2.5 Asacol 4.8 g versus 2.4 g/day	3	1459	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.78, 1.01]
5.2.6 MMX mesalazine 4.8 g versus 2.4 g/day	1	169	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.61, 1.33]
5.2.7 Pentasa 4 g versus 2.25 g/day	1	123	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.27, 0.71]
5.3 Development of any adverse event	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.3.1 Asacol 4.8 g versus 1.6 g/day	1	49	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.48, 1.21]
5.3.2 Salofalk 4.5 g versus 3 g/day	1	213	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.78, 1.20]
5.3.3 Salofalk 4.5 g versus 1.5 g/day	1	209	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.77, 1.19]
5.3.4 Salofalk 3 g versus 1.5 g/day	1	213	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.84, 1.29]
5.3.5 Pentasa 4 g versus 2.25 g/day	1	123	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.78, 1.11]
5.4 Serious adverse events	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.4.1 5.3.2 Salofalk 4.5 g versus 3 g/day	1	213	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.05, 5.48]
5.4.2 5.3.5 Pentasa 4 g versus 2.25 g/day	1	123	Risk Ratio (M-H, Fixed, 95% CI)	5.25 [0.26, 107.07]
5.5 Withdrawal from study due to adverse event	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.5.1 Asacol 4.8 g versus 2.4 g/day	1	268	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.24, 3.63]
5.5.2 Asacol 4.8 g versus 1.6 g/day	1	49	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.02, 4.26]
5.5.3 Asacol 2.4 g versus 1.6 g/day	1	106	Risk Ratio (M-H, Fixed, 95% CI)	5.00 [0.25, 101.73]
5.5.4 Salofalk 4.5 g versus 3 g/day	1	213	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.50, 3.36]
5.5.5 Salofalk 4.5 g versus 1.5 g/day	1	209	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.34, 1.84]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.5.6 Salofalk 3 g versus 1.5 g/day	1	210	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.25, 1.52]
5.5.7 Pentasa 4 g versus 2.25 g/day	1	123	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.01, 4.28]
5.6 Exclusions and withdrawals after entry	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.6.1 Salofalk 3 g versus 1.5 g/day	1	210	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.38, 0.99]
5.6.2 Asacol 4.8 g versus 2.4 g/day	1	386	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.40, 1.16]
5.6.3 Asacol 4.8 g versus 1.6 g/day	1	49	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.04, 1.01]
5.6.4 Asacol 3.6 g versus 2.4 g/day	1	48	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.10, 2.48]
5.6.5 Asacol 3.6 g versus 1.2 g/day	1	49	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.09, 1.95]
5.6.6 Asacol 2.4 g versus 1.6 or 1.2 g/day	2	155	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.60, 1.92]
5.6.7 Salofalk 4.5 g versus 3 g/day	1	213	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.59, 1.74]
5.6.8 Salofalk 4.5 g versus 1.5 g/day	1	209	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.38, 0.99]
5.6.9 Pentasa 4 g versus 2.25 g/day	1	123	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.24, 1.14]

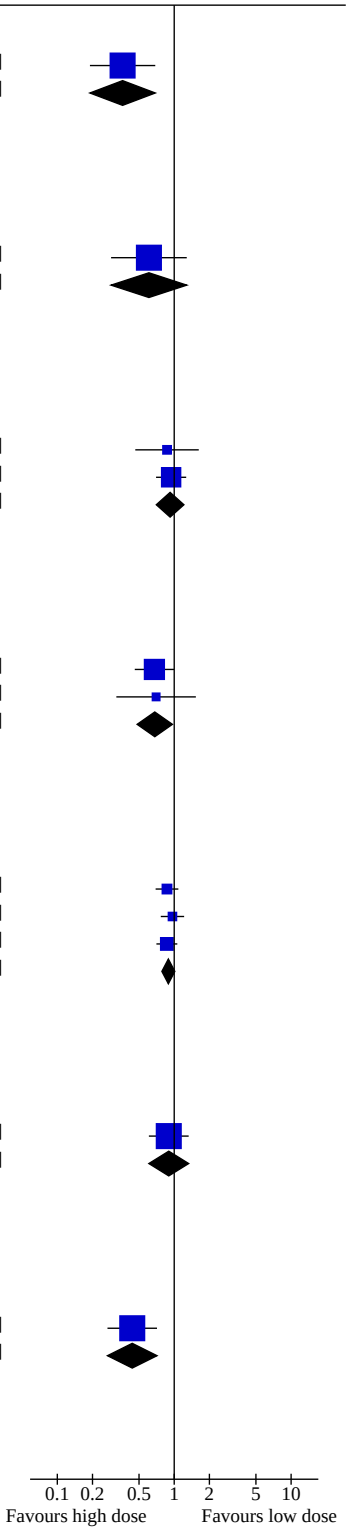
Analysis 5.1. Comparison 5: 5-ASA dose ranging, Outcome 1: Failure to Induce Global/Clinical Remission

Study or Subgroup	High dose mesalazine Events	Total	Low dose mesalazine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.1.1 Salofalk 4.5 g versus 3 g/day						
Kruis 2003	48	106	36	107	100.0%	1.35 [0.96 , 1.89]
Subtotal (95% CI)		**106**		**107**	**100.0%**	**1.35 [0.96 , 1.89]**
Total events:	48		36			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.72 (P = 0.09)						
5.1.2 Salofalk 4.5 g versus 1.5 g/day						
Kruis 2003	48	106	51	103	100.0%	0.91 [0.69 , 1.22]
Subtotal (95% CI)		**106**		**103**	**100.0%**	**0.91 [0.69 , 1.22]**
Total events:	48		51			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.61 (P = 0.54)						
5.1.3 Salofalk 3 g versus 1.5 g/day						
Kruis 2003	36	107	51	103	100.0%	0.68 [0.49 , 0.95]
Subtotal (95% CI)		**107**		**103**	**100.0%**	**0.68 [0.49 , 0.95]**
Total events:	36		51			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.30 (P = 0.02)						
5.1.4 Pentasa 4 g versus 2.25 g/day						
Hiwatashi 2011	47	60	54	63	100.0%	0.91 [0.77 , 1.08]
Subtotal (95% CI)		**60**		**63**	**100.0%**	**0.91 [0.77 , 1.08]**
Total events:	47		54			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.06 (P = 0.29)						
5.1.5 Asacol 3.6 g versus 2.4 g/day						
Ito 2010	36	65	46	66	100.0%	0.79 [0.61 , 1.04]
Subtotal (95% CI)		**65**		**66**	**100.0%**	**0.79 [0.61 , 1.04]**
Total events:	36		46			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.67 (P = 0.10)						
5.1.6 MMX mesalazine 4.8 g versus 2.4 g/day						
D'Haens 2006	9	11	10	14	15.1%	1.15 [0.74 , 1.77]
Kamm 2007	50	85	49	84	84.9%	1.01 [0.78 , 1.30]
Subtotal (95% CI)		**96**		**98**	**100.0%**	**1.03 [0.82 , 1.29]**
Total events:	59		59			
Heterogeneity: $Chi^2 = 0.26$, df = 1 (P = 0.61); $I^2 = 0\%$						
Test for overall effect: Z = 0.25 (P = 0.80)						
Test for subgroup differences: $Chi^2 = 10.19$, df = 5 (P = 0.07), $I^2 = 50.9\%$						



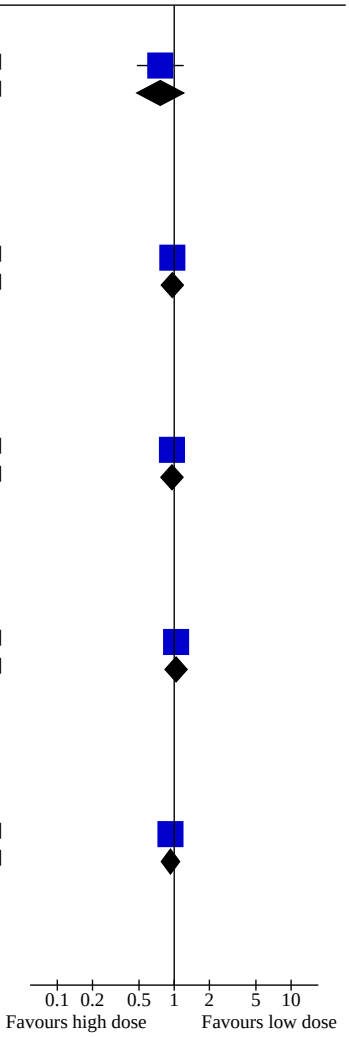
Analysis 5.2. Comparison 5: 5-ASA dose ranging, Outcome 2: Failure to Induce Global/Clinical Remission or Improvement

Study or Subgroup	High dose mesalazine Events	Total	Low dose mesalazine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.2.1 Asacol 4.8 g versus 1.6 g/day						
Schroeder 1987	10	38	8	11	100.0%	0.36 [0.19 , 0.69]
Subtotal (95% CI)		**38**		**11**	**100.0%**	**0.36 [0.19 , 0.69]**
Total events:	10		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.10 (P = 0.002)						
5.2.2 Asacol 3.6 g versus 1.2 g/day						
Miglioli 1990	7	24	12	25	100.0%	0.61 [0.29 , 1.28]
Subtotal (95% CI)		**24**		**25**	**100.0%**	**0.61 [0.29 , 1.28]**
Total events:	7		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.31 (P = 0.19)						
5.2.3 Asacol 2.4 g versus 1.6 or 1.2 g/day						
Miglioli 1990	10	24	12	25	25.7%	0.87 [0.46 , 1.62]
Sninsky 1991	32	53	34	53	74.3%	0.94 [0.70 , 1.27]
Subtotal (95% CI)		**77**		**78**	**100.0%**	**0.92 [0.70 , 1.21]**
Total events:	42		46			
Heterogeneity: Chi² = 0.05, df = 1 (P = 0.82); I² = 0%						
Test for overall effect: Z = 0.58 (P = 0.56)						
5.2.4 Asacol 3.6 g versus 2.4 g/day						
Ito 2010	24	65	36	66	78.1%	0.68 [0.46 , 1.00]
Miglioli 1990	7	24	10	24	21.9%	0.70 [0.32 , 1.53]
Subtotal (95% CI)		**89**		**90**	**100.0%**	**0.68 [0.48 , 0.97]**
Total events:	31		46			
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.94); I² = 0%						
Test for overall effect: Z = 2.16 (P = 0.03)						
5.2.5 Asacol 4.8 g versus 2.4 g/day						
Hanauer 2005	79	191	93	195	30.7%	0.87 [0.69 , 1.08]
Hanauer 2007	71	147	77	154	25.0%	0.97 [0.77 , 1.22]
Sandborn 2009	116	389	132	383	44.3%	0.87 [0.70 , 1.06]
Subtotal (95% CI)		**727**		**732**	**100.0%**	**0.89 [0.78 , 1.01]**
Total events:	266		302			
Heterogeneity: Chi² = 0.61, df = 2 (P = 0.74); I² = 0%						
Test for overall effect: Z = 1.77 (P = 0.08)						
5.2.6 MMX mesalazine 4.8 g versus 2.4 g/day						
Kamm 2007	30	85	33	84	100.0%	0.90 [0.61 , 1.33]
Subtotal (95% CI)		**85**		**84**	**100.0%**	**0.90 [0.61 , 1.33]**
Total events:	30		33			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.54 (P = 0.59)						
5.2.7 Pentasa 4 g versus 2.25 g/day						
Hiwatashi 2011	15	60	36	63	100.0%	0.44 [0.27 , 0.71]
Subtotal (95% CI)		**60**		**63**	**100.0%**	**0.44 [0.27 , 0.71]**
Total events:	15		36			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.32 (P = 0.0009)						
Test for subgroup differences: Chi² = 16.84, df = 6 (P = 0.010), I² = 64.4%						



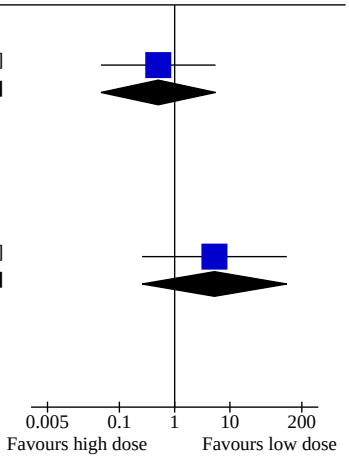
Analysis 5.3. Comparison 5: 5-ASA dose ranging, Outcome 3: Development of any adverse event

Study or Subgroup	High dose mesalazine Events	Total	Low dose mesalazine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.3.1 Asacol 4.8 g versus 1.6 g/day						
Schroeder 1987	21	38	8	11	100.0%	0.76 [0.48 , 1.21]
Subtotal (95% CI)		**38**		**11**	**100.0%**	**0.76 [0.48 , 1.21]**
Total events:	21		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.17 (P = 0.24)						
5.3.2 Salofalk 4.5 g versus 3 g/day						
Kruis 2003	63	106	66	107	100.0%	0.96 [0.78 , 1.20]
Subtotal (95% CI)		**106**		**107**	**100.0%**	**0.96 [0.78 , 1.20]**
Total events:	63		66			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.34 (P = 0.74)						
5.3.3 Salofalk 4.5 g versus 1.5 g/day						
Kruis 2003	63	106	64	103	100.0%	0.96 [0.77 , 1.19]
Subtotal (95% CI)		**106**		**103**	**100.0%**	**0.96 [0.77 , 1.19]**
Total events:	63		64			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.40 (P = 0.69)						
5.3.4 Salofalk 3 g versus 1.5 g/day						
Kruis 2003	66	107	63	106	100.0%	1.04 [0.84 , 1.29]
Subtotal (95% CI)		**107**		**106**	**100.0%**	**1.04 [0.84 , 1.29]**
Total events:	66		63			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.34 (P = 0.74)						
5.3.5 Pentasa 4 g versus 2.25 g/day						
Hiwatashi 2011	46	60	52	63	100.0%	0.93 [0.78 , 1.11]
Subtotal (95% CI)		**60**		**63**	**100.0%**	**0.93 [0.78 , 1.11]**
Total events:	46		52			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.80 (P = 0.42)						
Test for subgroup differences: $Chi^2 = 1.61$, df = 4 (P = 0.81), $I^2 = 0\%$						

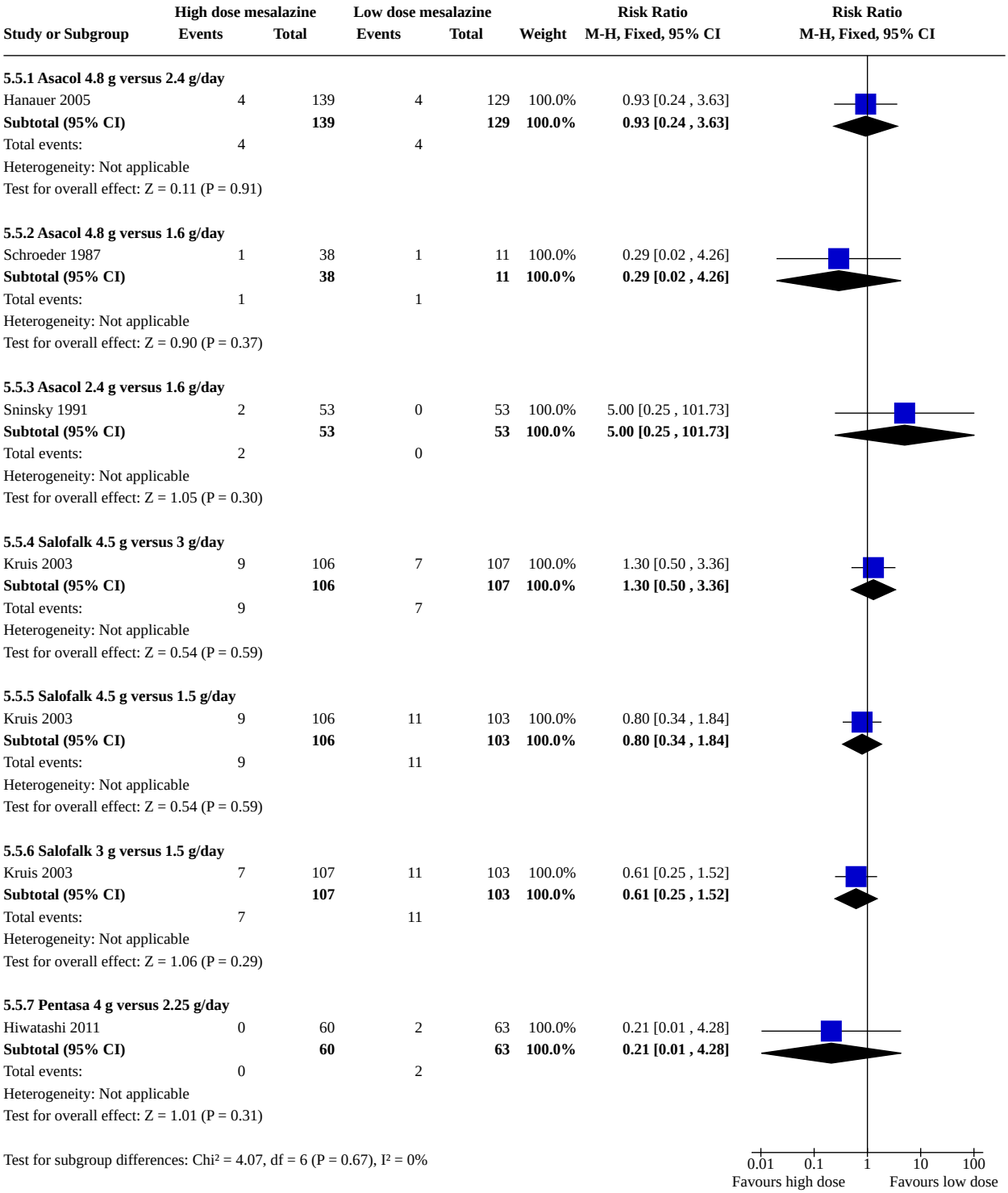


Analysis 5.4. Comparison 5: 5-ASA dose ranging, Outcome 4: Serious adverse events

Study or Subgroup	High dose mesalazine Events	Total	Low dose mesalazine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.4.1 5.3.2 Salofalk 4.5 g versus 3 g/day						
Kruis 2003	1	106	2	107	100.0%	0.50 [0.05 , 5.48]
Subtotal (95% CI)		**106**		**107**	**100.0%**	**0.50 [0.05 , 5.48]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.56 (P = 0.57)						
5.4.2 5.3.5 Pentasa 4 g versus 2.25 g/day						
Hiwatashi 2011	2	60	0	63	100.0%	5.25 [0.26 , 107.07]
Subtotal (95% CI)		**60**		**63**	**100.0%**	**5.25 [0.26 , 107.07]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.08 (P = 0.28)						
Test for subgroup differences: Chi² = 1.42, df = 1 (P = 0.23), I² = 29.8%						

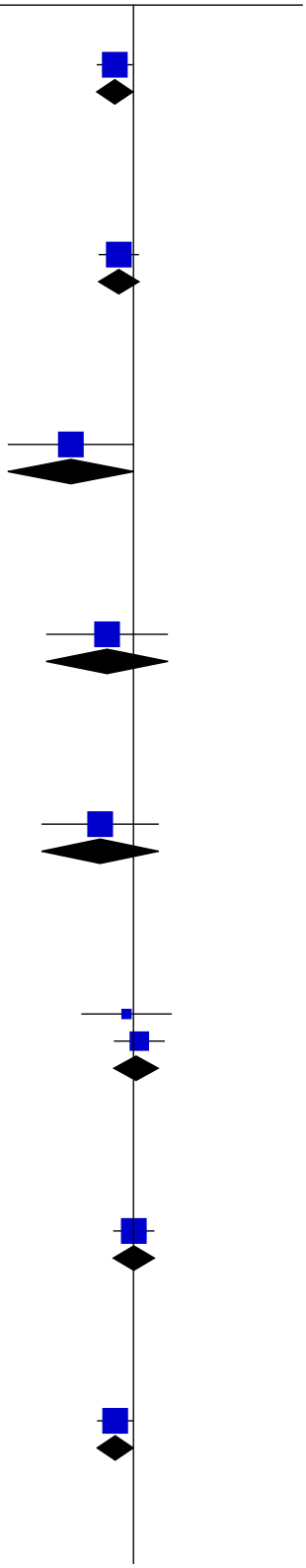


Analysis 5.5. Comparison 5: 5-ASA dose ranging, Outcome 5: Withdrawal from study due to adverse event



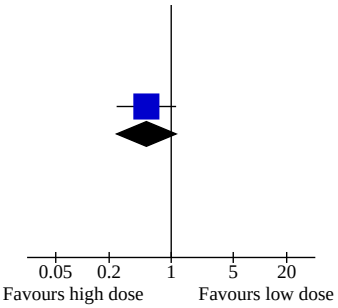
Analysis 5.6. Comparison 5: 5-ASA dose ranging, Outcome 6: Exclusions and withdrawals after entry

Study or Subgroup	High dose mesalazine Events	Total	Low dose mesalazine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.6.1 Salofalk 3 g versus 1.5 g/day						
Kruis 2003	21	107	33	103	100.0%	0.61 [0.38 , 0.99]
Subtotal (95% CI)		**107**		**103**	**100.0%**	**0.61 [0.38 , 0.99]**
Total events:	21		33			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.02 (P = 0.04)						
5.6.2 Asacol 4.8 g versus 2.4 g/day						
Hanauer 2005	20	191	30	195	100.0%	0.68 [0.40 , 1.16]
Subtotal (95% CI)		**191**		**195**	**100.0%**	**0.68 [0.40 , 1.16]**
Total events:	20		30			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.42 (P = 0.15)						
5.6.3 Asacol 4.8 g versus 1.6 g/day						
Schroeder 1987	2	38	3	11	100.0%	0.19 [0.04 , 1.01]
Subtotal (95% CI)		**38**		**11**	**100.0%**	**0.19 [0.04 , 1.01]**
Total events:	2		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.94 (P = 0.05)						
5.6.4 Asacol 3.6 g versus 2.4 g/day						
Miglioli 1990	2	24	4	24	100.0%	0.50 [0.10 , 2.48]
Subtotal (95% CI)		**24**		**24**	**100.0%**	**0.50 [0.10 , 2.48]**
Total events:	2		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.85 (P = 0.40)						
5.6.5 Asacol 3.6 g versus 1.2 g/day						
Miglioli 1990	2	24	5	25	100.0%	0.42 [0.09 , 1.95]
Subtotal (95% CI)		**24**		**25**	**100.0%**	**0.42 [0.09 , 1.95]**
Total events:	2		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.11 (P = 0.27)						
5.6.6 Asacol 2.4 g versus 1.6 or 1.2 g/day						
Miglioli 1990	4	24	5	25	29.0%	0.83 [0.25 , 2.74]
Sninsky 1991	14	53	12	53	71.0%	1.17 [0.60 , 2.28]
Subtotal (95% CI)		**77**		**78**	**100.0%**	**1.07 [0.60 , 1.92]**
Total events:	18		17			
Heterogeneity: $Chi^2 = 0.23$, df = 1 (P = 0.63); $I^2 = 0\%$						
Test for overall effect: Z = 0.23 (P = 0.82)						
5.6.7 Salofalk 4.5 g versus 3 g/day						
Kruis 2003	21	106	21	107	100.0%	1.01 [0.59 , 1.74]
Subtotal (95% CI)		**106**		**107**	**100.0%**	**1.01 [0.59 , 1.74]**
Total events:	21		21			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.03 (P = 0.97)						
5.6.8 Salofalk 4.5 g versus 1.5 g/day						
Kruis 2003	21	106	33	103	100.0%	0.62 [0.38 , 0.99]
Subtotal (95% CI)		**106**		**103**	**100.0%**	**0.62 [0.38 , 0.99]**
Total events:	21		33			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.98 (P = 0.05)						



Analysis 5.6. (Continued)

Test for overall effect: Z = 1.98 (P = 0.05)						
5.6.9 Pentasa 4 g versus 2.25 g/day						
Hiwatashi 2011	8	60	16	63	100.0%	0.53 [0.24 , 1.14]
Subtotal (95% CI)		**60**		**63**	**100.0%**	**0.53 [0.24 , 1.14]**
Total events:	8		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.64 (P = 0.10)						
Test for subgroup differences: Chi² = 7.82, df = 8 (P = 0.45), I² = 0%						



APPENDICES

Appendix 1. Search strategies

MEDLINE Search Strategy:

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. randomized controlled trial/
14. or/1-13
15. (colitis and ulcerat*).mp.
16. ulcerative colitis.mp. or exp ulcerative colitis/
17. (inflammatory bowel disease* or IBD).mp.
18. 19 or 20 or 21
19. 18 and 22
20. 5-aminosalicylic acid.mp. or exp Mesalamine/
21. Mesalazine.mp. or exp Mesalamine/
22. Sulfasalazine.mp. or exp Sulfasalazine/
23. sulphasalazine.mp. or exp Sulfasalazine/

24. 24 or 25 or 26 or 27

25. 23 and 28

EMBASE Search Strategy:

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. (colitis and ulcerat*).mp.

20. ulcerative colitis.mp. or exp ulcerative colitis/

21. (inflammatory bowel disease* or IBD).mp.

22. 19 or 20 or 21

23. 18 and 22

24. 5-aminosalicylic acid.mp. or exp Mesalamine/

25. Mesalazine.mp. or exp Mesalamine/

26. Sulfasalazine.mp. or exp Sulfasalazine/

27. sulphasalazine.mp. or exp Sulfasalazine/

28. 24 or 25 or 26 or 27

29. 23 and 28

Cochrane Library Search Strategy:

1. MeSH descriptor: [Colitis, Ulcerative] explode all trees

2. colitis

3. #1 or #2

4. 5-ASA

5. 5-aminosalicylic acid

6. Mesalamine

7. Sulfasalazine

8. Salazosulfapyridine

9. Sulphasalazine

10. #4 or #5 or #6 or #7 or #8 or #9

11. #3 and #10

Cochrane IBD Specialized Register:

1. 5-ASA (ab/ti)

2. 5-Amino* (ab/ti)

3. Mesala* (ab/ti)

4. Sulfa* (ab/ti)

5. Sulpha* (ab/ti)

6. 1 or 2 or 3 or 4 or 5

7. Colitis (ab/ti)

8. 6 and 7

Clinical Trials. Gov

5-ASA and Ulcerative Colitis

WHAT'S NEW

Date	Event	Description
11 June 2019	New citation required but conclusions have not changed	Updated review with new authors.
11 June 2019	New search has been performed	We conducted a new literature search on 11 June 2019, and added one study.

HISTORY

Review first published: Issue 4, 1997

Date	Event	Description
14 June 2016	Amended	Correction of minor error in study flow diagram
9 July 2015	New citation required but conclusions have not changed	Updated review with new authors

Date	Event	Description
9 July 2015	New search has been performed	A new literature was conducted on 9 July 2015. New studies added

CONTRIBUTIONS OF AUTHORS

Alistair Murray (AM) was involved in the search and selection of studies for inclusion in the review, collection of data for the review, assessment of the risks of bias, analysis of data, interpretation of data and writing the review.

Tran M Nguyen (TMN) was involved in the co-ordination of the review, search and selection of studies for inclusion in the review, collection of data for the review, assessment of the certainty of the body of evidence, analysis of data, interpretation of data and writing the review.

Claire E Parker (CEP) was involved in the design of the review and interpretation of data.

Brian G Feagan (BGF) was involved in the conception of the review, design of the review and interpretation of data.

John K MacDonald (JKM) was involved in assessment of the certainty of the body of evidence, interpretation of data and writing the review.

DECLARATIONS OF INTEREST

AM: no known conflicts of interest.

TMN: no known conflicts of interest.

CEP: no known conflicts of interest.

BGF has received fees from Abbott/AbbVie, Amgen, Astra Zeneca, Avaxia Biologics Inc., Bristol-Myers Squibb, Celgene, Centocor Inc., Elan/Biogen, Ferring, JnJ/Janssen, Merck, Nestles, Novartis, Novonordisk, Pfizer, Prometheus Laboratories, Protagonist, Salix Pharma, Takeda, Teva, TiGenix, Tillotts Pharma AG and UCB Pharma for Scientific Advisory Board membership; fees from Abbott/AbbVie, Actogenix, Akros, Albireo Pharma, Amgen, Astra Zeneca, Avaxia Biologics Inc., Avir Pharma, Axcan, Baxter Healthcare Corp., Biogen Idec, Boehringer-Ingelheim, Bristol-Myers Squibb, Calypso Biotech, Celgene, Elan/Biogen, EnGene, Ferring Pharma, Roche/Genentech, GiCare Pharma, Gilead, Given Imaging Inc., GSK, Ironwood Pharma, Janssen Biotech (Centocor), JnJ/Janssen, Kyowa Kakko Kirin Co Ltd., Lexicon, Lilly, Lycera BioTech, Merck, Mesoblast Pharma, Millennium, Nektar, Nestles, Novonordisk, Pfizer, Prometheus Therapeutics and Diagnostics, Protagonist, Receptos, Salix Pharma, Serono, Shire, Sigmoid Pharma, Synergy Pharma Inc., Takeda, Teva Pharma, TiGenix, Tillotts, UCB Pharma, Vertex Pharma, VHsquared Ltd., Warner-Chilcott, Wyeth, Zealand, and Zyngenia for consultancy; payment for lectures from Abbott/AbbVie, JnJ/Janssen, Takeda, Warner-Chilcott, UCB Pharma; his institution has received grants/grants pending from Abbott/AbbVie, Amgen, Astra Zeneca, Bristol-Myers Squibb (BMS), Janssen Biotech (Centocor), JnJ/Janssen, Roche/Genentech, Millennium, Pfizer, Receptos, Santarus, Sanofi, Tillotts, and UCB Pharma. Dr Feagan was the author of one study that was included in this review.

JKM: no known conflicts of interest.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We added in SAEs as a secondary outcome for this review. SAEs were not reported in the previously published version.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Anti-Inflammatory Agents, Non-Steroidal [*administration & dosage] [adverse effects]; Bias; Colitis, Ulcerative [*drug therapy]; Drug Administration Schedule; Induction Chemotherapy [methods]; Mesalamine [*administration & dosage] [adverse effects]; Patient Dropouts [statistics & numerical data]; Placebos [therapeutic use]; Randomized Controlled Trials as Topic; Remission Induction; Sulfasalazine [*administration & dosage] [adverse effects]; Treatment Failure

MeSH check words

Humans