American Gastroenterological Association Technical Review on the Management of Mild to Moderate Ulcerative Colitis

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ABSTRACT

Most patients with ulcerative colitis (UC) have mild to moderate disease activity, with low risk of colectomy, and are managed by primary care physicians or gastroenterologists. Optimal management of these patients decreases the risk of relapse and proximal disease extension, and may prevent disease progression, complications and need for immunosuppressive therapy. With several medications (sulfasalazine, diazo-bonded 5-aminosalicylates [ASA], mesalamines, corticosteroids including budesonide, etc.) and complex dosing formulations, regimens and routes, to treat a disease with variable anatomic extent, there is considerable practice variability in the management of patients with mild-moderate UC. Hence, the AGA prioritized clinical guidelines on this topic. To inform clinical guidelines, this technical review was developed in accordance with the GRADE framework for interventional studies. Focused questions included: (1) comparative effectiveness and tolerability of different oral 5-ASA therapies (sulfalsalazine vs. diazo-bonded 5-ASAs vs. mesalamine; low- (<2g) vs. standard (2-3g/d) vs. high-dose (>3g/d) mesalamine); (2) comparison of different dosing regimens (once-daily vs. multiple times per day dosing) and routes (oral vs. rectal vs. both oral and rectal); (3) role of oral budesonide in patients mild-moderate UC; (4) comparative effectiveness and tolerability of rectal 5-ASA and corticosteroid formulations in patients with distal colitis; and (5) role of alternative therapies like probiotics, curcumin and fecal microbiota transplantation in the management of mild-moderate UC.
INTRODUCTION

Ulcerative colitis (UC) is a chronic disabling inflammatory bowel disease that generally begins in young adulthood and lasts throughout life. Although the incidence and prevalence of UC has stabilized in Western Europe and North America (affecting >0.3% of the population), its incidence continues to rise in newly industrialized countries. Based on longitudinal population-based cohort studies, the majority of patients with UC have a mild-moderate course, generally most active at diagnosis and then in varying periods of remission or mild activity; about 14-17% of patients may experience an aggressive course. Almost 50% patients require UC-related hospitalization at some point during the disease course, and among those hospitalized once, the 5-year risk of re-hospitalization is about 50%. The 5- and 10-year cumulative risk of colectomy surgery is 10-15%, and though rates of early colectomy have declined, long-term colectomy rates have remained stable over time. Besides significantly impacting quality of life and work productivity due to debilitating symptoms, UC is also associated with an increased risk of colorectal cancer. Consistent predictors of an aggressive UC disease course and colectomy are young age at diagnosis (age <40y), extensive disease, severe endoscopic activity (presence of deep ulcers), presence of extra-intestinal manifestations, early need for corticosteroids and elevated inflammatory markers. In contrast, patients with limited anatomic extent and mild endoscopic activity may be at low risk of colectomy. Overall, about two-thirds of patients with UC have disease limited to the rectum or left colon at diagnosis, and approximately one-fourth of the patients with limited UC extend over time, usually within the first 10 years of diagnosis, with higher risk if the disease is inadequately controlled.

In population-based cohorts, >90% patients receive 5-aminosalicylates (5-ASA) within 1 year of diagnosis for management of UC, and on long-term follow-up, 60-87% patients continue 5-ASA use; only 50% of patients receive corticosteroids during the course of their disease, with even lower rates of use of immunosuppressive (20%) and biologic therapy (5-10%). Though considerable attention has focused on managing patients with moderate-severe UC at high
risk of colectomy, the majority of patients with UC have mild-moderate disease activity at low risk of colectomy. These patients are frequently managed by primary care physicians and gastroenterologists, and there is considerable practice variability. Successful management of patients with UC is based on: (a) accurate risk stratification with early identification of predicted mild vs. severe course, appropriately aggressive step therapy and close monitoring of patients at high risk of colectomy, and (b) optimal management of patients at low-risk of colectomy with mild-moderate disease activity, with the assumption that optimal control will reduce the risk of disease progression and complications. Prior guidelines have primarily focused on patients with moderate-severe UC, with limited evidence synthesis for management of mild-moderate UC. Moreover, there has been limited guidance on the role of probiotics, curcumin and fecal microbiota transplantation in this patient population. Hence, the American Gastroenterological Association (AGA) prioritized this topic for generation of clinical guidelines.

**Objectives of the Review**

This technical review focuses on treatment options and strategies for the management of adult (≥18 years) outpatients with UC with mild-moderate disease activity, the majority of whom would be at low risk of colectomy. Mild-moderate disease activity is loosely defined based on Truelove-Witts criteria and Mayo Clinic score, as patients with <4-6 bowel movements per day, mild-moderate rectal bleeding, absence of constitutional symptoms, and low inflammatory burden based on biochemical and endoscopic assessment, and absence of features suggestive of high disease severity (absence of deep endoscopic ulcers, high inflammatory burden, repeated hospitalizations and steroid-dependence). Disease extent was based on the Montreal classification as extensive (extending beyond splenic flexure), left-sided (up to splenic flexure) and proctitis. The focused clinical questions address:
• Comparative effectiveness and tolerability of different oral 5-ASA therapies (sulfasalazine, diazo-bonded 5-ASAs like balsalazide and olsalazine, and mesalamine) for induction and maintenance of remission in patients with extensive mild-moderate UC;

• Comparative effectiveness and tolerability of different mesalamine dosing regimens (low [<2g/d] vs. standard [2-3g/d] vs. high-dose [≥3g/d] mesalamine; once-daily vs. multiple times per day dosing, oral vs. rectal vs. oral + rectal therapy) for induction and maintenance of remission in patients with extensive mild-moderate UC;

• Comparative effectiveness and tolerability of rectal 5-ASA and corticosteroid formulations for induction and maintenance of remission in patients with ulcerative proctosigmoiditis or proctitis;

• Role of budesonide in the management of patients with mild-moderate UC;

• Role of alternative therapies like probiotics, curcumin and fecal microbiota transplantation in the management of mild-moderate UC

This technical review does not address the role of immunosuppressive or biologic therapy in patients with mild-moderate UC. The results of this technical review were used to inform the development of the accompanying clinical guidelines on the management of patients with mild-moderate UC.

METHODS

Overview

This technical review and the accompanying guideline were developed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework. The members of the technical review panel were selected by the AGA Clinical Guidelines Committee based on their clinical content and guidelines methodological expertise, and went through a thorough vetting process for potential conflicts of interest. Through an iterative process,
and in conjunction with the guideline panel, the participants developed focused clinical questions on the management of mild-moderate UC deemed relevant for clinical practice that the guideline would address. After the focused questions were approved by the AGA Governing Board (in April 2017), the technical review team formulated the clinical questions, identified relevant patient-important outcomes, systematically reviewed and summarized the evidence for each outcome across studies, and then rated the quality of the evidence across all outcomes for each clinical question.

**Formulation of Clinical Questions and Outcome Measurement**

Using the PICO format, which frames a clinical question by defining a specific Population (P), Intervention (I), Comparator (C), and Outcomes (O), the team finalized 12 questions (Table 1). Among potentially relevant patient-important outcomes, achieving clinical remission was considered a critical outcome for decision-making, whereas achieving endoscopic remission and tolerability (drug discontinuation due to adverse events) were considered important outcomes. Since the frequency of colectomy and hospitalization is very low in patients with mild-moderate UC, these outcomes were not deemed relevant for this review. Clinical remission was measured using various disease activity indices (DAI), most commonly, UCDAI, Mayo Clinic Score, simple clinical colitis activity index, Sutherland DAI, Rachmilewitz Clinical Activity Index, etc.19, 22-27 These DAI s generally combined measures of stool frequency, rectal bleeding and/or physician global assessment, with a measure of endoscopic disease activity. There were subtle differences in definition of remission across different DAI s; in some studies, if clinical and endoscopic outcomes were reported separately, then data on clinical remission was used for analysis. If clinical remission was not reported, then clinical response was abstracted as a surrogate outcome.

**Estimating Absolute Magnitude of Benefit**
In order to provide a synthesis of the risks and benefits of different management strategies, to calculate absolute effect estimates, the technical review team used either median placebo remission rates (for trials comparing oral 5-ASA therapy in patients with extensive mild-moderate UC), or trial-reported pooled remission rate (for trials comparing active interventions or rectal therapy). In trials of induction therapy with oral 5-ASA, the median calculated placebo remission rate was 10%, whereas in trials of maintenance therapy, the median calculated placebo remission rate was 58%. In a Cochrane meta-analysis of 61 placebo-controlled trials examining placebo response and remission rates in UC, Jairath and colleagues observed significant differences in placebo response and remission rates depending on baseline endoscopic disease severity, disease duration, rectal bleeding score, trial agent and time point of outcome assessment. Hence, median placebo remission rates in this review should be deemed illustrative.

**Search Strategy and Study Selection Criteria**

An experienced medical librarian performed a systematic literature search of multiple electronic databases (Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, EMBASE, and Wiley Cochrane Library) using a combination of controlled vocabulary terms supplemented with keywords. The search was conducted on July 21, 2017. In addition, the search was supplemented by a review of key Cochrane systematic reviews published on the topic in the last 5 years (2012-2017). For evidence synthesis, randomized controlled trials (RCTs) conducted in adults with mild-moderate UC evaluating interventions of interest (corresponding to relevant PICOs) were included. Minimum trial duration for induction and maintenance therapy was 2 weeks and 16 weeks, respectively. Trials in patients with Crohn’s disease were excluded; if a trial included both patients with UC and Crohn’s disease, it was included only if results were stratified by disease or if >70% participants had UC. Inclusion was limited to outpatients with mild-moderate UC defined by various disease activity indices. However, some older trials in which the baseline disease activity was not
explicitly stated, as in the initial trials of sulfasalazine, were also included if there was paucity of evidence, otherwise. Separate systematic literature reviews were performed to identify studies informing cost-effectiveness and patients' values and preferences for different management strategies in mild-moderate UC. In addition, studies on issues of racial, ethnic, and social disparities and issues of general health equity pertinent to the topic were identified. Details of the search strategy are reported in the Online Supplement. Total 3962 articles were identified.

**Statistical Analysis**

For trials of induction and maintenance therapy, outcomes were abstracted and reported as failure to induce clinical remission (in patients with active disease), and failure to maintain remission (in patients with quiescent disease at trial entry), respectively. All analyses were conducted using true intention-to-treat analysis; patients lost to follow-up or excluded from analysis for other reasons were deemed to be treatment failures. Summary estimates were reported as pooled relative risk (RR) and 95% confidence intervals (CI) were calculated using DerSimonian-Liard random-effects model; if a comparison had only 2 studies, then a fixed-effects model was used.\(^29\),\(^30\) Statistical heterogeneity was assessed using the \(I^2\) statistic, and values >50% were considered suggestive of significant heterogeneity.\(^31\) Small study effects were examined using funnel plot symmetry and Egger's regression test, although it is important to recognize that these tests are unreliable when the number of studies is <10.\(^32\) Statistical analyses were performed using RevMan v5.3 (Cochrane Collaboration, Copenhagen, Denmark) or Comprehensive Meta-Analysis (CMA) software, version 2 (Biostat, Englewood, NJ).

**Quality of Evidence**

The GRADE approach was used to rate the quality of evidence (or confidence in summary effect estimates).\(^33\) In this approach, direct evidence from RCTs starts at high quality and can be rated down based on risk of bias in the
body of evidence (or study quality), indirectness (addressing a different but related population, intervention, or outcome, from the one of interest), imprecision (of summary estimate and boundaries of 95% CI), inconsistency (or heterogeneity, both statistical in effect estimate, and conceptually in intervention or outcomes), and/or publication bias to levels of moderate, low, and very low quality. For imprecision, evidence was rated down even if the 95% CI did not cross unity if optimal information size was less than 200 events.34

Evidence-to-Decision Framework
Since this technical review was used to inform the development of clinical guidelines, besides a comprehensive risk-benefit analysis and the accompanying quality of evidence, information about additional factors such as patients' values and preferences, cost-effectiveness, and resource utilization were also considered.35 These studies are discussed in the corresponding PICOs to inform decision-making.

RESULTS

Question 1. In adults with extensive mild-moderate ulcerative colitis, what dose of mesalamine is effective for induction and maintenance of remission?

Key Message: Low- (<2g/d), standard- (2-3g/d) and high-dose (>3g/d) mesalamine is more effective than placebo for induction and maintenance of remission in patients with extensive mild-moderate UC (moderate to high quality evidence). High- and standard-dose mesalamine is more effective than low-dose mesalamine for inducing and maintaining remission in patients with mild-moderate UC (moderate quality evidence). High-dose mesalamine may have a small benefit over standard-dose mesalamine for induction and maintenance of remission (moderate quality evidence), particularly in a subset of patients with moderate UC.
Effect estimate:  

**Induction of Remission** – We identified 18 clinical trials comparing different doses of mesalamine with each other or placebo for inducing clinical remission in patients with mild-moderate UC. Of these, 14 trials reported outcomes based on validated disease activity indices combining clinical and endoscopic outcome; 3 reported on clinical and endoscopic outcomes separately and 2 used investigator-defined clinical improvement. Of note, we assumed comparability of different commercial preparations of mesalamine at equivalent doses based on an exhaustive systematic review that demonstrated that different mesalamine formulations have comparable efficacy and safety. Amongst mesalamine formulations available in the United States, a 4-arm trial comparing once-daily MMX mesalamine 2.4g/d vs. Asacol 2.4g/d administered in three divided doses, there was no significant difference in efficacy for induction of remission; however, the trial was not designed nor powered to evaluate differences in equimolar doses of different mesalamine formulations. Equimolar doses of different commercial preparations of mesalamine are shown in Table 2.

High-dose (6 RCTs, 904 patients; RR of failure to achieve remission, 0.75 [0.66-0.86]), standard-dose (8 RCTs, 1199 patients; RR, 0.84 [0.78-0.91]) and low-dose mesalamine (4 RCTs, 531 patients; RR, 0.88 [0.82-0.94]) were superior to placebo in inducing remission in patients with mild-moderate UC (eFigure 1). With estimated placebo rates of induction of remission of 10% in trials, this translates into 32.5%, 24.4% and 20.8% patients treated with high-, standard- and low-dose mesalamine achieving clinical remission with induction therapy, respectively. All doses of mesalamine were well tolerated, with lower rates of treatment discontinuation with active intervention as compared to placebo.

High-dose (6 trials, 519 patients; RR, 0.81 [0.71-0.92]) and standard-dose mesalamine (8 trials, 906 patients; RR, 0.88 [0.79-0.99]) were superior to low-dose mesalamine for induction of remission, with low heterogeneity (eFigure 2). Based on 12 trials with 2492 patients with mild-moderate UC, there was a trend favoring a small benefit of high-dose
mesalamine over standard-dose mesalamine for inducing clinical remission (RR, 0.94 [0.88-1.01]), with low heterogeneity (eFigure 3). In trials conducted only in patients with moderate UC (ASCEND II, ASCEND III, Hiwatashi et al.), high-dose mesalamine was significantly superior to standard-dose mesalamine in inducing remission (6 trials, 1589 patients; RR, 0.92 [0.86-0.99]), albeit with small magnitude of benefit. With a median 33% induction of remission rate with standard-dose mesalamine in these patients, the corresponding estimated rate with high-dose mesalamine was 38.4%.

**Maintenance of Remission** – We identified 11 trials comparing different doses of mesalamine with each other or placebo for maintenance of remission, all of which enrolled patients in clinical and endoscopic remission, with or without histologic remission, for varying time periods of 6-12 months; outcome was reported as combined clinical and endoscopic remission based on validated disease activity indices. Standard-dose (2 RCTs, 510 patients; RR of failure to achieve remission, 0.55 [0.43-0.70]) and low-dose mesalamine (3 RCTs, 579 patients; RR, 0.63 [0.51-0.79]) were superior to placebo in maintaining remission in patients with mild-moderate UC (eFigure 4). With estimated placebo rates of maintenance of remission of 58%, 76.9%, and 73.5% patients treated with standard- and low-dose mesalamine maintained remission, respectively.

Meta-analysis of four trials including 1798 patients demonstrated that standard-dose mesalamine was superior to low-dose mesalamine for maintaining remission (RR, 0.85 [0.72-0.99]), with minimal heterogeneity (eFigure 5). Only two trials compared high-dose vs. standard-dose mesalamine, and there was no significant benefit of high-dose mesalamine for maintenance of remission (RR, 0.93 [0.73-1.17]); neither trial reported whether patients received high-dose mesalamine for induction remission (eFigure 6).

**Potential Harms of Intervention:** All doses of mesalamine were well tolerated in RCTs for induction of remission, with lower rates of treatment discontinuation with active intervention as compared to placebo (eFigure 7). Among patients in remission, low- (RR, 0.83 [0.52-1.32]) and standard-dose mesalamine (RR, 0.62
were at least as well or better tolerated than placebo for maintenance of remission (Figure 8); standard-dose mesalamine was better tolerated than low-dose mesalamine, with lower rates of drug discontinuation (4 trials; RR, 0.82 [0.67-1.00]). Overall, mesalamine is a safe medication. Rare cases of interstitial nephritis have been observed, usually within 12 months of starting therapy. In an epidemiologic study of 19,000 patients from the UK, the incidence of any renal disease in patients with IBD taking 5-ASA was estimated at 0.17 per 100 patients/year, which was similar to the incidence in IBD patients not taking 5-ASAs (0.25), but higher than controls (0.08). Periodic renal function testing is suggested by the FDA, though no specific studies have evaluated the frequency of testing. Rare case reports of pancreatitis, pericarditis, myocarditis, and pneumonitis have also been observed. In addition, a small subset of patients (<5% in adults, 12% in pediatric patients) may develop paradoxical worsening of colitis-type symptoms due to a hypersensitivity reaction.

When treating patients with suboptimal response to standard-dose mesalamine, the potential small benefit of escalating to high-dose mesalamine should be weighed against the potential risk of delaying alternative, more effective therapy, such as corticosteroids, immunosuppressive and/or biologic therapy.

**Quality of Evidence:** The overall body of evidence regarding mesalamine for mild-moderate UC was deemed to be at low risk of bias, without considerable inconsistency or indirectness; most of the studies used validated disease activity metrics for patient enrollment and outcome ascertainment. High quality evidence supports the use of standard- or high-dose of mesalamine over placebo for induction and maintenance of remission; evidence supporting low-dose mesalamine over placebo was rated down due to serious imprecision due to low event rate (<200 events), resulting in moderate confidence in estimates (Table 3). There is moderate to high confidence in estimates supporting the use of standard- or high-dose mesalamine over low-dose mesalamine for achieving remission. There was no trial comparing high-dose mesalamine to low-dose mesalamine for maintenance of remission, but indirect evidence indicates it is
probably more efficacious (Table 4). There is moderate quality evidence suggesting a small benefit of high-dose mesalamine over standard-dose mesalamine, particularly in a subset of patients with moderate UC; low quality evidence suggests a small benefit for maintenance of remission, due to very imprecise estimates (Table 5).

**Discussion:** While all doses of mesalamine are effective in patients with mild-moderate UC, standard- (U.S. Food and Drug Administration approved) and high-dose mesalamine are more effective than low-dose mesalamine for induction and maintenance of remission. Given absence of dose-dependent toxicity and potential risk of suboptimal disease control with low-dose mesalamine, standard-dose mesalamine may be the preferred treatment strategy when using these medications. The magnitude of benefit with high-dose mesalamine over standard-dose mesalamine was small, and it is associated with higher costs. High-dose mesalamine may be considered for induction of remission in a subset of patients at high risk of treatment failure before escalating to immunosuppressive therapy, such as treatment-naïve patients with moderate disease activity, patients with suboptimal response to standard-dose mesalamine, and patients who require corticosteroids for achieving remission. This is based on indirect evidence suggesting dose-dependent efficacy of mesalamine; no clinical trials have specifically been conducted to address the benefit of dose escalation in patients with suboptimal response to standard-dose mesalamine. A British cost-utility analysis suggested that high-dose mesalamine is more cost-effective than standard-dose mesalamine over 12-weeks in patients with moderate UC. However, the small incremental benefit with high-dose mesalamine should be discussed with patients in the context of potential risks associated with delaying more effective, albeit immunosuppressive therapy. The benefit of continuing high-dose mesalamine for maintenance of remission is unclear, with moderate confidence in estimates supporting a small benefit, over standard-dose mesalamine. The two included maintenance trials did not report whether patients enrolled in this study required standard- vs. high-dose mesalamine for induction of remission. Since increasing time in remission is
associated with lower subsequent risk of relapse, de-escalation from high-dose to standard-dose mesalamine (in a subset of patients who achieved remission with high-dose mesalamine) may be considered after 12 months of high-dose mesalamine therapy, through shared decision-making. A cost-effectiveness analysis comparing two maintenance strategies – no maintenance mesalamine, with mesalamine 4.8 g/day given for flares vs. maintenance mesalamine 2.4 g/day, escalated and maintained at 4.8 g/day after the first flare – failed to demonstrate cost-effectiveness of a long-term maintenance strategy.70

Question 2. In adults with extensive mild-moderate ulcerative colitis, are diazo-bonded 5-aminosalicylates (balsalazide, olsalazine) effective for induction and maintenance of remission?

**Key Message:** In patients with extensive mild-moderate UC, diazo-bonded 5-aminosalicylates (balsalazide, olsalazine) are effective for induction (*moderate quality evidence*) and maintenance of remission (*low quality evidence*). Diazo-bonded 5-aminosalicylates may be slightly more effective than standard-dose mesalamine for induction and maintenance of remission, with comparable tolerability (*low quality evidence*). Diazo-bonded 5-aminosalicylates are probably more effective and better tolerated than sulfasalazine for induction of remission (*moderate quality evidence*), with comparable efficacy to sulfasalazine for maintenance of remission (*low quality evidence*).

**Effect estimate and Quality of Evidence:**

**Diazo-bonded 5-ASA vs. placebo** – We identified 6 trials comparing diazo-bonded 5-ASA (5 trials of olsalazine 2-3g/day,71-75 1 trial of balsalazide 6.6g/day76) with placebo for induction of remission and 2 trials comparing these medications for maintenance of remission. Diazo-bonded 5-ASA was significantly more effective than placebo in inducing clinical remission (RR, 0.86 [0.76-0.98]) with minimal heterogeneity ($I^2=29\%$) (eFigure 9). With illustrative median placebo rates of induction of remission of 10% in trials, this translates into 22.6% patients treated with diazo-bonded 5-ASA achieving clinical remission. Rate of treatment discontinuation was numerically higher with diazo-bonded 5-ASA, particularly
olsalazine (RR, 2.15 [0.71-6.50]) but not balsalazide (RR, 0.75 [0.35-1.59]), as compared to placebo during induction therapy (eFigure 10). Based on 2 trials of maintenance therapy comparing olsalazine 1-2g/day with placebo, there was numerically lower risk of relapse with diazo-bonded 5-ASA (RR, 0.71 [0.41-1.21])77, 78; no trials of maintenance therapy with balsalazide were identified (eFigure 11). In one trial that reported rate of treatment discontinuation, olsalazine was significantly more likely to be discontinued due to intolerance than placebo (24.9% vs. 3.8%).

Quality of Evidence: The overall body of evidence supporting the use of diazo-bonded 5-ASA over placebo for induction of remission was rated as moderate quality due to imprecision. There was low confidence in estimates supporting a moderate benefit of diazo-bonded 5-ASA for maintenance of remission due to inconsistency and imprecision.

Diazo-bonded 5-ASA vs. mesalamine: Based on 5 trials comparing diazo-bonded 5-ASA (1 trial of olsalazine 3g/day,79 4 trials of balsalazide 4.5-6.75 g/day80-83) with standard-dose mesalamine (2.4-3g/d) for induction of remission, rates of failing to achieve remission was numerically lower with diazo-bonded 5-ASA as compared to standard dose mesalamine (RR, 0.81 [0.60-1.08]) (eFigure 12). When analysis was limited to only balsalazide, results were similar (RR, 0.73 [0.52-1.02]). There was no significant difference in tolerability of diazo-bonded 5-ASA and mesalamine (RR of treatment discontinuation, 0.74 [0.39-1.39]); on limiting analysis only to balsalazide, there was a trend favoring superior tolerability of balsalazide for induction of remission (RR, 0.41 [0.15-1.11]) (eFigure 13). Based on 4 trials of maintenance therapy, risk of clinical relapse was significantly lower with diazo-bonded 5-ASA as compared to mesalamine (RR, 0.69 [0.51-0.98]);84-87 of note, all mesalamine trials used low-dose mesalamine (1-1.5g/day) for maintenance of remission (eFigure 14). There was no difference in tolerability of diazo-bonded 5-ASA and low-dose mesalamine for maintenance therapy (RR of treatment discontinuation, 0.99 [0.40-2.50]) (eFigure 15).
**Quality of Evidence:** Trials of induction therapy comparing diazo-bonded 5-ASA with standard-dose mesalamine yielded inconsistent results, and the overall effect estimates were imprecise. Hence, the overall evidence supporting a benefit of diazo-bonded 5-ASA over standard-dose mesalamine was rated as low quality. Though there was a statistically significant beneficial effect of diazo-bonded 5-ASA over mesalamine for maintenance of remission, this was based only on low quality evidence due to indirectness (trials used only low-dose mesalamine, as opposed to standard-dose mesalamine) and imprecision due to low event rate.

**Diazo-bonded 5-ASA vs. sulfasalazine:** Eight trials comparing diazo-bonded 5-ASA (olsalazine 1-3g/day, balsalazide 6.75g/day) with sulfasalazine (3-6g/day) for induction of remission demonstrated a lower risk of failing to achieve clinical remission with diazo-bonded 5-ASA (RR, 0.77 [0.61-0.96]) (eFigure 16); results were stable on sensitivity analysis after excluding studies using suboptimal doses of diazo-bonded 5-ASA. Diazo-bonded 5-ASA was better tolerated than sulfasalazine with significantly lower rates of treatment discontinuation (RR, 0.31 [0.14-0.70]) (eFigure 17). Based on 6 trials of maintenance therapy, there was no significant difference in rates of relapse between diazo-bonded 5-ASA-treated and sulfasalazine-treated patients (RR, 1.07 [0.98-1.16]) (eFigure 18). All trials used sulfasalazine 2g/day; 5 trials compared it with olsalazine (3 trials at dose of 1g/day and two trials used 2g/day) and one trial compared it with low-dose balsalazide (2g/day). Among patients in remission, there was no significant difference in tolerability of diazo-bonded 5-ASA and sulfasalazine (RR of treatment discontinuation, 1.02 [0.99-1.06]); as noted above, five trials used olsalazine (eFigure 19).

**Quality of Evidence:** For induction of remission, evidence supporting diazo-bonded 5-ASA over sulfasalazine was rated as moderate quality due to imprecision since optimal information size was not reached (<200 events) (Table 6). For maintenance of remission, the evidence supporting use of diazo-bonded 5-ASA over sulfasalazine was rated as low quality due to imprecision (wide confidence intervals) and indirectness (very limited data on balsalazide which
may be the preferred diazo-bonded 5-ASA given higher intolerability with olsalazine due to diarrhea).\textsuperscript{101, 102}

**Potential Harms of Intervention:** Diazo-bonded 5-ASAs are safe medications, with very low rates of idiosyncratic serious or life-threatening complications. However, approximately 20\% patients may develop watery diarrhea with olsalazine; this effect is not observed with balsalazide.\textsuperscript{101} They are better tolerated than sulfasalazine, and approximately 80\% patients intolerant or allergic to sulfasalazine tolerate 5-ASA medications. Renal dysfunction is very rare with 5-ASA, but periodic renal function tests are suggested.

**Discussion:** Based on the evidence presented above, diazo-bonded 5-ASA is an effective and safe alternative to mesalamine for treating the majority of patients with mild-moderate UC. Given the higher costs of mesalamine than diazo-bonded 5-ASA for some patients, diazo-bonded 5-ASA may be an alternative. The observed potential superiority of diazo-bonded 5-ASA over mesalamine should be interpreted with caution – olsalsazine, but not balsalazide, has a dose-dependent side effect of secretory diarrhea, in up to 20\% patients, which may limit its tolerability especially for maintenance therapy.\textsuperscript{101} Due to a high pill burden associated with balsalazide, compliance and adherence may be lower. Moreover, these studies compared diazo-bonded 5-ASA with low- or standard-dose mesalamine, both of which are inferior to high-dose mesalamine. Hence, the potential benefits of diazo-bonded 5-ASA may be offset by limited ability to dose-escalate to doses equivalent to high-dose mesalamine. Moreover, maintenance studies compared diazo-bonded 5-ASA to low-dose mesalamine, which itself is inferior to standard-dose mesalamine. As noted above, diazo-bonded 5-ASA (and mesalamine) are better tolerated than sulfalsazine, particularly during induction therapy in patients with active UC-related symptoms.\textsuperscript{102, 103} Rates of treatment discontinuation during maintenance therapy with diazo-bonded 5-ASA were not different than for sulfasalazine which may be due to self-selection of sulfasalazine-tolerant patients during maintenance trials.
Question 3. In adults with extensive mild-moderate ulcerative colitis, is sulfasalazine effective for induction and maintenance of remission?

**Key Message:** In patients with extensive mild-moderate ulcerative colitis, sulfasalazine is effective for induction (*moderate quality evidence*) and maintenance of remission (*low quality evidence*). Mesalamine may be slightly more effective than sulfasalazine for induction (*moderate quality evidence*) and maintenance of remission (*low quality evidence*) with lower rate of adverse events.

**Effect estimate and Quality of Evidence:**

**Sulfasalazine vs. placebo** – Based on two trials conducted in 1960s, sulfasalazine (dose range, 2-6g) was more effective than placebo for induction of remission (RR, 0.62 [0.45-0.87]); a larger effect size was observed in trial using 4-6g/d of sulfasalazine (*eFigure 20*). Sulfasalazine (2g/d) was also more effective than placebo for maintenance of remission based on 4 trials (RR, 0.45 [0.23-0.89]), with moderate heterogeneity ($I^2=52\%$) (*eFigure 21*). In trials of induction therapy, sulfasalazine was not very well tolerated with high rate of treatment discontinuation due to adverse events (7/41 vs. 1/43; RR of treatment discontinuation, 5.14 [0.95-27.96]) (*eFigure 22*); in contrast, in trials of maintenance therapy in patients who had previously achieved remission with and tolerated sulfasalazine, rate of treatment discontinuation was only slightly inferior to placebo (RR, 2.22 [0.67-7.35]) (*eFigure 23*).

**Quality of Evidence:** The overall body of evidence supporting the use of sulfasalazine over placebo for induction of remission was rated as moderate quality, with evidence being rated down for imprecision (low event rate). Evidence supporting sulfasalazine over placebo for maintenance of remission was rated down for imprecision and inconsistency in effect estimate, and was rated as low quality.

**Sulfasalazine vs. mesalamine:** Based on 7 trials of induction therapy, there was no significant difference in efficacy of sulfasalazine (3g/d) and mesalamine (1.5-4g/d) for induction of remission (RR, 1.07 [0.91-1.26]), without heterogeneity ($I^2=0\%$) (*eFigure 24*). On restricting comparison to 4 trials
comparing 3g/d sulfasalazine with standard-dose (2-3g/d) mesalamine, the effect estimate was more pronounced favoring superiority of mesalamine (RR, 1.27 [0.94-1.73]);\textsuperscript{47, 50, 111, 112} in contrast, there was no difference in efficacy of sulfasalazine and low-dose mesalamine (<2g/d) (RR, 1.00 [0.83-1.21]) for induction of remission.\textsuperscript{26, 110, 113} Rate of adverse events was significantly higher in sulfasalazine-treated patients as compared to mesalamine-treated patients (RR, 1.69 [1.12-2.55]), though rates of treatment discontinuation due to adverse events did not reach statistical significance (RR, 1.55 [0.64-3.77]) (\textsuperscript{eFigure 25}). Based on 6 trials, sulfasalazine (1-4g/d, most common dose, 2g/d) was numerically but not statistically inferior to mesalamine for maintenance of remission (RR, 1.13 [0.91-1.40]) without heterogeneity (\textsuperscript{eFigure 26}).\textsuperscript{110, 114-118} Of note, in five trials evaluating maintenance of remission, low-dose mesalamine was used (0.75-1.5g/d),\textsuperscript{110, 114, 116-118} and only one small trial compared sulfasalazine with standard-dose mesalamine.\textsuperscript{115} There was no difference in tolerability (RR, 1.11 [0.51-2.44]) or risk of adverse events (RR, 1.05 [0.43-2.57]) between sulfasalazine- and mesalamine-treated patients during maintenance therapy (\textsuperscript{eFigure 27}).

\textit{Quality of Evidence}: The overall body of evidence suggesting higher efficacy of standard-dose mesalamine over sulfasalazine for induction of remission was rated as moderate quality due to imprecision (\textsuperscript{Table 7}). Evidence suggesting higher efficacy of mesalamine over sulfasalazine for maintenance of remission was rated as low quality due to serious imprecision and indirectness. Of note, extrapolating results to comparisons with standard-dose mesalamine, the anticipated effect estimate would be more strongly in favor of mesalamine over sulfasalazine.

\textbf{Potential Harms of Intervention}: As noted above, sulfasalazine is not as well tolerated as mesalamine, with higher rate of treatment discontinuation due to adverse events. Between 10-45% patients may develop dose-related adverse effects, including nausea, dyspepsia, headache and fatigue with sulfasalazine.\textsuperscript{102, 119} Moreover, sulfasalazine has also been associated with serious cutaneous reactions such as toxic epidermal necrolysis and Stevens Johnson syndrome,
pancreatitis, hepatotoxicity, drug-induced connective tissue disease, bone marrow suppression, interstitial nephritis, and hemolytic anemia or megaloblastic anemia, which are primarily attributed to the sulfapyridine moiety. Periodic monitoring of complete blood count and liver function tests is suggested in patients being treated with sulfasalazine. Sulfasalazine has also been associated with reversible quantitative and qualitative changes in spermatogenesis, but has not been associated with birth defects, still births, miscarriages, low birth weights or pre-term delivery as compared to the general population or with untreated patients with IBD. However, patients who tolerate induction therapy with sulfasalazine are likely to tolerate maintenance therapy well. Mesalamine is better tolerated than sulfasalazine, and approximately 80% patients intolerant or allergic to sulfasalazine would tolerate 5-ASA medications. Renal dysfunction is very rare with 5-ASA.

**Discussion:** Sulfasalazine is metabolized by gut flora into sulfapyridine and 5-ASA, which act as anti-inflammatory agents. It is an effective option for induction and maintenance of remission, though it may not be as effective as standard-dose mesalamine. Sulfasalazine, especially at higher doses, may not be well tolerated, which limits dose escalation in patients with a sub-optimal response, whereas the dose of mesalamine may be escalated usually without any adverse events. Hence, mesalamine may be a preferred treatment option for the majority of patients with mild-moderate UC. However, patients who have tolerated and achieved remission with sulfasalazine tolerate it well long-term, and may be maintained on the same therapy. Sulfasalazine is very inexpensive, and may be considered when alternatives are cost-prohibitive. Additionally, sulfasalazine may be beneficial in patients with colitis-associated arthralgias, given its efficacy in management of mild rheumatoid arthritis.

**Question 4.** In adults with extensive mild-moderate UC, is combined oral and rectal 5-ASA therapy superior to oral 5-ASA therapy for induction and maintenance of remission?
**Key Message:** In patients with extensive mild-moderate UC, combined oral and rectal 5-ASA therapy is probably more effective than oral 5-ASA therapy alone for induction of remission (*moderate quality evidence*), and may be more effective for maintenance of remission (*low quality evidence*).

**Effect estimate:** We identified 4 trials comparing oral+rectal 5-ASA (either sulfasalazine 3g/d or standard-dose oral mesalamine combined with 1-4g rectal sulfasalazine or mesalamine enemas) with oral sulfasalazine or standard-dose mesalamine for induction of remission in patients with either left-sided colitis and/or extensive colitis (~94% patients in 3 trials with left-sided colitis; 100% patients in one trial with extensive colitis).\(^{123-126}\) Based on meta-analysis, risk of induction of remission was significantly higher with combination therapy compared with oral 5-ASA monotherapy (RR, 0.68 [0.49-0.94]) without significant heterogeneity \(I^2=31\%\) (eFigure 28). Two trials compared oral+rectal 5-ASA (low-dose mesalamine combined with 1-4g mesalamine enemas twice/week) with oral 5-ASA alone (low-dose mesalamine) for maintenance of remission over 52 weeks.\(^{127, 128}\) Outcomes was defined based on CAI defined remission or need for rescue medications in one trial, and maintenance of endoscopic remission with or without symptoms in the other trial. Based on these two trials, combination therapy with 5-ASA was superior to oral 5-ASA therapy for maintenance of remission (RR, 0.45 [0.20-0.97]) (eFigure 29).

**Quality of Evidence:** The overall body of evidence suggesting superiority of combination oral+rectal 5-ASA therapy for induction of remission was rated as moderate quality, due to low event rate leading to imprecision (Table 8). Evidence supporting combined 5-ASA therapy over oral 5-ASA monotherapy for maintenance of remission was rated as low quality, due to indirectness (comparator group received low-dose mesalamine, whereas combined mesalamine amount in intervention group exceeded 2g) and imprecision (low event rate).

**Potential Harms of Intervention:** Both oral and rectal 5-ASA were well tolerated in trials.
**Discussion:** Optimization of 5-ASA therapy is a critical step before escalating to immunosuppressive therapy in patients with mild-moderate UC. With moderate quality evidence supporting a benefit of combining oral+rectal 5-ASA over standard-dose 5-ASA, this combination regimen is potentially an effective strategy for all patients with extensive mild-moderate UC, particularly those who are sub-optimally controlled with oral 5-ASA therapy alone, or patients with moderate disease activity. Two studies suggested a quicker onset of action by combining oral and rectal 5-ASA,\textsuperscript{124, 125} whereas Vecchi et al did not observe any significant difference in time to achieving remission.\textsuperscript{126} In a survey of 100 patients with UC, rapidity of onset of relief was highly valued by patients over pill burden or once-daily dosing.\textsuperscript{129} This beneficial effect of combined therapy may be related either to higher effective 5-ASA dose delivered, or to an independent topical anti-inflammatory effect of adding rectal 5-ASA therapy. While induction studies used only standard-dose oral 5-ASA for both intervention and comparator arm, it is conceivable that adding 5-ASA enemas may increase efficacy of high-dose oral 5-ASA.

Maintenance therapy with combined oral+rectal 5-ASA may also be an effective strategy, especially in patients sub-optimally controlled with oral 5-ASA alone and who value avoiding potentially avoid immunosuppressive therapy. In a focus-group when presented with a scenario of achieving steroid-induced remission after failure of 5-ASA therapy, patients valued avoiding immunosuppressive therapy, and were willing to use higher doses of 5-ASA to avoid side effects.\textsuperscript{130} However, studies have also demonstrated low compliance with rectal therapy, and most patients wanted to reserve rectal therapy as adjunct to be used during acute flares.

**Question 5.** In patients with mild-moderate ulcerative colitis treated with oral mesalamine, is once-daily mesalamine comparable to multiple times per day administration of mesalamine?

**Key Message:** In patients with mild-moderate UC treated with oral mesalamine, there is probably no difference between equivalent doses of
mesalamine administered once daily vs. multiple-times per day for inducing and maintaining remission *moderate quality evidence*).

**Effect estimate:** We identified 4 trials comparing equivalent doses of mesalamine administered once daily vs. multiple times per day (2 or more divided doses) for induction of remission,\(^3^7, 4^0, 1^3^1, 1^3^2\) and 11 trials comparing different mesalamine dosing schema for maintenance of remission, in patients with mild-moderate UC.\(^6^0, 6^2, 1^3^3-1^4^1\) All studies used standard-dose mesalamine; no trials of once daily administration of diazo-bonded 5-ASA or sulfasalazine were identified. There was no significant difference in rates of induction of remission between once daily and multiple times daily mesalamine (4 trials, 944 patients; RR, 0.96 [0.85-1.08]), with minimal heterogeneity (eFigure 30). In trials of maintenance therapy, there was no significant difference in rates of maintaining remission when equivalent doses of mesalamine was administered once daily or multiple times per day (11 trials, 4465 patients; RR, 0.96 [0.85-1.07]) with minimal heterogeneity (eFigure 31). Within clinical trials, there was no difference in adherence to therapy (>80% of recommended doses taken) between once daily (pooled adherence, 92.4%; range, 41.7-98.3) and multiple times per day administration (93.6%; range, 37.5-99.6) (11 trials, 3305 patients; RR for failure to adhere to therapy, 1.09 [0.78-1.50] (eFigure 32).

**Potential Harms of Intervention:** There was no difference in rates of treatment discontinuation between patients treated with once daily or multiple times daily mesalamine (10 trials, 4081 patients; RR, 0.98 [0.90-1.06]) (eFigure 33). In contrast to clinical trials, adherence to multiple times per day regimens may be lower as compared to once daily regimen in clinical practice which may lead to higher rates of relapse.

**Quality of Evidence:** The overall body of evidence suggesting comparability of once daily vs. multiple times per day administration of equivalent doses of mesalamine for both induction and maintenance of remission was rated as moderate quality (Table 9). Evidence was rated down for imprecision due to wide confidence intervals on either side of unity.
Discussion: In contrast with clinical trials which are closely regulated with high adherence rates, real-world observational studies in patients with chronic diseases have consistently demonstrated significantly lower adherence to complex dosing regimens, involving multiple divided doses, over simplified once daily dosing regimens. In a meta-analysis of 51 prospective studies utilizing an electronic monitoring device to measure adherence, compared with once daily regimen, ‘taking’ adherence was 6.7%, 13.5%, and 19.2% lower in twice-, 3-times, and 4-times (n = 57) daily regimens and ‘regimen’ adherence was 13.1%, 24.9%, and 23.1% lower in twice-, 3-times, and 4-times daily regimen, respectively. In clinical practice, adherence to mesalamine is low (~40-60%) particularly during maintenance phase. Non-adherence is associated with significantly higher risk of disease relapse and burden and costs of hospitalization. Overall, non-adherence in patients with mild-moderate UC can be attributed to patient-related factors (young age, male sex, being single, full-time employment), disease-related factors (symptomatic remission, recent diagnosis) and treatment-related factors (complexity of dosing regimen, heavy pill burden, perception of lack of benefit of medications, side effects). One key modifiable factor to improving compliance is simplifying dosing regimens without compromising efficacy. Based on clinical trials, we observed moderate confidence in estimates supporting that once daily mesalamine is as effective and safe as multiple times per day mesalamine, both for induction and maintenance of remission. Studies on patient preferences have demonstrated that both patients and physicians value ease of once daily administration over multiple times per day administration, though it was not as highly valued by patients as perceived by physicians. A British cost-effectiveness analysis suggested superiority of once daily mesalamine over multiple times per day administration, at equivalent doses. None of the trials evaluated once daily administration of sulfasalazine and diazo-bonded 5-ASA, and these have conventionally been administered in multiple divided doses, in part due to high pill burden and pill size.
Question 6. In adults with mild-moderate UC, what is the role of budesonide formulations (budesonide MMX and controlled ileal-release budesonide)?

**Key Message:** In patients with mild-moderate UC, oral budesonide MMX is probably effective in inducing remission (*moderate quality evidence*), and controlled ileal-release budesonide may be effective in inducing remission (*low quality evidence*); these medications are unsuitable for maintenance of remission. Oral budesonide MMX is not more effective than oral mesalamine or controlled ileal-release budesonide for inducing clinical remission (*low quality evidence*). Controlled ileal-release budesonide is probably inferior to oral mesalamine for induction of remission (*moderate quality evidence*). Budesonide may not be inferior to prednisone for induction of remission, and has lower risk of adverse events (*low quality evidence*). In mesalamine-refractory patients with mild-moderate UC, addition of oral budesonide MMX to mesalamine may be modestly effective in inducing remission (*moderate quality evidence*).

**Effect estimate:**

**Budesonide MMX or controlled ileal release budesonide vs. placebo:** Based on three RCTs comparing oral budesonide MMX 9mg with placebo in patients with mild-moderate UC (32.8% with extensive colitis, 66.3% with moderate disease activity, 67% with prior 5-ASA exposure), budesonide MMX 9mg was more effective than placebo in inducting clinical remission (RR of failure to induce remission, 0.88 [0.83-0.94]) ([eFigure 34](#)). There was no significant difference in risk adverse events necessitating discontinuation of drug therapy (RR, 0.91 [0.46-1.80]) ([eFigure 35](#)). While no dedicated trial evaluated the efficacy of controlled ileal-release (CIR)-budesonide, a single four-arm RCT compared budesonide MMX 9mg vs. budesonide MMX 6mg vs. CIR-budesonide vs. placebo. In this trial, CIR-budesonide was modestly more effective than placebo in inducing remission (RR for failure to induce remission, 0.93 [0.87-0.99]), without significant differences in tolerability (RR, 1.19 [0.68-2.08]). In a single trial published only in abstract form comparing budesonide MMX 6mg and placebo for maintenance of remission in 122 patients with mild-moderate UC, 12-
month rates of clinical relapse was numerically lower in budesonide MMX treated patients (40.4% vs. 60.5%), but did not reach statistical significance (p=0.055).\textsuperscript{151}

**Quality of Evidence:** In comparing budesonide MMX with placebo, evidence was rated down for imprecision due to low event rate. Though in the CORE-II trial, some sites violated good clinical practice, and 15% patients suspected to have active clinical and endoscopic evidence of UC were deemed not to have active histological disease, the body of evidence was not deemed to be at high risk of bias; overall results were comparable on sensitivity analysis with inclusion of appropriate patients. Hence, the overall quality of evidence was rated as moderate favoring budesonide MMX over placebo for induction of remission (Table 10). In contrast, evidence supporting CIR-budesonide over placebo was rated as low quality due to imprecision (due to low event rate) and high risk of bias in the only included CORE-II trial.

**Budesonide MMX vs. CIR-budesonide vs. mesalamine:** In a single 4-arm RCT (CORE-I) designed to establish efficacy of budesonide-MMX over placebo with mesalamine included as an internal reference, there was no significant difference between budesonide MMX and mesalamine in inducing remission (failure to achieve induction of remission: 105/127 [82.7%] vs. 112/127 [88.2%], RR, 0.94 [0.85-1.04] and tolerability (RR, 1.07 [0.54-2.13]).\textsuperscript{44} Similarly, in the CORE-II study where CIR-budesonide was included as an internal reference, there was no significant difference between budesonide MMX and CIR-budesonide in inducing remission (failure to achieve induction of remission: 108/127 [85.0%] vs. 113/126 [89.7%], RR, 0.95 [0.86-1.04] and tolerability (RR, 1.07 [0.64-1.81]).\textsuperscript{150} In contrast in a head-to-head comparative, double-blind, double-dummy trial of CIR-budesonide 9mg/d and mesalamine 3g/d (20.1% with extensive colitis, 64.7% with mild activity, 42.3% with prior 5-ASA exposure), CIR-budesonide was inferior to mesalamine for induction of remission (failure to achieve induction of remission: 107/177 [60.5%] vs. 75/166 [45.2%],RR, 1.34 [1.09-1.64]), and was numerically more likely to be discontinued due to adverse events (RR, 1.88 [0.82-4.27]).\textsuperscript{152}
**Quality of Evidence:** Overall comparative evaluations of budesonide MMX vs. mesalamine and budesonide MMX vs. CIR-budesonide was rated as low quality due to serious imprecision and high risk of bias in the trials informing this evidence (Table 11). In contrast, evidence comparing CIR-budesonide to mesalamine was rated as moderate quality, rated down due to low event rate.

**Budesonide MMX vs. systemic corticosteroids:** No trials comparing budesonide MMX with oral systemic corticosteroids like prednisone, for mild-moderate UC were identified. Hence, we relied on indirect evidence from three trials comparing 2nd-generation corticosteroids (CIR-budesonide, beclomethasone, fluticasone) with oral prednisone for induction of remission in patients with mild-moderate UC.\(^{153-155}\) Of these trials, one trial comparing beclomethasone vs. prednisone was designed as a non-inferiority trial, using UCDAI-defined clinical remission as a secondary outcome at week 4;\(^{154}\) in the other trials, outcomes were defined either as 'investigator-defined' clinical remission or endoscopic remission (without data on clinical remission). Based on these 3 RCTs, there was no significant difference between 2nd-generation corticosteroids and oral prednisone (RR of failure to induce remission, 1.04 [0.96-1.13]), without heterogeneity (eFigure 36). Two trials reported rates of steroid-related adverse events. Rate of steroid-related adverse events was significantly lower in patients treated with 2nd-generation corticosteroids as compared to oral prednisone (RR, 0.32 [0.16-0.64]) (eFigure 37).

**Quality of Evidence:** Overall body of evidence comparing the efficacy of budesonide MMX with oral systemic corticosteroids was rated as low quality, due to indirectness (since evidence was derived from other 2nd-generation corticosteroids) and imprecision (wide confidence intervals crossing unity). While one of early trials was at high risk of bias due to inadequate description of allocation concealment and sequence generation, overall evidence was not rated down for risk of bias (Table 12).

**Adding budesonide MMX for mesalamine-refractory patients:** Based on a single, multi-center, double-blind, placebo-controlled trial comparing budesonide MMX 9mg and placebo in patients with mild-moderately active UC despite
ongoing therapy with mesalamine $\geq$2.4g/d, adding budesonide MMX was modestly more effective than placebo (failure to achieve induction of remission: 225/255 [88.2%] vs. 238/255 [93.3%], RR, 0.95 [0.89-1.00]) in true ITT analysis. In contrast, in the previously mentioned CORE-I and –II trials, patients discontinued oral 5-ASA therapy for at least 2 days prior to randomization. The overall results were comparable using study-reported modified ITT in which patients without histological evidence of active UC on centralized blinded reading (n=51/510, 10%) and infectious enteritis (n=1) were excluded (budesonide MMX vs. placebo: 13.0% vs. 7.5%; RR, 0.94 [0.88-1.00]). There was no significant difference in tolerability (RR, 1.33 [0.57-3.11]).

Quality of Evidence: Overall body of evidence supporting the addition of budesonide MMX in patients with ongoing mild-moderately active UC despite oral 5-ASA $\geq$2.4g/d was rated as moderate quality (serious imprecision since upper limit of confidence interval in true ITT was unity) (Table 13).

Potential Harms of Intervention: As noted in the analysis, budesonide MMX and CIR-budesonide were well tolerated. Due to extensive first-pass metabolism in the liver, systemic corticosteroid exposure with these medications is very low. In the CORE-I and –II trials, the incidence of potential glucocorticoid-related adverse events was observed in <10% patients, and the rate was similar in patients treated with budesonide MMX 9mg and placebo (mood changes, 2.7% vs. 3.9%; sleep changes, 2.7% vs. 4.3%; insomnia, 2.4% vs. 3.1%). Though an 18-28% reduction in baseline cortisol level was observed in budesonide-treated patients in these trials, overall morning cortisol remained within normal limits at the end of the trials. Hence, these medications appear to be safe for short-term use. If these medications are considered in place of mesalamine for patients with mild-moderate UC, then potential risks of lack of long-term maintenance therapy (risk of disease relapse) needs to be considered since budesonide is not approved for long-term use. Alternatively, if these medications are considered in addition to 5-ASA in patients with mild-moderately active UC despite standard-dose 5-ASA, then modest benefits and tolerability of
this combination needs to be weighed in the context of potentially delaying more effective therapy such as biologic agents, and risk of worsening disease.

**Discussion:** Budesonide is a corticosteroid with high potency and low systemic corticosteroid activity due to high first pass metabolism. While CIR-budesonide is primarily released in the distal ileum and right colon and is used in patients with Crohn’s disease, budesonide MMX was designed for release throughout the colon, for use in patients with UC. Based on the evidence presented above, budesonide MMX 9mg is a safe and effective alternative in inducing remission in patients with mild-moderate UC. However, there is paucity of data on long-term safety and low quality evidence of efficacy of budesonide for maintenance therapy; hence, it is unsuitable for and has not been approved for maintenance of remission. There is moderate quality evidence that budesonide MMX is probably effective in mesalamine-refractory patients as an add-on therapy; however, the magnitude of benefit is small, and risks and benefits needs to weighed in the context of severity of flare, risks of disease worsening and effectiveness and tolerability of alternative therapy. In clinical practice, in mesalamine-refractory patients with mild-moderate disease activity, the typical decision facing patients and physicians in the short-term is between choosing budesonide MMX vs. oral prednisone. Unfortunately, we did not identify any clinical trial comparing these two options, and hence, relied on indirect evidence from trials comparing other 2nd-generation corticosteroids with oral prednisone/prednisolone. Of three trials, one comparing beclomethasone vs. prednisone was a well-designed non-inferiority trial suggesting equivalence of both interventions for achieving clinical response by week 4. One trial comparing fluticasone with oral prednisolone suggested a more rapid onset of action with oral prednisolone with a higher proportion of patients achieving clinical remission by week 2; however, by week 4, the rates of achieving investigator-defined clinical remission was equivalent. In a small trial comparing budesonide with systemic prednisone in patients with UC, Lofberg and colleagues observed similar improvement in symptoms and endoscopic remission with both agents, though overall rates of clinical remission were not reported. However, this specific budesonide
formulation (acid-resistant pellets with a sustained-release profile to deliver the active drug during the passage throughout the colon) is not commercially available. Two trials reported a significantly lower risk of corticosteroid-related adverse events with use of 2nd-generation corticosteroids with high first-pass metabolism in the liver, as compared to conventional oral prednisone/prednisolone.154, 155

We opted to explore CIR-budesonide as a potential treatment option in patients with mild-moderate UC, though it has not been approved for this indication. Based on exploratory analyses, we observed low quality evidence suggesting that it may be effective in inducing remission in patients with mild-moderate UC; however, in a head-to-head trial, it was inferior to mesalamine in inducing remission in patients with mild-moderate UC, and hence, should not replace 5-ASA therapy. In another underpowered trial, exploratory analysis suggested no significant difference in efficacy and tolerability of budesonide MMX and CIR-budesonide, though rates of achieving remission were numerically higher in budesonide MMX-treated patients. On pooled analysis of the CORE-I and -II trials, efficacy of budesonide MMX 9mg was relatively higher in patients with left-sided colitis or proctosigmoiditis, as compared to patients with extensive colitis (32/145 [22.1%] vs. 8/85 [9.4%]; RR, 0.86 [0.77-0.96]). This suggests that while budesonide MMX may be the preferred budesonide formulation in patients with mild-moderate UC, CIR-budesonide may be considered as an alternative if the former is not available and patients are averse to or intolerant to 5-ASA. It is important to note that CIR-budesonide has not been studied in 5-ASA refractory patients with mild-moderate UC, and indirect evidence suggests limited efficacy.

**Question 7.** In adults with mild-moderate ulcerative proctosigmoiditis or ulcerative proctitis, is rectal 5-ASA therapy superior to oral 5-ASA therapy for induction and maintenance of remission?

**Key Message:** In patients with mild-moderate ulcerative proctosigmoiditis or ulcerative proctitis, rectal 5-ASA therapy may be superior to oral 5-ASA therapy for induction and maintenance of remission (very low quality evidence).
**Effect estimate:** We identified 4 trials comparing 4-8 weeks of rectal vs. oral 5-ASA for induction of remission, of which 3 were conducted exclusively in patients with ulcerative proctosigmoiditis (up to 50cms from anal verge) or ulcerative proctitis.\textsuperscript{125, 158-160} Rectal 5-ASA intervention included mesalamine enemas 4g/d (3 trials) or mesalamine suppository 400mg three times/day (1 trial), whereas oral 5-ASA intervention included standard-dose mesalamine (2 trials), high-dose mesalamine (1 trial) or sulfasalazine 4g/d (1 trial). Outcomes were variably defined based on standardized disease activity index or physician global assessment. On meta-analysis, there was a trend favoring efficacy of rectal 5-ASA over oral 5-ASA (RR, 0.43 [0.14-1.31]), with considerable heterogeneity ($I^2=80\%$) (eFigure 38). After excluding one trial comparing high-dose MMX mesalamine with mesalamine enemas in patients with left-sided colitis,\textsuperscript{160} overall effect favoring rectal 5-ASA was significant (RR, 0.28 [0.14-0.56]) without any heterogeneity ($I^2=0\%$). We identified 3 trials comparing intermittent rectal 5-ASA (mesalamine enemas 4g 2-3 times/week or 1 week/month) and oral 5-ASA (sulfasalazine 2g/day in 2 trials, and low-dose mesalamine in 1 trial) for maintaining 5-ASA induced remission in patients with mild-moderate ulcerative proctosigmoiditis.\textsuperscript{161-163} All trials were single-blinded, with unclear randomization and allocation concealment schemes. On meta-analysis, there was a trend favoring rectal 5-ASA over oral 5-ASA (RR, 0.69 [0.41-1.17]), without heterogeneity ($I^2=0\%$) (eFigure 39).

**Quality of evidence:** Trials of induction and maintenance therapy comparing topical vs. oral 5-ASA in patients with ulcerative proctosigmoiditis or ulcerative proctitis were at high risk of bias due to unclear randomization and allocation concealment scheme, heterogeneous outcome measures and single-blind trial (for trials of maintenance therapy). Additionally, the evidence was imprecise with wide 95\% CI crossing unity. Evidence for induction therapy was also rated down for inconsistency, whereas trials of maintenance therapy were rated down for indirectness since the comparator oral 5-ASA therapy was based on low-dose, not standard-dose 5-ASA. Hence, the overall body of evidence favoring rectal 5-ASA therapy over oral 5-ASA was rated as very low quality (Table 14).
**Potential harms of intervention:** Both oral and rectal 5-ASA were well tolerated in included trials and in clinical practice.

**Discussion:** For patients with distal colitis, evidence suggests that rectal 5-ASA therapy may be more effective than oral 5-ASA for induction and maintenance of remission although there is very low confidence in these estimates. This beneficial effect may be related to topical delivery of higher dose 5-ASA at site of most active disease. However, decisions on preferred route of treatment administration are patient-sensitive, with inter-individual variability. Rectal 5-ASA may be inconvenient for some patients, and in patients with active disease, retaining enemas may be difficult. In survey studies and focused group-based qualitative studies, effectiveness and route of administration were rated as most important attributes by patients with mild-moderate UC. Patients generally preferred oral administration over rectal therapy, and wanted to reserve rectal therapy as adjunct to be used during acute flares.

**Question 8. In adults with mild-moderate ulcerative proctosigmoiditis, what is the role of mesalamine enemas and/or corticosteroid enemas/foam for induction and maintenance of remission?**

**Key Message:** In adults with mild-moderate ulcerative proctosigmoiditis, mesalamine enemas are probably more effective than placebo for induction and maintenance of remission (*moderate quality evidence*). Rectal corticosteroid therapy (foam or enema) is more effective than placebo for induction of remission (*high quality evidence*). Rectal corticosteroids have not been studied for maintenance of remission. Rectal mesalamine enemas are probably more effective than rectal corticosteroids for induction of remission (*moderate quality evidence*).

**Effect estimates:**

**Mesalamine enema vs. placebo:** Based on 4 RCTs in patients with mild-moderate ulcerative proctosigmoiditis (extending up to splenic flexure or <50cm from anal verge), mesalamine enemas (2-4g/d, once at night) were more effective than placebo in inducing remission (RR, 0.50 [0.35-0.73]), with
significant heterogeneity (\(I^2=58\%\)) (eFigure 40).\textsuperscript{165-168} Trials of sulfasalazine enemas and 4-ASA enemas were excluded; from dose-ranging trials of mesalamine enemas, only data for 4g/d mesalamine enemas was included since that is most commonly available in the United States and is FDA-approved. In a single small trial of 25 patients with quiescent left-sided colitis, mesalamine enema 1g/d was superior to placebo for maintenance of remission (RR, 0.30 [0.11-0.81]); no trials of standard 4g/d mesalamine enemas were identified.\textsuperscript{169}

**Quality of evidence:** For induction and maintenance of remission, the overall body of evidence supporting mesalamine enema over placebo was rated as moderate, primarily due to imprecision attributed to low event rate (Table 15). Though statistically significant heterogeneity was observed, it relates primarily to the magnitude of benefit and not the direction, and hence, evidence was not rated down.

**Rectal corticosteroids vs. placebo:** We identified 4 RCTs comparing rectal corticosteroids (all budesonide; 3 trials of budesonide foam 2-4g/day, 1 trial of budesonide enema) with placebo for induction of remission in patients with mild-moderate ulcerative proctosigmoiditis, treated for 4 weeks (eFigure 41).\textsuperscript{170-172} On meta-analysis, rectal corticosteroid therapy was significantly more effective than placebo for inducing remission (RR, 0.73 [0.66-0.80]), without significant heterogeneity. In a single trial comparing budesonide foam with hydrocortisone foam, no difference in efficacy was identified (RR of failure to induce remission, 0.99 [0.76-1.28]).\textsuperscript{173} No trials of maintenance therapy with rectal corticosteroids in patients with quiescent ulcerative proctosigmoiditis were identified.

**Quality of evidence:** Overall body of evidence supporting rectal corticosteroids over placebo for induction of remission in patients with active mild-moderate proctosigmoiditis was rated as high (Table 16).

**Rectal 5-ASA vs. rectal corticosteroids:** Based on 13 trials comparing rectal 5-ASA (5-ASA enemas 1-4g/d or 5-ASA suppositories 1g/d) vs. rectal corticosteroids (hydrocortisone enema 100mg/d, prednisolone enema 25-30mg/d, budesonide enema 2mg/d, beclomethasone 3mg/d or comparable foam preparations) used for treatment of mild-moderate ulcerative proctosigmoiditis for
2-8 weeks, rectal 5-ASA was superior to rectal corticosteroids for induction of clinical remission (RR, 0.74 [0.61-0.90]) (eFigure 42). Substantial heterogeneity was observed ($I^2=62\%$), with considerable differences in rates of achieving remission across different trials. On limiting analysis to 4 trials using standard dose 5-ASA enemas (4g/d), a similar benefit was observed (RR, 0.39 [0.19-0.82]).

**Quality of evidence:** Overall body of evidence supporting rectal 5-ASA over rectal corticosteroids for induction of remission in patients with mild-moderate ulcerative proctosigmoiditis was rated as moderate (evidence rated down for heterogeneity) (Table 17).

**Potential harms of intervention:** Rectal mesalamine is safe and well-tolerated, without significant treatment-related adverse events. Rectal corticosteroid preparations are generally safe in studies of induction of remission; however, there is potential risk of corticosteroid-related side effects with long-term use especially with conventional corticosteroids such as prednisolone or hydrocortisone. Second-generation corticosteroids including budesonide have a very low risk of suppression of adrenocortical axis (decreased morning cortisol observed in <1% patients in trials).

**Discussion:** Rectal mesalamine and corticosteroids are both effective in inducing remission in patients with ulcerative proctosigmoiditis, with the former probably being more effective. Rectal mesalamine enemas are also effective for maintenance of remission; though the included study was based on maintenance with daily mesalamine enemas 1g/d, other trials comparing rectal mesalamine with oral mesalamine for maintenance of remission in patients with ulcerative proctosigmoiditis have demonstrated efficacy with twice/week enemas or enemas one week/month when used at 4g/d dose. Different rectal corticosteroid formulations were combined in this analysis. In a trial comparing budesonide foam with hydrocortisone foam for ulcerative proctosigmoiditis, Bar-Meir and colleagues reported comparable efficacy for induction of remission (53% vs. 52%). Though second-generation rectal corticosteroids like budesonide may be safer and better tolerated than conventional rectal corticosteroids, the overall
risk of corticosteroid-related side effects with short-duration topical therapy is low. Different formulations for administering topical therapies including enemas and foam have been developed. In a Cochrane review, there was no significant difference in the efficacy of 5-ASA enemas and 5-ASA foam (5 trials, OR of failing to achieve remission, 1.19 [0.60-2.33]). Similar comparable efficacy was observed in a trial comparing budesonide foam with budesonide enema. In this trial, patients preferred foam over enema because of easier delivery and better retention. This may be an important consideration in patients who are unable to retain liquid enemas. However, there is paucity of data on cost-effectiveness of budesonide foam over enemas. In a trial, corticosteroid enema combined with 5-ASA enema was superior to either of them alone for induction of clinical remission, and this may be considered in patients with refractory ulcerative proctosigmoiditis. In another trial of 120 patients with mild-moderately active distal UC despite standard-dose mesalamine, addition of rectal 5-ASA combined with rectal corticosteroid enemas was superior to rectal 5-ASA or rectal corticosteroid enemas alone.

**Question 9. In adults with mild-moderate ulcerative proctitis, what is the role of mesalamine suppositories and/or corticosteroid suppositories for induction and maintenance of remission?**

**Key Message:** In adults with mild-moderate ulcerative proctitis, mesalamine suppositories are probably more effective than placebo for induction of remission (*moderate quality evidence*) and maintenance of remission (*low quality evidence*). No randomized trials of corticosteroid suppositories were identified in patients with ulcerative proctitis; indirect evidence derived from efficacy of corticosteroid enemas in patients with ulcerative proctosigmoiditis suggests benefit of corticosteroid suppositories for induction of remission in patients with ulcerative proctitis (*low quality evidence*).

**Effect estimates:**

**Mesalamine suppositories vs. placebo:** Based on 4 RCTs in patients with mild-moderate ulcerative proctitis comparing mesalamine suppositories (1-
1.5g/d, administered once daily or in three divided doses) with placebo, mesalamine suppositories were more effective than placebo at inducing remission (RR, 0.44 [0.34-0.56]), without significant heterogeneity (eFigure 43). In these trials, proctitis was defined as disease extending <15-20cm from anal verge. Four trials compared mesalamine suppositories (0.5-1g dose, administered once/day to three times/week) with placebo for maintenance of remission in patients with ulcerative proctitis. On meta-analysis, mesalamine suppositories were superior to placebo for maintenance of remission (RR, 0.50 [0.32-0.79]), with significant heterogeneity ($I^2=59\%$), primarily in the magnitude of benefit (eFigure 44).

**Quality of evidence:** Overall body of evidence supporting mesalamine suppositories over placebo for induction of remission in patients with proctitis was rated as moderate, primarily due to imprecision attributed to low event rate (Table 18). Though statistically significant heterogeneity was observed, it was primarily in the magnitude of benefit and not the direction, and hence, the evidence was not rated down. Evidence favoring mesalamine suppositories for maintenance of remission was rated as low quality due to imprecision due to low event rate, and risk of bias in included trials due to inadequate description of randomization and allocation concealment scheme.

**Corticosteroid suppositories vs. placebo:** No trials or open-label cohort studies of corticosteroid suppositories for management of mild-moderate ulcerative proctitis were identified. Based on indirect evidence supporting the efficacy of corticosteroid enemas and/or foam in patients with ulcerative proctosigmoiditis and proctitis, there may be benefit of using corticosteroid suppositories for induction of remission in patients with ulcerative proctitis, albeit quality of evidence is low. Rectal corticosteroid therapies have not been studied for maintenance of remission.

**Potential harms of intervention:** Mesalazine suppositories are well tolerated. There is limited data on side effects of corticosteroid suppositories, though long-term use of corticosteroid enemas is associated with modest systemic absorption and may marginally lower serum cortisol.
**Discussion:** Mesalamine suppositories are safe and effective for patients with mild-moderate ulcerative proctitis, and are better retained than enemas. In trials comparing once daily vs. multiple times per day administration of mesalamine suppositories, no significant differences were observed in efficacy. As noted above, in a single trial comparing mesalamine suppository 400mg three times/day with standard-dose oral mesalamine in patients with ulcerative proctitis, mesalamine suppositories were more effective in inducing remission than oral mesalamine. The maximum dose of mesalamine suppositories studied in trials was 1.5g/day, though trials of mesalamine enemas frequently use 4g/day; no significant dose-dependent toxicity has been identified with use of rectal mesalamine within therapeutic range.

**Question 10. In patients with mild-moderate UC, what is the role of probiotics for induction and maintenance of remission?**

**Key Message:** In patients with mild-moderate UC, the benefit of probiotics over placebo, or over mesalamine for induction and maintenance of remission is uncertain (*low to very low quality evidence*).

**Effect Estimates:**

**Probiotics vs. placebo:** Based on 7 RCTs with 585 patients with mild-moderate UC, probiotics were not more effective than placebo for induction of remission (RR, 0.88 [0.69-1.12]), with considerable heterogeneity ([eFigure 45](#)). In a sub-analysis of 3 RCTs in which VSL#3 was used as the probiotic, VSL#3 was superior to placebo for induction of remission (RR, 0.74 [0.63-0.87]). In 2 RCTs comparing probiotics with placebo for maintenance of remission, probiotic-treated patients had numerically, but not statistically, lower rates of relapse at 12 months as compared to placebo-treated patients (RR, 0.82 [0.63-1.06]) ([eFigure 46](#)).

**Quality of evidence:** In trials of induction therapy with probiotics, evidence was rated down for imprecision, inconsistency (both in summary estimates as well as in nature of probiotic-intervention with use of different formulations) and risk of bias (unclear allocation concealment and method of
randomization). Hence, the overall body of evidence favoring probiotics over placebo was deemed very low quality (Table 19). Evidence on efficacy of probiotics over placebo for maintenance of remission was rated as low quality, due to imprecision (wide CIs, with only 15 events across both trials) and risk of bias (unclear allocation concealment) in included trials.

**Probiotics vs. Mesalamine:** Only a single small trial compared probiotics (*Escherichia coli* Nissle 1917) with standard-dose mesalamine for induction of remission. In this trial, there was no significant difference in rates of achieving remission between probiotic- and mesalamine-treated patients, though overall remission rate was lower in the probiotic group (61.4% vs. 74.5%; RR, 1.24 [0.70-2.22]). Based on two trials comparing probiotics and mesalamine for maintenance of remission, there was no significant difference in rates of maintaining remission at 12 months (RR, 1.01 [0.84-1.22]) (eFigure 47).

**Quality of evidence:** Overall evidence suggesting no difference in efficacy of probiotics and mesalamine for both induction and maintenance of remission was rated as low quality due to imprecision (very wide CIs) and high risk of bias (unclear allocation concealment and/or method of randomization) (Table 19).

**Potential harms of intervention:** While probiotics were well tolerated in all included trials with low rates of treatment-related adverse events, there is potential for harm since their use may delay use of potentially more effective therapy and risk progression of disease. Alternate therapies like mesalamine are effective, safe and well-tolerated interventions in these patients with mild-moderate UC.

**Discussion:** Patients with mild-moderate UC often discuss the role of probiotics in disease management. Different probiotic formulations including *E. coli* Nissle 1917, Bifidobacterium spp., Enterococci, *Lactobacillus acidophilus, Lactobacillus rhamnosus* GG, *Lactobacillus johnsonii* LA1, combination *Streptococcus faecalis*, *Clostridium butyricum*, and *Bacillus mesentericus* and VSL#3 have been studied. Based on evidence synthesized above, the benefit of probiotics for induction and maintenance of remission over placebo and over mesalamine is uncertain.
Benefit over placebo for induction of remission was observed in three trials using VSL#3; however, no trials of maintenance therapy with VSL#3 were identified. Even though probiotics are well tolerated, in the absence of clear evidence of benefit, there is potential for harm since use of probiotics may delay use of more effective therapy. There is limited regulation of quality of probiotic formulations.

**Question 11. In patients with mild-moderate UC despite 5-ASA therapy, what is the role of curcumin for induction and maintenance of remission?**

**Key Message:** In patients with mild-moderate UC despite 5-ASA therapy, the benefit of adding oral curcumin for induction of remission is unclear (*very low quality evidence*), but it may be beneficial for maintenance of remission (*low quality evidence*).

**Effect Estimates:** Based on 3 RCTs with 169 patients with mild-moderate UC despite standard-dose mesalamine, there was a trend towards benefit with addition of oral curcumin over placebo for induction of clinical remission, though it did not reach statistical significance (RR, 0.70 [0.48-1.03]) (*eFigure 48*).203-205 One trial of curcumin enema also showed comparable effect estimates.206 There was considerable heterogeneity in effect estimates, with one trial using curcumin 3g/d (containing 95% curcuminoid) showing markedly beneficial effect and another trial using low dose curcumin 150mg/d, showing no benefit. In a single trial of maintenance therapy in mesalamine-treated patients with quiescent UC, addition of oral curcumin was more effective than placebo in maintaining remission over 6 months (failure to maintain remission: 4/45 [8.9%] vs. 13/44 [29.5%]; RR, 0.30 [0.11-0.85]).207

**Quality of evidence:** Overall, the body of evidence favoring oral curcumin over placebo for induction of remission with active mild-moderate UC despite 5-ASA, was rated as very low quality due to high risk of bias in included trials (inadequate blinding, allocation concealment, protocol violation, and an unexpectedly low placebo remission rate), inconsistency (statistically, in summary estimate, and clinically, with studies using widely variable curcumin dosage), and imprecision (*Table 20*). In contrast, evidence supporting the use
curcumin 2g/d for maintenance of remission in 5-ASA treated patients with quiescent UC was rated as low quality due to imprecision and risk of bias.

**Potential harms of intervention:** Curcumin is well tolerated without any significant treatment-related side effects. However, the potential benefit of using curcumin for induction of remission in patients sub-optimally controlled on 5-ASA should be weighed against risks of delaying more effective therapy. Similarly, when curcumin is added to 5-ASA for maintenance of remission, it’s potential benefit should be weighed in the context of risk of relapse – for patients at low risk of relapse maintained on 5-ASA, adding curcumin increases pill burden and may contribute to inconvenience; for patients at high risk of relapse on 5-ASA, adding curcumin may potentially delay initially of a more effective, albeit probably immunosuppressive therapy.

**Discussion:** Similar to the general population, patients with UC also frequently use complimentary and alternative therapies with the hope of controlling disease using a ‘natural’, non-toxic approach. While several herbal and dietary supplements have been studied albeit in poorly designed studies, curcumin, a naturally occurring phenol, active yellow pigment of turmeric, belonging to the ginger family is one of the best studied. Biologically, curcumin has immunomodulating, proapoptotic, and antiangiogenic properties that make it potentially beneficial in patients with immune-mediated diseases. However, literature on use of curcumin in IBD has been limited by lack of dose-finding efficacy studies, inability to develop a true placebo indistinguishable from curcumin (due to taste and color of curcumin), and small study size. In the study by Lang *et al*, which was the only strongly positive study of curcumin for induction of remission, there was exceptionally low placebo remission (0%) and response (12.5%) rate, unlike that seen in other trials in patients with mild-moderate UC. Additionally, the majority of patients in this trial had normal serum inflammatory markers and may have had mild as opposed to moderate disease activity. Large, well-designed, phase II or III studies of curcumin are warranted in patients with mild-moderate UC, who do not adequately respond to induction therapy with optimized 5-ASA therapy, to adequately inform its role in these patients.
Similarly, larger studies confirming relative and absolute efficacy of add-on curcumin for maintaining remission in 5-ASA-treated patients are warranted, to inform its role in maintenance of remission.

**Question 12. In patients with mild-moderate UC, what is the role fecal microbiota transplantation for induction and maintenance of remission?**

**Key Message:** In patients with mild-moderate UC, fecal microbiota transplantation may be effective for induction of remission (*low quality evidence*), but there is very limited data to inform its role for maintenance of remission.

**Effect Estimates:** Four RCTs in 281 patients with active UC despite usual care comparing FMT with placebo were identified; most patients had mild-moderate disease activity at time of enrollment.\(^2^{10}-^{2}^{13}\) The studies were heterogeneous in design with inclusion criteria, route of FMT administration and follow-up periods varying between studies. FMT was delivered via colonoscopy (x1) followed by enemas (x2 in study by Costello *et al*;\(^2^{10}\) x39 administered 5 days/week for 8 weeks in study by Paramsothy *et al*\(^2^{12}\)) in the two Australian studies, via enemas (weekly, for 6 weeks)\(^2^{11}\) or nasoduodenal tube (x2, every 3 weeks)\(^2^{13}\) in one each of the other studies. Patient follow-up periods varied from 7 to 12 weeks. In two studies, stool was obtained from a single donor, whereas in two Australian studies, stool was pooled from 3-7 donors, and included a mix of fresh and/or frozen stool; varying quantities of stool was instilled ranging from 8.3g to 120g. Comparator was either autologous stool in two trials and water in two trials. Based on meta-analysis of these 4 trials, FMT was more effective than placebo at inducing clinical remission over a 6-12 week period (RR, 0.80 [0.71-0.89]) (*eFigure 49*) and endoscopic remission (RR, 0.77 [0.63-0.93]) without significant heterogeneity. FMT was well tolerated with similar rates of adverse events in the FMT and placebo groups (RR, 1.41 [0.55-3.60]) (*eFigure 50*). No trials evaluating the efficacy of FMT for maintenance of remission were identified. From a recent meta-analysis of FMT in ulcerative colitis, 5 non-comparative cohort studies on long-term effectiveness of FMT were identified.\(^2^{14}\) In these studies, of 44 patients who underwent 1-5 FMT treatments at time of active disease and were followed
from 4-72 months, 22 patients had clinical response, 16 patients were unchanged and 3 patients deteriorated.

**Quality of evidence:** The overall body of evidence supporting benefit of FMT over placebo for induction of remission was rated as low quality. Evidence was rated down for inconsistency (variability in intervention, with differences in route and frequency of administration, amount and source of stool) and imprecision (small sample size with low event rate) (Table 21). Though patients in these trials were along the entire spectrum of UC severity with a substantial proportion on immunomodulators and/or biologic agents, we did not rate down for indirectness since the majority of patients had mild-moderately active disease at enrollment, and the anticipated benefits are likely to be exaggerated in a population with milder disease, as compared to patients with severe disease (who are inherently more treatment resistance).

**Potential harms of intervention:** In RCTs, FMT was well tolerated with very low rates of serious adverse events (worsening colitis seen in 3/140 patients receiving FMT vs. 4/137 patients receiving placebo). In a meta-analysis of 50 studies of FMT for UC or alternative reasons (mainly recurrent *Clostridium difficile* infection), FMT was well tolerated, with the most common FMT-attributable adverse event being abdominal discomfort. The incidence of FMT-attributable adverse events was 43.6% (89/204) and 17.7% (76/430) for FMT delivered through upper and lower gastrointestinal routes, respectively. A total of 44 kinds of serious adverse events were reported in 9.2% patients, including death (3.5%, 38/1089), infection (2.5%, 27/1089), relapse of IBD (0.6%, 7/1089) and *Clostridium difficile* infection (0.9%, 10/1089). Besides direct FMT-attributable risks, risks of potentially ineffective therapy and delay in initiation of proven effective therapies are conceivable.

**Discussion:** With increasing recognition of the role of dysbiosis in the pathogenesis of IBD, FMT is an attractive intervention. While FMT has established itself as highly effective in the management of recurrent *C. difficile* infection, FMT for the treatment of UC is still experimental. As noted above in 4 small RCTs, there is low quality evidence supporting a beneficial effect of FMT.
Each trial used different stool processing and delivery protocols, with varying intensity and variable donor pool, which makes it difficult to recommend a particular protocol or technique over the other. The mechanism of action of FMT in UC is unclear. Besides generally increasing bacterial diversity, certain patterns of microbial changes have been associated with response to FMT in patients with UC. For example, an increase in *Clostridium* clusters IV and XVIII was observed in those who responded in two RCTs and *Bacteroidetes* including *Sutterella spp* and *Fusobacterium spp* have been associated with non-response to FMT.\(^{211, 212}\) How these changes in microbial composition result in a beneficial effect in some patients with UC is unclear, and may be related to functional alterations in luminal and epithelial metabolic and biochemical processes as well as mucosal immune responses to the microbiota. Overall, this new treatment approach warrants in-depth mechanistic as well as large-scale clinical evaluation.

**KNOWLEDGE GAPS AND FUTURE DIRECTIONS**

While several significant advancements have been made in the treatment of patients with mild-moderate UC, this technical review identified some key knowledge gaps which merit further evaluation.

1. **Risk stratification**: Better approaches to identify patients presenting with moderate symptoms but at high-risk of progression and evolution into a severe phenotype and development of disease-related complications are warranted. Though there is some understanding of various clinical, biochemical and endoscopic factors that may be associated with progression, there is lack of validated risk prediction models that may identify high-risk patients early in their disease course. Once these tools are available, comparative studies on gradual step therapy vs. early aggressive therapy in patients deemed to have mild-moderate disease activity would inform an optimal treatment approach.
2. **Impact of 5-ASA on natural history of disease**: Though 5-ASA forms the mainstay of treatment in patients with mild-moderate UC for induction and maintenance of remission, there is limited understanding on whether these medications given as maintenance therapy beyond 12 months, modify the natural history of disease, preventing disease progression and complications. Likewise, there is little evidence to inform whether 5-ASA therapy should be continued vs. stopped in patients who escalate to biologic therapy for moderate-severe UC.

3. **Dosing regimens for 5-ASA**: While plenty is known (and summarized above) regarding optimal use of 5-ASA therapies in patients with mild-moderate UC, there are important knowledge gaps to identify patients who may benefit from early use of high-dose 5-ASA or in combination with rectal therapy, rather than gradually stepping from standard 5-ASA therapy. Additionally, there is limited evidence regarding optimal maintenance 5-ASA dosing in patients who required high-dose 5-ASA to induce remission

4. **Escalating from 5-ASA therapy to immunosuppressive agents**: There is little evidence to inform when 5-ASA-treated patients should be escalated to immunosuppressive therapy, particularly for a subset of patients who intermittently require corticosteroids – for example, should all patients who require corticosteroids even once after maximal optimization of 5-ASA therapy, be escalated to immunosuppressive therapy vs. only patients with continued corticosteroid-dependence or frequent courses of corticosteroids (≥1 course/year, etc.).

Besides these questions, there are knowledge gaps pertaining to the use of FMT in patients with UC, for which there are several ongoing studies. Well-designed trials of probiotic therapy and food supplements such as curcumin would also be helpful to optimally inform whether these medications are effective for inducing and/or maintaining remission in patients with mild-moderate UC.
REFERENCES:


51. Hanauer SB, Sandborn WJ, Dallaire C, et al. Delayed-release oral mesalamine 4.8 g/day (800 mg tablets) compared with 2.4 g/day (400 mg tablets) for the treatment of mildly to moderately active ulcerative colitis: The ASCENDI trial. Canadian Journal of Gastroenterology 2007;21:827-834.


83. Tursi A, Brandimarte G, Giorgetti GM, et al. Low dose balsalazide plus a high potency probiotic preparation is more effective than balsalazide alone


86. Kruis W, Schreiber S, Theuer D, et al. Low dose balsalazide (1.5 g twice daily) and mesalazine (0.5 g three times daily) maintained remission of ulcerative colitis but high dose balsalazide (3.0 g twice daily) was superior in preventing relapses. Gut 2001;49:783-789.


110. Andreoli A CR, Trotti R, Berri F, Prantera C. 5-aminosalicylic acid versus salazopirin (SASP) in the oral treatment of active ulcerative colitis (UC)
and in remission. Clinical Controversies in Inflammatory Bowel Disease 1987:170.

tolerance of 5-aminosalicylic acid in short term treatment of patients with
ulcerative colitis at a low or medium phase of activity. International Journal

112. Mihas AA, Xynopoulos D, Mihas TA. A prospective trial of oral 5-
aminosalicylic acid vs sulfasalazine in ulcerative colitis. Gastroenterology.

sulfasalazine and controlled-release mesalazine tablets in the treatment of
active ulcerative colitis. Journal of gastroenterology. Volume 30 Suppl 8,

(Claversal) is equivalent to sulfasalazine for remission maintenance in
ulcerative colitis: A double-blind study. Journal of Clinical

ulcerative colitis with 5-amino salicylic acid in high doses by mouth. British

slow-release 5-aminosalicylate and sulfasalazine in remission

117. Riley SA MV, Goodman MJ, Herd ME, Dutt S, Turnberg LA. Comparison
of delayed-release 5-aminosalicylic acid (mesalazine) and sulfasalazine
as
maintenance treatment for patients with ulcerative colitis. Gastroenterology

118. Rutgeerts P. Comparative efficacy of coated, oral 5-aminosalicylic acid
(Claversal) and sulphasalazine for maintaining remission of ulcerative

119. Navarro F, Hanauer SB. Treatment of Inflammatory Bowel Disease:
Safety and Tolerability Issues. American Journal of Gastroenterology

120. Birnie GG, McLeod TI, Watkinson G. Incidence of sulphasalazine-induced


rheumatological manifestations of the inflammatory bowel diseases.
Rheumatol Int 2006;26:953-8.

123. Fruhmorgen P, Demling L. On the efficacy of ready-made-up commercially
available salicylazosulphapyridine enemas in the treatment of proctitis,
proctosigmoiditis and ulcerative colitis involving rectum, sigmoid and


134. Hawthorne AB, Stenson R, Gillespie D, et al. One-year investigator-blind randomized multicenter trial comparing asacol 2.4 g once daily with 800 mg three times daily for maintenance of remission in ulcerative colitis. Inflammatory Bowel Diseases 2012;18:1885-1893.


140. Suzuki Y, Iida M, Ito H, et al. 2.4 g Mesalamine (Asacol 400 mg tablet) Once Daily is as Effective as Three Times Daily in Maintenance of Remission in Ulcerative Colitis: A Randomized, Noninferiority, Multi-center Trial. Inflammatory Bowel Diseases 2017;23:822-832.


149. D'Haens GR, Kovacs A, Vergauwe P, et al. Clinical trial: Preliminary efficacy and safety study of a new Budesonide-MMX 9 mg extended-


181. Hartmann F, Stein J. Clinical trial: Controlled, open, randomized multicentre study comparing the effects of treatment on quality of life, safety and efficacy of budesonide or mesalazine enemas in active left-sided ulcerative colitis. Alimentary Pharmacology and Therapeutics 2010;32:368-376.


<table>
<thead>
<tr>
<th>S#</th>
<th>Focused Question</th>
<th>Patients</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>In adults with extensive mild-moderate ulcerative colitis, what dose of mesalamine is effective for induction and maintenance of remission?</td>
<td>Adults with extensive, mild-moderate UC, treated with mesalamine</td>
<td>• Low-dose (&lt;2g/d)</td>
<td>Placebo or alternative mesalamine dose</td>
<td>INDUCTION • Clinical remission • Tolerability \n MAINTENANCE • Clinical remission • Tolerability</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Standard-dose (2-3g/d)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• High-dose (&gt;3g/d)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>In adults with extensive mild-moderate ulcerative colitis, are diazo-bonded 5-ASA (balsalazide, olsalazine) effective for induction and maintenance of remission?</td>
<td>Adults with extensive, mild-moderate UC</td>
<td>Diazo-bonded 5-ASA (balsalazide, olsalazine)</td>
<td>• Placebo • Mesalazine • Sulfasalazine</td>
<td>INDUCTION • Clinical remission • Tolerability \n MAINTENANCE • Clinical remission • Tolerability</td>
</tr>
<tr>
<td>3.</td>
<td>In adults with extensive mild-moderate ulcerative colitis, is sulfasalazine effective for induction and maintenance of remission?</td>
<td>Adults with extensive, mild-moderate UC</td>
<td>Sulfasalazine</td>
<td>• Placebo • Mesalazine</td>
<td>INDUCTION • Clinical remission • Tolerability \n MAINTENANCE • Clinical remission • Tolerability</td>
</tr>
<tr>
<td>4.</td>
<td>In adults with mild-moderate UC, is combined oral and rectal 5-ASA therapy superior to oral 5-ASA therapy for induction and maintenance of remission?</td>
<td>Adults with extensive, mild-moderate UC</td>
<td>Combined oral and rectal 5-ASA</td>
<td>Oral 5-ASA</td>
<td>INDUCTION • Clinical remission \n MAINTENANCE • Clinical remission</td>
</tr>
<tr>
<td>5.</td>
<td>In patients with extensive mild-moderate ulcerative colitis treated with mesalamine, is once-daily mesalamine comparable to multiple times daily administration of mesalamine?</td>
<td>Adults with extensive, mild-moderate UC, treated with oral mesalamine</td>
<td>Once-daily mesalamine</td>
<td>Equivalent doses of mesalamine split into two or more doses per day</td>
<td>INDUCTION • Clinical remission \n MAINTENANCE • Clinical remission \n Adherence</td>
</tr>
<tr>
<td>6.</td>
<td>In adults with extensive mild-moderate UC, what is the role of budesonide formulations (budesonide MMX and controlled ileal release budesonide)?</td>
<td>Adults with extensive, mild-moderate UC</td>
<td>• Budesonide MMX \n • Controlled ileal release budesonide</td>
<td>• Placebo • Mesalazine • Controlled ileal release budesonide</td>
<td>INDUCTION • Clinical remission • Tolerability \n MAINTENANCE • Clinical remission</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clinical Questions</td>
<td>Comparison Groups</td>
<td>Induction Adverse Events</td>
<td>Maintenance Adverse Events</td>
<td></td>
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<td>7.</td>
<td>In adults with mild-moderate left-sided colitis or ulcerative proctitis, is oral 5-ASA therapy superior to topical 5-ASA therapy for induction and maintenance of remission?</td>
<td>Adults with mild-moderate UC extending up to splenic flexure (left-sided) or ulcerative proctitis</td>
<td>Oral 5-ASA</td>
<td>Rectal 5-ASA</td>
<td>Clinical remission</td>
</tr>
<tr>
<td>8.</td>
<td>In adults with mild-moderate left-sided UC, what is the role of mesalamine enemas and/or corticosteroid enemas/foam for induction and maintenance of remission?</td>
<td>Adults with mild-moderate UC extending up to splenic flexure (left-sided)</td>
<td>Mesalamine enemas, foam or gel, First- and second-generation corticosteroid enemas or foam</td>
<td>Placebo, Rectal mesalamine, Rectal corticosteroids</td>
<td>Clinical remission</td>
</tr>
<tr>
<td>9.</td>
<td>In adults with mild-moderate ulcerative proctitis, what is the role of mesalamine suppository and/or corticosteroid suppository for induction and maintenance of remission?</td>
<td>Adults with ulcerative proctitis</td>
<td>Mesalamine suppository, First- and second-generation corticosteroid suppository</td>
<td>Placebo, Rectal mesalamine, Rectal corticosteroids</td>
<td>Clinical remission</td>
</tr>
<tr>
<td>10.</td>
<td>In patients with mild-moderate UC, what is the role of probiotics for induction and maintenance of remission?</td>
<td>Adults with mild-moderate UC</td>
<td>Probiotics</td>
<td>Placebo, Mesalamine</td>
<td>Clinical remission</td>
</tr>
<tr>
<td>11.</td>
<td>In patients with mild-moderate UC despite 5-ASA therapy, what is the role of curcumin for induction and maintenance of remission?</td>
<td>Adults with mild-moderate UC</td>
<td>Curcumin (with or without mesalamine)</td>
<td>Placebo, Mesalamine</td>
<td>Clinical remission</td>
</tr>
<tr>
<td>12.</td>
<td>In patients with mild-moderate UC, what is the role fecal microbiota transplantation for induction and maintenance of remission?</td>
<td>Adults with mild-moderate UC</td>
<td>Fecal microbiota transplantation</td>
<td>Placebo</td>
<td>Clinical remission, Adverse events</td>
</tr>
</tbody>
</table>

**Table 1.** Focused clinical questions on the management of mild-moderate ulcerative colitis, and corresponding questions in PICO format addressed in this technical review.
<table>
<thead>
<tr>
<th>Formulations</th>
<th>Drug Names (tablet strength)</th>
<th>Mode of Delivery</th>
<th>Site of Delivery</th>
<th>Dosing range (5-ASA equivalence)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sulfasalazine</strong></td>
<td>Azulfidine (500mg), Salazopyrin</td>
<td>5-ASA linked to sulfapyridine by azo-bond</td>
<td>Colon</td>
<td>2-4g/d (=0.8-1.6g/d 5-ASA)</td>
</tr>
<tr>
<td><strong>Diazo-bonded 5-ASA</strong></td>
<td>Olsalazine (Dipentum, 250mg)</td>
<td>5-ASA dimer linked by azo-bond</td>
<td>Colon</td>
<td>2-3g/d (=1.6-2.4g/d 5-ASA)</td>
</tr>
<tr>
<td></td>
<td>Balsalazide (Colazaal, 750mg)</td>
<td>5-ASA linked to 4-aminobenzoyl-β-alanine by azo-bond</td>
<td>Colon</td>
<td>2-6.75g/d (=0.7-2.4g/d 5-ASA)</td>
</tr>
<tr>
<td><strong>Mesalmine</strong></td>
<td>pH-dependent release: Delzicol (400mg), Asacol-HD (800mg)</td>
<td>Eudragit-S coated tables (released at pH ≥7.0)</td>
<td>Terminal ileum, colon</td>
<td>1.6-4.8g/d (=1.6-4.8g/d 5-ASA)</td>
</tr>
<tr>
<td></td>
<td>Time-dependent release: Pentasa (250mg, 500mg)</td>
<td>Ethylcellulose-coated microgranules</td>
<td>Duodenum, jejunum, ileum, colon</td>
<td>1.5-4g/d (=0.8-3.0g/d 5-ASA)</td>
</tr>
<tr>
<td></td>
<td><strong>MMX mesalamine: Lialda (1200mg)</strong></td>
<td>Enteric coating (dissolves at pH ≥7.0), MMX of lipophilic and hydrophilic excipients</td>
<td>Terminal ileum, colon</td>
<td>1.2-4.8g/d (=1.2-4.8g/d 5-ASA)</td>
</tr>
<tr>
<td></td>
<td>Delayed and extended release mesalamines: Apriso (375mg)</td>
<td>Mesalazine granules in polymer matrix with enteric coating (dissolves at pH ≥6.0)</td>
<td>Mid-ileum, colon</td>
<td>1.5g/d (=2.4g/d 5-ASA)</td>
</tr>
</tbody>
</table>

[Abbreviations: 5-ASA=5-aminosalicylate; MMX=Multimatrix]

**Table 2.** Different 5-aminosalicylate formulations with comparable dosing adapted from Sandborn *et al*\(^\text{216}\) and Ye *et al*\(^\text{217}\)
### LOW-DOSE MESALAMINE (<2g/day) COMPARED TO PLACEBO FOR MILD-MODERATE ULCERATIVE COLITIS

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects(^*) (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Absolute effect</th>
<th>№ of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure to induce remission</td>
<td>Risk with placebo (median)</td>
<td>900 per 1,000 (738 to 846)</td>
<td>RR 0.88 (0.82 to 0.94)</td>
<td>108 fewer per 1,000 (from 54 fewer to 162 fewer)</td>
<td>511 (4 RCTs)</td>
</tr>
<tr>
<td></td>
<td>Risk with low-dose mesalamine</td>
<td>792 per 1,000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure to maintain remission</td>
<td>Risk with placebo (median)</td>
<td>420 per 1,000 (231 to 328)</td>
<td>RR 0.63 (0.55 to 0.78)</td>
<td>155 fewer per 1,000 (from 92 fewer to 189 fewer)</td>
<td>763 (3 RCTs)</td>
</tr>
<tr>
<td></td>
<td>Risk with low-dose mesalamine</td>
<td>265 per 1,000 (231 to 328)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### STANDARD-DOSE MESALAMINE (2-3g/day) COMPARED TO PLACEBO FOR MILD-MODERATE ULCERATIVE COLITIS

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects(^*) (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Absolute risk difference</th>
<th>№ of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure to induce remission</td>
<td>Risk with placebo (median)</td>
<td>900 per 1,000 (702 to 819)</td>
<td>RR 0.84 (0.78 to 0.91)</td>
<td>144 fewer per 1,000 (from 81 fewer to 198 fewer)</td>
<td>1138 (8 RCTs)</td>
</tr>
<tr>
<td></td>
<td>Risk with standard-dose mesalamine</td>
<td>756 per 1,000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure to maintain remission</td>
<td>Risk with placebo (median)</td>
<td>420 per 1,000 (181 to 294)</td>
<td>RR 0.55 (0.43 to 0.70)</td>
<td>189 fewer per 1,000 (from 126 fewer to 239 fewer)</td>
<td>510 (2 RCTs)</td>
</tr>
<tr>
<td></td>
<td>Risk with standard-dose mesalamine</td>
<td>231 per 1,000 (181 to 294)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### HIGH-DOSE MESALAMINE (>3g/day) COMPARED TO PLACEBO FOR MILD-MODERATE ULCERATIVE COLITIS

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects(^*) (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Absolute effect</th>
<th>№ of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure to induce remission</td>
<td>Risk with placebo (median)</td>
<td>900 per 1,000 (539 to 714)</td>
<td>RR 0.75 (0.65 to 0.86)</td>
<td>225 fewer per 1,000 (from 126 fewer to 198 fewer)</td>
<td>1138 (8 RCTs)</td>
</tr>
<tr>
<td></td>
<td>Risk with high-dose mesalamine</td>
<td>675 per 1,000</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**GRADE Working Group grades of evidence**

**High quality:** We are very confident that the true effect lies close to that of the estimate of the effect.

**Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

**Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

**Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

\(^1\)Rated down for imprecision since optimal information size not met (<200 events)

**Table 3.** GRADE Evidence Profile comparing different doses of mesalamine with placebo for induction and maintenance of remission in patients with mild-moderate ulcerative colitis
# STANDARD-DOSE MESALAMINE (2-3g/day) vs. LOW-DOSE MESALAMINE (<2g/day) FOR MILD-MODERATE ULCERATIVE COLITIS

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects’ (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Absolute risk difference</th>
<th>Nr of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure to induce remission</td>
<td>702 per 1,000</td>
<td>612 per 1,000 (555 to 695)</td>
<td>RR 0.88 (0.79 to 0.99)</td>
<td>84 fewer per 1,000 (from 7 fewer to 148 fewer)</td>
<td>906 (8 RCTs)</td>
</tr>
<tr>
<td>Failure to maintain remission</td>
<td>368 per 1,000</td>
<td>312 per 1,000 (265 to 364)</td>
<td>RR 0.63 (0.55 to 0.78)</td>
<td>55 fewer per 1,000 (from 4 fewer to 103 fewer)</td>
<td>1798 (4 RCTs)</td>
</tr>
</tbody>
</table>

# HIGH-DOSE MESALAMINE (>3g/day) vs. LOW-DOSE MESALAMINE (<2g/day) FOR MILD-MODERATE ULCERATIVE COLITIS

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Anticipated absolute effects’ (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Absolute risk difference</th>
<th>Nr of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure to induce remission</td>
<td>634 per 1,000</td>
<td>612 per 1,000 (555 to 695)</td>
<td>RR 0.81 (0.71 to 0.92)</td>
<td>120 fewer per 1,000 (from 51 fewer to 184 fewer)</td>
<td>519 (6 RCTs)</td>
</tr>
</tbody>
</table>

GRADE Working Group grades of evidence

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

1Rated down for imprecision since 95% CI approaches unity

Table 4. GRADE Evidence Profile comparing standard- and high-dose mesalamine with low-dose mesalamine for induction and maintenance of remission in patients with mild-moderate ulcerative colitis
## HIGH-DOSE MESALAMINE (>3g/day) vs. STANDARD-DOSE MESALAMINE (2-3g/day) FOR MILD-MODERATE ULCERATIVE COLITIS

### Outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Absolute risk difference</th>
<th>Nr of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk with standard-dose mesalamine</td>
<td>Risk with high-dose mesalamine</td>
<td>Absolute risk difference</td>
<td>RR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Risk with standard-dose mesalamine</td>
<td>Risk with high-dose mesalamine</td>
<td>Absolute risk difference</td>
<td>RR</td>
<td></td>
</tr>
<tr>
<td>Failure to induce remission</td>
<td>678 per 1,000</td>
<td>612 per 1,000</td>
<td>RR 0.94 (0.88 to 1.01)</td>
<td>41 fewer per 1,000 (from 7 more to 81 fewer)</td>
<td>2482 (12 RCTs)</td>
</tr>
<tr>
<td>Failure to maintain remission</td>
<td>490 per 1,000</td>
<td>456 per 1,000</td>
<td>RR 0.93 (0.73 to 1.17)</td>
<td>34 fewer per 1,000 (from 83 more to 132 fewer)</td>
<td>1798 (4 RCTs)</td>
</tr>
</tbody>
</table>

GRADE Working Group grades of evidence

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

*Rated down for imprecision since 95% CI crosses 1

Table 5. GRADE Evidence Profile comparing high-dose mesalamine with standard-dose mesalamine for induction and maintenance of remission in patients with mild-moderate ulcerative colitis
DIAZO-BONDED 5-AMINOSALICYLATES COMPARED TO PLACEBO FOR MILD-MODERATE ULCERATIVE COLITIS

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Absolute effect</th>
<th>Nr of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk with placebo (median)</td>
<td>Risk with diazo-bonded 5-ASA</td>
<td>Risk with diazo-bonded 5-ASA</td>
<td>Risk with diazo-bonded 5-ASA</td>
<td>Risk with diazo-bonded 5-ASA</td>
</tr>
<tr>
<td>Failure to induce remission</td>
<td></td>
<td>RR 0.86 (0.76 to 0.98)</td>
<td>126 fewer per 1,000 (from 18 fewer to 216 fewer)</td>
<td>725 (6 RCTs)</td>
<td>○○□□□□ MODERATE</td>
</tr>
<tr>
<td></td>
<td>900 per 1,000</td>
<td>774 per 1,000 (684 to 882)</td>
<td>RR 0.86 (0.76 to 0.98)</td>
<td>126 fewer per 1,000 (from 18 fewer to 216 fewer)</td>
<td>725 (6 RCTs)</td>
</tr>
<tr>
<td>Failure to maintain remission</td>
<td></td>
<td>RR 0.71 (0.41 to 1.21)</td>
<td>122 fewer per 1,000 (from 88 more to 248 fewer)</td>
<td>763 (3 RCTs)</td>
<td>○○○○○□ LOW</td>
</tr>
<tr>
<td></td>
<td>420 per 1,000</td>
<td>298 per 1,000 (172 to 508)</td>
<td>RR 0.71 (0.41 to 1.21)</td>
<td>122 fewer per 1,000 (from 88 more to 248 fewer)</td>
<td>763 (3 RCTs)</td>
</tr>
</tbody>
</table>

DIAZO-BONDED 5-AMINOSALICYLATES COMPARED TO STANDARD-DOSE MESALAMINE (2-3g/d) FOR MILD-MODERATE ULCERATIVE COLITIS

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Absolute risk difference</th>
<th>Nr of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk with standard-dose mesalamine</td>
<td>Risk with diazo-bonded 5-ASA</td>
<td>Risk with diazo-bonded 5-ASA</td>
<td>Risk with diazo-bonded 5-ASA</td>
<td>Risk with diazo-bonded 5-ASA</td>
</tr>
<tr>
<td>Failure to induce remission</td>
<td></td>
<td>RR 0.81 (0.60 to 1.08)</td>
<td>108 fewer per 1,000 (from 8 more to 202 fewer)</td>
<td>571 (5 RCTs)</td>
<td>○○○○○□ LOW</td>
</tr>
<tr>
<td></td>
<td>609 per 1,000</td>
<td>493 per 1,000 (365 to 658)</td>
<td>RR 0.81 (0.60 to 1.08)</td>
<td>108 fewer per 1,000 (from 8 more to 202 fewer)</td>
<td>571 (5 RCTs)</td>
</tr>
<tr>
<td>Failure to maintain remission</td>
<td></td>
<td>RR 0.69 (0.51 to 0.98)</td>
<td>189 fewer per 1,000 (from 126 fewer to 239 fewer)</td>
<td>319 (4 RCTs)</td>
<td>○○○○○□ LOW</td>
</tr>
<tr>
<td></td>
<td>413 per 1,000</td>
<td>285 per 1,000 (210 to 404)</td>
<td>RR 0.69 (0.51 to 0.98)</td>
<td>189 fewer per 1,000 (from 126 fewer to 239 fewer)</td>
<td>319 (4 RCTs)</td>
</tr>
</tbody>
</table>

DIAZO-BONDED 5-AMINOSALICYLATES COMPARED TO SULFASALAZINE FOR MILD-MODERATE ULCERATIVE COLITIS

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Absolute effect</th>
<th>Nr of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk with sulfasalazine</td>
<td>Risk with diazo-bonded 5-ASA</td>
<td>Risk with diazo-bonded 5-ASA</td>
<td>Risk with diazo-bonded 5-ASA</td>
<td>Risk with diazo-bonded 5-ASA</td>
</tr>
<tr>
<td>Failure to induce remission</td>
<td></td>
<td>RR 0.77 (0.61 to 0.96)</td>
<td>104 fewer per 1,000 (from 18 fewer to 176 fewer)</td>
<td>488 (8 RCTs)</td>
<td>□□□□□□□□ MODERATE</td>
</tr>
<tr>
<td></td>
<td>451 per 1,000</td>
<td>347 per 1,000 (275 to 433)</td>
<td>RR 0.77 (0.61 to 0.96)</td>
<td>104 fewer per 1,000 (from 18 fewer to 176 fewer)</td>
<td>488 (8 RCTs)</td>
</tr>
<tr>
<td>Failure to maintain remission</td>
<td></td>
<td>RR 1.07 (0.98 to 1.16)</td>
<td>23 more per 1,000 (from 7 fewer to 53 more)</td>
<td>911 (6 RCTs)</td>
<td>□□□□□□□□ LOW</td>
</tr>
<tr>
<td></td>
<td>329 per 1,000</td>
<td>352 per 1,000 (322 to 382)</td>
<td>RR 1.07 (0.98 to 1.16)</td>
<td>23 more per 1,000 (from 7 fewer to 53 more)</td>
<td>911 (6 RCTs)</td>
</tr>
<tr>
<td>Discontinuation of induction therapy due to adverse events (Tolerability; Important outcome)</td>
<td>206 per 1,000</td>
<td>64 per 1,000 (29 to 144)</td>
<td>RR 0.31 (0.14 to 0.70)</td>
<td>142 more per 1,000 (from 177 fewer to 62 fewer)</td>
<td>258 (5 RCTs)</td>
</tr>
</tbody>
</table>
# DIAZO-BONDED 5-AMINOSALICYLATES COMPARED TO PLACEBO FOR MILD-MODERATE ULCERATIVE COLITIS

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Absolute effect</th>
<th>No of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk with placebo (median)</td>
<td>Risk with diazo-bonded 5-ASA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**GRADE Working Group grades of evidence**

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- **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

1. Rated down for imprecision
2. Rated down for inconsistency
3. Rated down for indirectness (trials used only low-dose mesalamine, as opposed to standard-dose mesalamine)
4. Rated down for indirectness (very limited data on balsalazide which may be the preferred diazo-bonded 5-ASA given higher intolerability with olsalazine due to diarrhea)

**Table 6.** GRADE Evidence Profile comparing diazo-bonded 5-aminosalicylates with placebo, standard-dose mesalamine and sulfasalazine for induction and maintenance of remission in patients with mild-moderate ulcerative colitis
### SULFASALAZINE COMPARED TO PLACEBO FOR MILD-MODERATE ULCERATIVE COLITIS

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Absolute effect</th>
<th>Nr of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk with placebo (median)</td>
<td>Risk with sulfasalazine</td>
<td>RR</td>
<td>Absolute risk difference</td>
<td></td>
</tr>
<tr>
<td>Failure to induce remission</td>
<td>900 per 1,000 (405 to 783)</td>
<td>558 per 1,000 (405 to 783)</td>
<td><strong>RR 0.62</strong> (0.45 to 0.87)</td>
<td>342 fewer per 1,000 (from 495 fewer to 117 fewer)</td>
<td>81 (2 RCTs) SINCE <strong>MODERATE</strong></td>
</tr>
<tr>
<td>Failure to maintain remission</td>
<td>420 per 1,000 (97 to 374)</td>
<td>189 per 1,000 (97 to 374)</td>
<td><strong>RR 0.45</strong> (0.23 to 0.89)</td>
<td>231 fewer per 1,000 (from 46 fewer to 323 fewer)</td>
<td>204 (4 RCTs) SINCE <strong>LOW</strong></td>
</tr>
<tr>
<td>Discontinuation of induction therapy due to adverse events (Tolerability; Important outcome)</td>
<td>23 per 1,000 (22 to 650)</td>
<td>120 per 1,000 (22 to 650)</td>
<td><strong>RR 5.15</strong> (0.95 to 27.96)</td>
<td>97 more per 1,000 (from 1 fewer to 627 more)</td>
<td>84 (2 RCTs) SINCE <strong>MODERATE</strong></td>
</tr>
</tbody>
</table>

**GRADE Working Group grades of evidence**

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

1 Rated down for imprecision
2 Rated down for inconsistency
3 Rated down for indirectness (most trials used low-dose mesalamine as comparator, as opposed to standard-dose mesalamine)
Table 7. GRADE Evidence Profile comparing sulfasalazine with placebo and standard-dose mesalamine for induction and maintenance of remission in patients with mild-moderate ulcerative colitis
## ORAL+RECTAL 5-ASA COMPARED TO ORAL 5-ASA ALONE FOR MILD-MODERATE ULCERATIVE COLITIS

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Absolute effect</th>
<th>Nr of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk with oral 5-ASA</td>
<td>Risk with oral+rectal 5-ASA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure to induce remission</td>
<td>568 per 1,000 (278 to 534)</td>
<td>386 per 1,000 (278 to 534)</td>
<td>RR <strong>0.68</strong> (0.49 to 0.94)</td>
<td>182 fewer per 1,000 (from 34 fewer to 290 fewer)</td>
<td>321 (4 RCTs)</td>
</tr>
<tr>
<td>Failure to maintain remission</td>
<td>673 per 1,000 (135 to 653)</td>
<td>303 per 1,000 (135 to 653)</td>
<td>RR <strong>0.45</strong> (0.20 to 0.97)</td>
<td>370 fewer per 1,000 (from 20 fewer to 539 fewer)</td>
<td>96 (2 RCTs)</td>
</tr>
</tbody>
</table>

GRADE Working Group grades of evidence

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

1 Rated down for imprecision
2 Rated down for indirectness (comparator group received low-dose mesalamine, whereas combined mesalamine amount in intervention group exceeded 2g)

**Table 8.** GRADE Evidence Profile comparing oral+rectal 5-aminosalicylates with oral 5-aminosalicylates alone for induction and maintenance of remission in patients with mild-moderate ulcerative colitis
## ONCE-DAILY COMPARED TO MULTIPLE-TIMES DAILY MESALAMINE FOR MILD-MODERATE ULCERATIVE COLITIS

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Absolute effect</th>
<th>Nr of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk with multiple-times daily mesalamine</td>
<td>Risk with once-daily mesalamine</td>
<td>RR, CI</td>
<td>Absolute effect</td>
<td></td>
</tr>
<tr>
<td>Failure to induce remission</td>
<td>477 per 1,000 (405 to 515)</td>
<td>458 per 1,000 (405 to 515)</td>
<td>RR 0.96 (0.85 to 1.08)</td>
<td>19 fewer per 1,000 (from 38 more to 72 fewer)</td>
<td>944 (4 RCTs) ⬤ MODERATE</td>
</tr>
<tr>
<td>Failure to maintain remission</td>
<td>281 per 1,000 (238 to 300)</td>
<td>269 per 1,000 (238 to 300)</td>
<td>RR 0.96 (0.85 to 1.07)</td>
<td>11 fewer per 1,000 (from 20 more to 42 fewer)</td>
<td>4465 (11 RCTs) ⬤ MODERATE</td>
</tr>
</tbody>
</table>

### GRADE Working Group grades of evidence

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

*Rated down for imprecision

**Table 9.** GRADE Evidence Profile comparing once-daily mesalamine with multiple-times daily mesalamine for induction and maintenance of remission in patients with mild-moderate ulcerative colitis
## BUDESONIDE MMX COMPARED TO PLACEBO FOR MILD-MODERATE ULCERATIVE COLITIS

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Absolute effect</th>
<th>№ of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure to induce remission</td>
<td>900 per 1,000</td>
<td>792 per 1,000 (747 to 846)</td>
<td>RR 0.88 (0.83 to 0.94)</td>
<td>108 fewer per 1,000 (from 54 fewer to 153 fewer)</td>
<td>546 (3 RCTs)</td>
</tr>
</tbody>
</table>

### CONTROLLED ILEAL-RELEASE BUDESONIDE COMPARED TO PLACEBO FOR MILD-MODERATE ULCERATIVE COLITIS

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Absolute risk difference</th>
<th>№ of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure to induce remission</td>
<td>900 per 1,000</td>
<td>837 per 1,000 (783 to 891)</td>
<td>RR 0.93 (0.87 to 0.99)</td>
<td>63 fewer per 1,000 (from 9 fewer to 117 fewer)</td>
<td>255 (1 RCT)</td>
</tr>
</tbody>
</table>

*GRADE Working Group grades of evidence*
- **High quality:** We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possible that it is substantially different.
- **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

1 Rated down for imprecision since optimal information size not met (<200 events)
2 Rated down for risk of bias

**Table 10.** GRADE Evidence Profile comparing budesonide MMX and controlled ileal-release budesonide with placebo for induction of remission in patients with mild-moderate ulcerative colitis
### BUDESONIDE MMX COMPARED TO CONTROLLED ILEAL-RELEASE (CIR) BUDESONIDE FOR MILD-MODERATE ULCERATIVE COLITIS

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Absolute effect</th>
<th>N of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure to induce remission</td>
<td>897 per 1,000 (771 to 933)</td>
<td>RR 0.95 (0.86 to 1.04)</td>
<td>45 fewer per 1,000 (from 36 more to 126 fewer)</td>
<td>253 (1 RCT)</td>
<td>◯◯ ○○ 1,2 LOW</td>
</tr>
</tbody>
</table>

### BUDESONIDE MMX COMPARED TO STANDARD-DOSE MESALAMINE FOR MILD-MODERATE ULCERATIVE COLITIS

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Absolute risk difference</th>
<th>N of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure to induce remission</td>
<td>882 per 1,000 (750 to 917)</td>
<td>RR 0.94 (0.85 to 1.04)</td>
<td>53 fewer per 1,000 (from 35 more to 132 fewer)</td>
<td>254 (1 RCT)</td>
<td>◯◯ ○○ 1,2 LOW</td>
</tr>
</tbody>
</table>

### CONTROLLED ILEAL-RELEASE (CIR) BUDESONIDE COMPARED TO STANDARD-DOSE MESALAMINE FOR MILD-MODERATE ULCERATIVE COLITIS

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Absolute effect</th>
<th>N of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure to induce remission</td>
<td>452 per 1,000 (492 to 741)</td>
<td>RR 1.34 (1.04 to 1.64)</td>
<td>154 more per 1,000 (from 41 more to 289 more)</td>
<td>343 (1 RCT)</td>
<td>◯◯ ○○ 1 MODERATE</td>
</tr>
</tbody>
</table>

**GRADE Working Group grades of evidence**
- **High quality:** We are very confident that the true effect lies close to that of the estimate of the effect
- **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
- **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
- **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1 Rated down for imprecision
2 Rated down for risk of bias

**Table 11.** GRADE Evidence Profile comparing budesonide MMX with controlled ileal-release budesonide and standard-dose mesalamine for induction of remission in patients with mild-moderate ulcerative colitis
### BUDESONIDE MMX (second-generation corticosteroids) COMPARED TO SYSTEMIC CORTICOSTEROIDS FOR MILD-MODERATE ULCERATIVE COLITIS

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Absolute effect</th>
<th>Nr of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure to induce remission</td>
<td>771 per 1,000 (740 to 871)</td>
<td>RR 1.04 (0.96 to 1.13)</td>
<td>31 more per 1,000 (from 31 fewer to 100 more)</td>
<td>559 (3 RCTs)</td>
<td>◯◯◯◯1,2 LOW</td>
</tr>
</tbody>
</table>

**GRADE Working Group grades of evidence**

**High quality**: We are very confident that the true effect lies close to that of the estimate of the effect.

**Moderate quality**: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

**Low quality**: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.

**Very low quality**: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

1 Rated down for imprecision
2 Rated down for indirectness (all trials compared non-budesonide MMX second-generation corticosteroids with oral prednisone/prednisolone)

**Table 12.** GRADE Evidence Profile comparing MMX vs. oral prednisone/prednisolone, for induction of remission in patients with mild-moderate ulcerative colitis
**Table 13. GRADE Evidence Profile comparing adding budesonide MMX to mesalamine vs. placebo, for induction of remission in patients with oral mesalamine-refractory mild-moderate ulcerative colitis**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Absolute effect</th>
<th>Nr of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk with placebo</td>
<td>Risk with budesonide MMX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure to induce remission</td>
<td>933 per 1,000</td>
<td>887 per 1,000 (831 to 933)</td>
<td>RR 0.95 (0.89 to 1.00)</td>
<td>47 fewer per 1,000 (from 0 fewer to 103 fewer)</td>
<td>510 (1 RCT) MODERATE</td>
</tr>
</tbody>
</table>

**GRADE Working Group grades of evidence**

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

*Rated down for imprecision*
### Rectal 5-ASA Compared to Oral 5-ASA for Mild-Moderate Ulcerative Proctosigmoiditis or Proctitis

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Absolute effect</th>
<th>Nr of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure to induce remission</td>
<td>Risk with oral 5-ASA: 450 per 1,000 (63 to 589)</td>
<td>RR 0.43 (0.14 to 1.31)</td>
<td>256 fewer per 1,000 (from 139 more to 387 fewer)</td>
<td>213 (4 RCTs)</td>
<td>□ΟΟΟΟ1,2,3 VERY LOW</td>
</tr>
<tr>
<td></td>
<td>Risk with rectal 5-ASA: 193 per 1,000 (63 to 589)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure to maintain remission</td>
<td>Risk with oral 5-ASA: 369 per 1,000 (151 to 432)</td>
<td>RR 0.69 (0.41 to 1.17)</td>
<td>114 fewer per 1,000 (from 63 more to 218 fewer)</td>
<td>129 (3 RCTs)</td>
<td>□ΟΟΟΟ1,2,4 VERY LOW</td>
</tr>
<tr>
<td></td>
<td>Risk with rectal 5-ASA: 255 per 1,000 (151 to 432)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**GRADE Working Group grades of evidence**

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

1Rated down for risk of bias
2Rated down for imprecision
3Rated down for inconsistency
4Rated down for indirectness (comparator oral 5-ASA therapy was based on low-dose, not standard-dose 5-ASA)

**Table 14.** GRADE Evidence Profile comparing rectal 5-aminosalicylates with oral 5-aminosalicylates for induction and maintenance of remission in patients with mild-moderate ulcerative proctosigmoiditis or proctitis
<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Absolute effect</th>
<th>N of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk with placebo</td>
<td>Risk with rectal mesalamine enemas</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure to induce remission</td>
<td>732 per 1,000 (256 to 534)</td>
<td>366 per 1,000 (256 to 534)</td>
<td>RR <strong>0.50</strong> (0.35 to 0.73)</td>
<td>366 fewer per 1,000 (from 198 fewer to 476 fewer)</td>
<td>342 (4 RCTs)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Relative effect</td>
<td>Absolute effect</td>
<td>N of participants (studies)</td>
</tr>
<tr>
<td>Failure to maintain remission</td>
<td>846 per 1,000 (93 to 685)</td>
<td>254 per 1,000 (93 to 685)</td>
<td>RR <strong>0.30</strong> (0.11 to 0.81)</td>
<td>592 fewer per 1,000 (from 161 fewer to 753 fewer)</td>
<td>25 (1 RCT)</td>
</tr>
</tbody>
</table>

### GRADE Working Group grades of evidence

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

*)Rated down for imprecision since optimal information size not met (<200 events)

**Table 15.** GRADE Evidence Profile comparing rectal mesalamine with placebo for induction and maintenance of remission in patients with mild-moderate ulcerative proctosigmoiditis
### RECTAL CORTICOSTEROID THERAPY COMPARED TO PLACEBO FOR MILD-MODERATE ULCERATIVE PROCTOSIGMOIDITIS

#### Outcomes

<table>
<thead>
<tr>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Absolute effect</th>
<th>Nr of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk with placebo</strong></td>
<td><strong>Risk with rectal corticosteroid therapy</strong></td>
<td><strong>RR 0.73 (0.66 to 0.80)</strong></td>
<td><strong>216 fewer per 1,000 (from 160 fewer to 273 fewer)</strong></td>
<td><strong>827 (4 RCTs)</strong></td>
</tr>
<tr>
<td>Failure to induce remission</td>
<td>802 per 1,000 (529 to 641)</td>
<td><strong>585 per 1,000</strong></td>
<td></td>
<td><strong>HIGH</strong></td>
</tr>
</tbody>
</table>

**GRADE Working Group grades of evidence**

*High quality:* We are very confident that the true effect lies close to that of the estimate of the effect.

*Moderate quality:* We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

*Low quality:* Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.

*Very low quality:* We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

---

**Table 16.** GRADE Evidence Profile comparing rectal corticosteroids (enema or foam) with placebo for induction of remission in patients with mild-moderate ulcerative proctosigmoiditis
### RECTAL MESALAMINE COMPARED TO RECTAL CORTICOSTEROID FOR MILD-MODERATE ULCERATIVE PROCTOSIGMOIDITS

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Absolute risk difference</th>
<th>Nr of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk with rectal corticosteroids</td>
<td>589 per 1,000 (359 to 530)</td>
<td>Risk with rectal mesalamine</td>
<td>436 per 1,000 (0.61 to 0.90)</td>
<td>153 fewer per 1,000 (from 59 fewer to 230 fewer)</td>
<td>1407 (13 RCTs)</td>
</tr>
<tr>
<td><strong>Failure to induce remission</strong></td>
<td>589 per 1,000 (359 to 530)</td>
<td>RR 0.74 (0.61 to 0.90)</td>
<td>153 fewer per 1,000 (from 59 fewer to 230 fewer)</td>
<td>1407 (13 RCTs)</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>

**GRADE Working Group grades of evidence**

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

1 Rated down for inconsistency

**Table 17.** GRADE Evidence Profile comparing rectal mesalamine with rectal corticosteroids for induction of remission in patients with mild-moderate ulcerative proctosigmoiditis
## Rectal Mesalamine Suppositories Compared to Placebo for Mild-Moderate Ulcerative Proctitis

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Absolute effect</th>
<th>Nr of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure to induce remission</td>
<td>818 per 1,000</td>
<td>360 per 1,000 (278 to 458)</td>
<td>RR 0.44 (0.34 to 0.56)</td>
<td>458 fewer per 1,000 (from 360 fewer to 540 fewer)</td>
<td>342 (4 RCTs)</td>
</tr>
<tr>
<td>Failure to maintain remission</td>
<td>659 per 1,000</td>
<td>330 per 1,000 (211 to 521)</td>
<td>RR 0.50 (0.32 to 0.79)</td>
<td>330 fewer per 1,000 (from 138 fewer to 448 fewer)</td>
<td>302 (4 RCTs)</td>
</tr>
</tbody>
</table>

**GRADE Working Group grades of evidence**

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

¹Rated down for imprecision since optimal information size not met (<200 events)
²Rated down for risk of bias

**Table 18.** GRADE Evidence Profile comparing rectal mesalamine suppositories with placebo for induction and maintenance of remission in patients with mild-moderate ulcerative proctitis
<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects’ (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Absolute effect</th>
<th>Nr of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk with placebo (median)</td>
<td>Risk with probiotics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure to induce remission</td>
<td>900 per 1,000 (621 to 1000)</td>
<td>792 per 1,000 (621 to 1000)</td>
<td>RR 0.88 (0.69 to 1.12)</td>
<td>108 fewer per 1,000 (from 54 more to 162 fewer)</td>
<td>585 (7 RCTs) □□□□1,2,3 VERY LOW</td>
</tr>
<tr>
<td>Failure to maintain remission</td>
<td>420 per 1,000 (265 to 445)</td>
<td>344 per 1,000 (265 to 445)</td>
<td>RR 0.82 (0.63 to 1.06)</td>
<td>76 fewer per 1,000 (from 25 more to 155 fewer)</td>
<td>92 (2 RCTs) □□□□1,3 LOW</td>
</tr>
</tbody>
</table>

**PROBIOTICS COMPARED TO MESALAMINE FOR MILD-MODERATE UC**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects’ (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Absolute risk difference</th>
<th>Nr of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk with mesalamine</td>
<td>Risk with probiotics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure to induce remission</td>
<td>254 per 1,000 (178 to 564)</td>
<td>315 per 1,000 (178 to 564)</td>
<td>RR 1.24 (0.70 to 2.22)</td>
<td>61 more per 1,000 (from 76 fewer to 310 more)</td>
<td>116 (1 RCT) □□□□1,3 LOW</td>
</tr>
<tr>
<td>Failure to maintain remission</td>
<td>458 per 1,000 (385 to 558)</td>
<td>462 per 1,000 (385 to 558)</td>
<td>RR 1.01 (0.84 to 1.22)</td>
<td>5 more per 1,000 (from 73 fewer to 101 more)</td>
<td>452 (2 RCTs) □□□□1,3 LOW</td>
</tr>
</tbody>
</table>

**GRADE Working Group grades of evidence**

**High quality:** We are very confident that the true effect lies close to that of the estimate of the effect

**Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

**Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

**Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1Rated down for imprecision

2Rated down for inconsistency (both in summary estimates as well as in nature of probiotic-intervention with use of different formulations)

3Rated down for risk of bias

**Table 19. GRADE Evidence Profile comparing probiotics with placebo or mesalamine for induction and maintenance of remission in patients with mild-moderate ulcerative colitis**
## ADDING CURCUMIN COMPARED TO PLACEBO FOR ORAL MESALAMINE-REFRACTORY MILD-MODERATE ULCERATIVE COLITIS

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Absolute effect</th>
<th>N\o of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk with placebo</td>
<td>Risk with curcumin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure to induce remission</td>
<td>854 per 1,000 (410 to 879)</td>
<td>RR 0.70 (0.48 to 1.03)</td>
<td>256 fewer per 1,000 (from 26 more to 444 fewer)</td>
<td>159 (3 RCTs)</td>
<td>◯◯◯1,2,3 VERY LOW</td>
</tr>
<tr>
<td></td>
<td>295 per 1,000 (33 to 251)</td>
<td>RR 0.30 (0.11 to 0.85)</td>
<td>207 fewer per 1,000 (from 44 fewer to 263 fewer)</td>
<td>89 (1 RCT)</td>
<td>◯◯◯1,3 LOW</td>
</tr>
</tbody>
</table>

**GRADE Working Group grades of evidence**

- **High quality:** We are very confident that the true effect lies close to that of the estimate of the effect
- **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
- **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
- **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1Rated down for imprecision
2Rated down for inconsistency (both in summary estimates as well as in dose of curcumin used)
3Rated down for risk of bias

**Table 20.** GRADE Evidence Profile comparing adding curcumin to mesalazine vs. placebo, for induction and maintenance of remission in patients with oral mesalazine-refractory mild-moderate ulcerative colitis
### FECAL MICROBIOTA TRANSPLANTATION COMPARED TO PLACEBO FOR MILD-MODERATE ULCERATIVE COLITIS

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects*(95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Absolute effect</th>
<th>Ne of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk with placebo</td>
<td>Risk with rectal mesalamine suppositories</td>
<td>RR 0.80 (0.71 to 0.89)</td>
<td>181 fewer per 1,000 (from 100 fewer to 263 fewer)</td>
<td>![GRADE] LOW</td>
</tr>
<tr>
<td>Failure to induce remission</td>
<td>907 per 1,000</td>
<td>726 per 1,000 (644 to 807)</td>
<td>181 fewer per 1,000 (from 100 fewer to 263 fewer)</td>
<td>281 (4 RCTs)</td>
<td>![GRADE] LOW</td>
</tr>
</tbody>
</table>

**GRADE Working Group grades of evidence**

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

1. Rated down for imprecision since optimal information size not met (<200 events)
2. Rated down for inconsistency (variability in intervention, with differences in route and frequency of administration, amount and source of stool)

**Table 21.** GRADE Evidence Profile comparing fecal microbiota transplantation with placebo for induction of remission in patients with mild-moderate ulcerative colitis
eFigure 1. PICO#1 – Efficacy of low-, standard- and high-dose mesalamine vs. placebo for INDUCTION of remission in patients with mild-moderate UC.
**eFigure 2.** PICO#1 – Efficacy of high- and standard-dose vs. low-dose mesalamine for **INDUCTION** of remission in patients with mild-moderate UC.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Active intervention</th>
<th>Low dose 5-ASA</th>
<th>Total</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>2.1.1 Standard dose 5-ASA (2–3 g) versus Low dose 5-ASA (&lt;2 g)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D’Haens 2006</td>
<td>10</td>
<td>14</td>
<td>13</td>
<td>8.3%</td>
</tr>
<tr>
<td>Goei 1992</td>
<td>12</td>
<td>21</td>
<td>12</td>
<td>3.0%</td>
</tr>
<tr>
<td>Hanauer 1993</td>
<td>67</td>
<td>95</td>
<td>223</td>
<td>23.7%</td>
</tr>
<tr>
<td>Ho 2010</td>
<td>46</td>
<td>65</td>
<td>35</td>
<td>15.3%</td>
</tr>
<tr>
<td>Knus 2003</td>
<td>37</td>
<td>108</td>
<td>72</td>
<td>9.2%</td>
</tr>
<tr>
<td>Miglioli 1990</td>
<td>35</td>
<td>24</td>
<td>16</td>
<td>8.9%</td>
</tr>
<tr>
<td>Riley 1988</td>
<td>22</td>
<td>21</td>
<td>5</td>
<td>5.0%</td>
</tr>
<tr>
<td>String 1991</td>
<td>47</td>
<td>52</td>
<td>14</td>
<td>26.3%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>412</td>
<td>434</td>
<td>100.00%</td>
<td>0.88 [0.79, 0.99]</td>
</tr>
<tr>
<td>Total events</td>
<td>246</td>
<td>347</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Test for overall effect:** \( \chi^2 = 10.24, df = 7 (p = 0.018); I^2 = 32\%

**eFigure 3.** PICO#1 – Efficacy of high- vs. standard-dose mesalamine for **INDUCTION** of remission in patients with mild-moderate UC.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>High dose 5-ASA (&gt;3 g) versus Standard dose 5-ASA (2–3 g)</th>
<th>Standard dose 5-ASA (2–3 g)</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td></td>
<td></td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>3.1.1 High dose 5-ASA (&gt;3 g) versus Standard dose 5-ASA (2–3 g)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D’Haens 2006</td>
<td>9</td>
<td>11</td>
<td>14</td>
<td>2.3%</td>
<td>1.15 [0.74, 1.77]</td>
</tr>
<tr>
<td>Goei 1992</td>
<td>10</td>
<td>30</td>
<td>12</td>
<td>1.0%</td>
<td>0.86 [0.44, 1.69]</td>
</tr>
<tr>
<td>Hanauer 1993</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Hanauer 2005</td>
<td>104</td>
<td>129</td>
<td>116</td>
<td>18.0%</td>
<td>0.97 [0.86, 1.08]</td>
</tr>
<tr>
<td>Hanauer 2007</td>
<td>112</td>
<td>147</td>
<td>124</td>
<td>17.0%</td>
<td>0.95 [0.84, 1.07]</td>
</tr>
<tr>
<td>Hwang 2011</td>
<td>47</td>
<td>60</td>
<td>54</td>
<td>11.4%</td>
<td>0.91 [0.77, 1.08]</td>
</tr>
<tr>
<td>Ho 2010</td>
<td>35</td>
<td>64</td>
<td>42</td>
<td>5.3%</td>
<td>0.78 [0.60, 1.01]</td>
</tr>
<tr>
<td>Kamis 2007</td>
<td>50</td>
<td>85</td>
<td>115</td>
<td>18.0%</td>
<td>0.93 [0.75, 1.14]</td>
</tr>
<tr>
<td>Knus 2003</td>
<td>51</td>
<td>109</td>
<td>86</td>
<td>10.8%</td>
<td>1.13 [0.98, 1.30]</td>
</tr>
<tr>
<td>Lakemun 2007</td>
<td>66</td>
<td>74</td>
<td>21</td>
<td>2.6%</td>
<td>1.67 [0.88, 1.29]</td>
</tr>
<tr>
<td>Miglioli 1990</td>
<td>13</td>
<td>24</td>
<td>35</td>
<td>1.9%</td>
<td>0.87 [0.54, 1.40]</td>
</tr>
<tr>
<td>Sandborn 2009</td>
<td>240</td>
<td>392</td>
<td>232</td>
<td>13.9%</td>
<td>0.89 [0.81, 0.99]</td>
</tr>
<tr>
<td>Schroder 1987</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Sutherland 1990</td>
<td>17</td>
<td>47</td>
<td>30</td>
<td>2.2%</td>
<td>0.58 [0.37, 0.91]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>756</td>
<td>875</td>
<td>100.00%</td>
<td>0.94 [0.88, 1.01]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>756</td>
<td>875</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Test for overall effect:** \( \chi^2 = 5.90, df = 5 (p = 0.16); I^2 = 16\%
**eFigure 4.** PICO#1 – Efficacy of low-, standard- and high-dose mesalamine vs. placebo for MAINTENANCE of remission in patients with mild-moderate UC.

**eFigure 5.** PICO#1 – Efficacy of standard-dose vs. low-dose mesalamine for MAINTENANCE of remission in patients with mild-moderate UC.

**eFigure 6.** PICO#1 – Efficacy of high-dose vs. standard-dose mesalamine for MAINTENANCE of remission in patients with mild-moderate UC.
eFigure 7. PICO#1 – Tolerability of low-, standard- and high-dose mesalamine vs. placebo for INDUCTION of remission in patients with mild-moderate UC.

eFigure 8. PICO#1 – Tolerability of low-, standard- and high-dose mesalamine vs. placebo for MAINTENANCE of remission in patients with mild-moderate UC.
eFigure 9. PICO#2 – Efficacy of diazo-bonded vs. placebo for INDUCTION of remission in patients with mild-moderate UC.

eFigure 10. PICO#2 – Tolerability of diazo-bonded vs. placebo for INDUCTION of remission in patients with mild-moderate UC.
eFigure 11. PICO#2 – Efficacy of diazo-bonded 5-ASA vs. placebo for MAINTENANCE of remission in patients with mild-moderate UC.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Diazobonded 5-ASA</th>
<th>Placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>4.3.1. Olsalazine vs. Placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sandberg-Gertzen 1986</td>
<td>12</td>
<td>52</td>
<td>22</td>
</tr>
<tr>
<td>Weight 1993</td>
<td>25</td>
<td>49</td>
<td>30</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>101</td>
<td>101</td>
<td>100.00%</td>
</tr>
<tr>
<td>Total events</td>
<td>37</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.09; Ch^2 = 2.51; df = 1 (P = 0.11); I^2 = 60%</td>
<td>Test for overall effect: Z = 1.26 (P = 0.21)</td>
<td>Test for subgroup differences: Not applicable</td>
<td></td>
</tr>
</tbody>
</table>

eFigure 12. PICO#2 – Efficacy of mesalamine vs. diazo-bonded 5-ASA for INDUCTION of remission in patients with mild-moderate UC (Note: Kruis 1998 studied olsalazine and all other trials studied balsalazide)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mesalamine</th>
<th>Total</th>
<th>Diazobonded 5-ASA</th>
<th>Total</th>
<th>Weight</th>
<th>M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Green 1998 - induction</td>
<td>38</td>
<td>49</td>
<td>23</td>
<td>50</td>
<td>19.6%</td>
<td>1.69 [1.01, 2.80]</td>
</tr>
<tr>
<td>Kruis 1998</td>
<td>41</td>
<td>80</td>
<td>48</td>
<td>88</td>
<td>22.7%</td>
<td>0.94 [0.71, 1.25]</td>
</tr>
<tr>
<td>Levine 2002</td>
<td>29</td>
<td>36</td>
<td>27</td>
<td>35</td>
<td>25.9%</td>
<td>1.04 [0.82, 1.34]</td>
</tr>
<tr>
<td>Prutt 2002</td>
<td>51</td>
<td>89</td>
<td>45</td>
<td>84</td>
<td>24.0%</td>
<td>1.07 [0.82, 1.40]</td>
</tr>
<tr>
<td>Turs 2004</td>
<td>14</td>
<td>30</td>
<td>9</td>
<td>30</td>
<td>7.9%</td>
<td>1.56 [0.80, 3.03]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>284</td>
<td>152</td>
<td>287</td>
<td>100.00%</td>
<td>1.16 [0.94, 1.43]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>172</td>
<td></td>
<td>172</td>
<td>0.94 [0.94, 1.43]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.03; Ch^2 = 8.56; df = 4 (P = 0.07); I^2 = 53%</td>
<td>Test for overall effect: Z = 1.41 (P = 0.16)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

eFigure 13. PICO#2 – Tolerability of mesalamine vs. diazo-bonded 5-ASA for INDUCTION of remission in patients with mild-moderate UC (Note: Kruis 1998 studied olsalazine and all other trials studied balsalazide)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mesalamine</th>
<th>Total</th>
<th>Diazobonded 5-ASA</th>
<th>Total</th>
<th>Weight</th>
<th>M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Green 1998 - induction</td>
<td>1</td>
<td>49</td>
<td>1</td>
<td>50</td>
<td>5.4%</td>
<td>1.02 [0.97, 1.08]</td>
</tr>
<tr>
<td>Kruis 1998</td>
<td>9</td>
<td>80</td>
<td>11</td>
<td>88</td>
<td>59.0%</td>
<td>0.90 [0.39, 2.06]</td>
</tr>
<tr>
<td>Levine 2002</td>
<td>5</td>
<td>51</td>
<td>1</td>
<td>53</td>
<td>9.1%</td>
<td>5.20 [0.63, 42.96]</td>
</tr>
<tr>
<td>Prutt 2002</td>
<td>6</td>
<td>89</td>
<td>3</td>
<td>84</td>
<td>22.1%</td>
<td>1.89 [0.49, 7.31]</td>
</tr>
<tr>
<td>Turs 2004</td>
<td>2</td>
<td>30</td>
<td>0</td>
<td>30</td>
<td>4.5%</td>
<td>5.00 [0.25, 99.95]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>299</td>
<td>16</td>
<td>305</td>
<td>100.00%</td>
<td>1.35 [0.72, 2.55]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>23</td>
<td></td>
<td>23</td>
<td>0.72 [0.72, 2.55]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau^2 = 0.00; Ch^2 = 3.59; df = 4 (P = 0.46); I^2 = 0%</td>
<td>Test for overall effect: Z = 0.93 (P = 0.35)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**eFigure 14.** PICO#2 – Efficacy of mesalamine vs. diazo-bonded 5-ASA for MAINTENANCE of remission in patients with mild-moderate UC

**eFigure 15.** PICO#2 – Tolerability of mesalamine vs. diazo-bonded 5-ASA for MAINTENANCE of remission in patients with mild-moderate UC

**eFigure 16.** PICO#2 – Efficacy of sulfasalazine vs. diazo-bonded 5-ASA for INDUCTION of remission in patients with mild-moderate UC

**eFigure 17.** PICO#2 – Tolerability of sulfasalazine vs. diazo-bonded 5-ASA for INDUCTION of remission in patients with mild-moderate UC
**eFigure 18.** PICO#2 – Efficacy of sulfasalazine vs. diazo-bonded 5-ASA for MAINTENANCE of remission in patients with mild-moderate UC

**eFigure 19.** PICO#2 – Tolerability of sulfasalazine vs. diazo-bonded 5-ASA for MAINTENANCE of remission in patients with mild-moderate UC
**eFigure 20.** PICO#3 – Efficacy of sulfasalazine vs. placebo for INDUCTION of remission in patients with mild-moderate UC.

**eFigure 21.** PICO#3 – Efficacy of sulfasalazine vs. placebo for MAINTENANCE of remission in patients with mild-moderate UC.

**eFigure 22.** PICO#3 – Tolerability of sulfasalazine vs. placebo for INDUCTION of remission in patients with mild-moderate UC.

**eFigure 23.** PICO#3 – Tolerability of sulfasalazine vs. placebo for MAINTENANCE of remission in patients with mild-moderate UC.
**eFigure 24.** PICO#3 – Efficacy of sulfasalazine vs. mesalamine for INDUCTION of remission in patients with mild-moderate UC.

**eFigure 25.** PICO#3 – Tolerability of sulfasalazine vs. mesalamine for INDUCTION of remission in patients with mild-moderate UC.

**eFigure 26.** PICO#3 – Efficacy of sulfasalazine vs. mesalamine for MAINTENANCE of remission in patients with mild-moderate UC.

**eFigure 27.** PICO#3 – Tolerability of sulfasalazine vs. mesalamine for MAINTENANCE of remission in patients with mild-moderate UC.
**eFigure 28.** PICO#4 – Efficacy of oral + topical 5-ASA vs. oral 5-ASA for **INDUCTION** of remission in patients with mild-moderate UC.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Oral + Topical 5-ASA Events</th>
<th>Total</th>
<th>Oral 5-ASA Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fruhnergen 1980</td>
<td>2</td>
<td>12</td>
<td>6</td>
<td>10</td>
<td>5.2%</td>
<td>0.28 [0.07, 1.09]</td>
</tr>
<tr>
<td>Marteau 2005</td>
<td>34</td>
<td>71</td>
<td>36</td>
<td>56</td>
<td>46.2%</td>
<td>0.74 [0.55, 1.02]</td>
</tr>
<tr>
<td>Safdi 1997</td>
<td>4</td>
<td>20</td>
<td>12</td>
<td>22</td>
<td>10.0%</td>
<td>0.37 [0.14, 0.95]</td>
</tr>
<tr>
<td>Yersch 2001</td>
<td>26</td>
<td>63</td>
<td>34</td>
<td>67</td>
<td>38.5%</td>
<td>0.81 [0.56, 1.19]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>166</strong></td>
<td><strong>155</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td></td>
<td><strong>0.68 [0.49, 0.94]</strong></td>
</tr>
</tbody>
</table>

Total events: 66
Heterogeneity: Tau² = 0.03; Ch² = 4.37, df = 3 (P = 0.22); I² = 31%
Test for overall effect: Z = 2.33 (P = 0.02)

**eFigure 29.** PICO#4 – Efficacy of oral + topical 5-ASA vs. oral 5-ASA for **MAINTENANCE** of remission in patients with mild-moderate UC.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Oral + Topical 5-ASA Events</th>
<th>Total</th>
<th>Oral 5-ASA Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>D'Albisio 1997</td>
<td>13</td>
<td>36</td>
<td>23</td>
<td>36</td>
<td>72.0%</td>
<td>0.57 [0.34, 0.93]</td>
</tr>
<tr>
<td>Yelkenman 2007</td>
<td>2</td>
<td>11</td>
<td>10</td>
<td>13</td>
<td>27.1%</td>
<td>0.24 [0.07, 0.86]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>47</strong></td>
<td><strong>49</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td></td>
<td><strong>0.45 [0.26, 0.79]</strong></td>
</tr>
</tbody>
</table>

Total events: 35
Heterogeneity: Tau² = 0.15; Ch² = 1.61, df = 1 (P = 0.20); I² = 38%
Test for overall effect: Z = 2.03 (P = 0.04)
eFigure 30. PICO#5 – Efficacy of once-daily vs. multiple-times daily equivalent doses of mesalamine for INDUCTION of remission in patients with mild-moderate UC.

eFigure 31. PICO#5 – Efficacy of once-daily vs. multiple-times daily equivalent doses of mesalamine for MAINTENANCE of remission in patients with mild-moderate UC.

eFigure 32. PICO#5 – Adherence of once-daily vs. multiple-times daily equivalent doses of mesalamine in patients with mild-moderate UC.
**eFigure 33.** PICO#5 – Tolerability of once-daily vs. multiple-times daily equivalent doses of mesalamine in patients with mild-moderate UC.
**eFigure 34.** PICO#6 – Efficacy of budesonide MMX vs. placebo for INDUCTION of remission in patients with mild-moderate UC.

**eFigure 35.** PICO#6 – Tolerability of budesonide MMX vs. placebo in patients with mild-moderate UC.

**eFigure 36.** PICO#6 – Efficacy of 2nd-generation corticosteroids vs. oral prednisone/prednisolone for INDUCTION of remission in patients with mild-moderate UC.

**eFigure 37.** PICO#6 – Risk of steroid-related adverse events with 2nd-generation corticosteroids vs. oral prednisone/prednisolone for INDUCTION of remission in patients with mild-moderate UC.
**eFigure 38.** PICO#7 – Efficacy of topical 5-ASA vs. oral 5-ASA for INDUCTION of remission in patients with mild-moderate UC.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Topical 5-ASA Events</th>
<th>Total</th>
<th>Oral 5-ASA Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>G_TRACE 1998</td>
<td>3</td>
<td>29</td>
<td>17</td>
<td>29</td>
<td>25.4%</td>
<td>0.18 [0.06, 0.54]</td>
</tr>
<tr>
<td>Kam 1996</td>
<td>1</td>
<td>19</td>
<td>4</td>
<td>18</td>
<td>15.4%</td>
<td>0.24 [0.03, 1.92]</td>
</tr>
<tr>
<td>Prantera 2005</td>
<td>19</td>
<td>38</td>
<td>16</td>
<td>40</td>
<td>31.9%</td>
<td>1.25 [0.76, 2.05]</td>
</tr>
<tr>
<td>Saffi 1997</td>
<td>4</td>
<td>18</td>
<td>12</td>
<td>22</td>
<td>27.3%</td>
<td>0.41 [0.16, 1.05]</td>
</tr>
</tbody>
</table>

Total (95% CI) 104 109 100.0% 0.43 [0.14, 1.31]

Total events 27 49

Heterogeneity: Tau² = 0.94; Chi² = 14.73, df = 3 (P = 0.002); I² = 80%

Test for overall effect: Z = 1.48 (P = 0.14)

**eFigure 39.** PICO#7 – Efficacy of topical 5-ASA vs. oral 5-ASA for MAINTENANCE of remission in patients with mild-moderate UC.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Topical 5-ASA Events</th>
<th>Total</th>
<th>Oral 5-ASA Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andreoli 1994</td>
<td>4</td>
<td>16</td>
<td>6</td>
<td>15</td>
<td>25.1%</td>
<td>0.63 [0.22, 1.79]</td>
</tr>
<tr>
<td>D’Albasso 1990</td>
<td>9</td>
<td>29</td>
<td>12</td>
<td>31</td>
<td>56.0%</td>
<td>0.80 [0.40, 1.62]</td>
</tr>
<tr>
<td>Mantzaris 1994</td>
<td>3</td>
<td>19</td>
<td>6</td>
<td>19</td>
<td>18.3%</td>
<td>0.50 [0.15, 1.71]</td>
</tr>
</tbody>
</table>

Total (95% CI) 64 65 100.0% 0.69 [0.41, 1.17]

Total events 16 24

Heterogeneity: Tau² = 0.00; Chi² = 0.48, df = 2 (P = 0.79); I² = 0%

Test for overall effect: Z = 1.38 (P = 0.17)
**eFigure 40. PICO#8** – Efficacy of 5-ASA enemas vs. placebo for INDUCTION of remission in patients with mild-moderate left-sided UC.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mesalamine enema</th>
<th>Placebo</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Camplien 1991 (1)</td>
<td>4</td>
<td>29</td>
<td>27</td>
<td>11.5%</td>
</tr>
<tr>
<td>Camplien 1991b</td>
<td>6</td>
<td>18</td>
<td>13</td>
<td>14.18%</td>
</tr>
<tr>
<td>Hanauer 1998 (2)</td>
<td>41</td>
<td>73</td>
<td>69</td>
<td>40.2%</td>
</tr>
<tr>
<td>Pokrotnik 2000 (3)</td>
<td>19</td>
<td>54</td>
<td>34</td>
<td>29.5%</td>
</tr>
</tbody>
</table>

Total (95% CI) | 174 | 168 | 100.0% |

Total events 70 123
Heterogeneity: Tau² = 0.06; Chi² = 7.15, df = 3 (P = 0.07); I² = 58%
Test for overall effect: Z = 3.58 (P = 0.0003)

Footnotes:
(1) Includes patients with left sided disease n=32 (37% of data)
(2) combined 3 different doses for mesalamine
(3) includes patients with left sided disease

**eFigure 41. PICO#8** – Efficacy of budesonide enemas vs. placebo for INDUCTION of remission in patients with mild-moderate left-sided UC.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Budesonide Foam</th>
<th>Placebo</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hanauer 1998 (1)</td>
<td>33</td>
<td>56</td>
<td>48</td>
<td>14.1%</td>
</tr>
<tr>
<td>Naganuma 2016</td>
<td>56</td>
<td>111</td>
<td>40</td>
<td>15.3%</td>
</tr>
<tr>
<td>Sandborn 2015a</td>
<td>77</td>
<td>133</td>
<td>114</td>
<td>35.2%</td>
</tr>
<tr>
<td>Sandborn 2015b</td>
<td>83</td>
<td>124</td>
<td>113</td>
<td>35.4%</td>
</tr>
</tbody>
</table>

Total (95% CI) | 434 | 393 | 100.0% |

Total events 249 315
Heterogeneity: Tau² = 0.00; Chi² = 2.87, df = 3 (P = 0.41); I² = 0%
Test for overall effect: Z = 6.59 (P < 0.00001)

**eFigure 42. PICO#8** – Efficacy of topical 5-ASA vs. topical steroids for INDUCTION of remission in patients with mild-moderate left-sided UC.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Topical 5-ASA</th>
<th>Topical steroids</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anonymous 1987</td>
<td>34</td>
<td>43</td>
<td>62</td>
<td>13.1%</td>
</tr>
<tr>
<td>Bianchi Porro 1995</td>
<td>3</td>
<td>27</td>
<td>9</td>
<td>2.4%</td>
</tr>
<tr>
<td>Blanchard 2007</td>
<td>20</td>
<td>42</td>
<td>32</td>
<td>10.7%</td>
</tr>
<tr>
<td>Camplien 1981</td>
<td>3</td>
<td>44</td>
<td>42</td>
<td>2.5%</td>
</tr>
<tr>
<td>Fanup 1995</td>
<td>24</td>
<td>41</td>
<td>25</td>
<td>11.5%</td>
</tr>
<tr>
<td>Friedman 1986</td>
<td>2</td>
<td>9</td>
<td>7</td>
<td>2.1%</td>
</tr>
<tr>
<td>Giomini 2005</td>
<td>80</td>
<td>106</td>
<td>78</td>
<td>15.9%</td>
</tr>
<tr>
<td>Hartmann 2010</td>
<td>24</td>
<td>106</td>
<td>36</td>
<td>9.4%</td>
</tr>
<tr>
<td>Hedges 1996</td>
<td>90</td>
<td>167</td>
<td>122</td>
<td>15.6%</td>
</tr>
<tr>
<td>Lemann 1995</td>
<td>21</td>
<td>49</td>
<td>31</td>
<td>10.6%</td>
</tr>
<tr>
<td>Muerle 1988</td>
<td>4</td>
<td>15</td>
<td>3</td>
<td>2.0%</td>
</tr>
<tr>
<td>Mueler 1996</td>
<td>5</td>
<td>21</td>
<td>6</td>
<td>3.1%</td>
</tr>
<tr>
<td>Senagore 1992</td>
<td>2</td>
<td>19</td>
<td>2</td>
<td>1.1%</td>
</tr>
</tbody>
</table>

Total (95% CI) | 707 | 700 | 100.0% |

Total events 312 412
Heterogeneity: Tau² = 0.06; Chi² = 31.65, df = 12 (P = 0.002); I² = 62%
Test for overall effect: Z = 3.05 (P = 0.002)
eFigure 43. PICO#9 – Efficacy of 5-ASA suppositories vs. placebo for INDUCTION of remission in patients with mild-moderate ulcerative proctitis.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mesalazine suppositories</th>
<th>Placebo</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campieri 1990a (1)</td>
<td>21</td>
<td>63</td>
<td>32</td>
<td>0.47 [0.31, 0.71]</td>
</tr>
<tr>
<td>Campieri 1990b (2)</td>
<td>14</td>
<td>32</td>
<td>28</td>
<td>0.47 [0.31, 0.70]</td>
</tr>
<tr>
<td>Watanabe 2013 (3)</td>
<td>12</td>
<td>37</td>
<td>29</td>
<td>0.42 [0.25, 0.69]</td>
</tr>
<tr>
<td>Williams 1987 (4)</td>
<td>3</td>
<td>14</td>
<td>12</td>
<td>0.23 [0.08, 0.64]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>146</td>
<td>110</td>
<td>100.0%</td>
<td>0.44 [0.34, 0.56]</td>
</tr>
</tbody>
</table>

Footnotes:
(1) disease is up to 20cm
(2) disease is < 20cm
(3) Watanabe study included patients with all different extents of disease this is a subgroup
(4) Disease is < 15cm

---

eFigure 44. PICO#9 – Efficacy of 5-ASA suppositories vs. placebo for MAINTENANCE of remission in patients with mild-moderate ulcerative proctitis.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mesalazine suppositories</th>
<th>Placebo</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>D'Arcaise 1998 (1)</td>
<td>17</td>
<td>76</td>
<td>16</td>
<td>0.49 [0.28, 0.85]</td>
</tr>
<tr>
<td>D'Arcaise 1990 (2)</td>
<td>1</td>
<td>15</td>
<td>11</td>
<td>0.39 [0.01, 0.62]</td>
</tr>
<tr>
<td>Hanauer 2000</td>
<td>12</td>
<td>21</td>
<td>13</td>
<td>0.44 [0.28, 0.69]</td>
</tr>
<tr>
<td>Marteau 1998</td>
<td>22</td>
<td>48</td>
<td>29</td>
<td>0.74 [0.51, 1.09]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>52</td>
<td>170</td>
<td>132</td>
<td>0.50 [0.32, 0.79]</td>
</tr>
</tbody>
</table>

Footnotes:
(1) Combined the two doses of 1g and 0.5g suppositories
(2) Includes proctitis n=17 and ps n=13

Heterogeneity: Tau² = 0.12; Chi² = 7.38; df = 3 (P = 0.06); I² = 59%
**eFigure 45.** PICO#10 – Efficacy of probiotics vs. placebo for INDUCTION of remission in patients with mild-moderate ulcerative colitis.

**eFigure 46.** PICO#10 – Efficacy of probiotics vs. placebo for MAINTENANCE of remission in patients with mild-moderate ulcerative colitis.

**eFigure 47.** PICO#10 – Efficacy of probiotics vs. mesalamine for MAINTENANCE of remission in patients with mild-moderate ulcerative colitis.
eFigure 48. PICO#11 – Efficacy of curcumin vs. placebo for INDUCTION of remission in patients with mild-moderate ulcerative colitis.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Curcumin Events</th>
<th>Placebo Events</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total events</td>
<td>46</td>
<td>70</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.08, Ch² = 6.96, df = 2 (P = 0.03); I² = 71%
Test for overall effect: Z = 1.82 (P = 0.07)

1.1.2 Curcumin Enema
Singla 2014
Subtotal (95% CI) 23 22 100.0%
Total events 13 17
Heterogeneity: Not applicable
Test for overall effect: Z = 1.45 (P = 0.15)

eFigure 49. PICO#12 – Efficacy of fecal microbiota transplantation vs. placebo for INDUCTION of remission in patients with mild-moderate ulcerative colitis.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>FMT Events</th>
<th>Placebo Events</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total events</td>
<td>141</td>
<td>140</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00, Ch² = 0.55, df = 3 (P = 0.91); I² = 0%
Test for overall effect: Z = 3.97 (P < 0.0001)

eFigure 50. PICO#12 – Safety of fecal microbiota transplantation vs. placebo for INDUCTION of remission in patients with mild-moderate ulcerative colitis.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>FMT Events</th>
<th>Placebo Events</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total events</td>
<td>10</td>
<td>7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00, Ch² = 0.17, df = 3 (P = 0.98); I² = 0%
Test for overall effect: Z = 0.71 (P = 0.48)