National Clinical Guideline Centre

Ulcerative colitis

Appendix G

Evidence tables

Ulcerative colitis

Clinical guideline

June 2013

NICE's original guidance on Ulcerative colitis: management in adults, children and young people was published in June 2013 and has undergone an update, published in May 2019. The full, current recommendations can be found on the NICE website.

Final version

Commissioned by the National Institute for Health and Care Excellence

Royal College of Physicians
Royal College of Nursing
RCGP Royal College of General Practitioners
The Royal College of Surgeons of England
NICE accredited www.nice.org.uk/accreditation

Funding
National Institute for Health and Care Excellence

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1 Appendix G: Evidence tables

1.1 Clinical evidence tables

Table 1: ACEITUNO2008

Reference	Patient characteristics	Predictors & outcome measures	Effect sizes	Comments
M. Aceituno et al. Steroid-refractory Ulcerative Colitis: Predictive Factors of Response to Cyclosporine and Validation in an Independent Cohort. *Inflammatory Bowel Disease*; 14 (3):347-352. 2008. **Type of study: Prospective Cohort** **Setting:** Two University hospitals Spain **Follow up period:** 3 months **Model development:** Univariate screening **Model presentation:** Ho index was used as previously used in the HO2004 study. **Model evaluation:** External validation	**Sample size:** Derivation cohort: N=34 Validation cohort: N=38 **<5% missing data?** None reported. Unclear. **Type of analysis used:** Assume ITT. Unclear. Chi squared (qualitative), students t-test (quantitative). Stepwise multiple logistic regression. Receiver operating curve (ROC) analysis. **Appropriate?** Yes **Inclusion criteria:** • Steroid refractory ulcerative colitis (failed to respond to 1mg/kg/day prednisolone or equivalent for at least 5 days • Moderate to severe flare according to the modified Truelove & Witts activity index **Exclusion criteria:** • Cytomegalovirus infection **Data collection:** Prospectively collected from established databases in 2 Spanish University hospitals between 1998-2005.	**Univariate analysis results:** see the table below **Definitions of predictors:** As per HO2004. **Routinely measured?** Yes. **Outcome and definition:** Need of early surgery within 3 months since ciclosporine treatment. Response: Avoidance of colectomy at 3 months. A colectomy was performed if: clinical condition deteriorated during ciclosporine treatment, a clinical response was not obtained after 14 days of ciclosporine, or clinical condition deteriorated within 3 months after treatment with ciclosporine. **Blinding:** Not described. Unclear. **Risk of measurement error:** Low **Risk of inter-observer variability:** Low. Some variability likely measuring	**Results** **<u>Population 1 (in the study referred to as the derivation cohort)</u>** **Response:** 23/34 (67.64%) (60% IV, and 75% oral) **Colectomized (in 1st 3 months):** 11/34 due to • Lack of response (N=6) • Early relapse of disease activity (N=5) No serious adverse events. N=4 infectious complication associated with ciclosporin but none were severe (1 herpes simplex, 3 oral candidiasis). **<u>Population 2 (in the study referred to as the validation cohort)</u>** **Response:** 29/38 (76.3%) **Colectomized (in 1st 3 months):** 9/38 due to • Lack of response (N=7) • Early relapse of disease activity (N=2) **Variables** / **Score** Mean stool frequency <4 — 0 Mean stool frequency >4≤6 — 1 Mean stool frequency >6≤0 — 2 Mean stool frequency >9 — 4 Colonic dilatation — 4	**Source of funding**: None described. **Risk of bias:** • Unclear whether any missing data • Different cut off used compared to original study • Partially adequate event: covariate ratio (7-9) – inadequate for the exploratory analysis • <100 events, small sample size **Additional outcomes reported:** Exploratory analyses considering colectomy during the index admission as the endpoint. Exploratory analyses combining the derivation and validation cohorts

Reference	Patient characteristics	Predictors & outcome measures	Effect sizes		Comments
Model performance: Calibration- Not reported Discrimination – See Efficacy results.	**Treatment given:** All had received 1mg/kg/day prednisolone or equivalent for ≥5 days before ciclosporine. Ciclosporine was given orally or IV with starting doses of 10mg/kg/day and 4mg/kg/day respectively. Doses were then adjusted to blood levels (200-400ng/mL). Those reaching clinical remission (absence of blood in stool and no diarrhoea with ciclosporin changed to 2.5mg/kg of azathioprine. **Baseline characteristics:** (see table below) **Population 1 (derivation cohort):** 6 patients were on treatment with azathioprine prior to admission. 24 patients had oral, 10 IV ciclosporine (IV was given if presence of colonic dilatation or significant ileus). Ciclosporin was taken for a mean 28.65 days (SD 35.96), mean levels 386 +/- 133 ng/mL (95% CI 339-433). **Validation cohort:** All patients had IV ciclosporin for a mean duration of 14.5 days (SD 5.26).	colonic dilatation. **Continuous variable analysis:** continuous or categorical- mean stool frequency was continuous and made into categorical, as was the serum albumin level. Colonic dilation was binary (yes/no). **Key prognostic factors not included?** No.	Hypoalbuminaemia (<30g/L)	1	Adverse events **Note: population is steroid refractory treated with ciclosporin**
			Regression analysis results: Only the Ho index was an independent predictive factor of response (P=0.011). No other variable improved the prediction function. Model correctly predicted response to ciclosporine avoiding colectomy in 87% of cases in the derivation cohort, 82% in the validation cohort. Best specificity and sensitivity to predict failure to ciclosporine and need for colectomy was determined to be ≥5. **Note:** In the original HO2004 study the cut off was ≥4. **Sensitivity:** Population 1 (derivation cohort): 55 % Population 2 (validation cohort): 55.5% **Specificity:** Population 1 (derivation cohort): 91 % Population 2 (validation cohort): 82% **Positive predictive value:** Population 1 (derivation cohort): 66.6 % Population 2 (validation cohort): 50% **Negative predictive value:** Population 1 (derivation cohort): 80% Population 2 (validation cohort): 85% **Area under the curve:** Population 1 (derivation cohort): 0.79 (95CI 0.59-0.99) Population 2 (validation cohort): 0.74 (95%CI 0.53-0.96) When the two curves were compared they were not significantly different (z=0.03). **Exploratory analysis** **Only colectomies performed during the initial hospitalisation:** Optimum cut-off point of the Ho index: 6 Ho index <6: 93.1% (27/29) avoided colectomy in the		

Reference	Patient characteristics	Predictors & outcome measures	Effect sizes	Comments
			population 1 (derivation cohort), 96.7% (29/30)population 2 (validation cohort). Ho index ≥6, 60% (3/5) in the population 1 (derivation cohort), 57.1% (4/7) in the population 2 (validation cohort) required surgery during the initial hospitalisation. **Area under the curve:** Population 1 (derivation cohort): 0.87 (0.73-0.99) Population 2 (validation cohort): 0.82 (0.65-0.99) Despite some differences in the populations of the two cohorts, the AUC figures are very similar.	

Table 2: Derivation and validation cohort baseline characteristics

Characteristic	Population 1 (derivation cohort) (N=34)	Population 2 (validation cohort) (N=38)	Statistical significance
Sex (M/F)	21/13	22/16	NS
Age (years)	36.3 +/- 15.55	34.13 +/-11.61	NS
Disease duration	30.90 +/-36.28	55.24 +/- 77.08	NS
Disease location Proctitis Left-sided Extensive	 1 (2.9%) 8 (23.5%) 25 (73.5%)	 9 (23.7%) 9 (23.7%) 20 (52.6%)	P=0.033
C-reactive protein (mg/L)	8.53 +/- 8.15)	5.49 +/- 5.00	P=0.05
Erythrocyte sedimentation rate (mm/h)	51.47 +/- 32.57	50.72 +/- 26.08	NS
Haemoglobin (g/L)	11.91 +/- 2.03	9.80 +/- 1.57	P=0.000
Albumin (g/L)	34.84 +/- 5.99	30.06 +/- 5.89	P=0.002
Leukocyte count ($x10^6$)	10766 +/- 3018	12920 +/- 5812	NS
Antibiotic use	17	19	NS
Positive stool culture	3	3	NS
Colonic dilatation	10	5	NS

Characteristic	Population 1 (derivation cohort) (N=34)	Population 2 (validation cohort) (N=38)	Statistical significance
Ho Index	3.16 +/-2.65	2.59 +/-1.96	NS
Lindgren Index	15.45 +/- 9.06	10.19 +/- 7.25	P=0.006
Truelove	17.45 +/-2.58	12.84 +/-2.24	P=0.000
Corticosteroids duration (days)	17 +/- 31.39	37.28 +/-51.37	NS

Table 3: Univariate analysis- statistically significant results (P<0.05)

	Population 1 (derivation cohort)			Population 2 (validation cohort)		
Variable	**Colectomy**	**No colectomy**	**P- value**	**Colectomy**	**No colectomy**	**P- value**
CRP	14.01 +/- 8.37	6.62 +/- 6.91	0.012	9.06 +/-7.01	4.82 +/-4.40	Not reported
Ho index	5.5 +/- 3.21	2.3 +/-1.49	0.013	29.57 +/- 3.82	29.86 +/- 6.15	Not reported

(a) Variables of p<0.1 were included in the regression analysis (CRP, Ho Index, leukocyte counts and Hb level) and avoiding duplication of variables contained within indexes.

(b) The number of stools and colonic dilation were not included because they are contained in the Ho index and the Lindgren index was not included as it contained CRP as one of its parameters.

Table 4: ANDERSON2008

Reference	Study description	Findings	Comments
P. Anderson et al. Inflammatory Bowel Disease Specialist Nurse Patients survey. United Bristol Healthcare NHS Trust.2008 **REF ID: ANDERSON2008** Cross-sectional study	N=88 questionnaires were sent out to IBD patients Response rate: 34% (n=30), 1 returned by the post office as "no longer at that address". **Aim:** To find out how patients felt about the new dedicated IBD surgical clinic **Data collection:** Questionnaire that mainly consisted of tick boxes but with three text boxes, including general comments. 88 questionnaires with pre-paid envelopes were sent out. Piloted in	**Summary of findings that relate to the clinical review:** 97% received information prior to appointment 97% satisfied with amount of information given: "It would be useful to have some literature about the surgery as it's a lot to take in during the appointment. Particularly because it is something important and it is difficult to always remember what has been discussed. This would also be useful to give to family etc so they understand what is happening. It is also the practical issues that you want to know about e.g. time off work, how long before operation, next step, before and after operation, ongoing consultations after operation etc" 3/8 who did not have a specialist nurse with them at the appointment would have liked one Reasons why people would have liked a specialist nurse present with them: 1) "Because she could have explained and gone into more depth" 2) "The IBD nurse would have been able to explain more after the consultation" Reason why a patient liked having the specialist nurse present: 1) "I liked her being there because it was the first time I had met the surgeon and it was really helpful to have a familiar person there" Other comments: 1) "Patients need more help with their diet and the emotional support is very important as it greatly affects	**Source of funding:** None described **Limitations:** Indirect population: it is not clear whether the responses were UC or Crohn's patients, therefore cannot separate them out

Reference	Study description	Findings	Comments
	February 2008 and then rolled out over 3 months.	these conditions." 2)" Also help with relaxation is needed because constant stress causes repeated flare ups"	

Table 5: ANDREOLI1994

Author	Patients	Intervention	Outcome measures	Effect size	Comments
A. Andreoli et al. 5-ASA enema versus oral sulphasalazine in maintaining remission in ulcerative colitis. *Italian Journal of Gastroenterology; 26: 121-125. 1994.* **REF ID: ANDREOLI1994** **Study design and quality:** Single blind RCT Italy **6 month trial** **Randomisation:** Not described. Unclear. **Allocation concealment**: Not described. Unclear. **Blinding:** Single blind (endoscopy) **Outcome assessment:** Daily	**<u>All patients:</u>** **N=31 randomised** **Drop-outs** (don't complete the study): N=0 (0%) Only the patients who relapsed dropped out. **Two phases; 1 induction of remission, 2 maintenance of remission** **Inclusion criteria for phase 1:** • Active mild/moderate left sided colitis • Total colonoscopy documenting visible and biopsy confirmed mucosal inflammation extending proximal to the rectum but not above the splenic flexure • Typical histological findings including normal transverse colonic mucosa • At least two months without local or systemic therapy with steroids or immunosuppressive drugs **Exclusion:** • Any other pathology of colitis **Phase 1:** On entry oral 5-ASA or SASP maintenance was stopped. Patients were given daily 4g 5-ASA enemas (liquid). 31 patients who entered remission within 3 months were enrolled into	**Group 1: 2g SASP** N=15 randomised N=15 (completers) Enteric coated oral SASP, 1g taken twice a day, after meals. Total 14g SASP per week = 7g 5-ASA **Group 2: 4g 5-ASA enema twice a week** N=16 randomised N=16 (completers) One enema at bedtime on Mondays and Thursdays and to retain it as possible, recording the retention time of each. Type of 5-ASA was not specified. Total 8g 5-ASA per	**Outcome 1: Relapse** The p value given in the paper was assumed to be a log rank p value because it says that the difference between the two treatment groups in terms of survival function (Kaplan Meier) was tested using the log rank test, in the methods section. The hazard ratio has been calculated where possible. **Outcome 2: Adverse events** No patient had significant side effects on either treatment. No other details were given.	**Group1:** 6/15 **Group 2:** 4/16 **Log rank test p=0.37** **By extent of disease:** **<u>Left sided colitis</u>** **Group1:** 3/8 **Group 2:** 1/8 **<u>Proctosigmoiditis</u>** **Group1:** 3/7 **Group 2:** 3/8	**Funding:** None described. **Limitations:** Unclear method of randomisation and allocation concealment Single blind **Additional outcomes:** Mean time to new attack

Author	Patients	Intervention	Outcome measures	Effect size	Comments
diary card of bowel frequency, rectal bleeding and abdominal pain. Seen monthly. Laboratory tests. Suspected relapse and at the end of 6 months endoscopy was done (scored 0-3). **Sample size calculation:** None described. **Type of analysis: ITT** **Compliance rates:** 95% of enemas were retained all night. "Compliance was judged to be excellent". N=0 dropout/ withdrawal due to drug related AEs.	phase 2. They were randomised to the treatment as soon as they entered remission. **Phase 2 baseline characteristics** **Group 1: 2g SASP** **Mean age (range):** 44.0 (21-71) **Extent:** proctosigmoiditis n=7, left sided colitis n=8 **Clinical severity of relapse prior to phase 2:** mild n=10, moderate n=5 **Endoscopic remission achieved within:** 30 days n=1, 60 days n=7, 90 days n=7 **Frequency of relapses:** Not described **Drop outs:** 0 **Group 2: 5-ASA enema** **Mean age (range):** 39.1 (21-56) **Extent:** proctosigmoiditis n=8, left sided colitis n=8 **Clinical severity of relapse prior to phase 2:** mild n=11, moderate n=5 **Endoscopic remission achieved within:** 30 days n=3, 60 days n=9, 90 days n=4 **Frequency of relapses:** Not described **Drop outs:** 0 **Definitions** **Remission:** Clinical remission was achieved and microscopic inflammation cleared from biopsy specimens. **Relapse:** Endoscopic grade >0.	week. **Concomitant therapy:** Unclear. Oral 5-ASA or SASP was stopped on entry to Phase 2 of the trial.			

Table 6: Andus2008

Author	Patients	Intervention	Outcome measures	Effect size	Comments
T. Andus et al. Clinical Trial: A Novel High-dose 1g Mesalamine Suppository (Salofalk) Once Daily Is as Efficacious as a 500mg Suppository Thrice Daily in	**All patients:** **N=408 randomised** N=403 were treated and had at least one follow up value for safety analysis) **N=354 (PPA)**	**Group 1: 1g mesalazine (Salofalk) suppository at night** N=201 randomised/ITT N=200 (authors	**Outcome 1: Clinical remission** (DAI<4)	**ITT** **6 weeks** **Group1:** 168/201 **Group 2:**	**Funding:** None described. **Limitations:** Unclear method of

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Active Ulcerative Proctitis. *Inflammatory Bowel Disease. 16 (11): 1947-1956. 2010.* **REF ID: ANDUS2010** **and abstract:** **T. Andus et al.** **A novel high dose 1g mesalamine suppository (Salofalk) is efficacious as 500mg TID suppositories in mild to moderate active ulcerative proctitis: A mulitcenter, randomized trial. *Gastroenterology; 134 (4 Suppl 1): T1137. 2008.*** ***REF ID: ANDUS2008*** **Study design and quality:** Single investigator blind RCT Multicentre: Israel, Germany, Russia, Ukraine **6 week trial** **Randomisation:** No details of randomisation given. **Allocation concealment**: Unclear **Blinding:** Distribution, return of study medication and all checks of patient diaries were performed by a third person not involved in any of the assessment centres	**Drop-outs** (don't complete the study): It is not clear what the number of drop outs were. 3 were due to AEs. There were 54 patients excluded from the PPA due to major protocol deviations, non compliance or premature study termination (non drug related). It is not clear as to how many of these dropped out. **Inclusion criteria:** • 18-75 years • Established or newly diagnosed • Extent: Proctitis (maximum 15cm from the anus), confirmed by endoscopy & histology • Severity: Mild to moderate (3<DAI<11) **Exclusion:** • Crohn's disease • Proctitis of a different origin • Prior bowel resection leading to diarrhoea and/or pouch formation • Toxic megacolon • Haemorrhagic diathesis • Present or past colorectal cancer • Serious other secondary disease(s) • Use of steroids or cycloferon within 1 month • Immunosuppressants or ant TNF-α within 3 months prior to inclusion • Relapse during daily maintenance of >0.5g rectal or >2g oral mesalamine, or corresponding doses of rectal or oral sulphasalazine • Tranaminases or alkaline phosphatase levels ≥2 x upper limit of normal or serum creatinine >1.5mg/dL • Pregnant women **<u>Baseline characteristics</u>** **<u>Group 1: 1g mesalazine (Salofalk) suppository at night</u>** **Sex (m/f):** 85:115 **Mean age (SD):** 41.4 (13.2) **Course of the disease:** new diagnosis n=41, continuous n=16,	definition of ITT) 1g mesalazine suppository (Salofalk) to be given once a day, at night. **Group 2: 500mg mesalazine (Salofalk) suppository three times a day** N=207 randomised/ITT N=203 (authors definition of ITT) 500mg mesalazine suppository (Salofalk) to be given three times a day. **Concomitant therapy:** All oral or rectal treatment for UC had to have been stopped prior to study inclusion. The following were not permitted during the trial: Use of NSAIDs for >6 weeks, antibiotics, drugs containing psyllium, E. Coli Nissle 1917 and Loperamide.		172/207	randomisation and allocation concealment Unclear drop out rate Single blind **Additional outcomes:** Clinical remission by severity of disease Histological remission Physicians global assessment Patient acceptance and preference of treatment
			Outcome 2: Clinical improvement (≥1 point decrease in DAI from baseline to final visit, LOCF)	**ITT** **<u>6 weeks</u>** **Group1:** 186/201 **Group 2:** 184/207	
			Outcome 3: Endoscopic remission (EI<4 at the final visit, LOCF)	**ITT** **<u>6 weeks</u>** **Group1:** 153/201 **Group 2:** 164/207	
			Outcome 4: Adverse events Most frequently occurring were headache, nasopharyngitis and UC. Group 1: 48 events. 5 were considered to possibly be drug related. Group 2: 67 events. 7 were considered to possibly be drug related.	**ITT** **<u>6 weeks</u>** **Group1:** 38/201 **Group 2:** 43/207	
			Outcome 5: Serious adverse events	**ITT**	

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Outcome assessment: Disease Activity Index, Endoscopic Index. **Sample size calculation:** Estimated 380 patients. **Type of analysis: PPA and ITT** Last observation carried forward (LOCF) **Compliance rates:** 99.5% in the 1g group and 98.5% in the 1.5g group were considered compliant as they had taken ≥80% of the prescribed number of suppositories. N=3 dropout/ withdrawal due to AEs, 2 possibly drug related. They were all from the 500mg tds group and were due to, elevated liver values at baseline and 2 patients due to flatulence, pruritus, defecation urgency and constipation.	recurrent n=142 **Extent:** All proctitis **Mean DAI score (SD):** 6.2 (1.6) **Mean Endoscopic Index (SD):** 6.8 (2.0) **Drop outs:** unclear **Group 2: 500mg mesalazine (Salofalk) suppository three times a day** **Sex (m/f):** 93:110 **Mean age (SD):** 42.7 (13.9) **Course of the disease:** new diagnosis n=34, continuous n=8, recurrent n=161 **Extent:** All proctitis **Mean DAI score (SD):** 6.2 (1.5) (n=210) **Mean Endoscopic Index (SD):** 6.6 (2.0) **Drop outs:** unclear		Group 1: Due to a subclavian artery embolism. Group 2: Due to anxiety. **Outcome 6: Hospitalisations**	**6 weeks** **Group1:** 1/201 **Group 2:** 1/207 **ITT** **6 weeks** **Group1:** 1/201 **Group 2:** 1/207	

Table 7: ARDIZZONE1999

Author	Patients	Intervention	Outcome measures	Effect size	Comments
S. Ardizzone et al. Mesalazine foam (Salofalk foam) in the treatment of active distal ulcerative colitis. A comparative trial vs. Salofalk enema. *Italian Journal of*	**All patients:** **N=195 randomised** **N=185 Authors analysis** (10 patients did not have efficacy assessments post treatment) **Drop-outs** (don't complete the study):	**Group 1: 4g Mesalazine foam enema (Salofalk)** N=97 randomised 1g/30mls mesalazine foam enema. Two applications (2g) in the	**Outcome 1: Clinical remission** (CAI<4)	**ITT** **3 weeks** **Group1:** 55/97 **Group 2:** 74/98	**Funding:** Study mediations and support were given by Dr. Falk GmbH, Germany. Knoll Farmaceutici SpA (BASF Pharma) did the organization monitoring

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Gastroenterology **REF ID: ARDIZZONE1999** **Study design and quality:** Open Phase III RCT Multicentre: Italy **3 week trial (out of a 6 week trial).** Patients who showed remission at 3 weeks stopped treatment. Those with active disease continued receiving the alternative formulation for 3 weeks. Only the first 3 weeks of data is analysed in this review. **Randomisation:** No details given. Unclear **Allocation concealment**: No details given. Unclear. **Blinding:** None. **Outcome assessment:** CAI and EI. **Sample size calculation:** Not explicitly described, just that at least 190 patients should be enrolled. **Type of analysis: ITT** **Compliance rates:** Was assessed by quantifying the unused trial medication returned at the end of each treatment phase, diary card checking and asking the patient.	N=25 (12.8%) 16 in the foam group and 9 in the liquid enema group. It is unclear whether they dropped out in Phase 1 or 2. Missing data <10% difference between the two treatment arms **Inclusion criteria:** • 18-70 years old • Extent: endoscopically confirmed active proctitis, proctosigmoiditis or left sided UC • Severity: CAI≥4 and EI≥6 **Exclusion:** • Macroscopic lesions beyond the splenic flexure • Pregnant women or those intending to become pregnant • Use of glucocorticosteroids during the last month • Use of immunosuppressive drugs during the last three months • Use of rectal mesalazine during the last week • History of previous intolerance to mesalazine **<u>Baseline characteristics</u>** **<u>Group 1: 4g Mesalazine foam enema (Salofalk)</u>** **Age (m/f):** 60/37 **Mean age (SD):** 41.8 (12.2) **Extent:** proctitis n=23, proctosigmoiditis n=57, left sided UC n=17 **Concomitant oral treatment with aminosalicylates:** 29 **Drop outs:** 16 **<u>Group 2: 4g mesalazine liquid enema (Salofalk)</u>** **Age (m/f):** 56/42 **Mean age (SD):** 44.9 (13.4) **Extent:** proctitis n=26, proctosigmoiditis n=52, left sided UC n=20 **Concomitant oral treatment with aminosalicylates:** 40 **Drop outs:** 9 Drop outs were due to the following reasons but it was unclear which were from which group: Patients request or lack of cooperation n=13 Worsening of disease n=4	morning and two in the evening, if possible after evacuation. Total 4g/ day. **Group 2: 4g mesalazine liquid enema (Salofalk)** N=98 randomised 2g/60mls rectal suspension enema (Salofalk).One enema in the morning and one enema in the evening. Patients were advised to remain lying down on their left side for at least 15-30minutes after the enema administration. **Concomitant therapy:** Concomitant disease treatment was allowed if it didn't affect the assay methods used in the trial. Oral mesalazine or other aminosalicylates were permitted if the patient was on them when they relapsed and the dose was kept constant throughout the study.	**Outcome 2: Endoscopic remission** (EI<6) **Outcome 3: Clinical and endoscopic remission** (CAI<4, EI<6) **Adverse events:** It is unclear which phase of the trial patients got what adverse events. Overall, there were 6 reports with the foam and 2 with the liquid enema (one patient had an AE with both)	**ITT** **<u>3 weeks</u>** **Group1:** 51/97 **Group 2:** 67/98 **<u>3 weeks</u>** **Group1:** 48/97 **Group 2:** 64/98	and statistical analysis of the study. **Limitations:** Open study Unclear method of randomisation and allocation concealment More patients on oral SASP in one treatment group compared to the other **Additional outcomes:** Results of Phase 2 of the study.

Author	Patients	Intervention	Outcome measures	Effect size	Comments
3 patients discontinued due to poor compliance. N=2 dropout/ withdrawal due to drug related AEs (both foam group) related to the administration route. It is unclear whether this was in Phase 1 or 2 (anal burning and worsening of disease and burning and meteorism).	Lack of compliance n=3 Intercurrent disease n=2 Adverse event n=2 Pregnancy n=1				

Table 8: ARDIZZONE1999C

Author	Patients	Intervention	Outcome measures	Effect size	Comments
S. Ardizzone et al. Is maintenance therapy always necessary for patients with ulcerative colitis in remission? *Alimentary Pharmacology and Therapeutics; 13: 373-379. 1999.* **REF ID: ARDIZZONE1999C** **Study design and quality:** Double blind RCT Single centre **1 year trial** **Randomisation:** Patients were stratified into length of remission; 1-2 years and >2 years. Unclear randomisation. **Allocation concealment**:	**<u>All patients:</u>** **N=112 randomised** Due to a slower rate of inclusion, the sample sizes calculated could not be obtained. **Drop-outs** (don't complete the study): N=18 (16.1%) <10% missing data difference between treatment arms. **Inclusion criteria:** • Men and women aged 18-75 years • Confirmed diagnosis of intermittent chronic ulcerative colitis in stable clinical, endoscopic and histological remission for at least 1 year • Previously treated with 2g/day of SASP or 0.8-1.5g mesalazine formulation per day **Exclusion:** • Hepatic or renal dysfunction	**Group 1: 1.2g mesalazine** N=54 randomised 400mg mesalazine tablets (Asacol). One taken three times a day. **Group 2: Placebo** N=58 randomised Identical placebo tablets to the active tablets. One placebo tablet taken three times a day. **Concomitant therapy:** No further information given. See inclusion/ exclusion criteria.	**Outcome 1: Relapse** The hazard ratio has been calculated from the data given in the paper. The data was only available by years in remission, so the data is presented as if it were two different studies in the forest plots.	**<u>1-2years in remission</u>** **Group 1:**6/26 **Group 2:** 17/35 Log rank test (1.d.f)= 5.8885, P=0.0152 **<u>>2years in remission</u>** **Group 1:** 5/28 **Group 2:** 6/23 Log rank test (1.d.f) =0.7058,	**Funding:** Bracco S.p.A. supported this study. **Limitations:** Unclear method of randomisation and allocation concealment Double blind but no further information given **Additional outcomes:** None **Notes:** Withdrawal study Mean risk of relapse was statistically higher in

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Unclear. **Blinding:** Double blind. Identical active and placebo tablets. No further information given. **Outcome assessment:** Clinical and endoscopic activity was evaluated according to the criteria of Truelove & Witts. **Sample size calculation:** 86 per treatment arm, 80% power to detect a 30% difference in the proportions of patients having a relapse using a 0.05 statistical significance level. **Type of analysis: ITT** (all randomized patients with at least a value in the follow up) **Compliance rates:** Determined by tablet count and by review of the patient diaries at each study visit. Non compliance was defined as consuming <80% of the study drug. N=5 dropout/ withdrawal due to AEs. 3 in the mesalazine group (abdominal pain, bloating and diarrhoea) and 2 in the placebo group (abdominal pain and bloating).	• malignant disease • Salicylates allergy • Pregnancy or breast feeding or women of child-bearing age not taking adequate contraception • Patients with a single attack of colitis • Taken systemic and/or corticosteroid, topical mesalazine and immunosuppressive therapy during the year before entry **<u>Group 1: 1.2g mesalazine</u>** **<u>Remission 1-2years</u>** **Mean age (SD):** 36.1 (13.0) **Extent:** proctitis n=3, proctosigmoiditis n=8, left-sided colitis n=10, pancolitis n=5 **Mean duration of disease (SD):** 5.30 (4.41) **Mean duration of remission (SD):** 1.6 (1.8) **Mean risk of relapse per year (SD):** 0.05 (0.05) **Mean maintenance therapy in the last year (g):** SASP 2.3g n=14/26, mesalazine 1.3g n=12/26 **Severity of previous relapse:** Not described **Frequency of relapses:** Not described **<u>Remission >2 years</u>** **Mean age (SD):** 41.9 (13.3) **Extent:** proctitis n=4, proctosigmoiditis n=8, left-sided colitis n=10, pancolitis n=6 **Mean duration of disease (SD):** 9.00 (6.18) **Mean duration of remission (SD):** 4.8 (3.0) **Mean risk of relapse per year (SD):** 0.03 (0.02) **Mean maintenance therapy in the last year (g):** SASP 2.2g n=14/28, mesalazine 1.2g n=14/28 **Severity of previous relapse:** Not described **Frequency of relapses:** Not described **Drop outs:** 11 (5 due to poor compliance, 3 lost to follow up at 6 months, 3 due to AEs) **<u>Group 2: Placebo</u>** **<u>Remission 1-2years</u>** **Mean age (SD):** 35.9 (12.9) **Extent:** proctitis n=4, proctosigmoiditis n=12, left-sided colitis n=13, pancolitis n=6			P=0.4008 **Outcome 2: Adverse events** Only withdrawals due to adverse events were reported.	patients in 1-2years of remission compared to those >2years of remission. The >2 years of remission group were found to be older, with a longer duration of disease, a longer duration of remission and a lesser mean risk of relapse per year. **All patients taken SASP or mesalazine as maintenance prior to trial**

Author	Patients	Intervention	Outcome measures	Effect size	Comments
	Mean duration of disease (SD): 5.40 (4.55) **Mean duration of remission (SD):** 1.3 (1.5) **Mean risk of relapse per year (SD):** 0.05 (0.04) **Mean maintenance therapy in the last year (g):** SASP 2.2g n=18/35, mesalazine 1.2g n=17/35 **Severity of previous relapse:** Not described **Frequency of relapses:** Not described **Remission >2 years** **Mean age (SD):** 41.7 (13.1) **Extent:** proctitis n=5, proctosigmoiditis n=7, left-sided colitis n=6, pancolitis n=5 **Mean duration of disease (SD):** 9.02 (6.28) **Mean duration of remission (SD):** 5.1 (3.6) **Mean risk of relapse per year (SD):** 0.02 (0.01) **Mean maintenance therapy in the last year (g):** SASP 2.3g n=13/23, mesalazine 1.3g n=10/23 **Severity of previous relapse:** Not described **Frequency of relapses:** Not described **Drop outs:** 7 (2 due to poor compliance, 3 were lost to follow up, 2 due to AEs) **Definitions** **Remission:** Absence of active disease symptoms and no signs of active inflammation on sigmoidoscopy **Histological:** Grade 0 (absence of neutrophils) according to the criteria of Truelove & Richards. **Clinical and endoscopic relapse:** Increased stool frequency with blood or mucus and evidence of active disease on sigmoidoscopy.				

Table 9: AZADKHAN1980

Author	Patients	Intervention	Outcome measures	Effect size	Comments
A. K. Azad Khan et al. Optimum dose of sulphasalazine for maintenance treatment in ulcerative colitis.	**All patients:** **N=170 randomised** **Drop-outs** (don't complete the study):	**Group 1: 1g Sulphasalazine** N=57 randomised	**Outcome 1: Relapse** by 6 months Unable to calculate the hazard ratio.	**Group 1:** 19/57 **Group2:** 8/57 **Group 3:** 5/56	**Funding:** None described. **Limitations:**

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Gut; 21: 232-240.1980. **REF ID: AZADKHAN1980** **Study design and quality:** RCT **6 months trial** **Randomisation:** Allotted at random. No further information was given. **Allocation concealment**: Unclear. **Blinding:** Pathologist was blinded. It is unclear from the paper what estimations were done blindly, but assumed it was the blood tests. **Outcome assessment:** Seen 3 monthly. GP reported if any colitis symptoms were back. Sigmoidoscopy and biopsies were done on entry, 6 months or if a relapse was suspected. Blood tests were done on entry, 3 months, and 6 months and on relapse (some done by central laboratory of Pharmacia). **Sample size calculation:** None described. **Type of analysis: ITT** **Compliance rates:** Not described. N=0 dropout/ withdrawal due	N=0 (0%) **Inclusion criteria:** • Ulcerative colitis in remission **Exclusion:** • None described **Baseline characteristics** None were given. It is described in the paper that "the patients in the three treatment groups were closely similar in respect of age and sex distribution, body weight, and extent of colonic involvement as judged radiologically". All but 7 patients were on maintenance therapy with 2g SASP prior to commencing the study. **Definitions** **Remission:** Absence of colitic symptoms and the absence of signs of inflammation on sigmoidoscopy and on histological examination of rectal biopsy specimens as defined by Truelove & Richards. **Relapse:** Most relapses were associated with clinical symptoms of colitis but some patients remained free from symptoms but with inflammation on sigmoidoscopy and histology. Relapse was treated with oral prednisolone and topical corticosteroids in addition to the oral SASP. Intolerable side effects, drug was stopped for 1-2days then restarted on 1g lower dose. Additional blood samples were drawn before reducing the dose.	No further intervention details were given. **Group 2: 2g Sulphasalazine** N=57 randomised No further intervention details were given. **Group 3: 4g Sulphasalazine** N=56 randomised No further intervention details were given. **Concomitant therapy:** None described. Unclear.	Clinical + sigmoidoscopic + histological relapse, or sigmoidoscopic + histologic, or histologic relapse figures have been used. As this was the authors definition of relapse. Group 1 results have not been analysed as 1g SASP is below the recommended BNF dose for maintenance of remission. **Adverse events** This was only reported for the 4g SASP group. 21/56 Majority of the side effects occurred within 4 days of increasing the dose and they all manifest within one week (11 nausea, 5 malaise, 4 headache, 2 myalgia, 2 diarrhoea, 1 constipation, 2 anal soreness, 1 anal mucous discharge, 2 flatulence, 3 dysuria, 2 anorexia, 1 indigestion, 1 insomnia, 2 dizziness).		Very limited baseline characteristics Unclear method of randomisation and allocation concealment Unclear blinding. **Additional outcomes:** Acetylator status Serum concentrations of SASP and its metabolites Acetylator phenotype Biochemical and haematological effects **Notes:** **163/170 patients had already been taking 2g SASP prior to the trial.** 5 patients in the 4g SASP group decreased their dose to 2g after one week because they could not tolerate the high dose. Of them, 1 patient relapsed. Out of the 32 patients that relapsed; 28 had distal colitis, 2 extensive, 2 universal colitis. These were not statistically significant.

Author	Patients	Intervention	Outcome measures	Effect size	Comments
to drug related AEs.					

Table 10: BAUDET2010

Reference	Patient characteristics	Predictors & outcome measures	Effect sizes	Comments
A. Baudet et al. A fulminant colitis index greater or equal to 8 is not predictive of colectomy risk in infliximab-treated moderate – to-severe ulcerative colitis attacks. *Gastroenterologie Clinique et Biologique;* 34: 612-617. 2010. **Type of study: Retrospective cohort** **Setting:** Gastroenterology Departments of University Hospitals in the north western regions of France. **Follow up period: Unclear** 30 weeks for colectomy. **Model development:** Used FCI index as the predictor of colectomy. Explored different cut offs. **Model presentation:**	**Sample size:** N=43 **<5% missing data?** Not described **Type of analysis used:** Chi squared test, sensitivity, specificity, NPV, PPV, Yules Q coefficient, Youden's index. **Appropriate?** Yes **Inclusion criteria:** • All patients were treated with oral corticosteroids • Had received at least one infusion of infliximab to treat moderate-to-severe ulcerative colitis • Confirmed UC diagnosis using the Lennard-Jones criteria **Exclusion criteria** • Participation in a clinical trial involving infliximab **Data collection** Medical files of the 43 patients were retrieved. Disease activity was measured by the partial Mayo Clinic score (no endoscopy score).	**No Univariate analysis was carried out.** **Definitions of predictors: FCI (fulminant colitis index)** (number of stools/ day +0.14 x CRP (mg/L) was calculated from baseline to day 3 (as the third day after the initiation of corticosteroid treatment was used in the Lindgren et al. study. Median FCI of 2 (0-3 range). **Routinely measured?** Yes. **Outcome and definition:** Colectomy (from first infliximab infusion) **Maximum time 30 weeks.** **Blinding:** Not described. **Risk of measurement error: Low** **Risk of inter-observer variability: Low** **Continuous variable analysis:** yes- CRP and stool frequency, which were left as	**Results** Cut-off point: FCI≥8 (as this score had already been proposed as predictive of colectomy in patients suffering a severe UC attack treated with IV corticosteroids). Remission: N=10 (23.3%) Clinical response: N=21 (48.8%) Treatment failure: N=4 (9.3%) but did not need a colectomy Surgery: N=8 (18.6%) Median time from the first infliximab infusion to surgery was 6 weeks (range 4-30). See the table below for the results of the statistical tests. **Authors conclusion:** FCI is not a predictor of colectomy in patients treated with infliximab for moderate to severe ulcerative colitis.	**Source of funding**: None described. Three of the authors worked/ consulted for various Pharmaceutical companies (Astra Zeneca, Ferring, Beaufour Ipsen, Member of the advisory board, participation to the CME events for Schering Plough and Centocor Ortho Biotech, French centers study coordinator for Pfizer, French centers study coordinator for Millenium Pharmaceuticals). **Risk of bias:** • Retrospective cohort • Infliximab treated population • Unclear if any missing data • Partially inadequate event: covariate ratio

Reference	Patient characteristics	Predictors & outcome measures	Effect sizes	Comments
N/A **Model evaluation:** External validation. **Model performance:** Calibration- Not reported Discrimination – Did not report AUC value for the different cut offs. Sensitivity and specificity was reported.	**Treatment given** All patients had been treated with oral corticosteroids, 13 in association with immunosuppressants (azathioprine, 6-mercaptopurine, methotrexate), and four taking only immunosuppressants. Infliximab: 5mg/kg, infused over 3hrs and followed by 2hrs of surveillance. Patients received variable numbers of infusions depending on clinical response/ prescribing physician decisions. **Baseline characteristics:** Median number of infliximab infusions 5 (range 1-9). 37 (86%) received standard induction treatment at W0, W2, & W6 followed by maintenance therapy every 8 weeks. 3 received induction treatment only, and 3 on demand therapy.	continuous variables. **Key prognostic factors not included?** N/A as testing a recognised tool.		(3-6) **Additional outcomes reported:** None **Note: Infliximab population**

Table 11: Accuracy of the FCI

FCI threshold value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Chi^2 test
FCI≥8	100	20	22.22	100	>0.05
FCI≥10	75	37.14	21.43	86.67	>0.05
FCI≥12	75	57.14	28.57	90.91	>0.05
FCI≥14	62.5	68.57	31.25	88.89	>0.05
FCI≥16	50	85.71	44.44	88.24	≤0.05

Table 12: Bardazzi1994

Author	Patients	Intervention	Outcome measures	Effect size	Comments

Author	Patients	Intervention	Outcome measures	Effect size	Comments
G. Bardazzi et al. Intermittent versus continuous 5-aminosalicylic acid treatment for maintaining remission in ulcerative colitis. *Italian Journal of Gastroenterology; 26: 334-337. 1994.* **REF ID: BARDAZZI1994** **Study design and quality:** Open RCT Single centre, Italy **12 month trial** **Randomisation:** Not described. **Allocation concealment**: Not described. **Blinding:** Blind endoscopists and histological assessment. Physicians assessing clinical end points knew the patient groups. **Outcome assessment:** Diary (stool frequency, abdo pain, rectal bleeding). Seen every 2 months or earlier of symptoms occur. Endoscopy and histology every 6 months if asymptomatic. Disease activity assessed against Truelove's criteria. Endoscopy by Baron et al. Histology by Truelove & Richards criteria. **Sample size calculation:** Not	**All patients:** **N=50 randomised** **N=50 ITT** **Drop-outs** (don't complete the study): N=3 (6%) **Inclusion criteria:** • Presence of a recent (within 3 months) relapse treated successfully • Remission documented by clinical, histological and endoscopic criteria and maintained for a minimum period of 1 month • Extent: absence of ulcerative proctitis in the preceding relapse (s) documented by endoscopy (with disease extension for >15cm from anal verge) **Exclusion:** • None described. **Group 1: Continuous oral 5-ASA 1.6g** **Mean age (SD):** 45.73 (16.93) **Extent:** proctosigmoiditis n=7, left-sided colitis n=11, pancolitis n=7 **Mean duration of disease (SD), months:** 59.6 (57.1) **Severity of previous relapse:** Not described. **Frequency of relapses:** Not described. **Current use of immunomodulators:** Not described **Drop outs:** 2 (2 due to non compliance) **Group 2: Intermittent oral 5-ASA 2.4g** **Mean age (SD):** 44.32 (13.5) **Extent:** proctosigmoiditis n=7, left-sided colitis n=13, pancolitis n=5 **Mean duration of disease (SD), months:** 66.9 (43.1) **Severity of previous relapse:** Not described. **Frequency of relapses:** Not described. **Current use of immunomodulators:** Not described **Drop outs:** 1 (1 due to non compliance) **Definitions** **Remission:** Mild symptoms and normal mucosa (endoscopically)	5-ASA (slow release tablets coated with Eudragit S, dissolves above a pH of 7. **Group 1: Continuous oral 5-ASA 1.6g** N=25 randomised N=23 (ACA) 1.6g of oral 5-ASA (type not specified) given once a day. **Group 2: Intermittent oral 5-ASA 2.4g** N=25 randomised N=24 (ACA) 2.4g of 5-ASA (type not specified) given for the first 7 days of each month. **Concomitant therapy:** No topical therapy was permitted.	**Outcome 1: Relapse rate** by 12 months Group 1: 6 mild relapses, 2 severe relapses Group 2: 5 mild relapses, 1 moderate and 1 severe In both groups symptoms were present in all patients classified as endoscopic and histologic relapse. All relapses responded to subsequent medical treatment. **Adverse events** None of the patients developed side effects.	**Authors analysis** **Group1:** 8/23 (34.7%) **Group 2:** 7/24 (29.2%) **Log rank test (relapse free actuarial curve):** p=0.56 **Hazard ratio (95% CI):** 1.35 (0.49, 3.73)	**Funding:** None described. **Limitations:** Unclear method of randomisation and allocation concealment Open trial **Additional outcomes:** None.

Author	Patients	Intervention	Outcome measures	Effect size	Comments
described. **Type of analysis: ACA** **Compliance rates:** 3 non compliant (2 in the continuous group and 1 in the intermittent) N=0 dropout/ withdrawal due to drug related AEs.	**Relapse:** Erythematous and friable mucosa even in the absence of symptoms				

Table 13: BARMEIR2003

Author	Patients	Intervention	Outcome measures	Effect size	Comments
S. Bar-Meir et al. Budesonide Foam vs. Hydrocortisone Acetate Foam in the Treatment of Active Ulcerative Proctosigmoiditis. *The American Society of Colon & Rectal Surgeon; 46 (7): 929-936. 2003.* **REF ID: BARMEIR2003** **Study design and quality:** Open RCT Multicentre: 38 centres, Israel, Germany & Italy **8 week trial** **Randomisation:** no information given **Allocation concealment**: no information given	**<u>All patients:</u>** **N=251 randomised** N=248 ITT (3 were excluded as they did not receive any treatment) N=179 PPA **Drop-outs** (don't complete the study): Unclear. There are 69 major protocol violations but it is unclear which ones withdrew from the study before the end. Also no figures are given for those who withdrew for AEs. 5 people had SAEs but it does not state that they withdrew. Minimum drop out value estimated to be N=20. **Inclusion criteria:** • Adults, 18-70 years • Extent: proctitis or proctosigmoiditis • Severity: DAI≥4 **Exclusion:** • Colitis is <2 weeks duration • Infectious agent could be isolated • Lesions proximal to the sigmoid colon	**Group 1: 2mg Budesonide foam enema (Budenofalk)** N=122 randomised N=120 (ITT) N=88 PPA 2mg budesonide foam enema (Budenofalk) in 20mls. Given once daily at bedtime. **Group 2: 100mg hydrocortisone foam enema (Colifoam)** N=129 randomised N=128 (ITT) N=91PPA 100mg hydrocortisone	**Outcome 1: Clinical remission** (DAI≤3 at the end of the treatment period, LOCF) N values were calculated from percentages given in the paper. **Outcome 2: Adverse events** Virtually all were thought not to be drug related. **Outcome 3: Serious adverse events** None were related to the study medication.	**<u>At 8 weeks</u>** **Group1:** 64/120 **Group 2:** 67/128 **Group1:** 36/120 **Group 2:** 50/128 **Group1:** 1/120 **Group 2:** 4/128	**Funding:** Supported by Dr. Falk Pharma, Germany **Limitations:** Open Unclear method of randomisation and allocation concealment Unclear drop out rate Risk of indirect population: may include patients with severe disease **Additional outcomes:** Patient's global impression (subjective improvement) Mean DAI

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Blinding: Blinded pathologist otherwise open **Outcome assessment:** Disease activity index **Sample size calculation:** Type 1 error of 5%. 80% power, sample size of 240. **Type of analysis: ITT and PPA** **Compliance rates:** 35 patients were classed as non compliant N=0 dropout/ withdrawal due to drug related AEs.	• Received corticosteroids within one month or immunomodulators within 3 months before enrolment **Baseline characteristics** **Group 1: 2mg Budesonide foam enema** **Sex (m/f):** 62/38 **Mean age (SD):** 42 (13.5) **Extent:** proctitis n=38, proctosigmoiditis n=82 **Mean activity index (SD):** 7.2 (1.9) **Mean number of stools per week (range):** 31 (4-105) **Premedication for current episode:** oral mesalamine n=58, rectal mesalamine n=45, SASP n=5, systemic steroids n=3, topical steroids n=9 **Drop outs:** unclear **Group 2: 100mg hydrocortisone foam enema** **Sex (m/f):** 52/48 **Mean age (SD):** 42 (13.0) **Extent:** proctitis n=43, proctosigmoiditis n=85 **Mean activity index (SD):** 7.0 (2.0) **Mean number of stools per week (range):** 30 (4-136) **Premedication for current episode:** oral mesalamine n=78, rectal mesalamine n=38, SASP n=3, systemic steroids n=3, topical steroids n=11, immunosuppressants n=1 **Drop outs:** unclear Major protocol violations: 2mg Budesonide foam enema followed by 100mg hydrocortisone enema figures: non compliant n=13, 22, prior or concomitant treatment with prohibited medication n=13, 9, withdrawn for reasons other than lack of efficacy/ treatment related AE n=7, 8, late for final visit n=5, 15, no post baseline DAI score n=5, 4, did not remain in study until visit 2, n=3, 2, diagnosis not confirmed by histology n=3, 1, proctitis/ proctosigmoiditis not confirmed n=2, 2, lesion present proximal to the sigmoid colon n=1, 1, infectious bowel disease n=0, 1.	acetate foam enema (Colifoam) in 15mls. Given once daily at bedtime. **Concomitant therapy:** Patients could continue oral mesalamine if it was not >2mg/day and was kept at a stable level during the entire study.			Endoscopic improvement Histologic improvement Bone metabolism measures

Table 14: BARON1962

Author	Patients	Intervention	Outcome measures	Effect size	Comments

Author	Patients	Intervention	Outcome measures	Effect size	Comments
J. H. Baron et al Out-Patient Treatment of Ulcerative Colitis: Comparison Between Three Doses Of Oral Prednisone. *British Medical Journal; 2 (5302):441-443. 1962* **REF ID:BARON1962** United Kingdom Duration of **follow-up** 1,2,3,5 weeks **Study design and quality:** Open RCT Specialised out-patient clinic **Randomisation**: Folded slip with prednisone dose written on it was picked out from a box **Allocation concealment** :No information on allocation concealment **Sample size calculation**: No sample size calculation described **Type of analysis:** ITT **Compliance rates:** N=2 dropout/ withdrawal due to AEs	**All patients** N=58 randomised (but 60 courses of treatment as two relapses at one week re-entered the trial in the 20mg group but not clear were they re-entered) First attacks and relapses **Inclusion criteria:** • Already been treated for the present attack of colitis with drugs other than corticosteroids or with a prednisone dose of <20mg/day and it had been ineffective • Group 1=n=7 • Group 2= n=5 • Group 3= n=3 • Extent: > rectum involvement • Severity: Mild to moderate **Exclusion criteria :** • Corticosteroids treatment contraindicated • UC confined to the rectum only • UC improving spontaneously **Drop-outs** N=11 (6 by 2 weeks) **Group 1**: 6 patients in the 20mg group (2 due to side effects and 4 because of symptom deterioration) **Group 2**:3 patients in the 40mg group due to symptom deterioration **Group 3**:2 patients in the 60mg group due to side effects.	**Group 1** N=20 randomised 20mg prednisone/ day Dose spilt into 3-4 equal doses/day. Each tablet was 5mg of prednisone. 20mg was given for a max. of 5 weeks. **Group 2** N=20randomised 40mg prednisone/ day Dose spilt into 3-4 equal doses/day. Each tablet was 5mg of prednisone. 40mg was given for a max. of 5 weeks. **Group 3** N=20 60mg prednisone/ day Dose spilt into 3-4 equal doses/day. Each tablet was 5mg of prednisone. 60mg was given for a max. of 3 weeks	**Clinical and endoscopic remission** (no symptoms; inactive or normal mucosa) Patient reported bleeding or mucus in the stool, sense of wellbeing, sigmiodoscopy- grade according to Lennard-Jones et al (1960)- active, moderately active, inactive or normal Overall assessment – remission (no symptoms and inactive or normal)	**2 weeks** Group 1=4/20 Group 2=10/20 Group 3=10/20 **End of treatment (5 weeks)** Group 1=6/20 Group 2=13/20 **3 weeks (high dose given for shorter period of time)** Group 3=13/20	
			Clinical improvement **2 weeks**	Group 1=9/20 Group 2=18/20 Group 3=18/20	
			Hospital admissions by 5 weeks	Group 1=0 Group 2=2 Group 3=1	
			Adverse events	Group 1=4/20 Moonface, glycosiria,, dyspepsia (2) Group 2=4/20 Moon face, acne, dyspepsia (2) Group 3=6/20 Mooning (n=3), acne (2),weight gain, oedema , hypertension, dyspepsia	

Table 15: BELL1997

Author	Patients	Intervention	Outcome measures	Effect size	Comments
C. M. Bell et al. Safety of Topical 5-Aminosalicylic Acid in Pregnancy. *The American Journal of Gastroenterology; 92 (12): 2201-2202. 1997.* **REF ID: BELL1997** **Study design and quality:** Prospective case series study **Canada** **Years studied: 1989-1996**	**<u>All patients:</u>** Included population: • 16 patients prospectively identified from a group of gastroenterology outpatients • Known distal ulcerative colitis by history, endoscopy and biopsy • Negative stool cultures • Dependent on topical therapy to prevent relapse (failed 3 attempts to wean off it over 3-6 months prior to conception) • In remission on maintenance 5-ASA at time of conception Excluded population: None described **N=19 pregnancies (16 women)** <u>Data collection</u> Assessed along with an obstetrician every 8 weeks through their pregnancy monitoring for fetal growth. Some patients were evaluated by ultrasound every 3 months. Within 24 hours of delivery the baby was assessed by a paediatrician. Children were followed up at regular intervals from 6 months to 6 years. <u>Baseline characteristics</u> Mean age, range: 25.8 years (21-33years) Time of conception, mean duration of illness, range: 4.6 years (1-12 years) Extent: proctosigmoiditis n=7, disease involving the rectum n=9 Previous pregnancies: yes n=5, no n=11 Relapse definition: symptoms accompanied by negative stool cultures and a positive sigmoidoscopic examination.	**Patients continued on either:** **4g5-ASA enemas three times a week** **or** **500mg 5-ASA nightly suppository**	**In remission at conception and throughout pregnancy (14/16)** Two women stopped treatment but consequently relapsed and restarted the medication 12 weeks later. All other patients continued therapy until delivery.		**Funding:** None described **Limitations:** High risk of bias due to study design **Additional outcomes:** None
			Outcome 1: Normal birth	19/19	
			Outcome 2: Congenital abnormality	0/19	
			Outcome 3: Spontaneous abortion	0/19	
			Outcome 4: Premature birth	0/19	
			Outcome 5: Still birth	0/19	
			No children had any clinical or biochemical abnormalities noted in the perinatal period. Post partum follow up (2months – 5 years, median 2years): No abnormal growth or development found.		

Table 16: BIANCONE2007

Author	Patients	Intervention	Outcome measures	Effect size	Comments
L. Biancone et al. Beclomethasone dipropionate versus mesalazine in distal ulcerative colitis: A multicenter, randomized, double-blind study. *Digestive and Liver Disease; 39: 329-337. 2007.* **REF ID: BIANCONE2007** **Study design and quality:** Double blind only for the type of drug, not the preparation, RCT Multicentre: 15 centres, Italy **8 week trial** **Randomisation:** Block randomisation within each centre. Unclear. **Allocation concealment**: Unclear. **Blinding:** None for the preparation comparison **Outcome assessment:** Disease activity index. **Sample size calculation:** 0.05 two tailed test, 80% power, sample size of 240 (but low rate of recruitment). **Type of analysis: PPA**	**<u>All patients:</u>** **N=99 randomised** **N=92 authors analysis** Four treatment arms, 3mg beclomethasone foam & enema and 2mg mesalazine foam & enema. **Drop-outs** (don't complete the study): N=9 (10%) Due to protocol violation or drug discontinuation before week 4. **Inclusion criteria:** • Adults (>18 years) • Newly diagnosed or relapse • Extent: Distal (proctitis and proctosigmoiditis) • Severity: DAI score of 3-9, EI score of 1-2 • ≥3 months from last remission • Written informed consent **Exclusion:** • Steroid refractory disease • Clinical relapse while on topical steroids or 5-ASA • Pregnant/ lactating women • Concomitant diseases requiring oral steroids • Low compliance • Patients enrolled in other trials **<u>Baseline characteristics</u>** **<u>Group 1: 2g 5-ASA (Asacol) foam enema</u>** **Sex (m/f):** 10/10 **Mean age (SD):** No information given **Episode:** first attack of UC n=2, relapse n=18 **Extent:** Not described. All proctitis/ proctosigmoiditis **Drop outs:** 7 (3 due to AEs, 4 protocol violation)	**Group 1: 2g 5-ASA (Asacol) foam enema** N=24 randomised N=20 (PPA) 2g 5-ASA (Asacol) foam enema, given once a day at night. **Group 2: 2g 5-ASA (Asacol) liquid enema** N=24 randomised N=22 (PPA) 2g 5-ASA (Asacol) liquid enema given once a day at night. **Concomitant therapy:** The following were not permitted: corticosteroids (topical, oral, parenteral), SASP, 5-ASA topical, immunosuppressives. Oral SASP or 5-ASAS were allowed only in patients showing relapse while on maintenance treatment using these drugs.	**Outcome 1: Clinical improvement** (response rate at 4 and 8 weeks, decrease in DAI score of ≥1 point) **Note: Presented as authors analysis in the paper. Converted to ITT.**	**ITT** **<u>4 weeks</u>** **Group1:** 16/24 **Group 2:** 17/24 **<u>8 weeks</u>** **Group1:** 16/24 **Group 2:** 22/24	**Funding:** Unrestricted grant of the Valeas (Milan, Italy) who provided the treatment. Statistical analysis was performed by Sofar (Milan, Italy) **Limitations:** Un-blinded preparation Unclear method of randomisation and allocation concealment **Additional outcomes:** Outcomes for the other treatment arms
			The paper describes that 10/40 patients showed side effects. 3 in the foam group withdrew from the study due to AEs. No further information given.		

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Compliance rates: Assessed by diary card and enema retention time (<60 or >60mins) N=3 dropout/ withdrawal due to AEs (due to abdominal pain or bowel tenderness in the foam group). They are described not to be drug related.	**Group 2: 2g 5-ASA (Asacol) liquid enema** **Sex (m/f):** 14/8 **Mean age (SD):** No information given **Episode:** first attack of UC n=3, relapse n=19 **Extent:** Not described. All proctitis/ proctosigmoiditis **Drop outs:** 2 (2 protocol violations)				

Table 17: BINDER1987

Author	Patients	Intervention	Outcome measures	Effect size	Comments
V. Binder et al. **Danish 5-ASA group** Topical 5-aminosalicylic acid versus prednisolone in ulcerative proctosigmoiditis. A randomized, double-blind multicenter trial. *Digestive Diseases and Sciences; 32 (6): 598-602. 1987.* **REF ID: BINDER1987** **Study design and quality:** Double blind RCT Denmark **2 &4 week trial** **Randomisation:** Done by study centre. Patients randomly	**All patients:** **N=123 randomised** Patients who achieved total remission, deteriorated or had a serious AE withdrew after 2 weeks. **Drop-outs** (don't complete the study): N=9 (7.3%) (8 in the mesalazine group and 1 in the prednisolone group) 4 were protocol violations, 2 insufficient compliance, and 3 AEs but it is unclear which group they were in. **>10% difference in drop outs between treatment arms** **Inclusion criteria:** • Extent: Outpatients with proven UC localized to the sigmoid colon and/or rectum (no less than 5cm from the anus) • Severity: slight to moderate active disease and normal renal and hepatic functions **Exclusion:** • None were described at recruitment phase. However, patients who	**Group 1: 1g mesalazine (Pentasa) liquid enema** N=61 randomised N=56 at 2 weeks N=34 at 4 weeks 1g mesalazine in 100mls, liquid enema (Pentasa), once daily at night. **Group 2: 25mg prednisolone liquid enema** N=62 randomised N=61 at 2 weeks N=41 at 4 weeks	**Outcome 1: Clinical remission** (change in disease activity according to Binder, Grade 0) **Outcome 2: Clinical improvement** (change in disease activity according to Binder, Grade 1) The n values from clinical remission have been added to the clinical improvement to give all those that improved. **Outcome 3: Endoscopic remission** (change in disease activity according to Binder, Grade 0)	**2 weeks** **Group1:** 27/56 **Group 2:** 19/61 **2 weeks** **Group1:** 32/56 **Group 2:** 33/61 **2 weeks** **Group1:** 17/56 **Group 2:**	**Funding:** None provided. **Limitations:** Unclear method of randomisation and allocation concealment Stated to be double blind but no further information was given **>10% difference in missing data between treatment arms** **Additional outcomes:** Overall outcome

Author	Patients	Intervention	Outcome measures	Effect size	Comments
allocated to one of two treatment arms. No other information given. **Allocation concealment**: Unclear. **Blinding:** Double blind **Outcome assessment:** Clinical and endoscopic scores ranged from 0 to 3 according to Binder. **Sample size calculation:** 60 per group to obtain 95% CI for the difference in remission of 16% (i.e. therapeutic gain) **Type of analysis: PPA** **Compliance rates:** N=3 dropout/ withdrawal due to suspected drug related AEs (5-ASA arm).	showed lack of compliance or not following the protocol were excluded. **<u>Baseline characteristics</u>** **<u>Group 1: 1g mesalazine (Pentasa) liquid enema</u>** **Sex (m/f):** 21/32 **Mean age (range):** 36 (16-71) **Concurrent SASP therapy:** n=30 **Endoscopic grade; slight/moderate/severe:** 9/13/31 **Clinical activity; slight/moderate:** 29/24 **Extent:** Not described. **Drop outs:** 8 **<u>Group 2: 25mg prednisolone liquid enema</u>** **Sex (m/f):** 24/37 **Mean age (range):** 40 (14-70) **Concurrent SASP therapy:** n=37 **Endoscopic grade; slight/moderate/severe:** 14/18/29 **Clinical activity; slight/moderate:** 25/36 **Extent:** Not described. **Drop outs:** 1	25mg prednisolone in 100mls liquid enema, once daily at night. **Concomitant therapy:** If patient was already on sulphasalazine this treatment was maintained unchanged during the trial.		15/61	Data at 4 weeks was also reported but it was unclear who dropped out/ were in remission or double counted
			Outcome 4: Clinical and endoscopic remission	**<u>2 weeks</u>** **Group1:** 15/56 **Group 2:** 12/61	
			Outcome 5: Adverse events Reported AEs were: Nausea, abdominal distension, colic, fatigue, depression, difficulties in retaining enema, joint stiffness and minor complaints.	**Group1:** 13/61 **Group 2:** 6/62	

Table 18: BOOT1998

Reference	Patient characteristics	Predictors and outcome measures	Effect sizes	Comments
A. M. Boot et al. Bone mineral density and nutritional status in children with chronic inflammatory bowel disease. *Gut; 42: 188-194.1998.* **Type of study:** Cross-sectional and longitudinal data	**Sample size:** N=55 (34 boys and 21 girls) N=33 who had UC 36 patients were studied prospectively. **<5% missing data?** Not described. **Type of analysis used:** T-tests, Pearson correlation coefficient, Spearman's rank correlation coefficient, multiple regression analysis.	**Definitions of variables measured:** **Total lifetime cumulative dose of prednisolone** (mg) – calculated at the first measurement and also the cumulative dose between the yearly measurements. **Pubertal development**- determined according to Tanner. For patients in puberty, delay in puberty was calculated by comparison of Tanner stage and age of the patients with reference data of Dutch children. **Weight:** Assessed by a standard clinical balance. BMI was calculated as weight/ height^2 (kg/m^2)	**Results** • None of the patients experience a fracture during the study period **Multiple regression analysis** • Including diagnosis (Crohn's / UC), cumulative dose of prednisolone and BMI SAS as determinants and BMD SDS as the dependent variable, cumulative dose of prednisolone and diagnosis related significantly to lumbar spine BMD SDS and explained 20% of the variance	**Source of funding**: None described. **Risk of bias:** • Cross-sectional data, unclear whether the population is representative (unclear enrolment to the trial) • Unclear how the lifetime

Reference	Patient characteristics	Predictors and outcome measures	Effect sizes	Comments
Setting: Unclear. Netherlands. **Follow up period: 1-2 years** (36 patients were followed for 1 year, 21 patients for 2 years)	**Appropriate?** Yes **Inclusion criteria (for UC patients):** • Diagnosis made according to the Dutch children's IBD consensus guidelines **Exclusion criteria:** None described. **Data collection:** Prospective data collection. **Treatment given:** Not described. **Baseline characteristics:** Mean age: 13 years (range 4-18 years) Duration of the symptoms: 1 month – 12 years (median 2.2years) 20 patients had not been treated with corticosteroids before the first measurement, 3 of these received them before the second measurement. All patients had been treated on sulphasalazine or mesalazine. 2 patients with UC also had sclerosing pericholangitis and one also had UC with chronic active hepatitis. Mean levels of the variables explored were given overall for Crohn's and UC patients combined. The correlation coefficients were reported for some of the variables for UC patients only (see the table below).	compared to age and sex matched reference values, and expressed as SDS. **Diet:** Calcium and calorie intake was assessed in 36 patients by a dietician using a 3 day food intake diary. This was compared to the Dutch recommended daily intake for age and sex. **Bone age:** Assessed in 52 children by one investigator using an x-ray of the left hand according to the Tanner-Whitehouse radius-ulnar-short bone (RUS method). 2 x-rays were taken in 30 patients, 3 x-rays in 14 patients with a time interval of about 1yr. **1-25-dihydroxyvitamin D, 25-hydroxyvitamin D:** Assessed in 42 and 23 patients respectively. **Routinely measured?** Total vitamin D and DEXA scanning is not routinely measured. Weight is routinely measured. **Outcome and definition:** Bone mineral density: measured using a DEXA scan. This was carried out at intervals of about 1yr. The coefficient of variation has been reported as 1.04% for lumbar spine and 0. 64% for total body. In the study setting it was 1.1% (SD0.2). BMD was matched to age and sex Dutch reference valued (n=500) and expressed as SDS. BMD SDS <-1.5 were given calcium 500mg/day and vitamin D 400 units/day supplements **Blinding:** Not described. **Risk of measurement error:** Unclear if carried out by the same person or not. **Risk of inter-observer variability:** Unclear. **Key prognostic factors not included?** Out of the potential confounders listed by the GDG the following where not described in the paper: • Ethnicity	• Only diagnosis related significantly to total body BMD SDS in the regression mode (r^2=15%)	cumulative corticosteroid dose was calculated • Limited information reported for the multiple regression analysis • Unclear missing data **Additional outcomes reported:** Height Fat/ lean mass Physical activity Other blood tests (calcium, ALP etc.)

Reference	Patient characteristics	Predictors and outcome measures	Effect sizes	Comments
		• Chronic disease associated with osteoporosis • Family history		

Table 19: Correlation coefficients

Variable	Lumbar spine BMD SDS for ulcerative colitis	P value
Height SDS	0.59	p<0.001
BMI SDS	0.05	
Cumulative dose of prednisolone (mg)	-0.35	p<0.05
Lean tissue mass SDS	0.58	p<0.0001
Fat mass SDS	0.04	

Table 20: BORTOLI2011

Author	Patients	Intervention	Outcome measures	Effect size	Comments
A. Bortoli et al. Pregnancy outcome in inflammatory bowel disease: prospective European case-control ECCO-EpiCom study, 2003-200.*Alimentary Pharmacology and Therapeutics; 34: 724-734. 2011.* **REF ID:BORTOLI2011** **Study design and quality:** Prospective cohort study **12 European countries: 68 centres** **Years studied: January 2003-December 2006**	1:1:1 study on pregnant IBD women: pregnant non IBD women: non pregnant IBD women **<u>All patients:</u>** Included population • All consecutive pregnancies which occurred in women with IBD and followed by the participating centres from January 2003-December 2006 • At the time of enrolment (conception/ 1st trimester until 12th gestational week) all IBD pregnant women were intended to be matched (1:1) with non IBD pregnant controls by age at conception (=/-5 years) and number of previous pregnancies at the Obstetric and Gynaecology Department at each participating centre Excluded population: none described **N=520** enrolled (244 Crohn's, 264 UC, 12 indeterminate colitis) **N=373** matched to non IBD pregnant controls (eligible for the study)	**<u>Ulcerative colitis patients (N=187) – treatment at conception/ 1st trimester</u>** **No therapy** N=22 **Any therapy** N=165 **5-ASA monotherapy** N=88 Median dose 2400mg per day (range 800-4800) 37 women had ≥3000mg at conception, most maintaining the same dose throughout	**See the table below for the birth outcomes.** Unable to separate the results by disease activity but in the multivariate logistic regression, active disease was found to be associated with a lower birth weight (p=0.04).		**Funding:** Authors received funding from ECCO and a research fund in the department of Pia Munkholm. **Limitations:** Low risk of bias

<table>
<tr><th>Author</th><th>Patients</th><th>Intervention</th><th>Outcome measures</th><th>Effect size</th><th>Comments</th></tr>
<tr><td rowspan="2">Risk of bias:

Confounder adjustment

Comparable at baseline - matched case controls

Analysis: Matched logistic regression

OR adjusted for age of conception, smoking and alcohol use.

Disease specific parameters only measured for the cases – standard logistic regression for the cases only

Sample size: Not described. 5% significance used.</td><td colspan="3">Further 32 excluded (missing data on pregnancy outcome in their controls)

N=332 (145 Crohn’s and 187 UC) were included

250 of these were from Italian centres, the rest other European centres (no significant difference in pregnancy outcome geographically)

<u>Data collection</u>

Electronic case report forms were used to record the requested data. Prospectively collected by trained physicians at entry, then 3 monthly until the end of pregnancy by regular personal or telephone interviews and review of the patient’s medical records.
Completed forms were sent electronically to the central data base to be stored/ analysed etc.
Disease activity was measured by the Simple Clinical Colitis Activity Index (SCCAI) for UC patients.

<u>Baseline characteristics</u></td><td>pregnancy

Immunomodulator therapy (azathioprine, ciclosporin, corticosteroids, infliximab) N=14

Combination therapy (two or more preparations N=63

<u>Non IBD controls to UC</u>

N=187</td><td></td><td></td><td></td></tr>
<tr><td colspan="3"><table>
<tr><th>Characteristic</th><th>UC patients
N=187</th><th>Controls to UC
N=187</th></tr>
<tr><td>Age, median (range)</td><td>31 (19-42)</td><td>32 (19-42)</td></tr>
<tr><td>Previous pregnancies
0-1
>1</td><td>
150
37</td><td>
116
71</td></tr>
<tr><td>Smoking (%)</td><td>15 (8%)</td><td>26 (13.9%)</td></tr>
<tr><td>Alcohol (%)</td><td>8 (4.3%)</td><td>13 (7%)</td></tr>
<tr><td>Disease duration, months (range)</td><td>66 (1-270)</td><td>N/A</td></tr>
<tr><td>Extent of disease
Pancolitis
Left sided colitis
Proctosigmoiditis</td><td>
64 (34%)
55 (30%)
67 (36%)</td><td>
N/A
N/A
N/A</td></tr>
<tr><td>Previous intestinal surgery (%)</td><td>6 (3.2%)</td><td>N/A</td></tr>
</table></td><td></td><td></td><td></td></tr>
</table>

Author	Patients			Intervention	Outcome measures	Effect size	Comments
	Remission at conception/ 1st trimester	148 (79%)	N/A				
	Onset during pregnancy (%)	2 (1.1%)	N/A				
	Any therapy at conception/ 1st trimester Mesalazine Corticosteroids Azathioprine/ MPT Infliximab Ciclosporin	165 (88.2%) 156 (83.4%) 74 (39.6%) 19 (10.2%) 0 1(0.5%)	N/A				

Table 21: Birth outcomes by therapy at any time during pregnancy (multivariate logistic regression)

Therapy	Live birth	Spontaneous abortion	Preterm delivery (<37 weeks)	Congenital abnormalities
Any therapy	p=0.60	p=0.56	p=0.60	0
5-ASA monotherapy	p=0.75 High dose: 35/37 (95%), 4 were preterm, 31 term	p=1.00 High dose: 1/37	(1% vs. 10%) p=0.01 High dose: 4/37	0 High dose: 0/37
IS therapy	p=1.00	p=1.00	p=1.00	0
Combination therapy	p=1.00	p=1.00	13% vs. 1% p=0.004	0
Non IBD controls	167/187	15/187	14/187	3/187

(a) Multivariate logistic regression (age at conception, smoking status, alcohol use, previous surgery, disease activity, drug therapy)
(b) High dose 5-ASA: ≥3g
(c) IS (immunomodulators therapy- azathioprine, ciclosporin, corticosteroids, infliximab)
(d) No CA were observed in newborns of mothers taking ≥3000mg 5-ASA
(e) One UC patient with extensive active disease since conception had a subtotal colectomy at gestational week 12 (steroid refractory UC. Patient had a healthy baby girl at term by caesarean section (2850g).
(f) It was reported in the study that patients on 5-ASA were less likely to have a premature birth, those on combination therapy were more likely to have a premature birth.
(g) There were no congenital abnormalities reported in the ulcerative colitis patients. In the Non-IBD control group there were 3 babies (3 congenital hip dysplasias, 1 intestinal agenesia)
(h) Note: one birth is not accounted for in the Non IBD group. The figures in the paper were not found to add up.

Table 22: BOSSA2007

Author	Patients	Intervention	Outcome measures	Effect size	Comments
F. Bossa et al Continuous infusion versus bolus administration of steroids in severe attacks of ulcerative colitis: A randomised, double-blind trials. *American Journal of Gastroenterology;102: 601-608. 2007.* **REF ID: BOSSA2007** **Study design and quality:** Double blind RCT Single centre, Italy **7 days (primary end-point)** **One month (secondary end-point)** **Randomisation:** Random number table **Allocation concealment**: Not stated **Blinding:** Double-blind **Outcome assessment:** blinding not stated. Endoscopy assessment using the Mayo scoring system. **Sample size calculation:** α 90% β 0.05 **Type of Analysis: ITT**	**<u>All patients:</u>** **N=66 randomised** **N=66 ITT** **Drop-outs** (don't complete the study): N=0 (%) **Inclusion criteria:** Patients with severe ulcerative colitis. Patients already on oral steroids were eligible if they had been on therapy for more than 14 days without clinical benefit. Oral corticosteroids were discontinued at inclusion, and patients were converted to iv steroids Extent: 40 patients (60.6%) had disease extending beyond the splenic flexure, while in 26 patients (39.4%); the colitis was limited to the left colon. Severity: Severe defined according to Truelove and Witts criteria modified by Lennard-Jones, a severe attack was defined as the passage of six or more bloody stools daily with the occurrence of one or more of the following secondary criteria: temperature > 37.8 C, pulse rate > 90/min, haemoglobin < 10.5 g/dL, ESR > 30 mm/h, and serum albumin < 3..2 g/dL. **Exclusion:** A plain abdominal x-ray, to exclude colonic dilation or perforation. Patients with ova/parasites and C difficile were excluded. Renal insufficiency with serum creatinine level > 2 mg/dL and cardiac insufficiency with left ventricular ejection fraction under 30% were other exclusion criteria **<u>Group 1: Infusion</u>** **Mean age (SD):** 39.2 (14.7) **Extent:** Pancolitis 22/34 (64%) Left-sided colitis 12/34 (36%) **Truelove-Witts score mean** 8 (range 7 to 10) **Endoscopy score mean** 2 (range 1 to 3)	**Group 1: Infusion** N=34 randomised N=34 (ITT) N=34 (completers) Methyl-prednisolone 1 mg/kg up to a maximum dose of 60 mg/day. Given as continuous infusion. Up to 14 days of treatment **Group 2: Bolus** N=32 randomised N=32 (ITT) N=32 (completers) Methyl-prednisolone 1 mg/kg up to a maximum dose of 60 mg/day. Given as a bolus twice daily. Up to 14 days of treatment **Concomitant therapy:** Hydrocortisone 100 mg daily by rectal enema. Incomplete responders were defined as those patients with a stool frequency > 3/day or visible blood on day 7, who did not require urgent colectomy. These patients were treated with the same steroid dosage for a further week. In cases of clinical improvement (slow responders), steroids were tapered down (5	Outcome 1: **Colectomy** Early colectomy (one month) Outcome 2: **Clinical Remission** (complete response): Stool frequency < 3/day on day 7, with no visible blood in the stools. Truelove and Witts score <4. Outcome 3: **Adverse events** Only the number of patients experiencing steroid-related adverse events was reported.	**<u>2-4 weeks</u>** **Infusion:** 5/34 **Bolus:** 5/32 **<u>0 - ≤2 wks</u>** **Infusion:** 17/34 **Bolus:** 16/32 **Infusion:** 13/34 **Bolus:** 15/32	**Funding:** None reported **Limitations:** Unclear allocation concealment **Additional outcomes:** Reports clinical improvement but it was not a clear definition (slow responders) so it has not been included Parental nutrition ESR CRP

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Compliance rates: N=0 dropout/ withdrawal due to drug related AEs.	**Drop outs:** 0 **Group 2: Bolus** **Mean age (SD):** 37.7 (15.7) **Extent:** Pancolitis 16/32 (50%) Left-sided colitis 16/32 (50%) **Truelove-Witts score mean** 9 (range 8 to 10) **Endoscopy score mean** 2 (range 1 to 3) **Drop outs:** 0	mg/wk) starting from the 15th day. Patients without significant clinical improvement after 14 days of steroids, not requiring urgent colectomy were switched to rescue therapy with iv ciclosporin (4 mg/kg per day) for 7 days followed by oral ciclosporin (5 mg/kg daily) for 6 months. Patients responding to ciclosporin received azathioprine at a dosage of 2 mg/kg per day starting within 3 months. Patients with clinical worsening or intestinal complications underwent urgent colectomy.			

Table 23: BRANCHE2009

Author	Patients	Intervention	Outcome measures	Effect size	Comments
J. Branche et al. Cyclosporine Treatment of Steroid-Refractory Ulcerative Colitis During Pregnancy. *Inflammatory Bowel Disease; 15 (7): 1044-1048. 2009.* **REF ID: BRANCHE2009** **Study design and quality:** Retrospective case series study **France** **Years studied: 2001-2007**	**Severe ulcerative colitis** **All patients:** Included population • Patients with UC treated by cyclosporine during pregnancy between 2001-2007 at the 35 centres of the GETAID group • Severe attack of UC refractory to steroids and treated with ciclosporin during pregnancy Excluded population was not described. **N=8 women included from 5 GETAID centres** Data collection The following data were extracted from medical records:	All patients received oral steroid therapy for a median duration of 14 days (range 1-148) and then IV steroids for 7 days (range 6-7) All patients were initially given 2mg/kg (n=7) or 4mg/kg (n=1) of cyclosporine for a median duration of 7 days (range 5-17) 7/8 improved.	**See the table below for patient level data.**		**Funding:** None described **Limitations:** High risk of bias due to study design**:** **Notes:** No severe infections/ cyclosporine related complications found. Adverse events: Recurrent lip herpes (n=1)
			Outcome 1: Normal birth	7/8	
			Outcome 2: Spontaneous abortion Patient had received 90 days of ciclosporin. Thought to be related to maternal S-protein deficiency. Patient had a successful pregnancy 1 yr later.	1/8 (22 week gestation in utero death).	
			Outcome 3: Premature birth Note: the paper reports	4 /7	

Author	Patients	Intervention	Outcome measures	Effect size	Comments
	date of birth, date of pregnancy, date of diagnosis of UC, date of onset of the severe flare up, disease extent, Truelove and Witt's criteria, presence of severe endoscopic lesions (defined by extensive deep ulcerations found on rectosigmoidoscopy), need for erythrocyte transfusion, duration of oral and IV steroid therapy and ciclosporin therapy, and concomitant medications. The General Practitioners in charge of the patients and their children and/or patients themselves were contacted by phone in August 2008 to have the most follow up information on the children's health. <u>Baseline characteristics</u> Median age: 30.5 years (range 25-38 years) Median time to diagnosis: 34 months (range 8-144) Median duration of pregnancy at time of flare: 11.5 weeks gestation (range 4-25) Extent of disease: pancolitis n=7, left sided n=1 All patients had >3 Truelove and Witt's criteria Three patients had severe anaemia and needed an erythrocyte transfusion. 3/8 had severe endoscopic lesions.	The one that didn't was later found to have Crohn's disease (patient had 17 days ciclosporin, then infliximab). Azathioprine was added to two patient's oral ciclosporin. In the responders: cyclosporine was continued for median duration of 107 days (range 7-253) and were exposed in pregnancy for a median duration of 96 days (range 3-202). Ciclosporin target levels: 100-200ng/ml, never over 200ng/ml. This was monitored in 6/8 patients. The other two had cyclosporine for 7 and 17 days (2mg/kg). 4 patients were on steroids at time of delivery, 4 had stopped.	two premature births, but by our definition (<37 weeks) there were actually 4.		Gestational diabetes (treated with insulin which was stopped after stopping steroid therapy) No colectomies were needed during pregnancy. 2 colectomies were done, median 31 months (range 12-75) follow up (one presented immediately after delivery and the other relapsed 3 years after delivery).
			Outcome 4: Low birth weight	1/7 (was premature)	
			Outcome 5: Congenital abnormalities There were no birth defects reported and the newborns were said to be healthy.	0/7	
			Median follow-up time 38 months (range 12-79). No renal side effect was found in the children. No severe infection in first months of life in the children.		

Table 24: Patient birth outcomes

Patient no:	Age	Term of pregnancy	IV steroids (days)	IV ciclosporin (days)	Oral Ciclosporin (days)	Clinical response	Term of Delivery (gestation weeks)	Birth weight	Malformative syndrome	Colectomy
1	38	27	7	7	30	yes	**32** (vaginal delivery)	**1820g**	no	yes- post delivery
2	32	6	7	5	192	yes	37	2600g	no	yes – post delivery
3	29	15	7	5	98	yes	**36**	3000g	no	no
4	28	14	7	7	0	yes	**33** (vaginal delivery)	3340g	no	no
5	30	10	7	7	104	yes	**Fetal death at 22 weeks**	N/A	no	no
6	25	13	6	17	0	no	**35** – Caesarean section	3160g	no	no, Crohn's disease
7	31	24	7	9	244	yes	37- vaginal delivery	2710g	no	no
8	32	10	7	0	200	yes	37 – vaginal delivery	2920g	no	no

Table 25: CAMPIERI1988

Author	Patients	Intervention	Outcome measures	Effect size	Comments
M. Campieri et al. 5-Aminoslicylic Acid as Enemas or Suppositories in Distal Ulcerative Colitis. *Journal of Clinical Gastroenterology; 10 (4): 406-9. 1988.*	**All patients:** **N=39 randomised / ITT** **Drop-outs** (don't complete the study): N=0 (0%)	**Group 1: 2g 5-ASA suppository** N=19 randomised/ITT 1g 5-ASA suppository given twice a day. Once	**Outcome 1: Clinical remission** (when symptoms, such as motions, blood and mucus, had completely disappeared)	**ITT** **2 weeks** **Group1:** 9/19 **Group 2:** 8/19	**Funding:** None described **Limitations:** Single blind

Author	Patients	Intervention	Outcome measures	Effect size	Comments
REF ID: CAMPIERI1988 **Study design and quality:** Single investigator blind RCT Unclear if it was definitely based in Italy **4 week trial (30 days)** **Randomisation:** Predetermined random list by an independent physician not involved in the assessment of the patients. No further details were described. **Allocation concealment**: Adequate **Blinding:** Single investigator blind. Physicians were unaware of the form of treatment. **Outcome assessment:** Clinical, sigmoidoscopic and histologic assessments were done according to Truelove & Richards. **Sample size calculation:** Not described. **Type of analysis: ITT** **Compliance rates:** Not described. N=0 dropout/ withdrawal due to drug related AEs.	**Inclusion criteria:** • Extent: Distal UC (at least 10cm but <20cm). Determined by a rigid sigmoidoscope. • Severity: mild/ moderate **Exclusion:** • None described **<u>Baseline characteristics</u>** **<u>Group 1: 2g 5-ASA suppositories</u>** **Sex (m/f):** 7/12 **Mean age (unclear if SD or SE):** 40 (16) **Mean extent (unclear if SD or SE):** 13 (2) **Patients on no previous treatment:** 11 **Patients on maintenance treatment with Salazopyrin 2g daily:** 8 **Clinical activity:** mild n=9, moderate n=10 **Sigmoidoscopic appearance:** Grade 3 n=2, Grade 2 n=9, Grade 1 n=8 **Histological appearance:** Grade 3 n=4, Grade2 n=9, Grade 1 n=6 **Drop outs:** 0 **<u>Group 2: 2g 5-ASA liquid enema</u>** **Sex (m/f):** 15/5 **Mean age (unclear if SD or SE):** 40 (11) **Mean extent (unclear if SD or SE):** 13 (2) **Patients on no previous treatment:** 11 **Patients on maintenance treatment with Salazopyrin 2g daily:** 9 **Clinical activity:** mild n=9, moderate n=11 **Sigmoidoscopic appearance:** Grade 3 n=4, Grade 2 n=10, Grade 1 n=6 **Histological appearance:** Grade 3 n=5, Grade2 n=10, Grade 1 n=5 **Drop outs:** 0	at night and once in the morning after evacuation. **Group 2: 2g 5-ASA liquid enema** N=20 randomised/ITT 2g of 5-ASA in 100mls enema, given at night. **Concomitant therapy:** If the patients were on maintenance treatment with SASP this was continued.		**<u>4 weeks</u>** **Group1:** 15/19 **Group 2:** 16/20	**Additional outcomes:** Histological improvement and remission
			Outcome 2: Clinical improvement (a reduction of at least one grade of activity according to the adopted scale)	**ITT** **<u>2 weeks</u>** **Group1:** 16/19 **Group 2:** 17/20 **<u>4 weeks</u>** **Group1:** 17/19 **Group 2:** 18/20	
			Outcome 3: Endoscopic remission (repaired rectal mucosa)	**ITT** **<u>2 weeks</u>** **Group1:** 9/19 **Group 2:** 6/20 **<u>4 weeks</u>** **Group1:** 14/19 **Group 2:** 13/20	

Table 26: CAMPIERI1990

Author	Patients	Intervention	Outcome measures	Effect size	Comments
M. Campieri et al. Mesalazine (5-Aminosalicylic Acid) Suppositories in the Treatment of Ulcerative proctitis or Distal proctosigmoiditis. A Randomized Controlled Trial. *Scandinavian Journal of Gastroenterology; 25 (7): 663-668. 1990.* **REF ID: CAMPIERI1990** **Study design and quality:** Double blind RCT Multicentre: 11 centres, Italy **4 week trial** **Randomisation:** Computerized randomised list using blocks of three. Each centre had a definite series of packages, numbered consecutively **Allocation concealment**: Adequate **Blinding:** Double blind. Identical blister packs. No further information given. **Outcome assessment:** For endoscopy – Barons criteria. Patients kept a diary of their symptoms.	**All patients:** **N=94 randomised/ ITT** **Drop-outs** (don't complete the study): N=11 (11.7%) Missing data <10% difference between the treatment arms. **Inclusion criteria:** • Outpatients • First attacks of UC or relapses • Extent: Distal proctosigmoiditis (<20cm from the anus on sigmoidoscopy and confirmed by biopsies) • Severity: Mild to moderate **Exclusion:** • <18 or >75 years • Systemic signs of disease • Previous salicylates allergy • Received steroids for >7 days before entering the study • Pregnant or lactating women **Baseline characteristics** **Group 1: 1.0g mesalazine (Asacol) suppositories** **Sex (M/F):** 24/8 **Mean age (SD):** 42.1 (14.1) **Episode:** First attack n=2, Relapse n=30 **On concurrent maintenance therapy:** 16 (50%) **Extent:** proctitis n=23, distal proctosigmoiditis n=9 **Clinical activity:** mild n=14, moderate n=18 **Endoscopic grade:** 1 n=9, 2 n=18, 3 n=5 **Histological grade:** 1 n=4, 2 n=13, 3 n=15 **Drop outs:** 0	**Group 1: 1.0g mesalazine (Asacol) suppositories** N=32 randomised/ ITT One 500mg 5-ASA (Asacol), three times a day. **Group 2: 1.5g mesalazine (Asacol) suppositories** N=31 randomised/ITT N=29 (completers) One 500mg 5-ASA (Asacol), two times a day and one placebo suppository. **Group 3: Placebo suppositories** N=31 randomised/ ITT N=22 (completers) One placebo suppository, three times a day. **Concomitant therapy:** No rectal or oral steroids were permitted. Oral	**Outcome 1: Clinical remission** (symptomless, with no more than 2 bowel movements/ day without visible blood) N values at 2 weeks were calculated from the percentages reported in the paper.	**2 weeks** **Group 1:** 13/32 **Group 2:** 14/31 **Group 3:** 7/31 **4 weeks** **Group 1:** 22/32 **Group 2:** 23/31 **Group 3:** 12/31	**Funding:** Financed by Bracco SpA Milan. Suppositories were supplied by Giuliani SpA Milan. **Limitations:** Double blind no further information given **Additional outcomes:** Endoscopic improvement Histologic remission and improvement
			Outcome 2: Clinical improvement (a decrease in severity of symptoms and signs) **Note:** clinical improvement figures have been added to clinical remission figures to give all those patients who had clinical improvement N values at 2 weeks were calculated from the percentages reported in the paper.	**2 weeks** **Group 1:** 24/32 **Group 2:** 26/31 **Group 3:** 10/31 **4 weeks** **Group 1:** 26/32 **Group 2:** 28/31 **Group 3:** 13/31	
			Outcome 3: Endoscopic remission (according to the Baron criteria)	**4 weeks** **Group 1:** 19/32 **Group 2:** 17/31	

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Sample size calculation: Power of 90%, type 1 error of 5%, 30 patients in each arm. **Type of analysis: ITT** **Compliance rates:** The count of unused suppositories showed that each patient had complied with the instructions given for the study. No further information was given. N=1 dropout/ withdrawal due to drug related AEs (placebo arm for a headache)	**<u>Group 2: 1.5g mesalazine (Asacol) suppositories</u>** **Sex (M/F):** 13/18[a] **Mean age (SD):** 37.1 (14.7) **Episode:** First attack n=2, Relapse n=29 **On concurrent maintenance therapy:** 19 (61%) **Extent:** proctitis n=19, distal proctosigmoiditis n=12 **Clinical activity:** mild n=13, moderate n=18 **Endoscopic grade:** 1 n=8, 2 n=19, 3 n=4 **Histological grade:** 1 n=6, 2 n=15, 3 n=10 **Drop outs:** 2 (1 worsening of symptoms, 1 lost to follow up) **<u>Group 3: Placebo suppositories</u>** **Sex (M/F):** 21/10 **Mean age (SD):** 41.2 (15.1) **Episode:** First attack n=4, Relapse n=27 **On concurrent maintenance therapy:** 17 (55%) **Extent:** proctitis n=23, distal proctosigmoiditis n=8 **Clinical activity:** mild n=18, moderate n=13 **Endoscopic grade:** 1 n=14, 2 n=15, 3 n=2 **Histological grade:** 1 n=8, 2 n=14, 3 n=9 **Drop outs:** 9 (5 worsening symptoms, 2 lack of improvement, 1 headache, 1 lost to follow up)	maintenance treatment with SASP or mesalazine was allowed if the patient relapsed whilst taking it. The dose was the same throughout the study.	**Outcome 4: Adverse events** Group 1: facial erythema and mild fever, but it did not require the drug to be discontinued.	**Group 3:** 7/31 **<u>4 weeks</u>** **Group 1:** 1/32 **Group 2:** 0/31 **Group 3:** 1/31	

Table 27: CAMPIERI1990A

Author	Patients	Intervention	Outcome measures	Effect size	Comments
M. Campieri et al. Topical treatment with 5-aminosalicylic in distal ulcerative colitis by using a new suppository preparation. A double-blind placebo controlled trial. *International Journal of*	**<u>All patients:</u>** **N=62 randomised /ITT** **Drop-outs** (don't complete the study): N=0 (0%) **Inclusion criteria:**	**Group 1: 1.5g Asacol suppositories** N=32 randomised/ ITT One 500mg suppository of 5-ASA (Asacol) given three times a day.	**Outcome 1: Clinical remission** (complete disappearance of symptoms)	**ITT analysis** **<u>15 days</u> (analysed as 2 weeks)** **Group1:** 8/32 **Group 2:**	**Funding:** Asacol suppositories supplied by Guiliani Pharmaceutical company. Placebo suppositories supplied by the Hospital Pharmacy Department.

a P<0.05 compared with the other groups

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Colorectal Disease; 5: 79-81. 1990. **REF ID: CAMPIERI1990A** **Study design and quality:** Double blind RCT Italy **4 week trial** **Randomisation:** Predetermined random list. **Allocation concealment**: No information given **Blinding:** Double blind. Physicians were unaware of the treatment given. **Outcome assessment:** According to Truelove & Richards. **Sample size calculation:** Not described. **Type of analysis: ITT** **Compliance rates:** Described that all patients showed excellent compliance. Unclear how they measured it. N=0 dropout/ withdrawal due to drug related AEs.	• Extent: <20cm, distal sigmoid colon and rectum on sigmoidoscopy • Severity: Mild to moderate attacks • Fewer than 4-6 bowel actions/ day **Exclusion:** • Rectal or systemic steroids **<u>Baseline characteristics</u>** **<u>Group 1: 1.5g Asacol suppositories</u>** **Sex (M/F):** 18/14 **Mean age (SD):** 37 +/-7 **Extent:** 14 +/-3cm **Clinical activity, n:** mild n=15, moderate n=17 **Sigmoidoscopic appearance, n:** Grade 3 n=3, Grade 2 n=15, Grade 1 n=14 **Histological appearance, n:** Grade 3 n=4, Grade 2 n=16, Grade 1 n=12 **Drop outs:** 0 **<u>Group 2: Placebo suppositories</u>** **Sex (M/F):** 17/13 **Mean age (SD):** 34 +/-8 **Extent:** 13 +/-2cm **Clinical activity, n:** mild n=14, moderate n=16 **Sigmoidoscopic appearance, n:** Grade 3 n=2, Grade 2 n=16, Grade 1 n=12 **Histological appearance, n:** Grade 3 n=4, Grade 2 n=15, Grade 1 n=11 **Drop outs:** 0	**Group 2: Placebo suppositories** N=30 randomised/ITT One placebo suppository given three times a day **Concomitant therapy:** If taking oral SASP, the dose was maintained during the study		1/30 **<u>30 days</u> (analysed as 4 weeks)** **Group1:** 18/32 **Group 2:** 2/30	**Limitations:** Unclear allocation concealment **Additional outcomes:** Endoscopic improvement Histological improvement and remission
			Outcome 2: Clinical improvement (a reduction of at least one grade from the baseline value according to the adopted evaluation scale) **Note:** the remission and improvement figures have been added together to get the total number of patients who improved.	**ITT analysis** **<u>15 days</u> (analysed as 2 weeks)** **Group1:** 22/32 **Group 2:** 6/30 **<u>30 days (analysed as 4 weeks)</u>** **Group1:** 28/32 **Group 2:** 10/30	
			Outcome 3: Endoscopic remission (rectal mucosa was apparently repaired)	**ITT analysis** **<u>15 days</u> (analysed as 2 weeks)** **Group1:** 5/32	

Author	Patients	Intervention	Outcome measures	Effect size	Comments
				Group 2: 1/30 **<u>30 days</u> (analysed as 4 weeks)** **Group1:** 13/32 **Group 2:** 2/30	
			No adverse events were reported in either group.		

Table 28: CAMPIERI1991

Author	Patients	Intervention	Outcome measures	Effect size	Comments
M. Campieri et al. Optimum dosage of 5-aminosalicylic acid as rectal enemas in patients with active ulcerative colitis. *Gut; 32: 929-931. 1991.* **REF ID: CAMPIERI1991** **Study design and quality:** Double blind RCT Italy **4 week trial** **Randomisation:** No details given. Divided into two groups	**<u>All patients:</u>** **N=113 randomised/ ITT** **Drop-outs** (don't complete the study): N=0 (0%) **Inclusion criteria:** • Outpatients • >18 years old • Extent: up to the splenic flexure (colonoscopy confirmed) • Severity: mild to moderate active UC • Stool examination excluded the presence of pathogens **Exclusion:** • Hepatic or renal dysfunction	**Group 1: 1g mesalazine (Pentasa) liquid enema** N=27 randomised/ ITT 1g mesalazine (Pentasa) in 100mls liquid enema. **Group 2: 2g mesalazine (Pentasa) liquid enema** N=30 randomised/ ITT 2g mesalazine (Pentasa) in 100mls liquid enema. **Group 3: 4g mesalazine (Pentasa) liquid enema** N=29 randomised/ ITT	**Outcome 1: Clinical remission** (symptoms of active disease had resolved)	**<u>At 15 days</u> (analysed as 2 weeks)** **Group 1:** 9/27 **Group 2:** 11/30 **Group 3:** 13/29 **Group 4:** 1/27 **<u>At 30 days</u> (analysed as 4 weeks)** **Group 1:** 17/27 **Group 2:** 20/30 **Group 3:**	**Funding:** Enemas provided by CHIESI Pharmaceutical company, Italy. **Limitations:** Unclear method of randomisation and allocation concealment **Additional outcomes:** Histological improvement/ remission Separate results for those on maintenance SASP and those that weren't

Author	Patients	Intervention	Outcome measures	Effect size	Comments
depending on if they are on maintenance SASP therapy. Unclear. **Allocation concealment**: No information given. Unclear. **Blinding:** Double blind. Clinical and sigmoidoscopic assessments were made by the same 'blind' investigators. Lactose (white powder) was mixed with all the enemas to ensure blindness. **Outcome assessment:** According to Truelove & Richards. **Sample size calculation:** Not described. **Type of analysis: ITT** **Compliance rates:** Not described. N=0 dropout/ withdrawal due to drug related AEs.	**Baseline characteristics** **Group 1: 1g mesalazine (Pentasa) liquid enema** **Sex (M/F):** 13/14 **Mean age (no SD given):** 36 **Extent:** proctitis n=7, proctosigmoiditis n=8, left sided colitis n=12 **Clinical activity:** Moderate n= 15, Mild n=12 **Endoscopic grade:** 3 n=6, 2 n=12, 1 n=9 **Histological grade:** 3 n=9, 2 n=11, 1 n=7 **Drop outs:** 0 **Group 2: 2g mesalazine (Pentasa) liquid enema** **Sex (M/F):** 12/18 **Mean age (no SD given):** 42 **Extent:** proctitis n=10, proctosigmoiditis n=9, left sided colitis n=11 **Clinical activity:** Moderate n= 16, Mild n=14 **Endoscopic grade:** 3 n=8, 2 n=12, 1 n=10 **Histological grade:** 3 n=10, 2 n=12, 1 n=8 **Drop outs:** 0 **Group 3: 4g mesalazine (Pentasa) liquid enema** **Sex (M/F):** 13/16 **Mean age (no SD given):** 37 **Extent:** proctitis n=8, proctosigmoiditis n=12, left sided colitis n=9 **Clinical activity:** Moderate n= 16, Mild n=13 **Endoscopic grade:** 3 n=8, 2 n=14, 1 n=7 **Histological grade:** 3 n=9, 2 n=12, 1 n=8 **Drop outs:** 0 **Group 4: Placebo** **Sex (M/F):** 15/12 **Mean age (no SD given):** 40 **Extent:** proctitis n=8, proctosigmoiditis n=10, left sided colitis n=9 **Clinical activity:** Moderate n= 15, Mild n=12 **Endoscopic grade:** 3 n=7, 2 n=11, 1 n=9 **Histological grade:** 3 n=9, 2 n=11, 1 n=7 **Drop outs:** 0	4g mesalazine (Pentasa) in 100mls liquid enema. **Group 4: Placebo** N=27 randomised/ ITT Placebo 100mls liquid enema. **Concomitant therapy:** No rectal or systemic steroids were permitted.		21/29 **Group 4:** 3/27	**Notes:** Pentasa in the BNF is to be prescribed at 1g for a liquid enema per day. The paper describes that the overall outcome was not influenced by the maintenance treatment with SASP.
			Outcome 2: Clinical improvement (at least one grade of reduction in activity according to the criteria adopted)	**At 15 days (analysed as 2 weeks)** **Group 1:** 21/27 **Group 2:** 23/30 **Group 3:** 24/29 **Group 4:** 10/27 **At 30 days (analysed as 4 weeks)** **Group 1:** 23/27 **Group 2:** 25/30 **Group 3:** 25/29 **Group 4:** 11/27	
			Outcome 3: Endoscopic remission (rectal mucosa was repaired with the appearance of a vascular pattern)	**At 15 days (analysed as 2 weeks)** **Group 1:** 7/27 **Group 2:** 9/30 **Group 3:** 11/29 **Group 4:** 1/27 **At 30 days (analysed as**	

Author	Patients	Intervention	Outcome measures	Effect size	Comments
				4 weeks) **Group 1:** 12/27 **Group 2:** 13/30 **Group 3:** 15/29 **Group 4:** 2/27	
			Adverse events: The paper describes that five patients complained of minor troubles, 2 in the placebo group and 3 in the 5-ASA group. They were not thought to be drug related. No further information was given.		

Table 29: CAMPIERI1991A

Author	Patients	Intervention	Outcome measures	Effect size	Comments
M. Campieri et al. Sucralfate, 5-aminosalicylic acid and placebo enemas in the treatment of distal ulcerative colitis. *European Journal of Gastroenterology & Hepatology; 3: 41-44. 1991.* **REF ID: CAMPIERI1991A** **Study design and quality:** Double blind RCT Italy **4 week trial**	**All patients:** **N=50 randomised** (32 were in the 5-ASA and placebo arms, the remainder where in the sucralfate arm which is excluded from this review) **N=32 ITT** **Drop-outs** (don't complete the study): N=0 (0%) **Inclusion criteria:** • Outpatients • >18 years old • Extent: not beyond the splenic flexure (confirmed by flexible sigmoidoscopy)	**Group 1: 2g 5-ASA enema** N=18 randomised/ITT 100mls enema containing 2g of 5-ASA (type unknown) **Group 2: Placebo enema** N=14 randomised/ITT 100mls placebo liquid enema.	**Outcome 1: Clinical remission** (symptoms of active disease (such as bleeding or mucus) had disappeared)	**ITT** **2 weeks** **Group1:** 7/18 **Group 2:** 0/14 **4 weeks** **Group1:** 12/18 **Group 2:** 1/14	**Funding:** None described. **Limitations:** Unclear allocation concealment **Additional outcomes:** Histological outcomes **Notes:**
			Outcome 2: Clinical improvement	**ITT**	

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Randomisation: Predetermined randomisation code. No further information was given. **Allocation concealment**: No information was given. Unclear. **Blinding:** Double blind. Pharmacist was unaware of the type of treatment they were providing to the patients. Same investigators made the clinical and sigmoidoscopic assessments. Blind pathologist. **Outcome assessment:** A clinical, sigmoidoscopic and histological assessment was carried out before and at 15, 30 days using the criteria of Truelove and Witts. **Sample size calculation:** None described. **Type of analysis: ITT** **Compliance rates:** N=0 dropout/ withdrawal due to drug related AEs.	• Severity: mild or moderate attacks of UC **Exclusion:** • Severe colitis • Hepatic or renal dysfunction • Pregnant women **Baseline characteristics** **Group 1: 2g 5-ASA enema** **Sex (m/f):** 6/12 **Mean age (no SD given):** 36 **Extent:** proctitis n=3, proctosigmoiditis n=10, left sided n=5 **Severity:** mild n=6, moderate n=12 **Sigmoidoscopic appearance:** grade 3 n=2, grade 2 n=10, grade 1 n=6 **SASP maintenance treatment:** n=12 **Drop outs:** 0 **Group 2: Placebo enema** **Sex (m/f):** 5/9 **Mean age (no SD given):** 40 **Extent:** proctitis n=3, proctosigmoiditis n=9, left sided n=2 **Severity:** mild n=7, moderate n=7 **Sigmoidoscopic appearance:** grade 3 n=1, grade 2 n=7, grade 1 n=6 **SASP maintenance treatment:** n=7 **Drop outs:** 0	**Concomitant therapy:** No rectal or systemic steroid medications were allowed during the study. Oral SASP was allowed if it had been used as a maintenance treatment for >1month prior to entry.	(reduction of at least one grade of activity according to the adopted scale)	**2 weeks** **Group1:** 15/18 **Group 2:** 2/14 **4 weeks** **Group1:** 17/18 **Group 2:** 2/14	Some patients were also on maintenance SASP
			Outcome 3: Endoscopic remission (repaired rectal mucosa)	**ITT** **2 weeks** **Group1:** 6/18 **Group 2:** 0/14 **4 weeks** **Group1:** 10/18 **Group 2:** 0/14	
			No adverse events were described.		

Table 30: CAMPIERI1993

Author	Patients	Intervention	Outcome measures	Effect size	Comments
M. Campieri et al.	**All patients:**	**Group 1: 2g Mesalazine**	**Outcome 1: Clinical**	**10 days** **Group 1:**	**Funding:**

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Better Quality of Therapy with 5-ASA Colonic Foam in Active Ulcerative Colitis. A Multicenter Comparative Trial with 5-ASA Enema. *Digestive Diseases and Sciences; 38(10): 1143-1850. 1993.* **REF ID: CAMPIERI1993** **Study design and quality:** Single investigator blind RCT Multicentre: 12 centres, Italy **3 week trial** **Randomisation:** Two computer generated lists with a block size of four. Individual drug packaging labelled with the patients number. **Allocation concealment**: Adequate **Blinding:** Single investigator blind. **Outcome assessment:** Modified Baron's criteria. Physician's clinical global evaluation. **Sample size calculation:** None described. **Type of analysis: ITT** **Compliance rates:** Not described.	**N=233 randomised** (N=117 mild severity, N=116 moderate severity) **Drop-outs** (don't complete the study): N=22 (9.4%) Unclear if all the AEs dropped out or not. 6 in the mild severity groups (3 in the foam group, 1 in the liquid enema, unclear which group the other two were in), 16 in the moderate severity groups (9 in the foam group, 5 in the enema group, unclear which group the other two were in). **Inclusion criteria:** • Outpatients aged 18-75 years • Extent: Relapse of established proctosigmoiditis or distal ulcerative colitis • Severity: Mild or moderate according to Truelove & Witts criteria, regardless of endoscopic or histological grade • Mild: no more than 4 bowel movements daily, small amount of rectal bleeding and with no systemic signs and symptoms • Moderate: 5-8 bowel movements/ day, significant rectal bleeding, some systemic signs e.g. low grade fever, fatigue, anorexia, weight loss etc. **Exclusion:** • First attack of UC • Relapse lasting >2 weeks • Extent > splenic flexure or <15cm distal from anus at colonoscopy • Salicylate allergy • Oral or topical steroids >7 days prior to study entry • Chronic continuous symptoms of disease • Relapse during maintenance therapy with 5-ASA enemas **Baseline characteristics** **Group 1: 2g Mesalazine foam (Asacol) enema [mild]** **Sex (m/f):** 27/36 **Mean age (SD):** 38 (16) **Oral maintenance:** 48 **Extent:** rectum-sigmoid n=55, left colon n=8	**foam (Asacol) enema [mild]** N=63 randomised Mild severity of disease. 5-ASA foam (Asacol) enema 2g/day in 10mls (expands to 100-120mls), once a day. **Group 2: 2g mesalazine (Asacol) liquid enema [mild]** N=54 randomised Mild severity of disease. 5-ASA liquid enema (Asacol). 2g/day in 50mls. **Group 3: 4g mesalazine (Asacol) foam enema [moderate]** N=60 randomised Moderate severity of disease. 5-ASA foam (Asacol) enema, 4g/day in 20mls (expands to 180-200mls), once a day. **Group 4: 4g mesalazine (Asacol) liquid enema [moderate]** N=56 randomised Moderate severity of disease. 5-ASA liquid	**remission** (Physician gave a clinical global evaluation of disease activity. Remission-return to normal stool frequency, no visible blood in the stools, no abdominal symptoms) **Outcome 2: Clinical improvement** (decrease in the severity of symptoms not meeting the criteria for remission) Figures included those classed as improved and those in remission **Outcome 3: Endoscopic remission** (Grade 0, normal mucosa)	34/63 **Group 2:** 17/54 **Group 3:** 11/60 **Group 4:** 5/56 **3 weeks** **Group 1:** 52/63 **Group 2:** 40/54 **Group 3:** 38/60 **Group 4:** 29/56 **10 days** **Group 1:** 54/63 **Group 2:** 39/54 **Group 3:** 44/60 **Group 4:** 32/56 **3 weeks** **Group 1:** 56/63 **Group 2:** 46/54 **Group 3:** 51/60 **Group 4:** 47/56 **3 weeks** **Group 1:** 41/63	Supported by a grant from Bracco and Giuliani, Italy. **Limitations:** Single investigator blind **Additional outcomes:** Individual clinical variables e.g. stool frequency etc. Histological improvement and remission

Author	Patients	Intervention	Outcome measures	Effect size	Comments
N=8 dropout/ withdrawal due to drug related AEs. One patient in the mild foam group due to worsening of tenesmus. In the moderate severity foam group: one patient suffered tenesmus and flatulence, one patient had transient chills and three patients abdominal gas. In the moderate liquid enema group one patient recorded tenesmus and flatulence and one patient abdominal gas.	**Endoscopy grade:** Grade 1 n=38, Grade 2 n=24, Grade 3=1 **Histological grade:** Grade 1 n= 32, Grade 2 n=29, Grade 3 n=2 **Drop outs:** 3 (1 due to AE, 2 due to inadequate response). Unclear if the other 2 drop outs were from group 1, 2 or both. **Group 2: 2g mesalazine (Asacol) liquid enema [mild]** **Sex (m/f):** 30/24 **Mean age (SD):** 36 (12) **Oral maintenance:** 43 **Extent:** rectum-sigmoid n=48, left colon n=6 **Endoscopy grade:** Grade 1 n=39, Grade 2 n=15, Grade 3=0 **Histological grade:** Grade 1 n= 29, Grade 2 n=25, Grade 3 n=0 **Drop outs:** 1 due to inadequate response. Unclear if the other 2 drop outs were from group 1, 2 or both. **Group 3: 4g mesalazine (Asacol) foam enema [moderate]** **Sex (m/f):** 46/14 **Mean age (SD):** 40 (13) **Oral maintenance:** 50 **Extent:** rectum-sigmoid n=36, left colon n=24 **Endoscopy grade:** Grade 1 n=4, Grade 2 n=54, Grade 3=2 **Histological grade:** Grade 1 n= 7, Grade 2 n=49, Grade 3 n=4 **Drop outs:** 9 (4 due to inadequate response, 5 AEs) Unclear if the other 2 drop outs were from group 3, 4 or both. **Group 4: 4g mesalazine (Asacol) liquid enema [moderate]** **Sex (m/f):** 37/19 **Mean age (SD):** 40 (14) **Oral maintenance:** 48 **Extent:** rectum-sigmoid n=28, left colon n=28 **Endoscopy grade:** Grade 1 n=7, Grade 2 n=45, Grade 3=4 **Histological grade:** Grade 1 n= 5, Grade 2 n=47, Grade 3 n=4 **Drop outs:** 5 (3 due to inadequate response, 2 AEs) Unclear if the other 2 drop outs were from group 3, 4 or both.	enema (Asacol), 4g/day in 100mls. **Concomitant therapy:** No oral or rectal steroids were permitted. Patients on oral maintenance treatment with SASP or 5-ASA at entry were allowed to continue the same dose throughout the study		**Group 2:** 30/54 **Group 3:** 23/60 **Group 4:** 19/56	
			Outcome 4: Adverse events Group 1: Due to worsening of tenesmus Group 2: Due to diarrhoea Group 3:1 tenesmus and flatulence, 3 abdominal gas, 1 occasional transient chills after foam administration Group 4: 1 tenesmus and flatulence, 1 abdominal gas	**3 weeks** **Group 1:** 1/63 **Group 2:** 1/54 **Group 3:** 5/60 **Group 4:** 2/56	

Table 31: CAMPIERI2003

Author	Patients	Intervention	Outcome measures	Effect size	Comments
M. Campieri et al.	**All patients:**	**Group 1: 5-ASA**	Outcome 1: **Clinical**	**Group1:**	**Funding:** Chiesi

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Oral beclomethasone dipropionate in the treatment of extensive and left-sided active ulcerative colitis: a multicentre randomised study. *Alimentary Pharmacology and Therapeutics; 17: 1471-1480. 2003.* **REF ID:** CAMPIERI2003 **Study design and quality:** Single blind RCT Multicentre: 13 centres, Italy **4 week trial** **Randomisation:** blocks of four produced by computer-generated randomisation list **Allocation concealment**: Adequate **Blinding:** Single blind. Investigators who performed endoscopic and histological examinations and the evaluation of the clinical symptoms of UC were blinded **Outcome assessment:** Pancolonoscopy graded according to Baron's criteria. Histology graded according to criteria of Truelove and Richard. Clinical symptoms measured	**N=177 randomised** **Drop-outs** (don't complete the study): N=25 (14%) **Inclusion criteria:** • Extent: extensive or left-sided • Severity: mild to moderate (Disease Activity Index [DAI] score >3 and <10, maximum score is 12) • Age 18-70 years **Exclusion:** • Severe UC or clinical remission on the basis of the DAI score • Severe renal, liver or heart failure • Diabetes mellitus • Active gastroduodenal ulcer • Osteoporosis • Severe or moderate hypertension • Neoplastic disease • Psychotic disorders, drug or substance abuse disorder • Known hypersensitivity to corticosteroids or aminosalicylates • Pregnancy or lactation • Treatment with corticosteroid, 5-ASA or sulphasalazine ≥1 month prior to enrolment **<u>Group 1:</u> 5-ASA 2.4g** **Mean age (SEM):** 45.4 (1.5) **Extent:** Patients with left sided UC (%): 69/87 (79.3) Patients with extensive UC (%): 18/87 (20.7) **Mean duration of disease in years (SEM):** 5.4 (0.7) **Mean DAI score(SEM):** 5.30 (0.18)	**(2.4g/day)** N=87 randomised N=80 (completers)/ authors ITT 800mg tds (Asacol 400mg tablets) **Group 2: Beclomethasone dipropionate (5mg/day)** N=90 randomised N=72 (completers) N=73 Authors ITT 5mg od early in the morning **Concomitant therapy:** Not allowed– see exclusion criteria	**remission** (DAI score <3) The n values were calculated from the percentages given in the paper. Outcome 2: **Clinical remission** (DAI score <3) **Left sided UC subgroup** The n values were calculated from the percentages given in the paper. Outcome 3: **Clinical remission** (DAI score <3) **Extensive UC subgroup** The n values were calculated from the percentages given in the paper. Outcome 4: **Clinical improvement** (reduction of at least 3 points in DAI score from baseline). This is in addition to those in clinical remission.	50/80 (62.5%) **Group 2:** 46/73 (63.0%) **Group1:** 41/62 (66.1%) **Group 2:** 27/47 (57.4%) **Group1:** 9/18 (50%) **Group 2:** 19/26 (73.1%) **Group1:** 59/80 (74%) **Group 2:** 57/73 (78%)	Farmaceutici S.p.A., Italy manufacturers and suppliers of Beclomethasone and 5-ASA, and performed the statistical analyses. Farmaresa S.R.L., Italy (providers of clinical trial services such as randomisation schedules) for trial monitoring **Limitations:** Significant (p=<0.05) difference in mean DAI score and patients with extensive colitis between groups at baseline. Beclomethasone group more severe i.e. would favour 5-ASA. Single blind >10% difference in missing data between the treatment arms **Additional outcomes:** Histological remission Mean change in DAI score and Truelove and Richard score Mean change in ESR

Author	Patients	Intervention	Outcome measures	Effect size	Comments
using Disease Activity Index (DAI). Complete haematological evaluation including white cell count, ESR and CRP. **Sample size calculation:** 80 patients per arm based on 80% power, p=0.05 for a 20% difference in remission (DAI score <3) **Type of analysis:** ITT (authors definition being: had at least one dose and attended at least one visit), efficacy and safety analyses **Compliance rates:** Investigators who assigned treatment checked compliance by counting residual study medication at each visit. 7 patients had poor compliance. N=1 dropout/ withdrawal due to drug related AEs (in the beclomethasone group). Note: 7 dropouts (3 on 5-ASA and 4 on beclomethasone) due to poor compliance with taking medication.	**Drop outs:** 7 (3 due to poor compliance, 2 lost to follow up, 1 due to insufficient therapeutic response, 1 due to "concomitant disease") **<u>Group 2:</u> Beclomethasone dipropionate 5mg** **Mean age (SEM):** 41.1 (1.6) **Extent:** Patients with left sided UC (%): 58/90 (64.4) Patients with extensive UC (%): 32/90 (35.6) **Mean duration of disease in years (SEM):** 5.3 (0.5) **Mean DAI score(SEM):** 6.06 (0.20) **Drop outs:** 18 (4 due to poor compliance, 8 lost to follow up, 1 due to AE – profuse menstrual bleeding, 1 due to protocol violation) Note: significant (p=<0.05) difference in mean DAI score and patients with extensive colitis between groups at baseline		The n values were calculated from the percentages given in the paper.		Mean morning plasma cortisol levels
			Outcome 5: **Clinical improvement** (as above) **Left sided UC subgroup** The n values were calculated from the percentages given in the paper.	**Group1:** 45/62 (73 %) **Group 2:** 33/47 (70 %)	
			Outcome 6: **Clinical improvement** (as above) **Extensive UC subgroup** The n values were calculated from the percentages given in the paper.	**Group1:** 14/18 (78%) **Group 2:** 24/26 (92%)	
			Outcome 7: **Adverse events**	**Group1:** 1/87 (1.1%) influenza symptoms **Group 2:** 1/90 (1.1%) menorrhagia	

Table 32: CARLSSON2003

Reference	Study description	Findings	Comments
E. Carlsson et al. What Concerns Subjects with Inflammatory Bowel Disease and an Ileostomy? Scandinavian Journal of Gastroenterology; 38: 978-984. 2003. **REF ID: CARLSSON2003** **Cross-sectional study** Gothenberg, Sweden **Outcome measures:** Rating Form of IBD Patient Concerns (RFIPC)- disease specific questionnaire for IBD for non-operated IBD patients. 25 items, visual analogue scale 0-100 (highest score means a great deal). Having an ostomy bag question was excluded. Validated in the USA, France and Sweden but not in patients with IBD and an ileostomy. Open ended question was also included to capture any other concerns. SF-36 Perceived QofL (VAS0-100) Jalowiec coping scale (JCS-40)	Eligible N=25 (4 declined due to individual professional situation) N= 21 women of which 6 had ulcerative colitis (n=10 Crohn's disease, n=1 indeterminate colitis) **Aim of the study:** to describe the worries and concerns in subjects with IBD and an ileostomy, and aspects of quality of life and coping strategies. Questionnaire survey (October 1999-April2000) was used in a group of patients with IBD (from the Gothenberg area) **Inclusion criteria:** • IBD • Permanent ileostomy • Intestinal resection of <25cm • No ongoing inflammatory activity as evaluated by history, Hb, CRP and albumin **Baseline characteristics** Age: 36-65 years old (Mean 51 +/-7.8 years) BMI: 25.3 (+/-3.6) kg/m2 No patient was receiving steroids or other anti-inflammatory treatment Time elapsed since the ileostomy operation: mean 21 (+/-10) years (range 2-39 years) N=8 (have to get up at night to empty the stoma bag) of which 2 have to get up twice in the night At the time of the study: n=1 reported problems with leakage of the stoma bag No other stoma-related complications were reported in the group. N=4 on anti-depressive drugs.	**Results of the RFIPC:** RFIPC item / Total (n=21) Median (inter-quartile range), rank Intimacy: 51 (11-73), 1 Access to quality medical care: 41 (13-62), 2 Energy level: 39 (9-61), 3 Loss of sexual drive: 27 (8-68), 4 Producing unpleasant odours: 25 (5-68), 5.5 Being a burden on others: 25 (5-63), 5.5 Ability to perform sexually: 22 (14-83), 7 Attractiveness: 18 (7-76), 8.5 Feelings about my body: 18 (1-52), 8.5 Uncertain nature of the disease: 16 (3-51), 10 Pain or suffering: 15 (0-44), 11 Achieve full potential: 14 (1-62), 12 Financial difficulties: 12 (0-66), 13.5 Being treated as different: 12 (0-49), 13.5 Feeling alone: 11 (0-71), 15 Developing cancer: 10 (1-25), 16 Feeling dirty or smelly: 8 (3-54), 17.5 Loss of bowel control: 8 (0-44), 17.5 Feeling out of control: 6 (0-57), 19.5 Effects on medication: 6 (0-21), 19.5 Dying early: 5 (0-24), 21 Having surgery: 3 (0-47), 22 Passing the disease to others: 2 (0-74), 23 Ability to have a child: 0 (0-3), 24 Open ended question results: N=1, worried about having to take anti-depressants N=1, worried about not getting unemployment benefit N=1, worried about impotence and stoma leakage	**Source of funding:** Swedish medical Research Council, Goteborgs Lakarasallskap and IB och A Lundbergs Forskningsstiftelse **Other outcomes reported:** Percieved QofL Coping scores Attributes of quality of life SF-36 scores

Table 33: CORTOT2008

Author	Patients	Intervention	Outcome measures	Effect size	Comments
A. Cortot et al. Mesalamine Foam Enema Versus Mesalamine Liquid Enema in Active Left-Sided Ulcerative Colitis. *American Journal of Gastroenterology; 103 (12): 3106-3114.2008.* **REF ID: CORTOT2008** **Study design and quality:** Single investigator blind RCT Multicentre: 67 centres, France, Belgium, Netherlands **4 week trial** **Randomisation:** 1:1 ratio assignment by a central computer generated randomization scheme. Numbers were allocated sequentially in the order in which the patients were enrolled. After informed consent, an interactive voice response system was used by the investigators to assign the next randomization number to the patient. Central randomization stratified the patient on disease extent. **Allocation concealment**: Adequate **Blinding:** Single investigator	**<u>All patients:</u>** **N=375 randomised** **N=373 for safety analysis, 368 for ITT and 330 for PPA** **Drop-outs** (don't complete the study): Unclear N=64 (17%) Foam group (24 major protocol violators (12 of which prematurely withdrew), 9 premature withdrawals) and the liquid enema group (21 major protocol violators (14 of which prematurely withdrew) and 10 premature withdrawals) **Inclusion criteria:** • >18 years old • Newly diagnosed or relapsing UC • Extent: At least 5m from the ano-rectal junction and not above the splenic flexure • Severity: Clinical activity Index (1-4) score of ≥4 • At least one colonoscopy in the disease history **Exclusion:** • Pregnant women • Antibiotics, NSAIDs, and rectal steroids within 1 week prior to baseline • Oral steroids within 1 month or immunomodulators within 3 months prior to baseline • Significant hepatic or renal function abnormalities • Clearance creatinine ≤80ml/min **<u>Baseline characteristics</u>** **<u>Group 1: 1g mesalamine foam enema (data on n=189)</u>** **Sex (m/f):** 113/76 **Median age (range):** 44.0 (18-83) **Episode:** first episode n=61 **Extent:** proctitis and proctosigmoiditis n=178,proctitis n=81, proctosigmoiditis n=97, left sided n=11	**Group 1: 1g mesalamine foam enema** N=191 randomised/ safety population N=189 (ITT) 1g/80mls mesalamine (5-ASA) foam per day. **Group 2: 1g mesalamine (Pentasa) liquid enema** N=184 randomised N=182 safety population N=179 (ITT) 1g/100mls mesalamine liquid enema (Pentasa) per day **Concomitant therapy:** The following was permitted: if on oral 5-ASA maintenance treatment at a stable dose for at least one month or stable dose of azathioprine/ methotrexate for 6 months prior to the trial and the dose is maintained at the same level in the trial.	**Outcome 1: Clinical remission** (CAI 1-4 ≤2) N values were calculated from the percentages given in the paper.	**Authors definition of ITT** **<u>Week 2</u>** **Group1:** 91/189 **Group 2:** 91/179 **<u>Week 4</u>** **Group1:** 126/189 **Group 2:** 126/179	**Funding:** Sponsored by Ferring, France **Limitations:** Single blind **Additional outcomes:** Global acceptability
			Outcome 2: Endoscopic remission (score <4)	**Authors definition of ITT** **<u>Week 4</u>** **Group1:** 121/189 **Group 2:** 130/179	
			Outcome 3: Adverse events Mainly due to GI disorders.	**Authors safety population** **Group1:** 52/191 **Group 2:** 59/182	

Author	Patients	Intervention	Outcome measures	Effect size	Comments
blind. **Outcome assessment:** Clinical activity index (1-4) according to Rachmilewitz. Endoscopic index according to Rachmilewitz. **Sample size calculation:** 80% power, type 1 error of 5%, sample size calculation of 378 **Type of analysis: ITT and PPA** **Compliance rates:** At week 4 patients had to return the treatment box containing used and unused medication and answer questions about compliance. N= 15 withdrawals due to AEs. Doesn't report whether the AEs were drug related (foam 1 SAE and 7 non serious AE, liquid 1 SAE and 6 non serious AE). **Note: the figures for withdrawals due to AEs are also reported again in the text and do not add up to those quoted earlier on in the study.**	**CAI (1-4) at baseline, median (range):** 6.0 (4-11) **Drop outs:** 33 (24 major protocol violations (bad compliance, no efficacy criteria, inclusion criteria not fulfilled etc. of which 12 prematurely withdrew, in addition there were9 premature withdrawals) **<u>Group 2: 1g mesalamine (Pentasa) liquid enema (data on n=179)</u>** **Sex (m/f):** 83/96 **Median age (range):** 41.0 (17-78) **Episode:** first episode n=55 **Extent:** proctitis and proctosigmoiditis n=173,proctitis n=82, proctosigmoiditis n=91, left sided n=6 **CAI (1-4) at baseline, median (range):** 6.0 (4-11) **Drop outs:** 31(21 major protocol violations (bad compliance, no efficacy criteria, inclusion criteria not fulfilled etc. of which 14 prematurely withdrew, in addition there were10 premature withdrawals)		**Outcome 4: Serious adverse events** Reasons were not described.	**Group1:** 1/191 **Group 2:** 1/182	

Table 34: COURTNEY1992

Author	Patients	Intervention	Outcome measures	Effect size	Comments
M.G. Courtney et al. Randomised comparison of olsalazine and mesalazine in	**<u>All patients:</u>** **N=100 randomised**	**Group 1: 1g Olsalazine** N=50 randomised	**Outcome 1: Relapse** by 12 months (ITT)	**Group1:** 5/49 **Group 2:** 13/50	**Funding:** None described.

Author	Patients	Intervention	Outcome measures	Effect size	Comments
prevention of relapses in ulcerative colitis. *The Lancet; 339: 1279-1281. 1992.* **REF ID: COURTNEY1992** **Study design and quality:** Single blind RCT, Ireland Single centre **12 month trial** **Randomisation:** Computer generated code for random allocation **Allocation concealment**: Adequate **Blinding:** Single- observers unaware of treatment allocation **Outcome assessment:** Diary cards to document symptoms and adverse events. **Sample size calculation:** 73% power, 5% significance, reduction in relapse rate of 25%, 100 patients. **Type of analysis: ITT and PPA.** All patients were included in the ITT apart from one patient who was lost to follow up immediately after entry and no follow up data. **Compliance rates:** Compliance was classed as having taken less	**N=99 ITT** **Drop-outs** (don't complete the study): N=18 (18%) <10% difference in missing data between the treatment arms **Inclusion criteria:** • Aged 16-75 years • Presence of ulcerative colitis previously diagnosed by appropriate combination of clinical, endoscopic, histological and radiological criteria and now in remission **Exclusion:** • Administration of systemic steroids, azathioprine or metronidazole within the previous month • Existing or intended pregnancy • Substantial cardiac, pulmonary, hepatic or renal disease **<u>Group 1: 1g olsalazine</u>** **Mean age (range):** 40.7 (16-72) **Mean time since relapse (range), months:** 9.4 (1-48) **Mean disease duration (range), months:** 98 (1-408) **Number of bowel movements/day:** 2.2 (1-8) **Extent:** proctitis n=16, left sided colitis n=22, pancolitis n=12 **Severity of previous relapse:** Not described. **Frequency of relapses:** Not described. **Drop outs:** 8 (2 due to AE, 2 intercurrent illness (MI and LVF), 3 poor compliance) **<u>Group 2: 1.2g mesalazine</u>** **Mean age (range):** 43.9 (11-77) **Mean time since relapse (range), months: 11.2** (2-48) **Mean disease duration (range), months:** 98 (4-300) **Number of bowel movements/day:** 2.1 (0-6) **Extent:** proctitis n=15, left sided colitis n=22, pancolitis n=13 **Severity of previous relapse:** Not described. **Frequency of relapses:** Not described. **Drop outs:** 10 (4 protocol violation at entry, 2 due to AEs, 3 lost to	N=49 (ITT) N= 42 (PPA) 1g olsalazine (Dipentum) per day in divided doses with meals. **Group 2: 1.2g mesalazine** N=50 randomised N=50 (ITT) N= 40(PPA) 1.2g mesalazine (Asacol) per day in divided doses with meals. **Concomitant therapy:** None described. See inclusion/exclusion criteria.		**Life table analysis p=0.022**	**Limitations:** Single blind **Additional outcomes:** Mean daily bowel movements for completers Satisfaction rating **Notes:** Only 1 patient with pancolitis had a relapse.
			Adverse events The data was not analysed as it was unclear whether the figures given were all the adverse events and whether one person experienced more than one adverse event. **Group 1:** 6/49 **Group 2:** 5/50 9 probably/ definitely drug related AE: Diarrhoea in 2 olsalazine patients (1 withdrew), 2 patients in each group had abdo pain (both in mesalazine group withdrew and found to have duodenal ulcers and 1 from the olsalazine group withdrew), nausea and rash in 1 olsalazine patient and 2 mesalazine patients. End of the 12 months two patients had colon cancer, symptomless and small. One in each group. They had had UC for 14.5 and 19 years.		

Author	Patients	Intervention	Outcome measures	Effect size	Comments
than one week's medication from a 3 month supply had not been taken. Discreet tablet counting and analysis of urine for total 5-ASA. N=4 dropout/ withdrawal due to drug related AEs.	follow up, 1 poor compliance) **Definitions** **Remission:** Absence of symptoms or the presence of only mild stable symptoms of colitis **Relapse:** Development of new symptoms of colitis sufficiently severe to warrant the introduction of systemic steroid therapy (by an investigator unaware of study treatment). Withdrawal from the trial could be due to: relapse, side effects, lost to follow up, intercurrent illness or poor compliance.				

Table 35: DALBASIO1990

Author	Patients	Intervention	Outcome measures	Effect size	Comments
G. D'Albasio et al. Intermittent Therapy with High-Dose 5-Aminosalicylic Acid Enemas for Maintaining Remission in Ulcerative Proctosigmoiditis. *Diseases of the Colon and Rectum; 33(5):394-397. 1990.* **REF ID: DALBASIO1990.** **Study design and quality:** Single blind RCT **2 year trial** **Randomisation:** Randomly assigned, no further information given. Unclear. **Allocation concealment**: Unclear.	**All patients:** **N=60 randomised** **Drop-outs** (don't complete the study): N=15 **(25%)** (29% in group 1 and 20.7% in group 2. <10% missing data difference between the two treatment arms). **Inclusion criteria:** • Extent: rectosigmoid involvement • Severity: had previously had a mild or moderate relapse prior to remission • All patients were in remission, documented by clinical, histologic and endoscopic criteria • Minimum of 2 months in remission **Exclusion:** • None described. **Group 1: 2g SASP** **Mean age (SD):** 40.5 (14.3) **Extent:** proctosigmoiditis n=29, proctitis n=2	**Group 1: 2g SASP** N=31 randomised 2g Sulphasalazine daily, orally. **Group 2: Rectal 5-ASA** N=29 randomised 4g rectal 5-ASA enema daily for the first 7 days of each month. Given at night. Type of 5-ASA was not specified. **Concomitant therapy:** None described.	Outcome 1: **Relapse** Unable to calculate the hazard ratio from the information given in the paper. It was felt that reading values off the graph would not be an accurate measure, so the data will be presented narratively.	**Group1:** 12/31 (ITT) **Group 2:** 9/29 (ITT) **Log rank test: p>0.05** **Severity of relapse** **Mild** **Group 1:** 8/12 **Group 2:** 6/9 **Moderate** **Group 1:** 3/12 **Group 2:** 3/9	**Funding:** Servizio Farmaceutico, Ospedale di Careggi helped with the statistical analysis and the preparation of the 5-ASA enemas. **Limitations:** Unclear method of randomisation and allocation concealment Single blind **Additional outcomes:** Number of relapses with disease extension Note:

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Blinding: Physicians were blind to the patient's treatment. **Outcome assessment:** Diary was used to document clinical symptoms and regular administration of the drugs. Disease activity was evaluated according to Truelove and Richards. Mucosa was scored according to Baron et al. **Sample size calculation:** Not described. **Type of analysis: ITT** **Compliance rates:** 93% for 5-ASA enemas, 90% for SASP N=2 dropout/ withdrawal due to drug related AEs (intolerance to SASP).	**Severity of previous relapse:** all mild/moderate **Frequency of relapses:** >1 /yr n=5, approx 1/yr n=14, <1/year n=12 **Drop outs:** 9 (2 due to drug intolerance, 4 spontaneous discontinuation, 3 due to poor compliance) **<u>Group 2: 4g rectal 5-ASA (intermittent)</u>** **Mean age (SD):** 42.6 (10.3) **Extent:** proctosigmoiditis n=27, proctitis n=2 **Severity of previous relapse:** all mild/moderate **Frequency of relapses:** >1 /yr n=7, approx 1/yr n=10, <1/year n=12 **Drop outs:** 6 (4 due to spontaneous discontinuation, 2 due to poor compliance) <u>Definitions</u> **Remission:** Mild symptoms and normal mucosa. **Relapse:** Erythematous and friable mucosa, even in the absence of symptoms.			**Severe** **Group 1:** 1/12 **Group 2:** 0/9 **Group1:** 2/31 **Group 2:** 0/29	It is unclear whether these patients were SASP tolerant. In the discussion section of the paper it states "It should, however, be remembered that the latter (SASP treated)group comprised essentially a series of patients previously selected for their tolerance to the treatment with sulfasalazine". Definition of relapse used would still be classed as remission in many other studies.

Table 36: DALBASIO1997

Author	Patients	Intervention	Outcome measures	Effect size	Comments
G. d'Albasio et al. Combined Therapy with 5-Aminosalicylic Acid Tablets and Enemas for Maintaining Remission in Ulcerative Colitis: A Randomized Double-Blind Study. *The American Journal of Gastroenterology; 92 (7): 1143-1147. 1997.* **REF ID: DALBASIO1997**	**<u>All patients:</u>** **N=72 randomised** **N=72 ITT** **Drop-outs** (don't complete the study): N=8 (11.1%) **Inclusion criteria:** • 18-65 years	**Group 1: Oral and rectal mesalazine** N=36 randomised N=36 (ITT) N=31 (completers) 1.6g oral mesalazine daily and 4g/100ml mesalazine enema twice a week. Mesalazine used	Outcome 1: **Relapse** **Log rank test p=0.02.** Outcome 2: **Relapse by extent of disease**	**Group1:** 13/36 **Group 2:** 23/36 **<u>Proctosigmoiditis</u>** **Group1:** 6/11 **Group 2:** 9/13	**Funding:** Supported by Broacco S.p.A. **Limitations:** None. **Additional outcomes:**

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Study design and quality: **Double blind RCT** **Multicentre: 3 centres, Italy** **1 year trial** **Randomisation:** Randomisation by a computer which generated random codes. **Allocation concealment:** Adequate. **Blinding:** Double blind. Identical looking enemas. Physicians unaware of patient's treatment. **Outcome assessment:** Diary recording stool frequency, abdominal pain, rectal bleeding and regular administration of the drugs. Instructed to contact physicians if they experienced any untoward effects. Seen every 2 months. 6 monthly colonoscopy and laboratory tests. Clinical assessment according to Powell-Tuck score, endoscopy according to Baron et al., histology Truelove criteria. **Sample size calculation:** 30 patients per treatment group. 30% difference in recurrence rate, 80% power, 5% significance. **Type of analysis: ITT.** Drop outs for any other reason than relapse were censored.	• Extent: Disease extent greater than proctitis only • History of two or more UC relapses in the last year • Remission obtained in the last 3 months • Remission documented by clinical histological and endoscopic criteria and maintained for a minimum of 1 month; in this period all patients were maintained on a regimen of oral (1.6g/day) plus topical (4g/100mls, twice weekly) mesalazine. **Exclusion:** • Proctitis only • Severe hepatic or renal disease • Hypersensitivity to salicylates • Other usual criteria for excluding participation in a clinical trial • Patients who in the previous 12 months had experienced a disease activity unresponsive to a 12 week course with steroids and those patients in whom steroid dose tapering had been unsuccessful because they returned to be symptomatic. **<u>Group 1: Oral and rectal mesalazine</u>** **Extent:** proctosigmoiditis n=11, left sided colitis n=20, pancolitis n=5 **Mean duration of disease (SD):** 6 years (7years) **Severity of previous relapse:** Not described. **Frequency of relapses:** 2 relapses in last year n=22, ≥3 relapses in last year n=14 **Current use of immunomodulators:** Not described. **Drop outs:** 5 (2 lost to follow up, 3 poor compliance) **<u>Group 2: Oral mesalazine</u>** **Extent:** proctosigmoiditis n=13, left sided colitis n=18, pancolitis n=5 **Mean duration of disease (SD):** 7 years (5years) **Severity of previous relapse:** Not described. **Frequency of relapses:** 2 relapses in last year n=24, ≥3 relapses in last year n=12 **Current use of immunomodulators:** Not described. **Drop outs:** 3 (due to poor compliance) Mean age at randomization was 42 years (range 21-61 years) **<u>Definitions</u>** **Remission:** Mild symptoms and normal endoscopic appearance of the mucosa.	was Asacol. **Group 2: Oral mesalazine** N=36 randomised N=36 (ITT) N=33 (completers) 1.6g oral mesalazine daily and a placebo enema twice a week. Mesalazine used was Asacol. **Concomitant therapy:** Not described.		**<u>Left sided colitis</u>** **Group1:** 5/20 **Group 2:** 11/18 **<u>Pancolitis</u>** **Group1:** 2/5 **Group 2:** 3/5	Severity of relapses Relapse with disease extension **Notes: Withdrawal study**
			Outcome 3: **Adverse events** No side effects attributable to 5-ASA were observed.		

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Compliance rates: Unclear level for compliance. 6 patients were not compliant. **N=0 dropout/ withdrawal due to drug related AEs.**	**Relapse:** Presence erythematous and friable mucosa even in the absence of symptoms.				

Table 37: DALBASIO1998

Author	Patients	Intervention	Outcome measures	Effect size	Comments
G. d'Albasio et al. Maintenance Treatment of Ulcerative Proctitis With Mesalazine Suppositories: A Double-Blind Placebo-Controlled Trial. *The American Journal of Gastroenterology; 93 (5): 799-803. 1998.* **REF ID: DALBASIO1998** **Study design and quality:** Double blind RCT Multicentre: 7 centres, Italy **1 year trial** **Randomisation:** Carried out in blocks of three using centre as a single variable of stratification. Unclear. **Allocation concealment**: Unclear. **Blinding:** Double blind.	**<u>All patients:</u>** **N=111 randomised** **N=91 completers** **Drop-outs** (don't complete the study): N=20 (18%) **Inclusion criteria:** >18 years of age Confirmed diagnosis of ulcerative proctitis in clinical, endoscopic and histological remission and had suffered a recent relapse of the disease (during the last 6 months) Extent: Ulcerative proctitis (limited to the rectum ≤15cm from anus) **Exclusion:** Salicylate allergy Concomitant active peptic ulcer Clinically important hepatic, renal, cardiovascular or psychiatric conditions Pregnant or lactating women	**Group 1: 1g mesalazine suppositories** N=36 randomised N=30 (completers) Two 500mg mesalazine suppositories (Asacol) per day. **Group 2: 500mg mesalazine suppository** N=40 randomised N=33 (completers) One 500mg mesalazine suppository (Asacol) and one placebo suppository per day. **Group 3: Placebo** N=35 randomised N=28 (completers) Two placebo	Outcome 1: Cumulative **relapse** rate Hazard ratios have been calculated. **Note:** the figures used for the number who have relapsed have been taken from Figure 1 rather than calculating them from the percentages given in the text. Outcome 2: **Adverse events** Group 1:Anal canal irritation and	**<u>At 12 months</u>** **ITT** **Group 1:** 3/36 **Group 2:** 11/40 **Group 3:** 14/35 **Log rank test group 1 vs. 3:** p=0.007 **Log rank test group 2 vs. 3:** p=0.1175 **Log rank test group 1 vs. 2:** p=0.0334 **Group 1:** 2/32 **Group 2:** 2/35	**Funding:** Supported by Bracco S.p.A., Milano, Italy **Limitations:** Unclear method of randomisation and allocation concealment Double blind but no further information given on the investigator blinding **Additional outcomes:** Physician's Global Assessment

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Outcome assessment: Endoscopic score by Baron's criteria (0-3). Histological score according to Truelove & Richards (0-3) **Sample size calculation:** Minimum of 35 per treatment arm to detect a 25% difference in the recurrence rate between mesalazine and placebo, power of 80%, 5% significance level. **Type of analysis: ITT** **Compliance rates:** Checked by the study personnel by counting returned unopened blister packs and review of returned empty blister packs. Noncompliant patients, were those who took <75% of the study medication in the previous 3 months (recorded as drop outs) N=5 dropout/ withdrawal due to drug related AEs.	Immunosuppressive drugs>3 months prior to the study Corticosteroids >2 weeks before the study 5-ASA or SASP <3 days before the study Positive stool culture **Group 1: 1g mesalazine suppositories** **Mean age (range):** 41 (18-65) **Extent:** All proctitis **Severity of previous relapse:** Not described **Mean frequency of relapses (SD) per year:** 1.54 (1.01) **Current use of immunomodulators:** Not described **Drop outs:** 6 (4 due to poor compliance, 2 due to drug related adverse events (anal canal irritation, abdominal pain and constipation)) **Group 2: 500mg mesalazine suppository** **Mean age (SD):** 41 (18-63) **Extent:** All proctitis **Severity of previous relapse:** Not described **Mean frequency of relapses (SD) per year:** 1.26 (1.11) **Current use of immunomodulators:** Not described **Drop outs:** 7 (3due to poor compliance, 2 lost to follow-up, 2 due to drug related adverse events (abdominal pain and constipation with swelling)) **Group 3: Placebo** **Mean age (SD):** 41 (20-65) **Extent:** All proctitis **Severity of previous relapse:** Not described **Mean frequency of relapses (SD) per year:** 1.51 (1.76) **Current use of immunomodulators:** Not described **Drop outs:** 7 (4 due to poor compliance, 2 lost to follow-up, 1 treatment related adverse event (tenesmus and swelling)) **Definitions:** **Clinical remission:** absence of visible blood in the stools and no more than two bowel movements per day. **Endoscopic remission:** score of 0 (Baron's criteria) **Histological remission:** score of 1 (Truelove & Richard's criteria)	suppositories per day. **Concomitant therapy:** None described.	abdominal pain with constipation Group 2: abdominal pain and constipation and swelling Group 3: Tenesmus and swelling	**Group 3:** 1/29	

Author	Patients	Intervention	Outcome measures	Effect size	Comments
	Relapse: Development of symptoms together with evidence of endoscopic activity (grade>1 of Baron's classification). Patients who experienced a side effect were considered right-censored at the time of their last visit.				

Table 38: DANIELSSON1987

Author	Patients	Intervention	Outcome measures	Effect size	Comments
A. Danielsson et al. A Controlled Randomized Trial of Budesonide versus Prednisolone Retention Enemas in Active Distal Ulcerative Colitis. *Scandinavian Journal of Gastroenterology; 22: 987-992. 1987.* **REF ID: DANIELSSON1987** **Study design and quality:** Single investigator blind RCT Multicentre: 8 centres, unclear which country ?Sweden **4 week trial** **Randomisation:** Randomized in blocks of two. No other information was given. **Allocation concealment**: No information given. **Blinding:** Single investigator	**<u>All patients:</u>** **N=64 randomised** **Drop-outs** (don't complete the study): N=2 (3%) **Inclusion criteria:** • 16-65 years • Extent: Active distal UC (rigid sigmoidoscopy confirmation). No distal definition given. • Severity: not part of the inclusion criteria **Exclusion:** • Use of corticosteroids during the month preceding the trial • Pregnant or non contraceptive practicing women **<u>Baseline characteristics</u>** **<u>Group 1: 2mg budesonide liquid enema</u>** **Maintenance therapy with SASP:** n=10 **Drop outs:** 0 **<u>Group 2: 31.25mg prednisolone liquid enema</u>** **Maintenance therapy with SASP:** n=11 **Drop outs:** 2 (treatment failure)	**Group 1: 2mg Budesonide liquid enema** N=31 randomised 2mg budesonide liquid enema in 100mls. Once daily at bedtime. **Group 2: 31.25mg prednisolone liquid enema** N=33 randomised 31.25mg/100mls prednisolone disodium phosphate liquid enema. Once daily at bedtime. **Concomitant therapy:** Sulphasalazine and other drugs for concomitant diseases were permitted if medically justified.	**Outcome 1: Endoscopic remission** (score of 0)	**Group1:** 16/31 **Group 2:** 8/33	**Funding:** Financial support and drug provision by AB Draco, Lund, Sweden **Limitations:** Single investigator blind Unclear method of randomisation and allocation concealment Very limited baseline characteristics Risk of indirect population as no severity data given **Additional outcomes:** Responders and non responders endoscopically and histologically at 2 and 4 weeks Plasma cortisol levels

Author	Patients	Intervention	Outcome measures	Effect size	Comments
blind. **Outcome assessment:** Endoscopy scoring according to Truelove & Richards. **Sample size calculation:** Not described. **Type of analysis: ITT** **Compliance rates:** not described. N=0 dropout/ withdrawal due to drug related AEs.	**Overall:** **Sex (m/f):** 27/37 **Mean age (range):** 42 years (19-65 years) Age, sex and duration of disease was said not to differ between the groups.				Subjective well-being

Table 39: DARIENZO1990

Author	Patients	Intervention	Outcome measures	Effect size	Comments
A. D'Arienzo et al. 5-Aminosalicylic Acid Suppositories in the Maintenance of Remission in Idiopathic Proctitis or Proctosigmoiditis: A Double-Blind Placebo-Controlled Clinical Trial. *The American Journal of Gastroenterology; 85 (9): 1079-1082. 1990.* **REF ID: DARIENZO1990** **Study design and quality:** RCT **1 year trial**	**<u>All patients:</u>** **N=30 randomised** **Drop-outs** (don't complete the study): These were considered as censored data and evaluated in the statistical analysis. N=3 (10%) **Inclusion criteria:** Patients with clinically, endoscopically and histologically documented idiopathic proctitis or proctosigmoiditis were selected Not taken oral or enema steroids for at least one month Extent: Distal colitis in remission (proctitis or proctosigmoiditis) Complete remission	**Group 1: 800mg of 5-ASA suppositories** N=15 randomised N=13 (ACA) 400mg 5-ASA suppository (CHIESI Farmaceutici) twice a day. **Group 2: Placebo** N=15 randomised N=14 (ACA) Identical placebo suppository twice a	Outcome 1: **Relapse** Hazard ratios have been calculated where possible.	**<u>At 1 year:</u>** **Group1:** 1/15 **Group 2:** 11/15 **Log rank p value: p<0.001** **<u>By extent of disease: ITT</u>** **<u>Proctitis</u>** **Group1:** 1/9 **Group 2:** 6/8	**Funding:** None described. **Limitations:** Unclear allocation concealment Open study (unclear blinding) **Additional outcomes:** No other outcomes were listed. **Notes:** The data was also stratified

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Randomisation: Divided at random using a random numbers table. No stratification. **Allocation concealment**: Unclear. **Blinding:** None described. **Outcome assessment:** Patient diaries. Endoscopy by Balckstone's modified scoring criteria (0-4). Biopsies were scored according to the method of Friedman (0-3). **Sample size calculation:** None described. **Compliance rates:** Assessed by the number of used suppository containers returned at each check up by the participants. It was said to be satisfactory, no further details was given. N=0 dropout/ withdrawal due to drug related AEs.	**Exclusion:** Pregnant and lactating women Women of childbearing potential not taking adequate contraceptive measure Patients who were considered unlikely to follow the instructions correctly Patients with a history of colon neoplasm or diverticulitis Chronic cardiac, Kidney or liver disease **<u>Group 1: 5-ASA suppositories</u>** **Mean age (SD):** 41.1 (9.7) **Mean duration of complete remission before trial (SD):** 6.3 months (7.0) **Number of patients in prolonged (≥1 year) or remission:** 1 **Extent:** proctitis n=9, proctosigmoiditis n=6 **Severity of previous relapse:** Not reported **Frequency of relapses:** Not reported **Therapy for previous attack:** oral SASP or 5-ASA n=2, rectal steroids and SASP n=3, systemic steroids and SASP n=0, 5-ASA enemas or suppositories n=10 **Maintenance therapy prior to enrolment:** no therapy n=7, SASP or 5-ASA n=8 **Allergy or intolerance to SASP:** n=4 **Drop outs:** 2 (At the 3rd and 5th months for personal reasons unrelated to the treatment, while in remission) **<u>Group 2: Placebo</u>** **Mean age (SD):** 39.8 (10.3) **Mean duration of complete remission before trial (SD):** 5.5 months (2.7) **Number of patients in prolonged (≥1 year) or remission:** 2 **Extent:** proctitis n=8, proctosigmoiditis n=7 **Severity of previous relapse:** Not reported **Frequency of relapses:** Not reported **Therapy for previous attack:** oral SASP or 5-ASA n=1, rectal steroids and SASP n=4, systemic steroids and SASP n=1, 5-ASA enemas or suppositories n=9	day. **Concomitant therapy:** None described.		**<u>Proctosigmoiditis</u>** **Group1:** 0/6 **Group 2:** 5/7 No clinical or chemical side effect was seen.	by extent of disease as there was a greater number of patients with proctitis rather than proctosigmoiditis in the 5-ASA group. The significant difference in remission and relapse rates were independent of the extent of disease, p<0.001.

Author	Patients	Intervention	Outcome measures	Effect size	Comments
	Maintenance therapy prior to enrolment: no therapy n=9, SASP or 5-ASA n=6 **Allergy or intolerance to SASP:** n=5 **Drop outs:** 1 (In the 2nd month for personal reasons unrelated to the treatment, while in remission) In 8 patients, steroids had been administered for the treatment of the last attack until 3-6 months before study entry. The rest of the patients had not required any steroid treatment for at least a year. 14 patients stopped maintenance treatment with SASP or 5-ASA prior to the trial (enrolment); the rest had been stopped from 1-3 months prior to the trial. **Definitions used:** **Clinical remission:** Absence of blood in the stools and absence of diarrhoea, abdominal pain and tenesmus. **Endoscopic remission:** Grade 0 or 1 Histologically (Grade 2 or 3) **Relapse:** Identified by clinical activity endoscopically (grade 2, 3, 4) and histologically (grade 2 or 3) confirmed, or in the absence of clinical manifestations, by endoscopic and histological evidence of activity. Relapsers were removed from the study, those on the rectal ASA were given a rectal steroid and those on the placebo were given the rectal ASA.				

Table 40: DHAENS2001

Author	Patients	Intervention	Outcome measures	Effect size	Comments
G. D'Haens et al. Intravenous cyclosporin versus intravenous corticosteroids as single therapy for severe attacks of ulcerative colitis. *Gastroenterology; 120: 1323-1329. 2001.*	**All patients:** **N=30 randomised** **N=30 ITT** **Drop-outs** (don't complete the study): N=1 (3.33%)	**Group 1: Ciclosporin** N=15 randomised N=14 (ITT) N=14 (completers) Continuous infusion of 4 mg/kg	**Outcome 1: Clinical improvement (clinical response):** Improvement in the clinical-activity score. Response was defined as a score of < 10 on days 7 and 8 with a	**0- ≤2 weeks** **Ciclosporin:** 9/14 **Steroid:** 8/15	**Funding:** None reported **Limitations:** Unclear method of randomisation and allocation concealment

Author	Patients	Intervention	Outcome measures	Effect size	Comments
REF ID: DHAENS2001 **Study design and quality:** Double blind RCT Single centre **8 days of IV medication** **Randomisation:** Not reported **Allocation concealment**: Not reported **Blinding:** Double blind **Outcome assessment:** Unblinded **Sample size calculation:** None **Type of analysis:** Available case **Compliance rates:** Not described. N=1 dropout/ withdrawal due to drug related AEs.	**Inclusion criteria:** Hospitalised with severe attack of UC. Active inflammation confirmed by flexible proctosigmoidoscopy. Severity: Patients were only included if the clinical activity score at inclusion was ≥ 10 (max score 21; modified Truelove and Witts score developed by Lichtiger et al.) **Exclusion:** Dilation or perforation of the colon. Uncontrolled hypertension, renal insufficiency with a serum creatinine level of > 2 mg/dL, increased concentrations of liver enzymes (>2 upper limit of normal), active infection or pregnancy. Treated with azathioprine for less than three months or if the dose had been changed in the 4 weeks before admission. Oral glucocorticosteroids were allowed for up to 14 days unless there had been an improvement of symptoms, and were discontinued at inclusion. Rectal steroids including budesonide enemas were not permitted in the 4 weeks before inclusion. **<u>Group 1: Ciclosporin</u>** **Mean age (SD):** 36.7 (19.8) **Extent:** Left-sided/universal 2/13 Concomitant medication Oral corticosteroids (< 2 wk) 2/15 Sulphasalazine/mesalamine 14/15 Azathioprine 1/15 Mean clinical activity index 13.9 (3.3) **Drop outs:** 1 patients excluded with C. difficile toxins **<u>Group 2: Methylprednisolone (steroid)</u>** **Mean age (SD):** 37.3 (15.1) **Extent:** Left-sided/universal 2/13 Concomitant medication Oral corticosteroids (< 2 wk) 4/15 Sulphasalazine/mesalamine 9/15 Azathioprine 2/15 Mean clinical activity index 13.2 (4.9) **Drop outs:** 0	body weight per day in a 250-mL 0.9% NaCl. Patients who had a response to ciclosporin were switched to oral ciclosporin started in a dose of 8 mg/kg in 2 equally divided doses per day adjusted to serum levels between 200 and 350 ng/mL **Group 2: Methylprednisolone** N=15 randomised N=15 (ITT) N=15 (completers) 40 mg per day in 250 mL 0.9% NaCl. Patients who had responded were switched to oral methylprednisolone 32 mg/day At discharge, azathioprine treatment in a dose of 2 to 2.5 mg kg^{-1} day^{-1} orally (without escalation) was started in all patients who were responders to ciclosporin or to combination therapy and who had not experienced severe adverse reactions to the drug in the past; in those already receiving the drug, it was continued at the same dose. Patients who had no response were offered the option to receive combined open-label IV treatment with glucocorticosteroids plus ciclosporin for another 5-8 days. If clinically indicated or in case this	drop in the score from day 1 to day 8 of at least 3 points and the possibility to discharge the patient **Outcome 2: Colectomy** At day 8, blinding ended Additional colectomies occurred after the failures were tried on combination treatment 3 in the methylprednisolone group. The patient who had C. Difficile and was withdrawn from the study also had a colectomy. These figures have not been included in the analysis. **Outcome 3: Adverse events** Number of patients experiencing one or more AEs not reported. The following are the AEs during the trial: **Ciclosporin:** Hypertension 1/11 Superficial thrombophlebitis 1/11 Headache 2/11 Vomiting 1/11 Epigastric discomfort 0/11 Hypokalemia 4/22	**0- ≤2 weeks** **Ciclosporin:** 2/14 **Steroid:** 0/15	**Additional outcomes:** • Long-term response and colectomy rates • Endoscopy response • Scintigraphic evaluation • Renal impairment

Author	Patients	Intervention	Outcome measures	Effect size	Comments
		combination also failed, a colectomy was proposed **Concomitant therapy:** Patients were excluded if they had been treated with azathioprine for less than 3 months or if the dose had been changed in the 4 weeks before admission. Azathioprine was continued if patients had been using it for more than 3 months. Oral glucocorticosteroids were allowed for up to 14 days unless there had been an improvement in symptoms, and were discontinued at inclusion. Oral sulphasalazine or other mesalamine formulations were kept stable. Mesalamine enemas were continued if they could be retained. Patients already taking antibiotics continued to receive them only if clinically indicated. During the study, antibiotics were only initiated in case of intercurrent infection. Antidiarrheal drugs were continued if judged necessary and safe, but not initiated during the study; use of these drugs (loperamide, codeine) was accounted for in the clinical activity score. Antihypertensive drugs were continued or initiated as indicated.	Hypomagnesia 2/11 Myalgia 2/11 (side effects beyond the first week of treatment but stopped when the ciclosporin was discontinued were; gingival hyperplasia (3), hypertension (1), tremor (1), hair loss (1) and headache (1). **Steroids:** Superficial thrombophlebitis 1/15 Headache 1/15 Epigastric discomfort 1/15 Parasthesia 1/15 Myalgia 1/15		

Table 41: D'HAENS2006

Author	Patients	Intervention	Outcome measures	Effect size	Comments

Author	Patients	Intervention	Outcome measures	Effect size	Comments
G. D'Haens et al. Once daily mezavant XL mesalazine for the treatment of mild-to-moderate ulcerative colitis: a phase II, dose-ranging study. *Alimentary Pharmacology & Therapeutics; 24: 1087-1097. 2006.* **REF ID: DHAENS2006** **Study design and quality:** Double blind, Pilot Phase II, RCT Multicentre: 8 centres, Belgium, the Netherlands and the United Kingdom **8 week trial** **Randomisation:**1:1:1 ratio. Stratified by centre and randomization numbers were not reassigned in the event of patient withdrawal. **Allocation concealment**: Unclear. **Blinding:** Double blind. Identical tablets (mesalazine and placebo). No other information given. **Outcome assessment:** Sigmoidoscopy was score from 0-3. Ulcerative Colitis Disease Activity Index.	**<u>All patients:</u>** **N=40 enrolled** **N=38 randomised**(two were excluded for an allergy to 5-ASA and the other for no relapsing disease) **N=36 evaluable LOCF** (1 screen failure and 1 due to having a positive stool culture) **N=33 PPA** (3 protocol violators) **Drop-outs** (don't complete the study): N=10**(26%)** **Inclusion criteria:** Male and female patients ≥18 years Histologically confirmed, newly diagnosed or relapsing (≤6 weeks prior to baseline) Extent:>15cm Severity: Mild to moderate (score of 4-10 on the UCDAI, sigmoidoscopy score ≥1, PGA score of ≤2) Female patients were postmenopausal, sterile or had a negative urine pregnancy test prior to entering the study, and used adequate contraception during the study **Exclusion:** Crohn's disease Proctitis (≤15cm) Bleeding disorders Active peptic ulcer disease Asthma (if mesalazine-sensitive)	**Group 1: Mesalazine 1.2g** N=13 randomised N=12 evaluable N=11 PPA N=7 (completers) One active tablet (1.2g) and three placebo tablets given once per day (in the morning) Mezavant XL mesalazine tablets were used. **Group 2: Mesalazine 2.4g** N=14 randomised N=13 evaluable N=12 PPA N=11 (completers) Two active tablets (2 x 1.2g) and two placebo tablets given once per day (in the morning. Mezavant XL mesalazine tablets were used. **Group 3: Mesalazine 4.8g**	Outcome 1: **Clinical remission**(UCDAI score ≤1, with a score of 0 for rectal bleeding and stool frequency and at least a 1 point reduction from baseline in sigmoidoscopy score) Outcome 2: **Adverse events** No patient withdrew due to AEs. Most frequently reported was a headache (8 patients). Others were only in one patient (diarrhoea, nausea, upper abdominal pain, aphthous stomatitis, constipation and pruritis, somnolence. Outcome 3: **Serious Adverse events** The one SAE reported was not treatment related. It was a screen failure with autoimmune hepatitis.	**<u>ACA week 8</u>** **Group1:**0/13 **Group 2:**4/14 **Group 3:** 2/11 **Group1:**9/13 **Group 2:**9/14 **Group 3:** 10/11 **Group1:**1/13 **Group 2:**0/14 **Group 3:** 0/11	**Funding:** Shire Pharmaceuticals **Limitations:** Unclear method of randomisation and allocation concealment Unclear double blinding. There was no clear description. High dropout rate **Additional outcomes:** Change in UCDAI Change in sigmoidoscopy score Change in histology score Change in symptoms (rectal bleeding and stool frequency)

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Sample size calculation:80% power, 5% significance test, to detect a 28% difference (assuming a linear trend) **Type of analysis: ITT, safety population, PPA** **Last observation carried forward (LOCF)** **Compliance rates:** Determined through the amount of unused medication. There were no non-compliant patients described in the paper. N=0 dropout/ withdrawal due to drug related AEs.	Positive stool culture for enteric pathogens or with ova or parasites (detected by microscopy) Previous colonic surgery Moderate or severe renal impairment Current or recurrent disease that could affect the colon or the action, absorption or disposition of the study medication or clinical or laboratory assessments Current or relevant previous history of serious, severe or unstable (acute or progressive) physical or psychiatric illness Any medical disorder that may have required treatment or made the patient unlikely to fully complete the study Any condition that presented undue risk from the study medication or procedures Relapsed whilst on maintenance therapy (mesalazine dose >2.0g) Relapsed within 2 weeks of a mesalazine dose reduction from >2.0 to ≤2g/day Unsuccessfully treated a current relapse with steroids or with mesalazine doses>2.4g/day used systemic or rectal steroids within 4 weeks prior to baseline Use of immunosuppressant's within 6 weeks prior to baseline Used antibiotics or repeatedly used NSAIDs within 7 days prior to baseline (although prophylactic use of a stable dose of aspirin (up to 325mg/day) for cardiac disease was permitted **<u>Group 1: 1.2g mesalazine</u>** **Mean age (SD):**41 (no SD given, range 22-72years) **Extent:** left sided n=10, involvement of the transverse colon n=0, pancolitis n=2, missing n=1 **Use of 5-ASA (other than mesalazine) in the 6 weeks prior:** 38.5% **Drop outs:** 6 (1 screen failure, 2 subject requests, 3 treatment failures)	N=11 randomised N=11 evaluable N=10 PPA N=10 (completers) Four active tablets (4 x 1.2g) given once per day (in the morning). Mezavant XL mesalazine tablets were used. **Concomitant therapy:** Patients were not permitted to self medicate with topical 5-ASA preparations.			

Author	Patients	Intervention	Outcome measures	Effect size	Comments
	Group 2: 2.4g mesalazine **Mean age (SD):**39 (no SD given, range 23-74years) **Extent:** left sided n=11, involvement of the transverse colon n=0, pancolitis n=3, missing n=0 **Use of 5-ASA (other than mesalazine) in the 6 weeks prior:** 42.9% **Drop outs:** 3 (treatment failures) **Group 3: 4.8g mesalazine** **Mean age (SD):**48 (no SD given, range 31-79years) **Extent:** left sided n=7, involvement of the transverse colon n=1, pancolitis n=3, missing n=0 **Use of 5-ASA (other than mesalazine) in the 6 weeks prior:** 45.5% **Drop outs:** 1 (treatment failure) 31 patients had relapsing UC.				

Table 42: DHAENS2012

Author	Patients	Intervention	Outcome measures	Effect size	Comments
D'Haens G. et al. Once-Daily MMX Mesalamine for Endoscopic Maintenance of Remission of Ulcerative Colitis. *The American Journal of Gastroenterology; 107: 1064-1077. 2012.* **REF ID: DHAENS2012** **Study design and quality:** Double blind RCT Multicentre (113 sites in 27 countries) **6 month trial**	**All patients:** **N=829 randomised** N=826 ITT (received at least one dose of the trial treatment **Drop-outs** (don't complete the study): N= 52 (26 in the Asacol group, 26 in the mezavant XL group. For reasons see below). This excludes those that dropped out due to lack of efficacy. **Inclusion criteria:** • Male or female, 18 yrs + • Diagnosis of UC (confirmed by histology) that was in remission for ≥30 days on a stable dose of mesalamine (≤2.4g/day) or the equivalent dose of sulphasalazine (≤6.2g/day) • Endoscopy score ≤1	**Group 1: 2.4g mesalazine (mezavant XL)** N=416 randomised N=415 ITT N=343 PPA N=340 completers Given once a day. **Group 2: 1.6g mesalazine (Asacol)** N=413 randomised N=411 ITT	**Outcome 1: Relapse** (withdrew due to lack of efficacy) **Outcome 2: Serious adverse events** **Group 1:** 3 patients with 4 SAEs (UC, fallopian tube perforation, inter-vertebral disc	**6 months** **Group 1:** 51/415 **Group 2:** 57/411 **Log rank test: p=0.5455** **Group 1:** 6/415 **Group 2:** 3/411	**Funding:** Shire Development LLC, USA. They also gave funding to GeoMed and MedErgy for support in writing and editing the manuscript. **Limitations:** Double blind but no further information was given No baseline extent data (stated to be a subgroup, no data reported) Limited baseline

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Randomisation: 1:1 ratio. Sequentially allocating 4 digit unique treatment group numbers to subjects at their baseline visit. Following a subsequent protocol revision to increase the study sample size and interactive voice response system was used to , within each site, sequentially allocate the 4-digit randomization numbers along with 5 digit treatment pack numbers to each patient before the treatment pack was dispensed. **Allocation concealment**: Adequate. **Blinding:** Stated to be double blind. No further information was given. **Outcome assessment:** UCDAI score, Physician's global assessment, endoscopies and other modified UC-DAI assessments. Amended endoscopy scoring system (mucosal friability given a score of 2 rather than 1, therefore deemed not in remission). **Predefined subgroup: disease classification** **Sample size calculation:** True difference in proportions ≤-10%, 80% power, 330 pts per treatment group **Type of analysis: ITT** (all pts randomized and received at least	• Combined symptom score (stool frequency and rectal bleeding) of ≤1 • Have experienced at least one acute flare of UC (documented episode of increased bowel frequency with rectal bleeding for which UC therapy was intensified) in the past 12 months • At least 2 acute flares in their medical history **Exclusion:** • Use of rectal 5ASA or systemic or rectal corticosteroids within 30 days before baseline • Immunosuppressive agents or antitumor necrosis factor antibody therapy within 12 weeks before baseline • Repeatedly used anti-inflammatory drugs (including NSAIDs) within 7 days (except prophylactic stable dose aspirin up to 325mg/day for cardiac disease) • Received another investigational agent within 30 days • Renal impairment (serum creatinine >2mg/dl) • Moderate to severe hepatic impairment • Proctitis (maximum disease extent ≤15cm) • Surgical resection of a portion of the colon • Acute flare of UC within the past 30 days • Other diseases of the colon • Any current or relevant previous history of serious, severe or unstable (acute or progressive) physical or psychiatric illness or medical disorder that may require treatment • History of allergy or sensitivity to salicylates/ aspirin • Use of investigational products within the past 30 days • History of alcohol or other substance abuse within the past year • Pregnant and/or lactating women **<u>Group 1: 1.6g Asacol</u>** **Mean age (SD):** 45.2 (13.4) **Sex:** 214 male, 197 female **Mean time since diagnosis (SD):** 377.5 weeks (381.0) **Number of acute episodes of UC in the last year, n (%):** 0 =2 (0.5), 1-2= 393 (95.6), 3-4= 15 (3.6), 5-6= 0, ≥7=1 (0.2) **Extent:** Not described (not proctitis) **Severity of previous relapse:** Not described	N=336 PPA N=330 completers Given as 800mg b.d. **Concomitant therapy:** See exclusion list. No further information given.	protrusion and ectopic pregnancy) **Group 2:** 6 patients with 7 SAEs (colitis, UC, appendicitis, bronchitis, post-procedural haemorrhage, brachial radiculitis and asthma) **Adverse events:** these were only reported as treatment emergent, not all adverse events therefore the data has not been extracted.		characteristics **Additional outcomes:** Endoscopic remission Maintenance of mucosal healing with no or mild symptoms Modified UC-DAI score and its components **Notes:** Mesalazine or sulphasalazine tolerant population (been on it for at least 30 days prior to the trial).

Author	Patients	Intervention	Outcome measures	Effect size	Comments
one dose of the study medication), **PPA** **Compliance rates:** Not described. Although one patient dropped out due to non-compliance. N=9 dropout/ withdrawal due to AEs.	**Drop outs:** 26 (10 lost to follow up, 6 patient request, 3 AE/SAE, 3 protocol violations, 1 non-compliance, 1 pregnancy, 2 other) **Group 2: 2.4g mezavant XL** **Mean age (SD):** 45.0 (14.1) **Sex:** 212 male, 203 female **Mean time since diagnosis (SD):** 370.7 weeks (392.7) **Number of acute episodes of UC in the last year, n (%):** 0 =0, 1-2= 395 (95.2), 3-4= 18 (4.3), 5-6= 2 (0.5), ≥7=0 **Extent:** Not described (not proctitis) **Severity of previous relapse:** Not described **Drop outs:** 26 (5 lost to follow up, 10 patient request, 6 AE/SAE, 3 protocol violation, 2 other) **Definitions** **Relapse:** Defined as withdrawal due to lack of efficacy				

Table 43: DICK1964

Author	Patients	Intervention	Outcome measures	Effect size	Comments
A. P. Dick et al. Controlled trial of sulphasalazine in the treatment of ulcerative colitis. *Gut; 5: 437-442. 1964.* **REF ID: DICK1964** **Study design and quality:** Double blind RCT It is unclear what country the trial was carried out in (author's origin was the UK) **4 week trial**	**All patients:** **N=44randomised** **N=41 completed the study** **Drop-outs** (don't complete the study): N=3 (6.8%). Two patients stopped treatment due to vomiting and the other thought she had been cured after two weeks of treatment. All of these patients were in the sulphasalazine group. **Inclusion criteria:** Extent: Ulcerative colitis or proctitis Severity: Mild to moderate severity	**Group 1: Sulphasalazine** N=21 randomised N=18 (completers) Dose varied depending on their weight from 4-6g per day. **Group 2: Placebo** N=23 randomised N=23 (completers) Placebo tablets	Outcome 1: **Clinical improvement** (improved or much improved) **Outcome 2: Adverse events** Incidence of GI side effects was high. This tended to be in the form of nausea, vomiting, anorexia, indigestion, heartburn or abdominal discomfort.	**Group1:**14/18 (78%) **Group 2:**9/23 (39%) **Group 1:** 8/21 **Group 2:** 2/23	**Funding:** Pharmacia Laboratories supplied the sulphasalazine and dummy tablets. **Limitations:** Unclear randomisation Very limited baseline characteristics Unclear how accurate the clinical assessment was Double blind but no information on the blinding

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Randomisation: Random using random sampling numbers. For the purpose of assessing the trial, treated and control patients were subsequently paired at random with the restriction that colitis cases were paired with colitis cases and proctitis with proctitis. **Allocation concealment**: Hospital pharmacist allocated the treatment without the knowledge of the doctor in charge of the case. **Blinding:** Says double blind. Treatments looked identical. No further information given. **Outcome assessment:** Clinical state was of 'improved' or 'much improved' was based on improvement in the patients wellbeing, decrease in the frequency of the stools and a return towards normal of their consistency and decrease or disappearance in the amount of pus, mucus and blood in the stools. Sigmoidoscopy was scored from 0-4 by normally two observers who formed independent opinions. **Sample size calculation:** No sample size given. Describes 1/3 of patients in the placebo group to be estimated to have improvements by 4 weeks, and 60% in the sulphasalazine group.	Fit enough to be treated as out-patients Initial attack, relapse after a remission or were chronic cases in exacerbation **Exclusion:** Severe disease or with appreciable systemic upset Received sulphasalazine, corticosteroids or adrenoscorticotrophin during the preceding three months **Group 1: Sulphasalazine** **Severity:** Mild n=4, moderate n=14 **Extent:** Colitis n=10, proctitis n=8 **Drop outs:** 3 **Group 2: Placebo** **Severity:** Mild n=10, moderate n=13 **Extent:** Colitis n=17, proctitis n=6 **Drop outs:** 0 No baseline characteristic data was given apart from severity and extent. In the text the paper describes there to be 30 patients suffering colitis and 14 from proctitis. As the patients are paired it is thought that there were 15 and 7 patients respectively with those extents in the original randomised groups.	**Concomitant therapy:** No further information given apart from that in the exclusion criteria.			of the physicians was given **Additional outcomes:** Sigmoidoscopic improvement

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Type of analysis: N=2 dropout/ withdrawal due to drug related AEs.					

Table 44: DIGNASS2009

Author	Patients	Intervention	Outcome measures	Effect size	Comments
A. U. Dignass et al. Mesalamine Once Daily Is More Effective Than Twice Daily in Patients With Quiescent Ulcerative Colitis. *Clinical Gastroenterology and Hepatology; 7: 762-769.2009.* **REF ID: DIGNASS2009** **Study design and quality:** Single blind, Phase III RCT [PODIUM trial] Multicentre: 68 centres, Belgium. Czech Republic, Denmark, Finland, Germany, The Netherlands, Norway and Sweden. **12 month trial** **Randomisation:** Centrally randomised using an interactive voice response system, permuted blocks of variable size **Allocation concealment**:	**All patients:** **N=362 randomised, 1:1** **N=353 ITT** **Drop-outs** (don't complete the study): N=47 (13.0%) <10% difference in missing data between the treatment arms. **Inclusion criteria:** • Male and female aged ≥18 years • Extent: >15cm from the anal verge • In clinical remission (definition below) • Clinical relapse (requiring adjustment of maintenance therapy) within 12 months prior to study entry for each centre. • Maintenance treatment with oral mesalamine (≤2.5g/day), SASP (≤3.0g/day) or olsalazine (≤1.5g/day) at randomization • Patients not using these drugs at randomization but who had received oral mesalazine, SASP or olsalazine in the 12months prior to exclusion were also eligible • Severity: Mild to moderate (mentioned in the introduction) **Exclusion:** • Other forms of inflammatory bowel disease, idiopathic proctitis or infectious disease	**Group 1: 2g once a day mesalazine** N=175 randomised N=169 (ITT) [6 major entry violations] N=153 (completers) 2g sachet of mesalazine (Pentasa) taken once a day. **Group 2: 1g twice a day (2g/day in total)** N=187 randomised N=184 (ITT)[3 major entry violations] N=162 (completers) 1g sachet of mesalazine (Pentasa) taken twice a day. Total dose of 2g/day. **Concomitant therapy:**	**Outcome 1: Relapse** by 12 months PP1: ITT population with patients who dropped out of the study censored at the time of drop out. **Outcome 2: Adverse events** No difference in the types of adverse events. Most frequent were GI disorders, and infections/infestations. 14 events deemed possibly drug related. **Outcome 3: Serious adverse events** All unrelated/ unlikely to be drug related. Group 1: Due to metastatic prostate cancer, myocardial	**PP1 population** **Group1:** 40/146 **Group 2:** 62/157 **p=0.021** **Group1:** 75/175 (42.9%) **Group 2:** 68/187 (36.4%) **Group1:** 6/175 **Group 2:** 4/187	**Funding:** Funded by Ferring Pharmaceuticals. They were also involved in the design, collection, analysis and interpretation of the data. **Limitations:** Single blind **Additional outcomes:** UCDAI subscores and PGA classed as normal Mean UCDAI total score Patient acceptability Severity of relapse Mortality **Notes:** Post hoc subgroup analyses for extent of disease and

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Adequate **Blinding:** Single blind. **Outcome assessment:** UCDAI, endoscopy, laboratory tests. Seen at the visit every 4 months/ and final visit. Patients Global Acceptability of treatment. **Sample size calculation:** 10% non inferiority limit, 80% power, 1 sided α=0.025, 10% drop out rate, 360 patients were needed. **Type of analysis: ITT** (all those randomised who received at least 1 dose of treatment and 1 post baseline efficacy assessment). **PPA.** **Compliance rates:** Recording the number of sachets dispensed and returned. And a self reported validated questionnaire. Compliance ranged from 74.6-80.3% (ITT & PPA1).Although slightly lower for b.d. it was not significant. N=6 dropout/ withdrawal due to AEs.	• Abnormal hepatic or renal function • History of alcohol or drug abuse • Use of the following drugs within 1 month of study entry: oral mesalamine, Sulphasalazine or olsalazine at dose >2.5g/day, >3.0g/day or >1.5g/day respectively; rectal mesalamine >3g/week, or SASP >3g/week, orally or rectally administered corticosteroids or use of immunosuppressants within the previous 3 months • Pregnant and lactating women • Patients with an allergy to acetylsalicylic acid and other salicylates derivates **Group 1: Once a day** **Mean age (SD):** 48.7 (15.0) **Extent:** pancolitis n=44, left sided colitis n=131 **Severity of previous relapse:** Not described **Frequency of relapses:** Not described. **Patients in remission:** 173 (98.9%) **UCDAI mean total score (SD):** 0.53 (0.52), range 0-2. **Drop outs:** 22 (adverse events (5), consent withdrawn (5), did not meet criteria (5), other reason (7)) **Group 2: Twice a day** **Mean age (SD):** 47.2 (14.1) **Extent:** pancolitis n=59, left sided colitis n=128 **Severity of previous relapse:** Not described **Frequency of relapses:** Not described. **Patients in remission:** 184 (98.9%) **UCDAI mean total score (SD):** 0.48 (0.52), range 0-2. **Drop outs:** 25 (adverse events (1), consent withdrawn (6), did not meet criteria (4), other reason (13), no reason specified (1)). **Definitions** **Remission:** UCDAI score <2 at enrolment **Relapse:** UCDAI score of 3-8 is a mild/ moderate relapse and >8 is severe.	Not permitted to take concomitant therapy for UC during the trial, including >2 consecutive days medication for symptomatic relief of possible relapse, use of NSAIDs for >2days/week for symptoms of increased disease activity, antibiotics for the treatment of relapse and any medication proven to be efficacious for remission maintenance.	ischemia, pyrexia, postoperative wound infection, squamous cell carcinoma, coronary artery disease, gastrointestinal ulcer haemorrhage and cerebral haemorrhage resulting in patient death. Group 2: Due to meningioma, migraine with aura, spondylolisthesis, chest pain, convulsion and hypokalemia. **Median time to relapse** **Group1:** 202.0 days **Group 2:** 148.0 days **Log rank test: p=0.08**		UCDAI remission rates showed no significant effect. **All patients on maintenance ASA prior to trial**

Table 45: DISSANAYAKE1973

Author	Patients	Intervention	Outcome measures	Effect size	Comments

Author	Patients	Intervention	Outcome measures	Effect size	Comments
A. S. Dissanayake and S.C. Truelove A controlled therapeutic trial of long-term maintenance treatment of ulcerative colitis with sulphasalazine (Salazopyrin). *Gut; 14: 923-926. 1973.* **REF ID: DISSANAYAKE1973** **Study design and quality:** Double blind RCT **6 month trial** **Randomisation:** Stratified for number of years on SASP maintenance treatment. Restricted randomization. Master sheet indicating the type of tablet to be issued to patients was held by the hospital pharmacist. **Allocation concealment**: Codes were not broken until the entire trial was completed. **Blinding:** Physician, patient and pathologist was unaware of the treatments given. **Outcome assessment:** Patient reported symptoms, sigmoidoscopy and rectal biopsies. Grading not described. Blood tests including levels of salicylates and sulphapyridine and its metabolites.	**<u>All patients:</u>** **N=64 randomised** **Drop-outs** (don't complete the study): N=0 (0%) **Inclusion criteria:** • Proven UC • Prolonged remission while on maintenance therapy with sulphasalazine (usual dose 0.5g, 4 times a day) • Symptoms free and normal mucosa on sigmoidoscopy with no significant inflammation on rectal biopsy **Exclusion:** • None described. **<u>Baseline characteristics</u>** The data was not provided. The text describes "the two groups were closely similar in respect of all of the following factors: age, sex, length of history of ulcerative colitis, severity of the first attack and maximum extent of disease as judged radiologically". Minimum period of maintenance therapy was 1 year. Some patients had been on it for >5 years. **<u>Definitions</u>** **Failure:** Patient reports colitis symptoms and there is definite evidence of inflammation. These patients were then removed from the trial and given oral prednisolone and a topical corticosteroid and they returned to maintenance therapy with SASP.	**Group 1: 2g Sulphasalazine** N=33 randomised 500mg tablet taken four times a day (Salazopyrin) **Group 2: Placebo** N=31 randomised Placebo tablets. **Concomitant therapy:** Not described.	**Outcome 1: Relapse** rates by 6 months Unable to calculate the hazard ratio from the information given in the paper. **Outcome 2: Adverse events** Three AEs were: headache (1), nausea (2). All patients had been on the same dose prior to the trial. When they went back to open therapy, the side effects went.	**Group1:** 4/33 **Group 2:** 17/31 **Group1:** 3/33 **Group 2:** 0/31	**Funding:** Pharmacia (G.B.) provided the salazopyrin tablets. Aspro Nicholas provided the dummy tablets. **Limitations:** Unclear randomisation No baseline characteristic data given **Additional outcomes:** Relapse rates by length of maintenance therapy with SASP prior to the trial strata. Blood changes **Notes: SASP tolerant population, withdrawal study**

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Sample size calculation: Not described. **Type of analysis: ITT** **Compliance rates:** Checked by blood tests. SASP patients all had detectable sulphapyridine and its metabolites. 4 placebo patients had small amount of salicylates but this was thought to be due to taking aspirin for headaches etc. N=0 dropout/ withdrawal due to drug related AEs.					

Table 46: ELHODHOD2012

Reference	Patient characteristics	Predictors and outcome measures	Effect sizes	Comments
M. A-A. El-Hodhod et al. Fibroblast growth factor 23 contributes to diminished bone mineral density in childhood inflammatory bowel disease**.** *BMC Gastroenterology; 12: 44. 2012.* **Type of study:** Prospective cohort **Setting: Pediatric Gastroenterology unit** **Follow up period:** 4-9	**Sample size:** 47 IBD children, of which 27 had ulcerative colitis. **<5% missing data?** Not described. **Type of analysis used:** Students t-test. Chi square test. Multiple regression analysis. **Appropriate?** Yes **Inclusion criteria (for UC patients):** • Diagnosis of IBD based on the Porto criteria • Disease flare that was assessed using Pediatric Ulcerative Colitis Activity Index (PUCAI) for UC and modified Pediatric Crohn's disease Activity Index (PCDAI) for CD • No steroid therapy for at least three months prior to enrolment in this study **Exclusion criteria:**	**Definitions of Risk factor variables measured:** **Disease activity:** All patients have had an episode of disease activity measured by the PUCAI or PCDAI. **Systemic corticosteroid use:** Not described/ measured. **Weight:** BMI was measured. **1-25-dihydroxyvitamin D, 25-hydroxyvitamin D:** 25 (OH) D_3 measured using radioiodine based RIA kits. Values <15ng/ml were considered as vitamin D deficiency, <8ng/ml severe deficiency. 1, 25 $(OH)_2$ was done using Human 1, 25- Dihydroxy-Vitamin D RIA kit with unit of measurement being pg/ml. **Definitions of outcomes measured:** **Bone mineral density:** Determined by DXA Lunar scan. Calibrated daily, technical error calculated to be <1%. Z scores calculated for age and sex and	**Results** • BMI was significantly lower in UC patients during the flare (17.26 (SD 2.34)) and in remission (19.27 (2.07)) compared to the control group (25.43 (SD 2.65)), p<0.001. • Difference between BMI during flare and remission for UC patients, p=0.002 • BMD and z score of corrected BMD to bone age and sex were significantly lower during disease activity (p<0.0001) • 25 $(OH)VD_3$ was not significantly different between flare and remission (p=0.38) • 1.25 $(OH)_2VD_3$: significantly higher during flare compared to remission and control group (p<0.0001) **Frequency of osteopenia and**	**Source of funding**: None described. **Risk of bias:** • Limited information reported for the multiple regression analysis • Unclear missing data **Additional outcomes reported:** Other laboratory parameters: calcium, phosphorus, ALP, creatinine, FGF23 serum levels, height for age, PTH

Reference	Patient characteristics	Predictors and outcome measures	Effect sizes	Comments
months reassessment from December 2008-2010	• Critically ill patients who cannot be transferred for DXA procedure • Concomitant endocrinal, renal or genetic bone diseases **Data collection:** Recruited from amongst IBD patients followed up at the Pediatric Gastroenterology Unit, Ain Shams University Faculty of Medicine, December 2008- December 2010. Patients were studied during disease activity, either at initial diagnosis (6 UC) or during relapse (21 UC). 3 months after remission, patients had a clinical and laboratory reassessment. 50 healthy, age and sex matched children were recruited as the control group. **Treatment given:** Induction of remission all patients received oral prednisone (1-2mg/kg/day) for 3-4 weeks. Parenteral antibiotics and other supportive measures were individually adjusted. Post induction, maintenance treatment was 5ASA. One UC patient had a proctocolectomy and ilo-anal anastomosis Nutritional support: After enrolment in the flare state- Calcium (500-1000mg) daily, oral vitamin D3 supplementation as 1000 IU daily for non-deficient and 10000IU daily for deficient children. Physical activity: patients weren't bed ridden, were ambulant, most attending full school activities. 3-4 weeks hospital admission. Time until reassessment was normal activities (non strenuous). **Baseline characteristics:** **All IBD patients:** Mean age (SD): 11.6 years (3.5)	corrected to bone age which was assessed from X-rays of the left hand. Values of total body BMD were used for analysis. -1.0 to -2.5 were classed as a mild decrease in BMD, <-2.5 were diagnostic of severe disease. **Routinely measured?** Total vitamin D and DEXA scanning are not routinely measured. Weight is routinely measured. **Outcome and definition:** **Blinding:** Unclear. Not described. **Risk of measurement error:** Low **Risk of inter-observer variability:** Unclear **Key prognostic factors not included?** Out of the potential confounders listed by the GDG the following where not described in the paper: • Ethnicity • Tanner staging • Family history • Diet (vegetarian, vegan etc.)	**osteoporosis in flare and remission:** UC flare: normal BMD n=3 (11.1%), mild degree n=0, severe degree n=24 (88.9%) UC remission: normal BMD n=11 (40.7%), mild degree n=6 (22.2%), severe degree n=10 (37%) **Multiple regression analysis** • Regression analysis in the ulcerative colitis group during flare showed the only significant determining factors were FDF23 followed by serum calcium • No other information was given	**Notes: For Crohn's patients it is described that many factors affecting BMD were significant. The top ones being 1.21 (OH)2 VD, followed by urinary phosphorus and FGF23. No other details were given.**

Reference	Patient characteristics	Predictors and outcome measures	Effect sizes	Comments
	Duration between flare and reassessment (when in remission): range 4-9 months, mean 7.12 months (SD 2.8). **Controls:** Age range: 4-16 years Mean age (SD): 12.8 (3.77 years) **UC patients:** 14 males, 13 female Mean age (SD): 12.77 (1.71) years Mean levels of the variables explored were given overall for Crohn's and UC patients combined. The correlation coefficients were reported for some of the variables for UC patients only (see the table below). **Definitions** **Remission:** PUCAI < 10 points for UC, or PCDAI <15 points for Crohn's			

Table 47: FARUP1995

Author	Patients	Intervention	Outcome measures	Effect size	Comments
P.G. Farup et al. Mesalazine suppositories versus hydrocortisone foam in patients with distal ulcerative colitis. A comparison of the efficacy and practicality of two topical treatment regimens. *Scandinavian Journal of Gastroenterology; 30 (2): 164-70. 1995.* **REF ID: FARUP1995**	**All patients:** **N=79 randomised** Complete responders and non responders after 2 weeks terminated the study. While partial responders continued for another 2 weeks. **Drop-outs** (don't complete the study): Unclear. There were 17 non responders at 2 weeks. **Inclusion criteria:** • Extent: n=50 had proctitis and n=29 proctosigmoiditis • Severity: with symptoms of at least 1 weeks duration severe enough	**Group 1: 1g mesalazine suppositories** N=41 randomised 500mg mesalazine suppository given twice a day (Mesasal). **Group 2: 356mg hydrocortisone foam enemas** N=38 randomised	**Outcome 1: Clinical remission** (complete responders- DAI≤2)	**2 weeks** **Group1:** 11/41 **Group 2:** 6/38 **4 weeks** **Group1:** 17/41 **Group 2:** 13/38	**Funding:** SmithKline Beecham, Norway **Limitations:** Open study Unclear method of randomisation and allocation concealment Clinical improvement was

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Study design and quality: Open RCT Norway **2 or 4 week trial** **Randomisation:** patients were stratified into 2 groups according to extent of disease and then randomized. Unclear. **Allocation concealment**: no information given. **Blinding:** Open study. Pathologist who examined biopsies was blind to patients' treatment. **Outcome assessment:** Disease activity index. **Sample size calculation:** Not described. **Type of analysis: ITT** **Compliance rates:** ≥80% prescribed dose. 24/28 and 19/22 in group 1 and 2 respectively were compliant in the first 2 weeks, and 19/19 and 11/15 in the last 2 weeks. N=0 dropout/ withdrawal due to drug related AEs.	to warrant treatment. DAI≥6. • Long term treatment that has not changed in the last 14 days **Exclusion:** • UC proximal to sigmoid • Severe or fulminant proctosigmoiditis • Recent history of receptive anal intercourse, bowel complications • Hypersensitivity to salicylates or steroids • Rectally installed drug during last 14 days • Drug abuse • Unstable co-morbidities • Pregnant and breast feeding women **Baseline characteristics** **Group 1: 1g mesalazine suppositories** **Sex (m/f):** 27/14 **Mean age (SD):** 49 (19-70) **Extent:** proctitis n=24, proctosigmoiditis n=17 **Drop outs:** unclear **Group 2: 356mg hydrocortisone foam enemas** **Sex (m/f):** 22/16 **Mean age (SD):** 39 (17-70) **Extent:** proctitis n=26, proctosigmoiditis n=12 **Drop outs:** unclear	178mg of hydrocortisone foam enema twice a day (Colifoam). **Concomitant therapy:** No numbers or details were provided, except to say patients were included if treatment has not changed in last 14 days.	**Outcome 2: Adverse events** Group 1: 1 erythema mulitforma like exanthema and fever, 1 transient exanthema, 3 burning sensation of the anus, 1 minor events Group 2: 1 transient exanthema, 1 burning sensation of the anus, 4 minor events	**Group1:** 6/41 **Group 2:** 6/38	defined as a partial responder but data was not reported Risk of indirect population (no upper limit to severity given) Unclear drop out rate **Additional outcomes:** Clinical remission by extent of disease Histological improvement

Table 48: FARUP2001

Author	Patients	Intervention	Outcome measures	Effect size	Comments
P. G. Farup et al. Mesalazine 4g Daily Given as Prolonged-Release Granules Twice Daily and Four Times Daily Is at Least as Effective as Prolonged-Release Tablets Four Times Daily in Patients with Ulcerative Colitis. *Inflammatory Bowel Disease; 7: 237-242. 2001.* **REF ID: FARUP2001** **Study design and quality:** RCT Multicentre: 30 GI units. It was unclear in which countries the trial was based. **8 week trial** **Randomisation:** Unclear, no description given. **Allocation concealment**: Unclear. **Blinding:** Open trial. **Outcome assessment:** Ulcerative Colitis Disease Activity Index (UCDAI), score from 0-12. Enhanced UCDAI (UCDAI with the addition of the patient's functional assessment) **Sample size calculation:**80%	**<u>All patients:</u>** **N=231randomised** **N=227 (APT- equivalent of modified ITT)** **N=147 (PPA)** **Drop-outs** (don't complete the study): N=84 (36%) due to the following: Did not meet inclusion/exclusion criteria: 4 Intake of <75% of prescribed drugs: 4 Incorrectly randomised: 13 Missing laboratory data at last visit: 4 Medication received before baseline assessments: 7 Time window for the last visit after 8 weeks (+/-4days) was exceeded: 45 Intake of disallowed concomitant medication: 14 **Inclusion criteria:** Adult outpatients Diagnosis had to be established by sigmoidoscopy, colonoscopy or barium enema and verified by histological examination of biopsy specimens from the diseased bowel Newly diagnosed and relapse patients Extent: verified by endoscopy or barium enema within the last 12 months. ≥15 cm from the anal verge Severity: Mild to moderate (DAI of 3-5 and 6-8 respectively)	**Group 1: 2g mesalazine granules b.d.** N=74 (APT) 1g mesalazine granule packets. 2 packets (2g) taken twice a day). Total dose 4g/day **Group 2: 1g mesalazine granules q.d.s.** N=76 (APT) 1g mesalazine granule packets. 1 packet (1g) taken four times a day. Total dose 4g/day. **Group 3: 1g (2 tablets) mesalazine q.d.s.** N=77 (APT) 500mg mesalazine tablets. Two tablets (1g) taken four times a day. Total dose 4g/day. **Concomitant therapy:** See inclusion/exclusion criteria.	Outcome 1: **Clinical remission** (EN/UCDAI 0-1) Outcome 2: **Clinical improvement** (EN/UCDAI reduction of ≥2). This is added to those in remission to give all those that improved. Adverse event data was not given separately for the treatment arms, but the text describes no clinical or significant differences between the groups. 70 patients reported AEs, 20 of which had adverse events thought to be related to the drug treatment. 9 patients withdrew due to AEs and 15 due to aggravation of the disease and other treatment was required. There were 4 SAEs, none of which were thought to be treatment related (back pain, UC aggravation, amputation of a finger at work, alcohol intoxication).	**Group1:**29/74 (39%) **Group 2:**28/76 (37%) **Group 3:** 24/77 (31%) **Group1:**58/74 (78%) **Group 2:**58/76 (76%) **Group 3:** 52/77 (67%)	**Funding:** None described. **Limitations:** Unclear method of randomisation and allocation concealment Open trial High dropout rate **Additional outcomes:** Mean clinical improvement

Author	Patients	Intervention	Outcome measures	Effect size	Comments
power, 5% one sided significance level, 61 patients per arm to detect a difference of 1 point in the UCDAI. **Type of analysis: All patients treated (APT) and PPA** (this included those who withdrew due to AEs or worsening of symptoms and they were given the highest UCDAI score of 12) **Compliance rates:** Remaining drugs collected and compliance calculated. 4 patients had poor compliance (<75% of the drugs taken).97% compliance in all three treatment arms. N=0 dropout/ withdrawal due to drug related AEs.	**Exclusion:** <15 cm above the anal verge (proctitis) Use of corticosteroids and anti-inflammatory drugs (oral or rectal) during the last 7 days Use of immunosuppressives in the last 90 days Patients receiving maintenance treatment with sulfasalazine >4g or mesalazine >2g daily during the last month (Note: patients taking lower doses of these drugs were just switched to the study drugs) Diseases that could influence the evaluation Pregnant and lactating women and women of child-bearing potential (and not taking adequate contraceptive precautions) **Group 1: 2g mesalazine granules b.d.** **Mean age (SD):**43 (no SD, range 17-77) **Previous flare ups:** 51 (69%) **Extent:** distal[b] n=33, extensive n=41 **Disease activity:** mild n=25, moderate n=49 **Drop outs:** unclear **Group 2: 1g mesalazine granules q.d.s.** **Mean age (SD):**45 (no SD, range 20-76) **Previous flare ups:** 57 (75%) **Extent:** distal n=33, extensive n=43 **Disease activity:** mild n=30, moderate n=46 **Drop outs:** unclear **Group 3: 1g (2 tablets) mesalazine q.d.s.** **Mean age (SD):**43 (no SD, range 17-77) **Previous flare ups:** 58 (75%) **Extent:** distal n=41, extensive n=36				

[b] Distal: disease confined to the rectum and sigmoid
Extensive: disease proximal to the sigmoid

Author	Patients	Intervention	Outcome measures	Effect size	Comments
	Disease activity: mild n=25, moderate n=52 **Drop outs:** unclear				

Table 49: FERRY1993

Author	Patients	Intervention	Outcome measures	Effect size	Comments
G. D. Ferry et al. Olsalazine Versus Sulfasalazine in Mild to Moderate Childhood Ulcerative Colitis: Results of the Pediatric Gastroenterology Collaborative Research Group Clinical Trial. *Journal of Pediatric Gastroenterology and Nutrition; 17: 32-38. 1993.* **REF ID: FERRY1993** **Study design and quality:** Double blind RCT Multicentre, 13 centres, United States, Canada **12 week trial** **Randomisation:** Patients were stratified by new diagnosis and relapse. Randomisation schedule by centre. No further information **Allocation concealment**:	**<u>All patients:</u>** **N=59[c] randomised** **N=56 (for analysis as 3 patients had micro colitis and so were excluded)** **Drop-outs** (don't complete the study): N=6[d] (10%) **Inclusion criteria:** **Children 2-17 years old** Severity: Mild to moderate (see below for criteria) Newly diagnosed or relapse while off all medications (patients who had relapsed had been off all medications for at least 1 week prior to trial start) Diagnosis confirmed histologically after colonoscopy, or barium enema and limited colonoscopy **Exclusion:** Severe UC Significant abdominal distension or tenderness associated with	**Group 1: Olsalazine (up to 2g)** N=28 randomised N=26 (completers) 30mg/kg/day of Olsalazine (maximum 2g/day) Medication was started at one dose per day or 25% of the calculated daily dose and increased by one dose every 3 days until four doses per day were achieved. All medications were stopped in those with a relapse 1 week prior to the trial. **Group 2: Sulphasalazine (up to 4g)**	Outcome 1: **Clinical remission (**Asymptomatic -free from all symptoms, formed bowel movements, no visible blood (all of the above for at least 7 days)) Outcome 2: **Endoscopic remission** (normal mucosa) Outcome 2: **Clinical and endoscopic remission** (normal mucosa and	**<u>At 1 month</u>** **Group1:**4/28 **Group 2:**6/28 **<u>At 2 months</u>** **Group1:**5/28 **Group 2:**8/28 **<u>At 3 months</u>** **Group1:**4/28 **Group 2:**9/28 **<u>At 2 months</u>** **Group1:**5/17 **Group 2:**11/24 **<u>At 2 months</u>** **Group1:**2/17	**Funding:** Supported in part by the Food and Drug Administration Grant, Pharmacia, Inc., the Bob and Vivian Smith Foundation and the Kelsey-Seybold Foundation. **Limitations:** Unclear method of randomisation and allocation concealment **Additional outcomes:** Mean change in colonoscopic score Colonoscopy improvement Time to remission

[c] Only one third of the expected patients were enrolled in the trial. It was decided that it would take too long to complete the trial waiting for further patients so enrolment was then stopped.

[d] Olsalazine group: Two patients were non compliant. In the Sulfasalazine group four patients discontinued the drug due to adverse drug reactions.

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Unclear **Blinding:** Double blind. Identical capsules. Drugs were dispensed in a double blind fashion. **Outcome assessment:** Colonoscopy score was modified by Roth, score from 0-3 for 5 characteristics. Severity based on temperature and stool frequency. **Sample size calculation:**90 patients per arm based on 80% power, p=0.05 for a 25% difference in adverse events **Type of analysis: ITT** **Compliance rates:** >85% of the prescribed dose taken was considered compliant. This was verified by tablet counts. Unclear if 2 patients were non compliant in the olsalazine group. N=4 dropout/ withdrawal due to AEs in the sulphasalazine group (they were thought to be possibly drug related (neutropenia, 3 for rash and/or headache)	guarding or rebound Localized proctitis History of allergy to salicylates or sulfa-containing drugs Previous intolerance to olsalazine or sulfasalazine Significant glucose-6- phosphate dehydrogenase deficiency If judged to be non compliant or if the patients refused **<u>Group 1: Olsalazine (up to 2g)</u>** **Mean age (SD):**10.5 (4.1), range 2.1-17.9 years **Extent:** rectosigmoid n=9, left colon n=5, beyond splenic flexure n=14 **Mean colonoscopy score:** 1.3 (0.5) **Drop outs:** 2 (non compliant) **<u>Group 2: Sulphasalazine (up to 4g)</u>** **Mean age (SD):**10.9 (4.2), range 3.1-17.5 years **Extent:** rectosigmoid n=6, left colon n=8, beyond splenic flexure n=14 **Mean colonoscopy score:** 1.2 (0.6) **Drop outs:**4 (Adverse events)	N=28 randomised N=24 (completers) **Standard paediatric** dose of sulfasalazine, 60mg/kg/day (maximum 4g/day) Medication was started at one dose per day or 25% of the calculated daily dose and increased by one dose every 3 days until four doses per day were achieved. All medications were stopped in those with a relapse 1 week prior to the trial. **Concomitant therapy:** No antibiotics, anticholinergic or antidiarrheal drugs were permitted during the study. Starting prednisone or enemas was left to the discretion of the attending gastroenterologist at each centre.	asymptomatic) Outcome 3: **Adverse events** Olsalazine: headache, nauseas, vomiting rash, increased diarrhoea, fever, pruritus) Sulphasalazine: all of the above apart from pruritus plus neutropenia and anorexia. Two patients on each drug reported increased diarrhoea which was thought to be drug related. Also reports clinical improvement but no definition was given so this has not been included in the analysis. 10 of 28 patients on olsalazine had received prednisone, 8 for worsening of symptoms and two for lack of response.1 patient in the sulphasalazine group was put on prednisone.	[e] **Group 2:**3/24[f] **Group1:**11/28 **Group 2:**13/28	

[e] 17 patients on olsalazine did not have a repeat colonoscopy at 2 months (concurrent medication or did not return for the procedure)
[f] 4 patients on sulphasalazine did not have a repeat colonoscopy (concurrent medication, adverse reactions to sulphasalazine, did not return for the procedure)

Table 50: FEURLE1989

Author	Patients	Intervention	Outcome measures	Effect size	Comments
G. E. Feurle Olsalazine versus placebo in the treatment of mild to moderate ulcerative colitis: a randomised double blind trial. *Gut; 30: 1354-1361. 1989.* **REF ID: FEURLE1989** **Study design and quality:** Double blind RCT West Germany, multicentre (eight hospitals, four in private practice) **4 week trial** **Randomisation:** Central randomisation, stratified in blocks of 10 for each of the 12 centres. **Allocation concealment**: Adequate **Blinding:** Double blind. Histology was analysed blindly. No further information given. **Outcome assessment:** Endoscopic score was the mean of redness or hyperaemia, contact bleeding, spontaneous bleeding and erosions each graded from 0-2. Clinical score was based on the number of stools, presence of	**<u>All patients:</u>** **N=105randomised** **Drop-outs** (don't complete the study): N=11 (10.5%) **Inclusion criteria:** Extent: None described. Severity: Mild (occasional bloody stools and occasional mild diarrhoea. Sigmoidoscopy should show slight mucosal changes, such as light hyperaemia and granularity or petechial bleeding) to moderate (bloody diarrhoea not seriously affecting the patient's general wellbeing. Sigmoidoscopy should show pronounced hyperaemia and enhanced mucosal fragility with occasional ulceration), as defined by Truelove and Richards criteria) 18-75 years old First attack or patients who had discontinued treatment and experienced a relapse **Exclusion:** Severe ulcerative colitis Allergy to salicylates Carcinoma, at present or in the past Cardiopulmonary, hepatic, renal or haematologic disorders Chronic oral or rectal use of salicylates Colonic or anal infection Large bowel resection	Capsules were taken four times a day, two capsules at a time. Total 8 capsules per day. Patients were advised to start on less than 8 capsules per day and gradually build up to the full 8 by day 3-4. **Group 1: Olsalazine 2g** N=52 randomised N=46 (completers) There were 10 protocol violations. 4 x2 capsules per day. Total dose 2g/day. **Group 2: Placebo** N=53 randomised N=48 (completers) There were 11 protocol violations. 8 placebo capsules per day. **Concomitant therapy:** None.	Outcome 1: **Adverse events** Adverse events included; diarrhoea, nausea, abdominal pain and loss of appetite. Clinical improvement (at least 3 of the 4 parameters measures were improved) was stated to be an outcome but there was no data reported on it, only that there was no significant difference between the two groups for the clinical score.	**Group1:**12/52 (ITT) **Group 2:**9/53 (ITT)	**Funding:** None described. **Limitations:** No baseline data on extent and severity Limited information on double blinding **Additional outcomes:** Gain/loss of weight Laboratory values Significant levels for clinical parameters Improvement in endoscopy score and histology score

Author	Patients	Intervention	Outcome measures	Effect size	Comments
blood, stool consistency and mucus (grade 0-2). Appetite was also graded this way. **Sample size calculation:** None described. **Type of analysis: Unclear** **Last observation carried forward (LOCF)** **Compliance:** 38/46 (82.6%). This was based on plasma and urine drug levels. N=3 dropout/ withdrawal due to AEs (it is not stated whether these were drug related). They were all in the olsalazine group (2 diarrhoea, 1 nausea). Rectal bleeding was not considered an adverse event.	Pregnancy or planned pregnancy Current treatment for ulcerative colitis with sulphasalazine, 5-aminosalylate derivates, steroids, metronidazole, azathioprine, or similar drugs Uncertain diagnosis, doubtful cooperation **Group 1: Olsalazine 2g** **Mean age (SD):**42.9 (15.8) **General wellbeing (%):** 18,2 (16.1) **Stools last week (n):**24 (17.2) **Stool consistency (%):** 45.7 (28.6) **Rectal bleeding:** 67.1 (29.3) **Mucus discharge (%):** 55.7 (33.6) **Endoscopic index:** 1.1 (0.5) **Drop outs:** 6 (2 due to diarrhoea, 1 due to nausea, 1 due to increased rectal bleeding and 2 people wished to terminate the trial) **Group 2: Placebo** **Mean age (SD):**42.9 (16.0) **General wellbeing (%):** 16.1 (13.6) **Stools last week (n):** 25.5 (22.2) **Stool consistency (%):** 48.6 (34.3) **Rectal bleeding:** 60.0 (32.9) **Mucus discharge (%):** 47.9 (27.9) **Endoscopic index:** 1.0 (0.4) **Drop outs:** 5 (3 due to increased rectal bleeding and 2 people wished to terminate the trial) No data was given for the extent of disease or the percentage with mild and moderate severity of disease at baseline.				

Table 51: FORBES2005

Author	Patients	Intervention	Outcome measures	Effect size	Comments
A. Forbes et al.	**NOTE: the author describes this as not an equivalence study**	**Group 1: 2.4g mesalazine(Ipocol)**	Outcome 1: **Clinical remission** (as defined	**Week 4**	**Funding:** Provision of the drugs,

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Multicentre randomized-controlled clinical trial of Ipocol, a new enteric-coated form of mesalazine, in comparison with Asacol in the treatment of ulcerative colitis. *Alimentary Pharmacology & Therapeutics; 21: 1099-1104. 2005.* **REF ID: FORBES2005** **Study design and quality:** Double blind RCT Multicentre: 8 hospitals, United Kingdom **8 week trial** **Randomisation:** Lagap Pharmaceuticals randomization centre; computer generated random numbers with stratification for extent (distal, or extensive) **Allocation concealment**: Adequate as central randomisation **Blinding:** Double blind. The tablets were not identical, so patients were advised they may get a different sized tablet to normal and investigators took care neither to see nor enquire about the nature of the tablets. **Outcome assessment:** Modified St. Mark's Colitis Activity Score. Endoscopic scoring is on a 4	**<u>All patients:</u>** **N=90randomised (2 patients consequently withdrew consent)** **N= 88 ITT/ safety** **Drop-outs** (don't complete the study): N=22 (24%) Unclear what the reasons were. **Inclusion criteria:** Acute exacerbation of UC, defined as a deterioration in symptoms to the extent that the supervising clinician considered it suitable to amend the therapeutic regimen >18yrs Otherwise in good health Prior topical therapy up to the date of enrolment was allowed Prior therapy with oral 5-ASA if <2.4g/day of mesalazine was permitted Severity: mild to moderate **Exclusion:** Systemic steroids in the previous 4 weeks Immunosuppressant or immunomodulatory drug in the previous 3 months Oral GI therapies other than the trial drug was not permitted "usual exclusions in terms of other important medical conditions" **<u>Group 1:2.4g mesalazine (Ipocol)</u>** **Mean age (SD):**47.9 (15.3) **Extent:** Extensive disease 38% **Sigmoidoscopy score:** of 1 (34%), of 2 (35%), of 3 (26%) **Mean St Mark's score (SD):** 5.4 (2.09) **Using mesalazine at permitted levels/routes prior to trial:** n=14	N=46 randomised N=37 (completers) 2.4g mesalazine (Ipocol – thinner Eudragit S coating than Asacol) Two 400mg tablets, three times a day **Group 2: 2.4g mesalazine (Asacol)** N=44 randomised N=42 (ITT- as 2 withdrew consent) N=31 (completers) 2.4g mesalazine (Asacol). Eudragit S coating. Two 400mg tablets, three times a day **Concomitant therapy:** Topical therapy was allowed if it was a stable dose for the previous 4 weeks and was continued at the same level throughout the trial. Steroids was permitted if the patient deteriorated sufficiently to need it (withdrawal from trial and classed	by the investigators global assessment) There is only graphical representation of clinical remission at week 8 which looks to be similar to that of week 4. The text describes no significant difference.	**Group1:**12/46 (26.1%) **Group 2:** 12/42 (28.6%)	blinded packaging, telephone randomization service and modest running expenses was given by Lagap Pharmaceuticals Ltd **Limitations:** High dropout rate and unclear reasons Limited information on double blinding **Additional outcomes:** Sigmoidoscopy improvement Histological improvement Graphs: St. Marks colitis score
			Outcome 2: **Adverse events** Great majority were classed as mild and 'unrelated' or 'likely to be unrelated' to the medication	**Group1:**34/46 (73.9%) with 140 AEs **Group 2:**31/42 (73.9%) with 93AEs	
			Outcome 5: **Colectomy** (Interval colectomy)	**Group 1:** 0/46 **Group 2:** 1/42	
			Outcome 3: **Quality of Life** (EuroQoL)- reduction in score **Group1:**0.7 **Group 2:**0.5 It is reported to not be statistically significant. As no SD was reported, this data could not be analysed.		

Author	Patients	Intervention	Outcome measures	Effect size	Comments
point scale encompassing normal as the lowest score. Investigator's global assessment. **Sample size calculation:**45 per arm with 80% power to detect a 30% difference **Type of analysis: ITT, but all patients in the safety analysis** (i.e. the two withdrawals of consent) **Compliance rates:** Checked by the pharmacist who looked at tablet counting. Apart from the protocol violations, compliance was >90% and similar between both groups. N=2 dropout/ withdrawal due to AEs (due to abdominal pain)	**Drop outs:** 9 **<u>Group 2: 2.4g mesalazine (Asacol)</u>** **Mean age (SD):**44.8 (13.7) **Extent:** Extensive disease 39% **Sigmoidoscopy score:** of 1 (29%), of 2 (52%), of 3 (19%) **Mean St Mark's score (SD):** 5.1 (2.32) **Using mesalazine at permitted levels/routes prior to trial:** n=13 **Drop outs:** 11 Note: Oral prednisolone was taken because of inadequate efficacy of the trial medication in 9.1% overall. (Asacol 11.9%, Ipocol 6.5%, not statistically significant). Topical steroids were used by 15.7% overall (11.0% Asacol, 17.4% Ipocol, not statistically significant). Protocol violations: Two patients in the Asacol group tool supplementary mesalazine (4.8%) and one patient in the Ipocol group (2.2%) due to prescriptions made by nontribal physicians.	as a treatment failure)			

Table 52: FRIEDMAN1986

Author	Patients	Intervention	Outcome measures	Effect size	Comments
L. S. Friedman et al. 5-Aminosalicylic acid enemas in refractory distal ulcerative colitis: a randomized controlled trial. *American Journal of Gastroenterology; 81 (6):412-8. 1986.* **REF ID: FRIEDMAN1986** **Study design and quality:**	**<u>All patients:</u>** **N=18 randomised** **Drop-outs** (don't complete the study): N=2 (11%) **Inclusion criteria:** • Extent: at least 5 cm and no more than 60cm from anal verge • Severity: mild to moderate • ≥18 years	**Group 1: 4g 5-ASA liquid enema** N=9 randomised 4g 5-ASA liquid enema given once a day at night. Type of 5-ASA unclear. **Group 2: 100mg hydrocortisone liquid enema**	**Outcome 1: Clinical remission** (Clinical score of 1) **Outcome 2: Clinical improvement** (change of clinical score by 1 point) **Outcome 3: Endoscopic remission** (score of 0) Only 8 people in each group had an	**Group1:** 4/9 **Group 2:** 1/9 **Group1:** 7/9 **Group 2:** 2/9 **Group1:** 2/8 **Group 2:** 0/8	**Funding:** National Institute of Health **Limitations:** Unclear method of randomisation and allocation concealment Double blind, no further information given

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Double blind RCT United States **3 week trial** **Randomisation:** Patients randomly assigned by means of prearranged random allocation of patient accession numbers **Allocation concealment**: No information given. **Blinding:** Double blind. **Outcome assessment:** Endoscopic score of 0-4. Clinical scores base on stool frequency and consistency. Unclear validation. **Sample size calculation:** None described. **Type of analysis:** ACA **Compliance rates:** Assessed by the returning of enema containers at the end of the trial. Compliance was >90%. N=2 dropout/ withdrawal due to possible drug related AEs. One in each treatment group.	**Exclusion:** • Fever >39◦C • Chills in the week prior to entry • Extra-intestinal manifestations • Weight loss of >2.5kg in preceding month • History of cardiac, renal or liver disease • Treated for their acute attack with corticosteroids or other immunosuppressant drugs • Women at risk of pregnancy **Baseline characteristics** **Group 1: 4g 5-ASA liquid enema** **Sex (m/f):**7/2 **Mean age (SD):** 40 (17) **Duration of disease:** 4 (5) **Extent:** 24 cm +/-17 **Recent sulphasalazine therapy:** 4 **Drop outs:** 1 (peri-rectal fistula and required surgery) **Group 2: 100mg hydrocortisone liquid enema** **Sex (m/f):**5/4 **Mean age (SD):** 48 (17) **Duration of disease:** 12 (12) **Extent:** 32 cm +/-17 **Recent sulphasalazine therapy:** 5 **Drop outs:** 1 (fever and bloody diarrhoea and required hospitalisation)	N=9 randomised 100mg hydrocortisone liquid enema given once a day at night. **Concomitant therapy:** Patients on chronic, stable doses of systemic corticosteroids or immunosuppressive agents had not been increased in the previous months. One week before the start of the trial SASP was discontinued in patients taking the drug. In no case did symptoms worsen during the next week.	endoscopy score pre and post treatment. **Outcome 4: Adverse events** **Outcome 5: Hospitalisation** **Outcome 6: Colectomy**	 **Group1:** 1/9 **Group 2:** 1/9 **Group1:** 1/9 **Group 2:** 1/9 **Group1:** 0/9 **Group 2:** 1/9	**Additional outcomes:** Pre and post treatment clinical, endoscopic and histological scores

Table 53: GIBSON2006

Author	Patients	Intervention	Outcome measures	Effect size	Comments

Author	Patients	Intervention	Outcome measures	Effect size	Comments
P. R. Gibson et al. Comparison of the efficacy and safety of Eudragit-L-coated mesalazine tablets with Ethylcellulose-coated mesalazine tablets in patients with mild to moderately active ulcerative colitis. *Alimentary Pharmacology & Therapeutics; 23: 1017-1026. 2006.* **REF ID: GIBSON2006** **Study design and quality:** Double blind, double dummy, Phase III RCT Multicentre: 38 centres (18 in Australia, 20 in Eastern Europe (Czech and Slovak Republics) **8 week trial** **Randomisation:** Use of randomization table generated by a program 'Rancode +'. This was done in blocks of four. Emergency envelopes containing the patient's treatment were provided to the investigators. Random code was broken after closing the database. Emergency envelopes were collected. None had been opened.	**All patients:** **N=260randomised**(85 in Australia, 175 in Europe) **N=258 safety analysis**(2 patients did not receive any medication) **N=257 modified ITT** (1 other patient had a baseline CAI of 1 and no other follow up values) **N=215 PPA**(22 from Australia, 21 from Europe) **Drop-outs** (don't complete the study): N=30 (12%) mainly due to lack of patient's co-operation, lack of efficacy or an intolerable adverse event. **Inclusion criteria:** 19-70 years old Diagnosis confirmed at least 14 days prior to screening for the study by standard endoscopic and histopathological criteria No infection (negative stool microscopy and culture) Extent:>15cm from the anus Severity: mild to moderately active UC (CAI between 6-12, EI≥4) **Exclusion:** ≤15cm from the anus (extent) Prior bowel surgery other than appendicectomy Serious co-morbidity Previous diagnosis of cancer	**Group 1: 3g mesalazine (Eudragit-L-coated) tablets** **Salofalk** N=131 randomised N=109 (PPA) 1000mg Eudragit-L-coated mesalazine tablets (2 tablets of 500mg) and placebo Ethylcellulose tablets (2 tablets) three times a day **Group 2: 3g mesalazine (Ethylcellulose-coated) tablets** N=127 randomised N=106 (PPA) 1000mg Ethylcellulose-coated mesalazine tablets (2 tablets of 500mg) and placebo Eudragit-L-coated tablets (2 tablets) three times a day. **Concomitant therapy:** Maintenance ASA	Outcome 1: **Clinical remission at the final/withdrawal examination** (CAI≤4) N values are calculated from the percentages given in the text. Outcome 2: **Endoscopic remission** (EI<4) (PPA) n values were calculated from the percentages given in the text. Outcome 3: **Clinical improvement** (Clinical remission or improved CAI by ≥3 from baseline) (PPA) n values were calculated from the percentages given in the text.	**ITT** **Group1:**83/131 (63%) **Group 2:**81/127 (64%) **PPA** **Group1:**75/109 (69%) **Group 2:**73/106 (69%) **Group1:**46/109 (42%) **Group 2:**46/106 (43%) **Group1:**87/109 (80%) **Group 2:**82/106 (77%)	**Funding:** Dr. Falk Pharma funded the drugs. **Limitations:** Some cluster differences at baseline **Additional outcomes:** Number of stools per week Number of bloody stools per week Time to first symptomatic remission Endoscopic improvement Histological remission Histological improvement Therapeutic success or benefit using the PGA Other subgroups for clinical remission (all baseline characteristics) **Notes:**

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Allocation concealment: Adequate. **Blinding:** Double blind. **Outcome assessment:** Clinical Activity Index (based on the previous 7 days of symptoms), Endoscopic Index **Sample size calculation:**20% difference in remission rates, Power 80%, sample size of 99-74 depending on response rate of the comparator **Type of analysis: ITT and PPA** **Compliance rates:** Calculated from the number of used/ unused tablets and diary records. 98% adherence rate in both treatment groups. Dropout/ withdrawal due to drug related AEs was unclear. It says in the discussion 'no patient discontinued therapy because of intolerance to the drug treatment' but some of the patients withdrew due to an intolerable adverse event, so this would mean that they were non drug related reasons.	Active peptic ulceration Maintenance aminosalicylate therapy dose not constant 7 days prior to enrolment and >2g/day for mesalazine and 5.2g for sulphasalazine (or equivalent of olsalazine) Oral or rectal steroids use on more than 3 days within 1 week of enrolment Immunosuppressants within 3 months of starting the study Previous intolerance of or contraindication to mesalazine Regular ingestion of NSAIDs (aspirin of 150mg or less was permitted) <u>**Group 1: 3g mesalazine (Eudragit-L-coated) tablets**</u> **Mean age (SD):**40 (no SD given, range 18-69 years) **Course:** continuous n=18, first episode n=31, episodic n=82 **Extent:** rectosigmoid n= 71, left sided n=27, extensive n=24, unknown n=9 **Duration of disease, mean (SD):** 6.5 (7.2) **Mean Clinical Activity Index (SD):** 8.2 (1.8) **Median Endoscopic Index (range):** 8 (5-12) **Drop outs:** 16 <u>**Group 2: 3g mesalazine (Ethylcellulose-coated) tablets**</u> **Mean age (SD):**40 (no SD given, range 18-81 years) **Course:** continuous n=12, first episode n=38, episodic n=77 **Extent:** rectosigmoid n= 63, left sided n=32, extensive n=23, unknown n=9 **Duration of disease, mean (SD):** 5.9 (7.7) **Mean Clinical Activity Index (SD):** 8.2 (1.9) **Median Endoscopic Index (range):** 8 (4-12) **Drop outs:** 14 **Note:** Duration of disease was numerically longer in the Eudragit-L group. There were differences between the geographical clusters; more patients had the continuous type in Australia (20% compared to 8%), duration of present acute episode was longer (median 10 weeks vs. median 5 weeks). Smoking history differed; smokers 4% vs. 14%,	therapy and other medications as per inclusion/exclusion criteria. Treatment of concurrent illnesses not subject to the exclusion criteria was permitted if it wasn't expected to impact on the outcomes of the trial. Permitted concurrent therapy was continued at the same dose. Topical mesalazine or corticosteroids was not permitted. Drugs not permitted: metronidazole, ciprofloxacin, immune modulating drugs, corticosteroids, other mesalazine-containing drugs, loperamide and other opioid -like drugs, nicotine patches, NSAIDS (except aspirin- see above).	Outcome 5: **Adverse events** Drug related AEs were: Group 1: 24 Group 2: 28 Most frequent AEs for Group 1 and 2 respectively were: Headache (26%, 17%) Abdo pain (5%, 4%) Nausea (4%, 5%) Viral infection (2%, 5%)	**Group 1:**74/131 (57%) **Group 2:**66/127 (52%)	
			Outcome 6: **Serious adverse events** None were considered to be drug related. (two other patients had SAEs in the screening period)	**Group 1:**4/131 **Group 2:**2/127	
			Outcome 6: **Hospitalisations** Note: these are the same patients who had the SAEs. This was due to deterioration or complications of the underlying disease.	**Group 1:**4/131 **Group 2:**2/127	

Author	Patients	Intervention	Outcome measures	Effect size	Comments
	ex-smokers 52% vs. 17%, non-smokers 44% vs. 69%. A European cohort, higher proportions in the Ethylcellulose group was freshly diagnosed (35% compared to 22% in the Eudragit-L group) and was current smokers (19% vs. 9%).				

Table 54: GIONCHETTI1998

Author	Patients	Intervention	Outcome measures	Effect size	Comments
P. Gionchetti et al. Comparison of Oral with Rectal Mesalazine in the Treatment of Ulcerative Proctitis. *Diseases of the Colon & Rectum; 41 (1): 93-97. 1998.* **REF ID: GIONCHETTI1998** **Study design and quality:** Single investigator blind RCT Single centre **4 week trial** **Randomisation & allocation concealment**: Randomised, allocation by previous computer pre-determined list. **Blinding:** Single investigator blind **Outcome assessment:** Disease Activity Index **Sample size calculation:** On PGA, 28 per group.	**<u>All patients:</u>** **N=58 randomised / ITT** **Drop-outs** (don't complete the study): N=0 (0%) **Inclusion criteria:** • >18 years • Extent: Active ulcerative proctitis not extending beyond 15cm from the anus • Severity: DAI>3 **Exclusion:** • Salicylate allergy • Concomitant active peptic ulcer • Clinically important hepatic, renal, cardiovascular or psychiatric conditions • Pregnancy or lactating women • Previous ineffective 5-ASA treatment • Receiving maintenance therapy with oral sulphasalazine or 5-ASA products • Immunosuppressive treatment less than 3 months previously • Corticosteroids less than 2 weeks previously **<u>Baseline characteristics</u>**	**Group 1: 2.4g mesalazine (Asacol)** N=29 randomised/ ITT 800mg of mesalazine (Asacol) taken orally three times a day. Total dose 2.4g. **Group 2: 1.2g mesalazine suppositories** N=29 randomised/ITT 400mg mesalazine suppositories, three times a day. Total dose 1.2g. **Concomitant therapy:** See exclusion criteria.	**Outcome 1: Clinical remission** (DAI=0 on clinical section) **Outcome 2: Clinical improvement** (Much improved, PGA score of 1) **Outcome 3: Endoscopic remission** (DAI=0 on	**<u>2 weeks</u>** **Group1:** 6/29 **Group 2:** 18/29 **<u>4 weeks</u>** **Group1:** 12/29 **Group 2:** 26/29 **<u>2 weeks</u>** **Group1:** 5/29 **Group 2:** 19/29 **<u>4 weeks</u>** **Group1:** 10/29 **Group 2:** 24/29 **<u>2 weeks</u>**	**Funding:** None described. **Limitations:** Single investigator blind Risk of an indirect population (no upper DAI inclusion criteria) **Additional outcomes:** Histological remission

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Type of analysis: ITT **Compliance rates:** Non-compliant if they consumed <75% N=0 dropout/ withdrawal due to drug related AEs.	**Group 1: 2.4g oral mesalazine** **Sex (m/f):** 15/14 **Mean age (no SD given):** 34 **Disease duration:** 5.6 years **Mean disease activity index score:** 7.42 **Extent:** All proctitis **Drop outs:** 0 **Group 2: 1.2g rectal mesalazine (suppositories)** **Sex (m/f):** 16/13 **Mean age (no SD given):** 36 **Disease duration:** 6.2 years **Mean disease activity index score:** 7.70 **Extent:** All proctitis **Drop outs:** 0		the sigmoidoscopic section) **Outcome 4: Adverse events** These were reported as mild. Group 1: 1 headaches, 2 abdominal pain, 3 nausea.	**Group1:** 4/29 **Group 2:** 15/29 **4 weeks** **Group1:** 10/29 **Group 2:** 21/29 **4 weeks** **Group1:** 6/29 **Group 2:** 0/29	

Table 55: GREEN1992

Author	Patients	Intervention	Outcome measures	Effect size	Comments
J. R. B. Green et al. Short report: comparison of two doses of balsalazide in maintaining ulcerative colitis in remission over 12 months. *Alimentary Pharmacology and Therapeutics; 6: 647-652. 1992.* **REF ID: GREEN1992** **Study design and quality:**	**All patients:** **N=108 randomised** **Drop-outs** (don't complete the study): N=17 (15.7%) <10% difference in missing data between the treatment arms **Inclusion criteria:** • Biopsy proven chronic ulcerative colitis	**Group 1: 3g Balsalazide** N=54 randomised N=44 (completers) 3g balsalazide (Colazide) per day. 750mg capsules taken with placebo capsules. **Group 2: 6g Balsalazide**	**Outcome 1: Relapse** rates by 12 months (Not significant from the Kaplan-Meier life table estimate. Figure not given.) Unable to calculate hazard ratio. **Outcome 2: Adverse events**	**ITT analysis** **Group1:** 10/54 **Group 2:** 15/54	**Funding:** Supported by a grant from Biorex Laboratories Ltd, UK. **Limitations:** Unclear method of randomisation and allocation concealment Double blind but no further information was given.

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Double blind RCT Multicentre: 4 centres, United Kingdom **12 month trial** **Randomisation:** No description given. Unclear. **Allocation concealment**: Unclear. **Blinding:** Stated to be double blind. No further information was given. **Outcome assessment:** Patients recorded any unexpected symptoms. Reviewed 3 monthly. Each review, patient recorded specific symptoms and global assessment of overall health. Sigmoidoscopy, 3 monthly and at relapse/withdrawal. Blood tests 6 monthly or at relapse. **Sample size calculation:** 40$ difference in remission rates, over 100 patients was deemed enough. No power or statistical significance described. **Type of analysis: ITT** **Compliance rates:** Blood and urine samples to analyse balsalazide concentrations at 6 months and 1 year. N=9 dropout/ withdrawal due	• Extent:≥15cm at some time in their illness • Clinical and sigmoidoscopic remission • Maintained on a 5-ASA preparation alone **Exclusion:** • None described. **<u>Group 1: 3g Balsalazide</u>** **Mean age (range):** 46 (21-78) **Extent:** proctosigmoiditis n=13, left sided colitis n=23, total colitis n=18 **Previous 5-ASA medication:** SASP n=51, mesalazine n=13, olsalazine n=3 **Adverse reactions to previous SASP:** yes n=20 **Time since previous relapse:** ≤one year n=31, >one year n=23 **Severity of previous relapse:** Not described. **Frequency of relapses:** Not described. **Drop outs:** 10 (6 due to AEs and 4 due to defaulters) **<u>Group 2: 6g Balsalazide</u>** **Mean age (range):** 47 (19-77) **Extent:** proctosigmoiditis n=16, left sided colitis n=20, total colitis n=18 **Previous 5-ASA medication:** SASP n=52, mesalazine n=9, olsalazine n=4 **Adverse reactions to previous SASP:** yes n=30 **Time since previous relapse:** ≤one year n=20, >one year n=34 **Severity of previous relapse:** Not described. **Frequency of relapses:** Not described. **Drop outs:** 7 (3 due to AEs and 4 defaulters) **<u>Definitions</u>** **Relapse:** Symptomatic (7 days of increased stool frequency with or without blood and mucus), Sigmoidoscopic (friable mucosa or spontaneous haemorrhage) and histological grounds (active disease) to distinguish it from non inflammatory diarrhoea. Central nurse coordinator who was the central point of contact for all the centres.	N=54 randomised N=47 (completers) 6g balsalazide (Colazide) per day. 750mg capsules taken. **Concomitant therapy:** None.	Data was only given for those that withdrew due to AEs. It is unclear whether there were additional patients with AEs that did not withdraw.		**Additional outcomes:** None. **Notes:** There was no difference in time from entry to relapse between the two groups. Those that did relapse could not be differentiated from those who didn't in terms of disease extent, age, gender, length of time from previous relapse or type/dose of previous 5-ASA medication. **All on 5-ASA previously (but not balsalazide).**

Author	Patients	Intervention	Outcome measures	Effect size	Comments
to drug related AEs (6 in the 3g group (1 headache, 2 nausea, 2 diarrhoea and abdo pain, 1 rash) and 3 (1 nausea, 2 diarrhoea and abdo pain) in the 6g group). All AEs were in the first 7 weeks.					

Table 56: GREEN1998

Author	Patients	Intervention	Outcome measures	Effect size	Comments
J. R. B. Green et al. Balsalazide Is More Effective and Better Tolerated Than Mesalamine in the Treatment of Acute Ulcerative Colitis. *Gastroenterology; 114: 15-22. 1998.* **REF ID: GREEN1998** **Study design and quality:** Double blind, double dummy RCT Multicentre: 19 centres, United Kingdom **12 week trial** **Randomisation:** Not described. Unclear. **Allocation concealment**:	**All patients:** **N=101 randomised** **N=99 (evaluable data)**– one patient did not have UC and the other did not take any study treatment **Drop-outs** (don't complete the study): N=38**(37.6%)** **Inclusion criteria:** 18-80 years old Extent: ≥12cm beyond the anal margin Severity: Moderate or severe (but this was based on the patient's overall evaluation of symptoms not Truelove & Witts[g]) and grade 2-4 on sigmoidoscopy Extent and grade were verified by sigmoidoscopy or colonoscopy more than 3 days before initiation of the study therapy **Exclusion:**	**Group 1: Balsalazide 6.75g** N=50 (evaluable) N=36 (completers) 2.25g balsalazide (0.75mg capsules), three times a day and placebo tablets three times a day. **Group 2: Mesalamine 2.4g** N=49 (evaluable) N=27 (completers) 0.8g mesalamine (0.4g tablets coated in Eudragit-S), three times a day and placebo	Outcome 1: **Clinical remission** (symptom free; If the following variables: consistency, stool frequency, blood on stools, blood on toilet paper, mucus, abdominal pain, need to go to the lavatory and other symptoms interfering with sleep, symptoms interfering with normal daily activities, other relevant symptoms, use of rectal hydrocortisone, were classed as none, absent, normal or no , as appropriate)	**2 weeks** **Group1:**32/50 (64%) **Group 2:**21/49 (43%) **4 weeks** **Group1:**35/50 (70%) **Group 2:**25/49 (51%) **8 weeks** **Group1:**39/50 (78%) **Group 2:**22/49	**Funding:** None described **Limitations:** Unclear method of randomisation and allocation concealment Double blind but no further information was given High drop out rate Indirect population: Likely to have included patients with severe disease **Additional outcomes:** Patients overall evaluation of symptoms Median time to complete

[g] No symptoms (excluded at entry), mild (aware of symptoms, easily tolerated, no interference with normal activities. They were also excluded at entry), moderate (occasional interference with normal activities), severe (frequent interference with normal activities)

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Unclear. **Blinding:** Double blind **Outcome assessment:** Sigmoidoscopy grading from 0-4, with 0 being normal. **Sample size calculation:** None described. **Type of analysis: All those treated.** **Last value extended principle was used for the symptom assessment** **Compliance rates:** Not described. N=2 dropout/ withdrawal due to AEs (1 in the balsalazide group due to increased bowel motions, 1 patient in the mesalamine group due to headaches).	Co existing Crohn's disease Idiopathic proctitis Non- inflammatory bowel disease Stool parasites, toxins or pathogens Received oral or IV steroids within the last month Received immunosuppressive agents within the last 3 months Required the daily use of a rectal steroid to maintain remission Received in the last 14 days a dose of mesalamine releasing compound from which >1.2g mesalamine per day was available **<u>Group 1: Balsalazide 6.75g</u>** **Mean age (SD):**39.7 (12.7), range 23-76 years **Previous use of mesalamine/ balsalazide in the last year:** n=6/ n=3 **Symptoms at entry:** moderate n=35, severe n=15 **UC grade at entry:** 2 n=25, 3 n=19, 4 n=6 **Extent in cm (SD):** 38.2 (20.8) **Extent:** left sided n=32, involvement of transverse colon n=5, pancolitis n=4 **Drop outs:** 15 (6 due to treatment failure, 6 noncompliance to the review protocol, 1 AEs, 1 treatment with excluded medication, 1 patient did not have UC) **<u>Group 2: Mesalamine 2.4g</u>** **Mean age (SD):**43.2 (13.9), range 22-70 years **Previous use of mesalamine/ balsalazide in the last year:** n=5/ n=2 **Symptoms at entry:** moderate n=33, severe n=16 **UC grade at entry:** 2 n=29, 3 n=13, 4 n=7 **Extent in cm (SD):** 35.4 (21.8) **Extent:** left sided n=35, involvement of transverse colon n=5, pancolitis n=3 **Drop outs:** 23 (16 due to treatment failure, 3 due to non compliance to the review protocol, 1 AEs, 1 treatment with excluded medication, 1 patient was not on adequate contraceptives, 1 patient was included after the recruitment date had passed)	capsules three times a day. **Concomitant therapy:** Rectal steroid foam as relief medication for use as required (Colifoam)		(45%) **<u>12 weeks</u>** **Group1:**44/50 (88%) **Group 2:**28/49 (57%)	relief of symptoms Daytime use of rescue steroids
			Outcome 2: **Clinical and endoscopic remission -** Complete remission (symptomatic remission with no use of relief medication in the previous 4 days and grade 0 or 1 UC on sigmoidoscopy) Apart from 12 weeks, the n values have been calculated from the 95% confidence intervals which were given in graphical and numerical formats.	**<u>4 weeks</u>** **Group1:**19/50 (38%) **Group 2:**6/49 (12%) **<u>8 weeks</u>** **Group1:**27/50 (54%) **Group 2:**11/49 (22%) **<u>12 weeks</u>** **Group1:**31/50 (62%) **Group 2:**18/49 (37%)	
			Outcome 3: **Adverse events** Most common were headaches, GI symptoms, and pain (in	**Group1:**24/50 (48%) **Group 2:**35/49 (71%)	

Author	Patients	Intervention	Outcome measures	Effect size	Comments
			various parts of the body), with patients receiving mesalamine reporting more adverse events in each category. Thought to be drug related: Group 1: 11% Group 2: 21%		
			Outcome 4: **Serious adverse events** Due to severe deteriorations or complications (rheumatoid arthritis and erythema nodosum) of UC	**Group1:**0/50 **Group 2:**4/49	

Table 57: GREEN1998A

Author	Patients	Intervention	Outcome measures	Effect size	Comments
J. R. B. Green et al. Maintenance of remission of ulcerative colitis: a comparison between balsalazide 3g daily and mesalazine 1.2g daily over 12 months. *Alimentary Pharmacology and Therapeutics; 12: 1207-1216. 1998.* **REF ID: GREEN1998A** **Study design and quality:**	**All patients:** **N=99 randomised** **N=95 (evaluable)** 4 were lost to follow up after initial entry visit. **Drop-outs** (don't complete the study): N=22 (22%) **Inclusion criteria:** • 18-80 years old • UC symptoms requiring treatment with maintenance therapy	**Group 1: 3g Balsalazide** N=49 randomised 3g Balsalazide (Colazide) is the equivalent of 1.04g of 5-ASA. 750mg capsules. Two capsules and one placebo tablet in the morning, two capsules and two placebo tablets in the evening.	Outcome 1: **Symptomatic relapse** at 12 months (Paper also reports symptomatic and asymptomatic relapses, and asymptomatic relapses. It is not clear what the primary outcome was but as the HR can only be calculated for the symptomatic relapse,	**Group1:** (13/49) **Group 2:** (16/46) Survival analysis p value = 0.4275	**Funding:** Financial support from Astra Pharmaceuticals Ltd. **Limitations:** Unclear method of randomisation and allocation concealment No extent data given at baseline

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Double blind, double dummy RCT Multicentre: 21 centres, United Kingdom and Ireland **12 month trial** **Randomisation:** Not described. Unclear. **Allocation concealment**: Unclear. **Blinding:** Double blind, double dummy. Identical placebo tablets/capsules. **Outcome assessment:** Sigmoidoscopy (graded 0-4).3 monthly assessment of clinical symptoms, compliance, examination and AEs. AEs assessed by asking a standard open ended health question. **Sample size calculation:** None described. **Type of analysis: all patients treated** **Compliance rates:** Verified by the amount of medication returned. 85% balsalazide and 93% mesalazine compliance rates, not statistically significant (p=0.3109) N=4 dropout/ withdrawal due to AEs (3 in the balsalazide group and 1 in the mesalazine).	• Asymptomatic (none or only mild symptoms) and had a sigmoidoscopic grade of 0 or 1 (verified by sigmoidoscopy or colonoscopy no more than 3 days before initiation of the study therapy • Previously had a relapse involving haemorrhagic mucosa, verified by sigmoidoscopy, and remission was declared up to a maximum of 1 year before entry to the study **Exclusion:** • Crohn's disease, idiopathic proctitis or non inflammatory bowel diseases • Received oral or IV steroids within the last month • Received immunosuppressants within the last 3 months • Required the daily use of a rectal steroid to maintain remission • Used rectal steroids outside the product license within the last 2 weeks • Received a dose of 5-ASA releasing compound from which more than 1.2g 5-ASA /day was available in the last two weeks • Unable to discontinue treatment with a rectal 5-ASA preparation on entry to the study **<u>Group 1: 3g Balsalazide</u>** **Mean age (SD):** 43.3 (12.5) **Extent:** Not described. **Severity of previous relapse:** Not described. **Number of acute attacks in the last year Mean (SD):** 1.5 (0.9) n=49 **Previous use of mesalazine/ balsalazide in the last year:** 30:17 **Symptoms on entry (None: Mild):**21:28 **UC grade at entry (grade 0:1):** 24:25 **Drop outs:** 13 (2 non compliance, 3 due AEs (2 of which were unacceptable AEs due to mild intermittent headaches which then became severe, the other due to severe headaches and lethargy), 6 were erroneously included, 2 not practicing adequate contraception) **<u>Group 2: 1.2g mesalazine</u>** **Mean age (SD):** **Mean age (SD):** 46.4 (13.4) **Extent:** Not described. **Severity of previous relapse:** Not described. **Number of acute attacks in the last year Mean (SD):** 1.4 (0.8) n=46	**Group 2: 1.2g Mesalazine** N=50 randomised N=46 (analysed) Mesalazine (Asacol) 400mg tablets. Two placebo capsules and one tablet in the morning, two placebo capsules and two tablets in the evening. **Concomitant therapy:** See inclusion/exclusion criteria.	this has been used as the outcome). **Outcome 2: Adverse events** Most common were headaches, GI symptoms, respiratory infections, abnormal lab tests (related to UC disease), pain (various parts of the body), and flu like disorders. Investigators thought 19% and 20% were probable or possibly drug related in mesalazine and balsalazide groups respectively. **Outcome 3: Serious adverse events** Group 1: 1 due to a fracture of the left scaphoid and the other a Spigelian hernia. Group 2: Suspected urinary tract infection, severe complication of UC and a death resulting from a cardiac arrest and ischaemic heart disease.	**Group1:** 30/49 (61%) **Group 2:** 30/46 (65%) **Group1:** 2/49 **Group 2:** 3/46	High drop out rate **Additional outcomes:** Asymptomatic relapses Symptomatic and asymptomatic relapses Night time symptoms GP visits Relapse of symptoms at 3 months Patients overall evaluation of symptoms in relation to symptomatic relapse.

Author	Patients	Intervention	Outcome measures	Effect size	Comments
	Previous use of mesalazine: balsalazide in the last year: 19:20 **Symptoms on entry (None: Mild):**22:24 **UC grade at entry (grade 0:1):** 26:19 **Drop outs:** 9 (1 due to urgency and increased frequency of bowel movements but it resolved by the time they attended clinic, 5 non compliance, 1 due to AEs, 2 were erroneously included) **Definitions** **Symptomatic relapse:** Recurrence of moderate or severe symptoms on the patients' overall evaluation. **Asymptomatic relapse:** Grade 3 or 4 on sigmoidoscopy in the absence of symptoms. Reasons for discontinuations: Patient wish, use of excluded medication, non compliance, development of an excluded medical condition, unacceptable AE or complication of UC requiring active intervention.				

Table 58: GROSS2006

Author	Patients	Intervention	Outcome measures	Effect size	Comments
V. Gross et al. Budesonide foam versus budesonide enema in active ulcerative proctitis and proctosigmoiditis. *Alimentary Pharmacology & Therapeutics; 23: 303-312. 2006.* **REF ID: GROSS2006** **Study design and quality:** Double blind, double dummy, Phase III RCT Multicentre: 52 centres, Germany, Hungary, Israel,	**All patients:** **N=541 randomised** **N=533 authors ITT** N=449 PPA **Drop-outs** (don't complete the study): N=34 (6%) were protocol violators that were premature discontinuations **Inclusion criteria:** • Adults 18-70 years • Extent: active ulcerative proctitis or proctosigmoiditis (confirmed by endoscopy, histology and a –ve stool culture)	**Group 1: 2mg Budesonide foam enema & placebo liquid enema** N=269 randomised N=265 (ITT) N=210 PPA N=267 safety population Budesonide 2mg/25mls (Budenofalk) and a placebo enema. Patients were stratified	**Outcome 1: Clinical remission** (CAI≤4) at the final/ withdrawal visit N values were calculated from the percentages given in the paper. **Outcome 2: Clinical improvement** (based on the CAI, no further information given)	**Authors ITT** **4 weeks** **Group1:** 151/265 **Group 2:** 174/268 **Authors PPA** **4 weeks** **Group1:** 177/210	**Funding:** Supported by Dr. Falk Pharma. **Limitations:** Unclear method of randomisation and allocation concealment Unclear drop out rate Double blind but no further information was given Risk of indirect population: no upper limit on the

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Lithuania, Latvia, Estonia, Netherlands **4 week trial** **Randomisation:** No information given. **Allocation concealment**: No information given. **Blinding:** Double blind, no further information given **Outcome assessment:** Clinical Activity Index (CAI). Endoscopic index according to Rachmilewitz. **Sample size calculation:** 0.05 significance, 80% power, sample size of 344 **Type of analysis: ITT and PPA** **Compliance rates:** 29 had inadequate compliance. N=0 dropout/ withdrawal due to drug related AEs.	• Severity: Clinical disease activity (CAI, according to Rachmilewitz >4), Endoscopic index of ≥4 **Exclusion:** • Uncertain diagnosis of UC • Symptoms of disease present for <2 weeks • Macroscopic lesions proximal to the sigma (>40cm ab ano) • Crohn's disease • Prior bowel operation • Use of oral/rectal steroids within 1 month prior to baseline • Use of immunosuppressant's within 3 months prior to baseline • Long-term NSAID treatment **<u>Baseline characteristics</u>** **<u>Group 1: 2mg Budesonide foam enema</u>** **Sex (m/f):** 117/148 **Mean age (SD):** 44.4 (12.9) **Extent:** No % given. All proctitis or proctosigmoiditis. **Type of disease:** new n=55, established n=210 **Mean CAI (SD):** 7.6 (2.0) **Mean DAI (SD):** 7.2 (1.8) **Endoscopic index, mean (SD):** 7.7 (1.9) **Drop outs:** unclear **<u>Group 2: 2mg Budesonide liquid enema</u>** **Sex (m/f):** 134/134 **Mean age (SD):** 43.1 (13.7) **Extent:** No % given. All proctitis or proctosigmoiditis. **Type of disease:** new n=69, established n=199 **Mean CAI (SD):** 7.5 (2.0) **Mean DAI (SD):** 7.3 (2.0) **Endoscopic index, mean (SD):** 7.7 (1.8) **Drop outs:** unclear	for sequence of application for example, enema in the morning and foam in the evening and vice versa. **Group 2: 2mg Budesonide liquid enema & placebo foam enema** N=272 randomised N=268 (ITT) N=239 PPA N=268 safety population Budesonide 2mg/100mls liquid enema (Entocort) and placebo foam enema. Patients were stratified for sequence of application for example, enema in the morning and foam in the evening and vice versa. **Concomitant therapy:** 5-ASA containing or releasing drugs- discontinued at the latest at baseline. Rectal administration of other medication was not allowed.		**Group 2:** 205/239	severity inclusion criteria **Additional outcomes:** Clinical remission by extent of disease, by baseline CAI, duration of disease, smoking history, extra intestinal manifestations, non response to rectal 5-ASA (present episode), non response to oral 5-ASA (present episode) Histological improvement Physicians' global assessment
			Outcome 3: Endoscopic remission (according to Rachmilewitz)	**Authors PPA** **<u>4 weeks</u>** **Group1:** 106/204 **Group 2:** 127/234	
			Outcome 4: Adverse events Most frequent AEs were; headache, UC deterioration, nausea and abdominal pain.	**Group1:** 86/267 **Group 2:** 87/268	
			Outcome 5: Serious adverse events Group 1: UC aggravated, unstable angina Group 2: 2 UC aggravation, renal colic, pneumonia and cerebrovascular accident It was stated that none of the SAEs were thought to be drug related.	**Group1:** 2/267 **Group 2:** 4/268	

Table 59: GROSS2009/2011

Author	Patients	Intervention	Outcome measures	Effect size	Comments
V. Gross et al. 3g mesalazine granules are superior to 9mg budesonide for achieving remission in active ulcerative colitis: A double blind, double-dummy, randomised trial. *Journal of Crohn's and Colitis; 5: 129-138. 2011.* **REF ID:** GROSS2011 And the abstract: **V. Gross et al.** Efficacy and Tolerability of a Once Daily Treatment with Budesonide Capsules Versus Mesalamine Granules for the Treatment of Active Ulcerative Colitis: A Randomized, Double-Blind, Double-Dummy, Multicentre Study. *Gastroenterology; 136:5 Suppl 1; A15. 2009.* **REF ID: GROSS2009** **Study design and quality:** Double blind, double dummy, phase III multicentre RCT Multicentre: 48 centres, Germany, Russia, Ukraine, Latvia, Hungary, Lithuania, Czech Republic, Slovakia, Poland	**<u>All patients:</u>** **N=343 randomised** **N=343 ITT** **N= 302 PPA** **Drop-outs** (don't complete the study): N=55 (16.0%) **Inclusion criteria:** Extent: proctosigmoiditis, left sided, subtotal/pancolitis Severity: mild to moderate Age 18-75 years **Exclusion:** • Proctitis limited to 15cm above anus • Crohn's disease, indeterminate colitis, ischaemic colitis, radiation colitis or microscopic colitis • Toxic megacolon • Baseline stool positive for microbial pathogens causing bowel disease • Diarrhoea due to other symptomatic gastrointestinal disease • Active peptic ulcer disease • Haemorrhagic diathesis • Active colorectal cancer or history of colorectal cancer • Treatment with immunosuppressants within previous 3 months and/or corticosteroid therapy (any route) within previous 4 weeks, NSAIDS for >6 weeks except acetylsalicylic acid ≤350mg/day, CYP3A inhibitors for > 7 days, oral antibiotics unless ≤ 7 days for conditions unrelated to UC • Current relapse under maintenance treatment with mesalazine >2.4g/day	All patients received 3 sachets and 3 capsules in the morning, **Group 1: Mesalazine 3g** N=166 randomised N= 166 (ITT) N= 146 (completers) Mesalazine granules (delayed and extended release [Salofalk]) 3g od (1g sachets) with placebo capsules **Group 2: Budesonide 9mg** N=177 randomised N=177 (ITT) N= 142 (completers) Budesonide capsules 9mg od (3mg capsules [Budenofalk]) with placebo sachets **Concomitant therapy:** Not allowed– see exclusion criteria	Outcome 1: **Clinical remission** (CAI ≤4 with stool frequency <18/week and 0-1 bloody stool/week) Outcome 2: **Clinical remission** (as above) **proctosigmoiditis /left sided colitis subgroup** Outcome 3: **Clinical remission** (as above) **subtotal/pancolitis subgroup** Outcome 4: **Clinical improvement** (complete marked, moderate or slight improvement of symptoms on the Physician's Global Assessment). This is including those in clinical remission. Outcome 5: **Endoscopic remission** (EI ≤3) Outcome 6: **Endoscopic remission** (EI ≤3)	**Group1:** 91/166 (54.8%) **Group 2:** 70/177 (39.5%) **Group1:** 72/134 (53.7%) **Group 2:** 56/140 (40.0%) **Group1:** 19/32 (59.4%) **Group 2:** 14/37 (37.8%) **Group1:** 142/166 (85.5%) **Group 2:** 136/177 (76.8%) **Group1:** 105/166 (63.3%) **Group 2:** 88/177 (49.7%) **Group1:** 82/134	**Funding:** Dr. Falk Pharma GmbH, Freiburg, Germany (manufacturers and suppliers of both drugs) contributed to study design, interpretation of data and reviewed the draft manuscript **Limitations:** **Additional outcomes:** Median time to first resolution of symptoms Histological remission (Histological Index ≤1) Mean treatment duration (days) Mean reduction in CAI from baseline Morning cortisol levels Global Assessment of Tolerability

Author	Patients	Intervention	Outcome measures	Effect size	Comments
8 week trial **Randomisation:** Computer generated randomisation list using randomly permuted blocks, held by staff at ClinResearch GmbH who were not involved in the study conduct **Allocation concealment**: Adequate **Blinding:** Double blind, double dummy **Outcome assessment:** Clinical symptoms measured using Clinical Activity Index (CAI) and endoscopy graded by Endoscopic Index (EI) (based on Rachmilewitz 1989) **Sample size calculation:** 180 patients per arm based on 80.5% power assuming a 50% remission rate in both treatment arms with a non-inferiority margin of 15% **Type of analysis:** ITT and per protocol (PP) **Compliance rates:** Ratio between the administered medication and the expected intake. 1 patient was classed as non compliant in the budesonide group. N=24 were classed as dropout/ withdrawal due to AEs (8 in mesalazine group and 16 in budesonide group) but the	**Group 1: Mesalazine 3g** **Mean age (SD):** 43.5 (14.1) **Extent:** subtotal/pancolitis n=32 (19%), left-sided colitis n=42 (25%), proctosigmoiditis n=92 (55%) **Severity:** mild (CAI ≤8) n=115 (69%), moderate (CAI >8) n=51 (31%) **New diagnosis (%):** 23 (14) **Established disease (%):** 143 (86) **Drop outs:** 20 (9 lack of efficacy,3 adverse events,7 lack of cooperation, 1 "other") **Group 2: Budesonide 9mg** **Mean age (SD):** 43.5 (13.8) **Extent:** subtotal/pancolitis n=37 (21%), left-sided colitis n=42 (24%), proctosigmoiditis n=98 (55%) **Severity:** mild (CAI ≤8) n=107 (60.5%), moderate (CAI >8) n=70(39.5%) **New diagnosis (%):** 28 (16) **Established disease (%):** 149 (84) **Drop outs:** 35 (25 lack of efficacy,2 adverse events,3 lack of cooperation, 5 "other")		**proctosigmoiditis /left sided colitis subgroup**	(61.2%) **Group 2:** 67/140 (47.9%)	
			Outcome 7: **Endoscopic remission** (EI ≤3) **subtotal/pancolitis subgroup**	**Group1:** 23/32 (71.9%) **Group 2:** 21/37 (56.8%)	
			Outcome 8: **Adverse events (excludes serious AEs)** **ASA vs. steroids** Most frequent were UC deterioration (3%, 10.2%), headache (5.4%, 5.6%), nasopharngitis (1.7%, 1.2%), increase lipase (2.4%, 0%), respiratory tract infection (0.6%, 1.8%).	**Group1:** 40/166 **Group 2:** 44/177	
			Outcome 9: **Serious adverse events**	**Group1:** 2/166 (1.2%) – both appendicitis **Group 2:** 3/177 (1.7%) – all deterioration of UC	

Author	Patients	Intervention	Outcome measures	Effect size	Comments
majority were deterioration of UC, only 5 were actual AEs. Unclear if these were drug related.					

Table 60: HABAL1993

Author	Patients	Intervention	Outcome measures	Effect size	Comments
F. M. Habal et al. Oral 5-Aminosalicylic Acid for Inflammatory Bowel Disease in Pregnancy: Safety and Clinical Course. *Gastroenterology; 105: 1057-1060. 1993.* **REF ID: HABAL1993** **Study design and quality:** Prospective case series **Canada** **Years studied: 1985-1992** **Risk of bias:** High due to study design	**<u>All patients:</u>** Included population • Identified by a group of gastroenterology outpatients • Known to have UC or Crohn's disease (proven by endoscopy and biopsy or by radiographic studies) • Intolerant or allergic to SASP • Symptomatically in remission on 5-ASA at the time of conception • Unable to discontinue 5-ASA because of a recurrence of symptoms after the drug had been stopped on at least one previous occasion before conception Excluded population **N=10 patients with ulcerative colitis (12 pregnancies)** 7 patients had Crohn's disease (excluded from this review) <u>Data collection</u> Prospective evaluation. 6 week obstetric review or earlier if a flare up of their disease occurred. Evaluation: weight, no. of bowel movements, rectal bleeding. 3 month ultrasound. Assessed by a paediatrician within 24hrs, then regularly from 1-6 years for height, weight and rate of development. <u>Baseline characteristics</u> Continued on the same dose of 5-ASA as prior to conception (Asacol).	**Oral 5-ASA (Asacol)** **All patients were previously in remission on 5-ASA, mean dose of 1.7g/ day (range 0.8-2.4g).** Other medication was added as clinically indicated in the event of a flare up of symptoms.	**All were in remission at conception.** One patient required a Colectomy but carried on to a full term pregnancy. One patient miscarried, but she had miscarried on 4 previous occasions before taking the 5-ASA.		**Funding:** None described **Limitations:** High risk of bias due to study design **Additional outcomes:** Outcomes for the Crohn's patients. **Notes:** **Sulphasalazine intolerant population**
			Outcome 1: Normal live birth	11/12 pregnancies	
			No fetal abnormalities were found at delivery. No clinical or biochemical abnormalities in the neonatal period. Every infant had a normal Apgar score of >6 and birth weight of >2.5kg. All Children were presently well with normal growth and development (overall including the Crohn's patients children, 1-6.5years old)		

Author	Patients						Intervention	Outcome measures	Effect size	Comments
	Two patients had two pregnancies during the time period.									
	Patient	**Mean age at delivery (yr)**	**Disease extent**	**Disease duration (yr)**	**Post partum follow up (yr)**	**Previous pregnancy**				
	1	29	PS	2	2.5	No				
	2[b]	30	PS	3	1.0	Yes				
	3	27	PC	5	3.5	Yes				
	4	31	LS	3	2.0	No				
	5[c]	32	LS	4	0.5	Yes				
	6	29	LS	1	1.5	No				
	7	30	LS	7	3.5	No				
	8	30	PC	7	1.5	Yes				
	9	26	LS	3	1.5	Yes				
	10	31	LS	6	1.5	No				
	11	30	LS	5	3.5	No				
	12	24	LS	1	4.5	Yes				

(a) Disease extent: PS (proctosigmoiditis), PC (pancolitis), LS (left sided colitis)
(b) Second pregnancy of patient 1
(c) Second pregnancy of patient 4

Table 61: Patient drug history and outcome of pregnancy

Patient	Duration of 5-ASA treatment before pregnancy	Duration during pregnancy	Dose (g/day)	Other drugs	Flare up?	Outcome of pregnancy
1	2	Term	1.6		No	Full term
2	3	12 weeks[a]	1.6		Yes	Full term
3	5	Term	2.4	Prednisone 10mg	No	Full term
4	0.5	9 weeks[b]	2.4		No	**Spontaneous abortion**

Patient	Duration of 5-ASA treatment before pregnancy	Duration during pregnancy	Dose (g/day)	Other drugs	Flare up?	Outcome of pregnancy
5	1	Term	2.4	5-ASA enema	Yes	Full term
6	1	Term	1.6		No	Full term
7	1	Term	2.4	Hydrocortisone enema	Yes	Full term
8	5	Term	1.2	Prednisone 10mg	No	Full term
9	2	Term	1.6	5-ASA enema	Yes	Full term
10	4	Term	0.8		No	Full term
11	2	Term	1.2		No	Full term
12	1	Term	2.0	Prednisone 5mg	No	Full term

(a) Patient underwent a Colectomy
(b) Patient had a spontaneous abortion
(c) Those who had a flare responded to hydrocortisone or 5-ASA enemas, apart from patient 2 who underwent a colectomy

Table 62: HANAUER1993

Author	Patients	Intervention	Outcome measures	Effect size	Comments
S. Hanauer et al. Mesalamine Capsules for Treatment of Active Ulcerative Colitis: Results of a Controlled Trial. *The American Journal of Gastroenterology; 88 (8): 1188-1197. 1993.* **REF ID: HANAUER1993** **Study design and quality:** Double blind RCT Multicentre: 20 centres, unclear if these were all in the	**All patients:** **N=374randomised**to four groups 1g,2g,4g mesalamine (Pentasa) and placebo **Drop-outs** (don't complete the study): N=82**(21.9%)** **Inclusion criteria:** Extent: No restriction described. Severity: Mild to moderate >18 years old	250mg capsules where used in identical looking blister packs. **Group 1: 2g mesalamine (Pentasa)** N=97 randomised N=81 (completers) Two active capsules and two placebo capsules, four times a day. **Group 2: 4g mesalamine (Pentasa)**	Outcome 1: **Clinical remission** (PGA score of 1; complete relief of symptoms) Outcome 2: **Endoscopic remission** (sigmoidoscopic score of 0-4, out of 15)	**Group 1:**28/97 (29%) **Group 2:** 28/95 (29%) **Group 3:** 11/90 (12%) **Group 1:** 43/97 (44%) **Group 2:** 46/95 (48%) **Group 3:** 28/90 (31%)	**Funding:** Grant was provided by Marion Merrell Dow Inc. **Limitations:** Unclear method of randomisation and allocation concealment Double blind but no further information given No detail on severity at baseline

Author	Patients	Intervention	Outcome measures	Effect size	Comments
United States or not. **8 week trial** **Randomisation:** Stratified on the basis of their extent of disease (distal to the splenic flexure is classed as left-sided colitis). No information on the method of randomisation was described. **Allocation concealment:** Unclear **Blinding:** Says double blind but no further information was given. **Outcome assessment:** Different form of the PGA, graded from 1-6. Sigmoidoscopy looked at erythema, friability, granularity/ulceration, mucopus and the appearance of mucosal vascular pattern. Each was scored from 0-3, maximum score of 15. **Sample size calculation:**70 patients per treatment arm based on 80% and a two sided 5% significance. **Type of analysis: ITT** **Last observation carried forward (LOCF)** Imputation was employed for data missing at baseline or endpoint.	Diagnosis of UC Presence of active disease confirmed by both clinical symptoms and colonoscopic evidence of active inflammation of ≥5 on a 15point index scale. 7 day washout period if prior use of steroids, sulfasalazine or other mesalamine products prior to baseline evaluations 90 day washout of immunosuppressant's Women of non child-bearing potential or women taking birth control **Exclusion:** Positive stool culture for enteric pathogens, ova, parasites or C. Difficile Pregnant or lactating women **<u>Group 1: 2g mesalamine (Pentasa)</u>** **Mean age (SD):**40.1 (14.6) **Extent:** Distal n=66 (68%), pancolitis n=31 (32%) **Recent use of:** **Steroids:** n=20, 21% **Sulphasalazine:** n=40, 41% **Drop outs:** 16 (16%) (4 due to insufficient therapeutic effect, 9 due to AEs, 2 due to voluntary withdrawal/lost to follow up and 1 for other reasons) **<u>Group 2: 4g mesalamine (Pentasa)</u>** **Mean age (SD):**40.9 (13.0) **Extent:** Distal n=68 (72%), pancolitis n=27 (28%) **Recent use of:** **Steroids:** n=27, 29% **Sulphasalazine:** n=38, 40% **Drop outs:** 13 (14%) (5 due to insufficient therapeutic effect, 7 due to AEs and 1 due to voluntary withdrawal/lost to follow up) **<u>Group 3: Placebo</u>** **Mean age (SD):**39.6 (13.4) **Extent:** Distal n=62 (69%), pancolitis n=28 (31%)	N=95 randomised N=82 (completers) Four active capsules, four times a day **Group 3: Placebo** N=90 randomised N=60 (completers) Four placebo capsules, four times a day. **Concomitant therapy:** Not permitted to continue with steroids, sulfasalazine, or other mesalamine formulations. Not permitted to use any drug which can mask symptoms (antispasmodics, antidiarrheals except loperamide), change absorption (cholestyramine) or possibly worsen the disease (antibiotics, NSAIDs). Loperamide was only dispensed when absolutely necessary for control of the diarrhoea.	Outcome 3: **Clinical improvement** (treatment benefit: complete relief of symptoms, marked, moderate or slight improvement of symptoms, PGA 1,2 3 &4) Outcome 4: **Adverse events** Only treatment related events were reported: **Outcome 5: Serious adverse events** Most frequently reported adverse events were diarrhoea, nauseas, headache, melena and abdominal pain of which they were all higher in the placebo group. Extent data was reported for the outcome 'treatment success' (complete relief of symptoms or marked improvement). The definition of clinical improvement also included those with slight improvement, therefore this was not one of our outcomes and so the data has not been reported. The paper describes that for treatment success there was no significant difference found between the two treatment groups for	**Group 1:**77/97 (79%) **Group 2:** 80/95 (84%) **Group 3:** 49/90 (54%) **Group 1:**15/97 **Group2:**19/95 **Group 3:**20/90 **Group 1:**10/97 **Group2:**4/95 **Group 3:**5/90	High dropout rate **Additional outcomes:** Treatment benefit Mean change in sigmoidoscopic index Treatment failure Reduction in biopsy score Clinical improvement by disease location Mean changes for the individual symptom assessments Biopsy remission

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Compliance: 338/374 (90%) were considered compliant (≥70% of medication for the duration of the study, patients had not been off medication for >2 days prior to final visit, and patients consumed study medication for at least 4 days prior to terminating study participation. N=32 dropout/ withdrawal due to AEs (it is not clear which of these were treatment related).	**Recent use of:** **Steroids:** n=25, 28% **Sulphasalazine:** n=38, 42% **Drop outs:** 30 (33%)(18 due to insufficient therapeutic effect, 11 due to AEs and 1 for other reasons)		distal and pancolitis.		

Table 63: HANAUER1996

Author	Patients	Intervention	Outcome measures	Effect size	Comments
S. B. Hanauer et al. A Multi-Center, Double Blind, Placebo-Controlled Dose-Ranging Trial Of Olsalazine For Mild –Moderately Active Ulcerative Colitis. *Gastroenterology; 110;A921. 1996.* **REF ID: HANAUER1996** **Study design and quality:** Abstract	**All patients:** **N=Xrandomised**(unclear) N=273 analysed **Drop-outs** (don't complete the study): N= 121[i](44%) **Inclusion criteria:** Extent: Not described Severity: Mild-moderate	**Group 1: 2g Olsalazine** N=92 randomised Given qid after meals and titrated up during the first week. **Group 2: 3g Olsalazine** N=91 randomised Given qid after meals and titrated up during the first week.	Outcome 1: **Clinical remission** (according to the number of bowel movements and the amount of blood in the stool[j])	**Group1:**11/92 **Group 2:**16/91 **Group 3:** 12/90	**Funding:** None described in the abstract. **Limitations:** Unclear method of randomisation and allocation concealment No baseline data reported only an overarching text description

[i] This value was taken from the Cochrane Systematic Review on Oral ASAs
[j] This definition was taken from the Cochrane Systematic Review on Oral ASAs.

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Double blind RCT [Abstract] Multicentre: 24 centres This abstract has been included because it was included in the Cochrane systematic review on oral ASAs for the induction of remission in ulcerative colitis. **12 week trial** **Randomisation: Unclear, not described.** **Allocation concealment**: Unclear, not described. Cochrane review describes it as adequate. **Blinding:** Double blinding described in the Cochrane review, but no information was given on this in the abstract. **Outcome assessment: Unclear.** **Sample size calculation:** None described in the abstract. **Type of analysis: Unclear.** **Compliance rates: Unclear/ not described.** N=19 dropouts/ withdrawals due to AEs(9 in the 2g group, 8 in the 3g group and 2 in the placebo[h]). It is unclear if these were drug related. Data taken from the Cochrane review.	**Exclusion:** **None described.** **Baseline characteristics:** **The abstract says that there were "no important differences in baseline demographics (age, gender, and length of disease, duration of attack, endoscopy score, and extent of disease, % newly diagnosed, stools/day and days with blood in stool".** Group 1: 2g Olsalazine Drop outs:47 Group 2: 3g Olsalazine Drop outs: 34 Group 3: Placebo Drop outs: 40	**Group 3: Placebo** N=90 randomised No intervention details were given **Concomitant therapy:** No anti-diarrhoeals were allowed.			Extent of UC unclear High dropout rate and unclear if their characteristics where the same as those who completed the trial **Additional outcomes:** Endoscopic improvement

[h] This information was taken from the Cochrane Systematic Review on Oral ASAs. It was unclear what the causes were.

Table 64: HANAUER1996A

Author	Patients	Intervention	Outcome measures	Effect size	Comments
S. B. Hanauer et al. An Oral Preparation of Mesalamine as Long-Term Maintenance Therapy for Ulcerative Colitis. *Annals of Internal Medicine; 124: 204-211. 1996.* **REF ID: HANAUER1996A** **Study design and quality:** Double blind RCT Multicentre: 17 centres (8 private practices, 5 university based medical centres and 4 hospitals or clinics, countries **6 month trial** **Randomisation:** Done by centre, using randomization codes with specific patient's numbers generated for each study site before the study began. Randomisation was done by a computer. No stratification was carried out. **Allocation concealment**: Unclear. **Blinding:** Double blind, no further information given. **Outcome assessment:** Proctosigmoidoscopy or colonoscopy scoring from 0 to	**<u>All patients:</u>** **N=264 randomised** **Drop-outs** (don't complete the study): N=75 (28.4%) The paper describes the numbers of patients excluded to be similar in the three groups. The reasons listed were; failure to meet study entry criteria (n=36), non compliance with study medication (n=18), non compliance with study procedure (n=3), concomitant medication violation (n=10), loss to follow-up (n=4) and voluntary withdrawal (n=4). **Inclusion criteria:** • 18-75 years old • Documented diagnosis of Ulcerative Colitis • Been in remission for at least 1 month as indicated by the endoscopic appearance of the bowel and by the passage of five or fewer bloodless stools per day • Score of 0 on the proctosigmoidoscopic grading • Presence of colitis symptoms such as loose stools or abdominal cramps was not a reason for exclusion from the study, provided that endoscopic examination showed remission of disease • Previously treated with 2-4g of SASP per day or 0.8-1.6g of any oral mesalazine product per day. The dose had to be kept constant for at least 1 month before study entry • No patient had received corticosteroid or topical rectal therapy within 1 month of study entry • Female patients with child bearing potential were required to practice a reliable method of birth control throughout the study **Exclusion:** • Pregnant or nursing women • History of allergy or intolerance to aspirin or salicylates • History of extensive bowel resection causing the short-bowel syndrome	**Group 1: 0.8g mesalamine** N=90 randomised N=68 (primary efficacy analysis) 400mg mesalamine (Asacol) tablets. Two active and two placebo tablets per day. Active tablet was taken at breakfast and bedtime. **Group 2: 1.6g mesalamine** N=87 randomised N=58 (primary efficacy analysis) 400mg mesalamine (Asacol) tablets. Four tablets per day. **Group 3: Placebo** N=87 randomised N=63 (primary efficacy analysis) Four placebo tablets per day. **Concomitant therapy:**	**Outcome 1: Relapse** The Group 1 results have not been used as it is below the BNF recommended dose for maintenance. **Outcome 2: Adverse events** The Group 1 results have not been used as it is below the BNF recommended dose for maintenance. Most frequent AEs reported were headache, flu syndrome, diarrhoea, rhinitis and abdominal pain. **Outcome 3: Serious adverse events** The Group 1 results have not been used as it is below the BNF recommended dose for maintenance. Group 2: miscarriage, unrelated to the treatment	**<u>Authors analysis</u>** **Group 1:** 24/68 **Group 2:** 18/58 **Group 3:** 33/63 **Group 2 vs. 3 log rank p value:** 0.011 **Group 1:** 29/90 **Group 2:** 36/87 **Group 3:** 34/87 **Group 1:** 1/90 **Group 2:** 1/87 **Group 3:** 1/87	**Funding:** Grant from Procter and Gamble **Limitations:** Unclear allocation concealment (unclear if the computer was secure/locked file) Unclear who dropped out from which treatment group Double blind, but no further information was given **Additional outcomes:** None **Note:** in supplemental analysis looking at stratification by disease extent, the distribution of time to relapse were similar in the five groups (p=0.907)

Author	Patients	Intervention	Outcome measures	Effect size	Comments
3. A score of 0 was required at baseline. Patient diaries. **Sample size calculation:** 64 patients per arm to detect a 25% difference in proportions of patients having a relapse, two sided 0.05 significance level, 80% power. **Type of analysis: ITT and efficacy analysis** (all those compliant with the protocol, completed 6 months or had a relapse or withdrew due to AEs) Patients who did not have a relapse were censored from the last date of study participation; patients in whom treatment was discontinued prematurely because of an AE were censored at the date of discontinuation. **Compliance rates:** Monitored by the tablet count and by review of patient diaries at each study visit. Non compliance was defined as missing >15% of the study medication over the duration of treatment or >50% of the study medication for 4 consecutive days (for reasons other than intolerance). 6 in the placebo group, 11 in the 0.8g and 4 in the 1.6g mesalamine groups were non compliant. N=10 dropout/ withdrawal due to AEs.	• Laboratory evidence of renal or hepatic dysfunction **<u>Group 1: 0.8g mesalamine</u>** **Mean age (SE):** 41.9 (1.37) **Extent:** proctitis n=10, proctosigmoiditis n=28, left-sided disease n=18, pancolitis n=26, unknown n=8 **Duration of UC:** <1yr n=13, 1-5yrs n=23, >5-10years n=22, >10years n=31, unknown n=1 **Previous medication for UC:** SASP n=58, any oral mesalamine n=31, other n=1 **Stool frequency:** 1/day n=41, 2/day n=31, 3/day n=12, four or more/day n=6, mean number/day n=1.83 SE 0.103 **Severity of previous relapse:** Not described **Frequency of relapses:** Not described **Drop outs:** unclear **<u>Group 2: 1.6g mesalamine</u>** **Mean age (SE):** 42.1 (1.45) **Extent:** proctitis n=16, proctosigmoiditis n=15, left-sided disease n=17, pancolitis n=23, unknown n=16 **Duration of UC:** <1yr n=13, 1-5yrs n=22, >5-10years n=23, >10years n=29, unknown n=0 **Previous medication for UC:** SASP n=54, any oral mesalamine n=32, other n=1 **Stool frequency:** 1/day n=30, 2/day n=40, 3/day n=10, four or more/day n=7, mean number/day n=1.95 SE 0.102 **Severity of previous relapse:** Not described **Frequency of relapses:** Not described **Drop outs:** unclear **<u>Group 3: Placebo</u>** **Mean age (SE):** Unclear as there is a typo in the paper. **Extent:** proctitis n=13, proctosigmoiditis n=20, left-sided disease n=13, pancolitis n=24, unknown n=17 **Duration of UC:** <1yr n=9, 1-5yrs n=23, >5-10years n=22, >10years n=33, unknown n=0 **Previous medication for UC:** SASP n=48, any oral mesalamine n=37, other n=2 **Stool frequency:** 1/day n=27, 2/day n=37, 3/day n=14, four or more/day n=9, mean number/day n=2.08 SE 0.109 **Severity of previous relapse:** Not described **Frequency of relapses:** Not described	Patients were not permitted to use corticosteroids (except topically for dermatologic reasons), SASP, antibiotics for more than 1-0 consecutive days, topical rectal therapies, or investigational drugs other than mesalamine.	Group 3: chest pain, hypertension and dyspnoea, which was considered unrelated to the treatment		

Author	Patients	Intervention	Outcome measures	Effect size	Comments
	Drop outs: unclear **Definitions:** **Relapse:** Score of ≥1 on endoscopy at any time. Note: During the course of the study the proctosigmoidoscopic grading scale was changed to allow entry of patients with mild findings, because the investigators agreed that patients with longstanding UC in remission may have had mild granularity, oedema, hyperaemia or erythema or mildly diminished vascular markings. There is a high drop out rate to patients not meeting the initial inclusion criteria relating to this scoring.				

Table 65: HANAUER1998

Author	Patients	Intervention	Outcome measures	Effect size	Comments
S. B. Hanauer et al. Dose-Ranging Study of Mesalamine (PENTASA) Enemas in the Treatment of Acute Ulcerative Proctosigmoiditis: Results of a Multicentered Placebo-Controlled Trial. *Inflammatory Bowel Disease; 4 (2): 79-83. 1998.* **REF ID: HANAUER1998** **Study design and quality:** Double blind RCT 18 centres, America **8 week trial**	**All patients:** **N=287 randomised/ ITT** **Drop-outs** (don't complete the study): N=47[k] (16.4%) These were treatment failures. It is unclear whether anyone else dropped out. **Inclusion criteria:** • Male or non pregnant female patients >18 years • Extent: limited to the rectum or sigmoid colon (<30cm maximum from anal verge) • Severity: mild to moderately active UC. Minimal sigmoidoscopic score of 5. **Exclusion:** • Severe/ fulminant UC • Required hospitalisation or systemic steroids or both	**Group 1: 1g mesalamine (Pentasa) enema** N=73 randomised/ITT 1g of mesalamine (Pentasa) in 100mls liquid enema. **Group 2: 2g mesalamine (Pentasa) enema** N=71 randomised/ITT 2g of mesalamine (Pentasa) in 100mls liquid enema. **Group 3: 4g**	**Outcome 1: Clinical remission** (PGA score of 1, complete resolution of symptoms) N values are calculated from the percentages reported in the paper. **Outcome 2: Clinical improvement** (PGA score of 1 or 2)	**8 weeks** **Group 1:** 34/73 **Group 2:** 35/71 **Group 3:** 32/73 **Group 4:** 10/70 **8 weeks** **Group 1:** 49/73 **Group 2:** 46/71 **Group 3:** 55/73 **Group 4:** 19/70	**Funding:** None described. **Limitations:** Unclear method of randomisation and allocation concealment No extent baseline information given Double blind, no further information given **Additional outcomes:** Histological remission

k Estimated drop out rate from the percentages given in the paper of patients who prematurely discontinued treatment as treatment failures.

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Randomisation: No details given. Unclear. **Allocation concealment**: No details given. Unclear. **Blinding:** Double blind. No further information given. **Outcome assessment:** 7 variables were score from 0-3 (sigmoidoscopic index) Maximum score of 15. Physicians global assessment. **Sample size calculation:** Not described. **Type of analysis: ITT** **Compliance rates:** ≥70% of doses, was uniformly good, averaging 81%, without differences between treatment groups. N=0 dropout/ withdrawal due to drug related AEs.	• Evidence of other forms of inflammatory bowel disease or infectious colitis • Received steroid or aminosalicylate therapy within 7 days of study entry or immunosuppressive use within 90 days of study entry • Allergic to aspirin or salicylate derivatives **Baseline characteristics** **Group 1: 1g mesalamine (Pentasa) enema** **Sex (m/f):** 29/44 **Mean age (SD):** 40.7 (15.1) **Episode:** new onset n=20, relapse n=53 **Concurrent SASP therapy:** n=25 **Mean sigmoidoscopic index (SD):** 9.9 (2.5) **Extent:** Not described – but all proctitis or proctosigmoiditis **Drop outs:** 6 (treatment failures) **Group 2: 2g mesalamine (Pentasa) enema** **Sex (m/f):** 32/39 **Mean age (SD):** 42.4 (14.6) **Episode:** new onset n=9, relapse n=62 **Concurrent SASP therapy:** n=32 **Mean sigmoidoscopic index (SD):** 10.6 (2.1) **Extent:** Not described – but all proctitis or proctosigmoiditis **Drop outs:** 8 (treatment failures) **Group 3: 4g mesalamine (Pentasa) enema** **Sex (m/f):** 25/48 **Mean age (SD):** 37.7 (11.8) **Episode:** new onset n=15, relapse n=58 **Concurrent SASP therapy:** n=36 **Mean sigmoidoscopic index (SD):** 10.4 (2.6) **Extent:** Not described – but all proctitis or proctosigmoiditis **Drop outs:** 7 (treatment failures) **Group 4: Placebo enema** **Sex (m/f):** 34/36 **Mean age (SD):** 39.5 (12.2) **Episode:** new onset n=14, relapse n=56 **Concurrent SASP therapy:** n=27 **Mean sigmoidoscopic index (SD):** 10.5 (2.7) **Extent:** Not described – but all proctitis or proctosigmoiditis	**mesalamine (Pentasa) enema** N=73 randomised/ITT 4g of mesalamine (Pentasa) in 100mls liquid enema. **Group 4: Placebo** N=70 randomised/ ITT Placebo 100mls liquid enema. **Concomitant therapy:**	**Outcome 3: Endoscopic remission** (score of <4 at week 8 or on discontinuation) **Adverse events** were described as having no significant differences between the mesalamine intervention groups and the placebo group, and no evidence of a dose relationship. No total figures were given in the paper.	**8 weeks** **Group 1:** 43/73 **Group 2:** 46/71 **Group 3:** 48/73 **Group 4:** 17/70	Individual symptom scores

Author	Patients	Intervention	Outcome measures	Effect size	Comments
	Drop outs: 26 (treatment failures)				

Table 66: HANAUER1998A: Budesonide (2mg, 8mg) versus placebo

Author	Patients	Intervention	Outcome measures	Effect size	Comments
S. B. Hanauer et al. Budesonide Enema for the Treatment of Active, Distal Ulcerative Colitis and Proctitis: A Dose-Ranging Study. *Gastroenterology: 115; 525-532. 1998.* **REF ID: HANAUER1998A** **Study design and quality:** Double blind RCT Multicentre: 33 centres, United States **6 week trial** **Randomisation:** No information given. **Allocation concealment**: No information given. **Blinding:** Double blind. Describes a blind pathologist. **Outcome assessment:** Sigmoidoscopy scored 0-4, unclear if validated. **LOCF: last observation carried**	**<u>All patients:</u>** **N=233 randomised** Four treatment arms. 0.5mg budesonide enema has been excluded as it is a dose lower than recommended in the BNF and is not available. **Drop-outs** (don't complete the study): N=63 (27%) Missing data: >10% between the placebo and active treatment arms **Inclusion criteria:** • Adults, >18yrs • Newly diagnosed or ongoing active UC • Extent: Distal (to splenic flexure, 5-50cm from anal ring) • Severity: sigmoidoscopic inflammation grade score of ≥2 • Symptoms - ≥1 of the following: frequency and urgency of stools, diarrhoea, grossly visible blood **Exclusion:** • Pregnant/ nursing women • Presence of symptomatic organic disease of the GI tract (except hiatus hernia, rectal haemorrhoids) • Laboratory abnormalities • History of active UC proximal to splenic flexure • Hypersensitivity to glucocorticosteroids • Ova or parasites, pathogens and/or toxins in stools	**Group 1: 2mg Budesonide liquid enema** N=56 randomised N=54 authors ITT analysis Budesonide liquid enema 2mg/100mls. Once daily at bedtime. **Group 2: 8mg Budesonide liquid enema** N=60 randomised/ authors ITT analysis Budesonide liquid enema 8mg/100mls. Once daily at bedtime. **Group 3: Placebo liquid enema** N=60 randomised N=57 authors ITT analysis Placebo enema 100mls, given once daily at	**Outcome 1: Endoscopic remission** (Grade 0) **Outcome 2: Clinical and endoscopic remission** (≤3 stools/day, no blood, no urgency, no abdo pain or painful evacuations, sigmoidoscopic score of 0. This had to be achieved in the preceding 2 days to the visit. n values were calculated from the percentages given in the paper. **Outcome 3: Adverse events** The most frequently reported adverse events were headache, back pain,	**<u>6 weeks Authors analysis</u>** **Group1:** 19/54 **Group 2:** 27/60 **Group 3:** 9/57 **<u>6 weeks Authors analysis</u>** **Group1:** 10/54 **Group 2:** 16/60 **Group 3:** 2/57	**Funding:** Research Grant: Astra Draco AB, Sweden and Astra USA **Limitations:** Unclear method of randomisation and allocation concealment **Missing data >10% between treatment arms** Unclear validation of sigmoidoscopy scoring Risk of indirect population: unclear severity of disease **Additional outcomes:** Investigators global evaluation score Patients global quality of life score (not a validated measure) Cortisol levels

Author	Patients	Intervention	Outcome measures	Effect size	Comments
forward **Sample size calculation:** 0.05 significance, 80% power, sample size of 200 **Type of analysis: ITT** (authors definition of all patients who received double blind medication , had baseline data and had double blind observation for a t least one visit) **and PPA** **Compliance rates:** 3 people had unsatisfactory compliance. N=5 dropout/ withdrawal due to AEs.	• Topical steroids within the last 2 weeks before screening **<u>Baseline characteristics</u>** **<u>Group 1: 2mg Budesonide liquid enema</u>** **Sex (m/f):** 28/28 **Mean age (no SD given):** 42 **Sigmoidoscopy:** Grade 2 n=22, Grade 3 n=32 **No. patients using mesalamine products:** 29 **Mean baseline total histopathology scores (no SD given):** 5.36 **Mean Investigator global evaluation (no SD given):** 1.95 **Mean patient global quality of life (no SD given):** 1.45 **Extent:** Not described **Drop outs:** 11 (3 inadequate response, 2 protocol violations, 2 AEs, 2 unsatisfactory compliance, 2 lost to follow up) **<u>Group 2: 8mg Budesonide liquid enema</u>** **Sex (m/f):** 36/24 **Mean age (no SD given):** 40 **Sigmoidoscopy:** Grade 2 n=37, Grade 3 n=23 **No. patients using mesalamine products:** 20 **Mean baseline total histopathology scores (no SD given):** 5.56 **Mean Investigator global evaluation (no SD given):** 1.93 **Mean patient global quality of life (no SD given):** 1.58 **Extent:** Not described **Drop outs:** 12 (9 inadequate response, 1 protocol violation, 2 withdrew consent) **<u>Group 3: Placebo liquid enema</u>** **Sex (m/f):** 30/30 **Mean age (no SD given):** 43 **Sigmoidoscopy:** Grade 2 n=36, Grade 3 n=21 **No. patients using mesalamine products:** 22 **Mean baseline total histopathology scores (no SD given):** 5.55 **Mean Investigator global evaluation (no SD given):** 2.06 **Mean patient global quality of life (no SD given):** 1.74 **Extent:** Not described **Drop outs:** 24 (17 inadequate response, 2 protocol violations, 3 AEs, 1 unsatisfactory compliance, 1 withdrew consent)	bedtime. **Concomitant therapy:** Rectally administered drugs needed to be discontinued 2 weeks prior to randomization. Oral mesalamine was permitted if constant dose during last 2 months.	dyspepsia and nausea. The AEs reported were the drug related ones, therefore they have not been analysed as it will underestimate the AE rate. **Group1:** 20/54 **Group 2:** 24/60 **Group 3:** 18/57		
			Outcome 4: Serious adverse events Group 2: 2 Patients developed Cushing's syndrome and one patient adrenal insufficiency Group 3: All due to Cushing's syndrome events	**Group1:** 0/54 **Group 2:** 3/60 **Group 3:** 4/57	

Table 67: HANAUER2005

Author	Patients	Intervention	Outcome measures	Effect size	Comments
S. B. Hanauer et al. Delayed-Release Oral mesalamine at 4.8g/day (800mg tablet) for the Treatment of Moderately Active Ulcerative Colitis: The ASCEND II Trial. *The American Journal of Gastroenterology; 100: 2478-2485. 2005.* **REF ID: HANAUER2005** **Study design and quality:** Double blind RCT Multicentre: 55 centres, United States, Canada **6 week trial** **Randomisation: P**ermutated blocks of four were used. The randomization scheme was generated for each centre. No stratification variables. **Allocation concealment**: Unclear **Blinding:** Double blind. **Outcome assessment:** Physician's Global Assessment. Patient's Functional Assessment (PFA). Electronic diaries to	**<u>All patients:</u>** **N=386randomised**(268 had moderate disease[l]) **N=268 ITT** **Drop-outs** (don't complete the study): N=42 (15.7%) **Inclusion criteria:** 18-75 years old Diagnosis confirmed by endoscopy or radiography in the last 24 months Severity: **Moderately** active UC Extent not specified **Exclusion:** Short bowel syndrome Intolerance or allergy to salicylates or 5-ASA Renal or hepatic disease Positive stools for bacterial pathogens, ova, parasites or *C. Difficile* History of alcohol or drug abuse Used oral 5-ASA products at a dose >1.6g/day or rectal therapies within the last 7 days Corticosteroid use within the last month	**Group 1: 2.4g mesalamine (Asacol)** N=139 (randomised) N=130 (analysed for treatment success) N=113 (completers) 2.4g mesalamine (5-ASA, Asacol) per day (400mg tablets) Two tablets, three times a day of mesalamine 400mg and the same of placebo tablets (size of 800mg tablets) **Group 2: 4.8g mesalamine (Asacol)** N=129 (randomised) N=124 (analysed for treatment success) N=113 (completers) 4.8g mesalamine (5-ASA) per day (800mg tablets) Two tablets, three times a day of	Outcome 1: **Clinical and endoscopic remission** (Complete remission (complete resolution of: stool frequency (normal), rectal bleeding (none), PFA score (generally well), endoscopy (normal) and a PGA score of 0)) Outcome 2: **Clinical improvement** (treatment success: complete remission or a clinical response to therapy(improvement in the baseline PGA score and improvement in at least one other clinical assessment (stool frequency, rectal bleeding, PFA, endoscopy findings) and no worsening in any other clinical assessment)	**<u>Moderate disease</u>** **<u>Week 6</u>** **Group1:**23/130 **Group 2:**25/124 **<u>Mild disease</u>** **<u>Week 6</u>** **Group1:**21/52 (40.4%) **Group 2:**19/58 (32.8%) **<u>Moderate disease</u>** **<u>Week 3</u>** **Group1:**67/130 (51.5%) **Group 2:**76/124 (61.3%) **<u>Week 6</u>**	**Funding:** Funded and provided the drugs: Procter & Gamble Pharmaceuticals **Limitations:** Unclear method of randomisation and allocation concealment No further details on double blinding **Additional outcomes:** Improvement from baseline in each of the clinical assessment subscores at weeks 3 and 6 Time to normalisation of stool frequency Time to resolution of rectal bleeding Change from baseline in the UCDAI Subgroup analyses on age, sex, race, smoking status, extent, length of disease history, drug use, sulphasalazine intolerance,

[l]Protocol changed after randomisation and still during screening to only include moderately active UC patients.

Author	Patients	Intervention	Outcome measures	Effect size	Comments
collect patient information on symptoms. **Sample size calculation:** Power of 80%, 5% significance level, 1:1 ratio, 112 subjects per arm. **Type of analysis: ITT analysis** (those randomised with moderate severity and ingested at least one dose of trial drug) **Compliance rates:** Not described. N=8 dropout/ withdrawal due to AEs (4 in each treatment arm, it is unclear whether they were drug related)	Immunomodulator use in the past 3 months Received anti-diarrhoeal or antispasmodic medications after the screening visit Treated with a nicotine patch or any product containing fish oils within the last week Received antibiotics in the last week Treated with any investigational drug in the last month Pregnant and lactating women **<u>Group 1: 2.4g mesalamine (Asacol)</u>** **Mean age (SD):**42.3 (no SD given) **Extent:** proctitis n=20, proctosigmoiditis n=49, left sided colitis n=42, pancolitis n=28 **Prior treatment:** Steroids (oral or IV) n=47, immunomodulators n=3, sulphasalazine n=53, sulfa-free oral 5-ASAs n=57, any oral 5-ASAs n=83, rectal therapies n=50 **Known intolerance to sulphasalazine:** yes n=12, no n=41 **Drop outs:** 26 (2 protocol violations, 4 AEs, 6 voluntary withdrawals, 3 investigator recommendation, 11 lack of treatment effect) **<u>Group 2: 4.8g mesalamine (Asacol)</u>** **Mean age (SD):**42.0 (no SD given) **Extent:** proctitis n=21, proctosigmoiditis n=32, left sided colitis n=49, pancolitis n=27 **Prior treatment:** Steroids (oral or IV) n=38, immunomodulators n=5, sulphasalazine n=40, sulfa-free oral 5-ASAs n=53, any oral 5-ASAs n=73, rectal therapies n=48 **Known intolerance to sulphasalazine:** yes n=8, no n=32 **Drop outs:** 16 (1 protocol violation, 4 AEs, 5 voluntary withdrawal, 1 investigator recommendation, 5 lack of treatment effect)	mesalamine 800mg and the same of placebo tablets (size of 400mg tablets) **Concomitant therapy:** None of the following drugs were permitted during the trial: Topical rectal therapies, anti-diarrhoeals and antispasmodics, immunomodulatory agents, nicotine patches, any products containing fish oils, or any investigational or marketed drug that may interfere with the evaluation of the study drug. And the following were also not permitted for longer than 10 days: Aspirin (apart for cardiac reasons), NSAIDs, mesalamine containing products, corticosteroids, sulfasalazine, 6-mercaptopurine, azathioprine, cyclosporine, metronidazole, antibiotics (other than topical).		**Group1:**77/130 (59%) **Group 2:**89/124 (72%)	relapse frequency, baseline disease activity measures
			Outcome 2: **Adverse events** (Similar in both the treatment groups for the most frequent causes which were headache, abdominal pain, diarrhoea and infection) In patients with mild disease, the safety population was similar to that seen with the moderate patient population (no data was given).	**<u>Moderate disease</u>** **Group1:**49/139 (35.3%) **Group 2:**57/129 (44.2%)	
			Outcome 3: **Serious adverse events**	**<u>Moderate disease</u>** **Group1:**2[m]/139 (1.4%) **Group 2:**1[n]/129 (0.8%)	

[m] Due to cholecystitis and pancreatitis
[n] Due to pericarditis

Table 68: HANAUER2007

Author	Patients	Intervention	Outcome measures	Effect size	Comments
S. B. Hanauer et al Delayed-release oral mesalamine 4.8g/day (800mg tablets) compared with 2.4g/day (400mg tablets) for the treatment of mildly to moderately active ulcerative colitis: The ASCEND I trial. *Canadian Journal of Gastroenterology; 21 (12): 827-834. 2007.* **REF ID: HANAUER2007** **Study design and quality:** Double blind RCT Multicentre:41 sites, United States and Canada **6 week trial** **Randomisation:**1:1 using permutated block of 4. Each random assignment scheme was generated from each centre. **Allocation concealment**: Unclear **Blinding:** Double blind; investigators and patients blinded to the treatment assignment.	**<u>All patients:</u>** **N=301randomised** **N=286 (ITT – author definition)** **Drop-outs** (don't complete the study): N=45 (15%) **Inclusion criteria:** 18-75 years old Extent: proctitis to pancolitis (confirmed by endoscopy or radiography within the preceding 24 months Severity: Mild to moderate (PGA score of 1 or 2) **Exclusion:** Short bowel syndrome Intolerance of or allergy to salicylates or 5-ASA compounds Current renal or hepatic disease Current alcohol or drug abuse Medical contraindication to study participation Blood urea nitrogen or serum creatinine more than 1.5 times the upper limit of normal Hepatic enzymes more than 2.0 time the upper limits of normal Positive stool examination for bacterial pathogens, ova and parasites	**Group 1: 2.4g mesalamine (Asacol)** N=154 randomised N=150 (ITT-author definition) N=133 (completers) Two 400mg tablets plus two placebo tablets, three times a day **Group 2: 4.8g mesalamine (Asacol)** N=147 randomised N=136 (ITT- author definition) N=123 (completers) Two 800mg tablets plus two placebo tablets, three times a day **Concomitant therapy:** Prohibited medication during the trial: Acetylsalicylic acid (other than a max. of 325mg for a cardio protective reason)	Outcome 1: Complete remission (normal stool frequency, no rectal bleeding, a PFA score of 0 (generally healthy), normal endoscopy findings and a PGA score of 0 (quiescent disease activity)**Clinical and endoscopic remission**	**<u>Week 6</u>** **Group1:**30/150 **Group 2:**35/136	**Funding:** Supported by Procter & Gamble Pharmaceuticals **Limitations:** Unclear what the random assignment scheme consisted of Unclear allocation concealment **Additional outcomes:** Physician's Global Assessment Differences in stool frequency, rectal bleeding, PFA and sigmoidoscopy scores at weeks 3 and 6 Median time to return to normal stool frequency and no rectal bleeding Analysis of the moderate severity patients for all of the outcomes at week 3 and 6. Mean plasma 5-ASA concentrations
			Outcome 2: **Clinical improvement** (overall improvement: complete remission or response to therapy from baseline to week 6)	**<u>Week 3</u>** **Group 1:** 63/150 (42%) **Group 2:** 53/137 (39%) **<u>Week 6</u>** **Group 1:** 77/150 (51%) **Group 2:** 76/136 (56%)	
			Outcome 2: **Adverse events**	**Group1:**60/154 **Group 2:**48/147	

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Outcome assessment: Patient's functional assessment (PFA). Physician's Global Assessment (PGA). Inflammatory Bowel disease Questionnaire. **Sample size calculation:**90% power to detect a 20% difference, 280 patients required. **Type of analysis: ITT** (all those mild/moderate randomised who had a least one dose of the drug and treatment outcome could be determined) **and PPA** **Compliance rates:** Was assessed at 3 and 6 weeks. It is not described how it was assessed. N=13 dropout/ withdrawal due to AEs. It is unclear whether these are drug related.	or *Clostridium difficile* Use of 5-ASA containing products by any route from which a total dose of >1.6g/day was available within 7 days before screening Use of corticosteroids within one month before the baseline visit Topical rectal therapy within one week before screening Immunomodulatory drugs within 3 months before baseline visit Use of antibiotics (other than topical), nicotine patches, products containing fish oils, acetylsalicylic acid (except for a cardio-protective dose of no more than 325mg), or NSAIDs within 1 week of screening Use of anti- diarrhoeal and/or antispasmodic medication after screening Treatment with any experimental or investigational medication within 1 month before baseline visit Pregnancy or lactation **<u>Group 1: 2.4g Mesalamine (Asacol)</u>** **Mean age (SD):**43.5 (no SD given) **Extent:** proctitis n=25, proctosigmoiditis n=45, left-side colitis n=45, pancolitis n=39 **Prior treatment:** Steroids (oral or IV) n=51, immunomodulators n=7, sulfasalazine n=57, sulfa-free oral 5-ASAs n=61, rectal therapy n=67 **Intolerant to sulfasalazine:** yes n=8, no n=49 **Drop outs:** 21 (1 protocol violation, 8 adverse events, 2 voluntary withdrawal,2 investigator recommendations, 8 lack of effect) **<u>Group 2: 4.8g Mesalamine (Asacol)</u>** **Mean age (SD):**45.0 (no SD given) **Extent:** proctitis n=29, proctosigmoiditis n=38, left-side colitis n=46, pancolitis n=34 **Prior treatment:** Steroids (oral or IV) n=43, immunomodulators n=7,	NSAIDs Mesalamine containing products Corticosteroids Immunomodulatory agents Metronidazole antibiotics (other than topical) for >10days Topical rectal therapies Ant diarrhoeal or anti spasmodic medications Metronidazole Nicotine patches Products containing fish oils Investigational or marketed drug which could interfere with the drug evaluation	Outcome 3: **Serious adverse events** **Improvement in Quality of Life (IBDQ)** The results are displayed graphically with no data given. Total IBDQ scores and all subcategory score were said to improve significantly from baseline to weeks 3 and 6 for mild and moderate UC in both treatment groups. Apart from the social sub-score , all subgroup scores and total IBDQ score demonstrated a significantly greater improvement in the 4.8g/day mesalamine group compared to the 2.4g/day group. See IRVINE2008 for the reported data. The rates of overall improvement for left sided (proctitis, proctosigmoiditis and left sided colitis) and pancolonic involvement were reported in the text to be greater at weeks 6 in the higher dose group (4.8g/day) compared to the lower dose group (2.4g/day) but this was not significant.	**Group1:**3[o]/154 **Group 2:**1[p]/147	

[o] Twice in the text it describes 3 SAEs in the 2.4g Mesalazine group but it has 8 in the table. As the text describes what the SAEs were, 3 have been used in the data analysis (uterine fibroids and ovarian cyst, worsening of UC and cholecystitis.

[p] Due to epigastric pain.

Author	Patients	Intervention	Outcome measures	Effect size	Comments
	sulfasalazine n=43, sulfa-free oral 5-ASAs n=70, rectal therapy n=60 **Intolerant to sulfasalazine:** yes n=8, no n=35 **Drop outs:** 24 (4 protocol violation, 5 adverse events, 6 voluntary withdrawal,2 investigator recommendations, 7 lack of effect)				

Table 69: HARTMANN2010

Author	Patients	Intervention	Outcome measures	Effect size	Comments
F. Hartmann et al. 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; 32: 368-376. 2010.* **REF ID: HARTMANN2010** **Study design and quality:** Open RCT Multicentre: 37 centres, Germany **8 week trial** **Randomisation:** In a 1:1 ratio based on a central computer generated randomization scheme **Allocation concealment**: Numbers allocated sequentially	**<u>All patients:</u>** **N=237 randomised** **N=193 ITT** (authors definition: all randomized patients who received at least one enema) **Drop-outs** (don't complete the study): N=44 (19%) (24 in the budesonide group and 20 in the mesalazine group) **Inclusion criteria:** • Men or non-pregnant women • 18-70 years • Newly diagnosed (at least one attack) or relapsing active UC • Extent: Left-sided • Severity: Mild to moderate. CAI >4, EI>2 • The above confirmed by endoscopy, histology and a negative stool culture **Exclusion:** • Uncertain diagnosis of UC • Symptoms of disease present for <2 weeks • Macroscopic lesions proximal to the sinistrial flexure • Crohn's disease • Prior bowel operation • Use of oral/rectal steroids within 2 weeks prior to baseline	**Group 1: 4g mesalazine enema (Salofalk)** N=119 randomised N=99 (completed the study) 4g mesalazine liquid enema once a day in 60mls (Salofalk). **Group 2: 2mg budesonide enema (Entocort)** N=118 randomised N=94 (completed the study) 2mg in 100mls budesonide liquid enema (Entocort). **Concomitant therapy:** See exclusion criteria.	**Outcome 1: Clinical remission** (CAI<4) **Outcome 2: Quality of life** (Inflammatory Bowel Disease Questionnaire, IBDQ)	**Authors ITT** **<u>Week 4</u>** **Group1:** 78/101 **Group 2:** 66/104 **<u>Week 8</u>** **Group1:** 82/106 **Group 2:** 65/101 **<u>Baseline</u>** **Group1:** n=67, 138.1 +/-32.6 **Group 2:** n=70, 145.0 +/-32.6 **<u>Week 4</u>** **Group 1:**	**Funding:** Sponsored by AstraZeneca **Limitations:** Open study Risk of an indirect population due to severity of disease **Additional outcomes:** Histological remission

Author	Patients	Intervention	Outcome measures	Effect size	Comments
in the order in which the patient were enrolled. No re-enrolment for a second time. **Blinding:** Open. Patients were unaware of treatment assignment due to the anonymous packaging although they were different in size. **Outcome assessment:** Clinical activity Index. Endoscopic index according to Loftberg. Inflammatory bowel disease questionnaire. **Sample size calculation:** Type 1 error of 0.05, and type II error of -.2, 80% power. Sample size was 115 per group. **Type of analysis: ITT and PPA** **Compliance rates:** Not described. N=3 dropout/ withdrawal due to drug related AEs.	• Use of immunosuppressants (azathioprine, mercaptopurine, methotrexate, tacrolimus, ciclosporin) within 6 month prior to baseline • NSAID treatment for >3 consecutive days • Antibiotics during the preceding 2 weeks other than following a defined infection for <10 days • 5-ASA, sulphasalazine or olsalazine in variable dosages within the preceding 2 weeks • Known significant hepatic or renal function abnormalities and/or clearance creatinine ≤80ml/min **Baseline characteristics** **Group 1: 4g mesalazine enema (Salofalk)** **Sex (m/f):** 74/45 **Mean age (no SD given):** 43.6 **Extent:** proctitis n=5, proctosigmoiditis n=70, left sided n=44 **CAI at baseline, median (range):** 7.1 (4-15) **Concurrent use of oral remission maintaining therapy (5-ASA, SASP, olsalazine):** n=74 **Drop outs:** 20 (1 hospitalisation due to aggravation, 1 erroneous inclusion, 1 other AE, 10 failure of therapy, 6 failure to show up, 0 improvement/healing, 3 other reasons) **Group 2: 2mg budesonide enema (Entocort)** **Sex (m/f):** 69/49 **Mean age (no SD given):** 41.8 **Extent:** proctitis n=5, proctosigmoiditis n=67, left sided n=45 **CAI at baseline, median (range):** 7.0 (4-15) **Concurrent use of oral remission maintaining therapy (5-ASA, SASP, olsalazine):** n=73 **Drop outs:** 20 (2 hospitalisation due to aggravation, 2 other AE, 16 failure of therapy, 2 failure to show up, 1 improvement/healing, 7 other reasons)			n=60, 176.0 +/-27.8 **Group2:** n=63, 168.8 +/- 31.4 **Week 8** **Group 1:** n=66, 179.5 +/-29.6 **Group 2:** n=65, 172.4 +/- 30.1	
			Outcome 3: Endoscopic remission (Endoscopic index <2)	**Authors ITT** **Week 8** **Group1:** 76/106 **Group 2:** 76/103	
			Outcome 4: Adverse events	**Group1:** 31/119 **Group 2:** 36/118	
			Outcome 5: Serious adverse events Reasons unclear.	**Group 1:** 2/119 **Group 2:** 1/118	
			Outcome 6: Hospitalisations Due to aggravation of	**Group1:** 1/119 **Group 2:** 2/118	

Author	Patients	Intervention	Outcome measures	Effect size	Comments
			UC.		

Table 70: HAWKEY1997

Author	Patients	Intervention	Outcome measures	Effect size	Comments
C. J. Hawkey et al. A Trial of Zileuton Versus Mesalazine or Placebo in the Maintenance of Remission of Ulcerative Colitis. *Gastroenterology; 112: 718-724. 1997.* **REF ID: HAWKEY1997** **Study design and quality:** Double blind RCT Multicentre: 30 centres **6 month trial** **Randomisation:** In blocks of 6, randomised to receive one of the three study drugs for 26 weeks or until relapse. **Allocation concealment**: Concealed randomization schedules were held at each participating hospital for code break in the event of serious adverse events. **Blinding:** Double blind, no further information given. **Outcome assessment:** Patient	**<u>All patients:</u>** **N=323 randomised** (all three arms) **N=210 randomised in the two arms** **Drop-outs** (don't complete the study): Unclear N=28 (13.3%) 11 Protocol violations (5 in the mesalazine group and 6 placebo) 17 withdrew due to AEs (unclear, included all those reported for worst case scenario). **Inclusion criteria:** • Patients with ulcerative colitis in remission (diagnosis established by sigmoidoscopy, colonoscopy or air-contrast barium enema and based on previous rectal or colonic biopsy findings) • In remission (normal Sigmoidoscopic appearances with no rectal bleeding during the week before entry and stools that were not liquid) • Patients already receiving salicylates could enter the study • Receiving oral or rectal steroids could only be included if they were tapered successfully over 2 weeks before study entry • Men and non-pregnant non-lactating women older than 18 years • Women with child bearing potential had to be prepared to use effective contraception during and for 90 days after the study • Extent: No restriction • Severity of previous relapse was not described. **Exclusion:** • No additional exclusions to the opposite of the inclusion criteria.	**Group 1: Mesalazine 1.6g** N=99 randomised N=94 (evaluable) 400mg mesalazine four times a day. One 400mg tablet and two placebo tablets were taken, four times a day. **Group 2: Placebo** N=111 randomised N=105 (evaluable) 3 placebo tablets were taken four times a day. **The third treatment arm was Zileuton which is not included in the scope; therefore the data has not been presented.** **Concomitant therapy:** See inclusion criteria. No further information given.	**Outcome 1: Hospitalisations** It is unclear from the paper what the reasons for the hospitalisations were. Group 2: This patient died. No reasons were given. Overall **adverse events** were not reported, only severe (7 in the mesalazine group and 5 in the placebo group). 2 and 3 patients respectively discontinued treatment due to AEs. An additional 12 patients discontinued treatment due to AEs (unclear which arms they were in). Headache was the most common adverse events (30.3%, 25.2%). Kaplan Meier curve demonstrating the proportion of patients remaining in remission for the two treatment groups do not overlap, p<0.001 for all evaluable patients. A hazard ratio was unable to be calculated.	**Group1:** 6/99 **Group 2:** 1/111	**Funding:** Funded and designed by Abbott Laboratories. **Limitations:** Unclear method of randomisation No information given on the double blinding More patients in the mesalazine group with distal disease **Additional outcomes:** Percentage with loose stools, rectal bleeding, abdominal pain, urgency, moderate or severe inflammation on sigmoidoscopy and low or high inflammation grade on biopsy Proportion in remission (unable to calculate the proportion who relapsed as drop outs were unclear) **Note: About 50% of patients were on**

Author	Patients	Intervention	Outcome measures	Effect size	Comments
diary. Sigmoidoscopy score based on Baron et al (4 point scale). **Sample size calculation:** 100 patients per group, 89% power (α=0.05) to detect a 15% difference. **Type of analysis: ITT** **Compliance rates:** Recorded in the patient's diary. N=17 dropout/ withdrawal due to AEs.	**Group 1: 1.6g Mesalazine** **Mean age (SD):** 45 (14) **Extent:** ≤50cm disease 74% **Mesalazine within 30 days:** 51% **Steroids within last 90 days:** 28% **Remission <6 months:** 54% **Severity of previous relapse: Not described** **Frequency of relapses: Not described** **Drop outs:** unclear **Group 2: Placebo** **Mean age (SD):** 45 (14) **Extent:** ≤50cm disease 55% **Mesalazine within 30 days:** 50% **Steroids within last 90 days:** 33% **Remission <6 months:** 50% **Severity of previous relapse: Not described** **Frequency of relapses: Not described** **Drop outs:** unclear **Definitions** **Relapse:** Sigmoidoscopic score of ≥1 or experienced 3 consecutive days of rectal bleeding caused by UC or liquid stools for 1 week. **Note: There were statistically more patients with distal disease in the mesalazine group (p=0.01)**				**mesalazine prior to trial entry**

Table 71: HAWTHORNE1992

Author	Patients	Intervention	Outcome measures	Effect size	Comments
A. B. Hawthorne et al. Randomised controlled trial of azathioprine withdrawal in ulcerative colitis. *British Medical Journal; 305: 20-22. 1992.*	Two parts to the trial. One randomised those in full remission and another randomised patients with chronic low grade or corticosteroids dependent disease. **Withdrawal study** **All patients:**	**Full remission** **Group 1: Azathioprine** N=33 randomised N=31 (completers)	**Outcome 1: Relapse** **P value = 0.039** Reported hazard ratio (95% CI) in the paper: 0.5 (0.25-1.0).	**Group1:** 12/33 (36%) **Group 2:** 20/34 (59%) Excluding the	**Funding:** None described. **Limitations:** Unclear method of randomisation and

Author	Patients	Intervention	Outcome measures	Effect size	Comments
REF ID: HAWTHORNE1992 **Study design and quality:** Double blind RCT Multicentre: Outpatient clinics of 5 hospitals, United Kingdom **1 year trial** **Randomisation:** Carried out in the hospital pharmacies in blocks of 4. Separate randomisation schedules for the patients in remission and with chronic stable disease. **Allocation concealment**: Unclear. **Blinding:** Double blind. No further details given. **Outcome assessment:** Endoscopy assessment (Baron et al.). Daily symptom diary. **Sample size calculation:** 35% increase in relapse, 80% power, two tailed α=0.05, 70 patients would be required. **Type of analysis: ITT and PPA** **Compliance rates:** Record of tablet consumption in the diary cards. N=0 dropout/ withdrawal due to drug related AEs.	**N=67 randomised** (full remission) **N=12 randomised** (chronic low grade or corticosteroid dependent disease- chronic stable colitis- the data for this has not been reported as it is not in the protocol and it is unclear how many went into remission. 2 patients were found to have Crohn's disease that completed the trial. They were included in the primary analysis and excluded from the secondary. **Drop-outs** (don't complete the study): N=2 (3.0%) <10% difference in missing data between the treatment arms **Inclusion criteria:** • In full remission for ≥2 months • **Already established on azathioprine prior to the trial for a minimum of 6 months** • Ulcerative colitis diagnosis based on a rectal biopsy and barium enema or colonoscopy • In those with chronic stable disease they must have been no change in dose of Prednisolone if taking corticosteroids for a minimum of two months before entering the trial. **Exclusion:** • None described **<u>Group 1: Azathioprine</u>** **Mean age (range):** 44 (19-82) **Extent:** total n=19, left sided n=8, sigmoid n=7, proctitis n=0 **Mean (range) azathioprine dose (mg):** 100 (10-150) **Concurrent therapy, n (mean dose, range):** SASP n= 22 (2g, 1-4g), mesalazine n=13 (1.2g (1.2-2.4g), not taking any ASAs n=4 **Mean (range) duration of disease before trial (years):** 7 (1-28) **Mean (range) duration of azathioprine treatment before trial (months):** 21 (7-93) **Mean (range) duration of remission before entry (months):** 11 (4-45) **Severity of previous relapse:** Not described.	Same dose was taken as prior to the trial. **Group 2: Placebo** N=34 randomised N=34 (completers) Same number of identical placebo tablets was taken as the azathioprine dose prior to the trial. **Concomitant therapy:** 5- ASA drugs taken prior to the trial were continued at the same dose.	**Note:** this is slightly different from the HR calculated using the log rank p value.	two Crohn's patients: **Group 1:** 11/31 (35%)	allocation concealment Double blind but no further information was given **Additional outcomes:** Relapse rates in the subgroup of long and shorter term remission **Notes:** Cox proportional hazards model: highly significant fall in relapse rate with increasing age (HR:0.95), longer duration of remission before trial entry was inversely related to relapse rate (HR:0.97).

Author	Patients	Intervention	Outcome measures	Effect size	Comments
	Frequency of relapses: Not described. **Drop outs:** 2 (1 due to default, 1 due to a misunderstanding) **Group 2: Placebo** **Mean age (range):** 44 (23-73) **Extent:** total n=18, left sided n=5, sigmoid n=8, proctitis n=2 **Mean (range) azathioprine dose (mg):** 100 (50-200) **Concurrent therapy, n (mean dose, range):** SASP n= 17 (2g, 1-4g), mesalazine n=15 (1.2g (0.8-3.2g), not taking any ASAs n=8 **Mean (range) duration of disease before trial (years):** 9 (2-30) **Mean (range) duration of azathioprine treatment before trial (months):** 19 (7-96) **Mean (range) duration of remission before entry (months):** 12 (2-48) **Severity of previous relapse:** Not described. **Frequency of relapses:** Not described. **Drop outs:** 0 **Definitions** **Remission:** Absence of symptoms of active disease in patients not taking corticosteroids and with a sigmoidoscopic appearance of grade 0 or 1 (Baron et al.). **Relapse:** Worsening symptoms recognised by the patient as active disease (such as rectal bleeding, loose motions, or bowel frequency) with a sigmoidoscopic appearance of grade 1 or above or grade 2 or 3 appearance at routine sigmoidoscopy regardless of symptoms. **Chronic stable disease:** Low grade symptoms or symptom control with low doses of corticosteroids (10mg Prednisolone or less0. With a sigmoidoscopic appearance of grade 0 or 1.				

Table 72: HAWTHORNE2012/2011

Author	Patients	Intervention	Outcome measures	Effect size	Comments
A. B. Hawthorne et al. One-year Investigator-blind Randomized Multicenter Trial Comparing Asacol 2.4g Once Daily with 800mg Three Times Daily for Maintenance of	**All patients:** **N=213 randomised/ITT** **Drop-outs** (don't complete the study): N=25 (11.7%)	**Group 1: 2.4g mesalazine (Asacol) once a day** N=103 randomised/ITT N=94 (complete case population)	**Outcome 1: Relapse** The percentages reported in the paper were failures (relapse and withdrawals). The	**ITT analysis** **Group1:** 23/103 **Group 2:** 33/110	**Funding:** Supported by an unrestricted education grant from Warner Chilcott Pharmaceuticals Ltd. The South East Wales Trials Unit is funded by the National

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Remission in Ulcerative Colitis. *Inflammatory Bowel Disease; 18 (10): 1885-1893. 2012* and the following abstract: **A. B. Hawthorne et al.** Once daily Asacol in maintenance therapy for ulcerative colitis: a one-year single-blind randomised trial. *Gut; 60 (Supplement I): A37-A38.* **REF ID: HAWTHORNE2012** **& HAWTHORNE2011** **Study design and quality:** Single investigator blind RCT [CODA study, Colitis Once Daily Asacol] Multicentre: 32 centres, United Kingdom **1 year trial** **Randomisation:** 1:1 ratio. Carried out in advance within the South East Wales Trials Unit who generated sequence codes to allocate patients to either group. Kept in each centres pharmacy (opaque, sequentially numbered, sealed envelopes). Stratified centers, allocation using random permuted blocks of size four or six (randomly selected). Adequate.	<10% difference in missing data between the treatment arms. **Inclusion criteria:** • UC in remission on maintenance therapy with mesalazine, sulfasalazine, olsalazine or balsalazide for at least 4 weeks • At least one relapse within the previous 2 years • >18 years • If female: taking adequate contraception (if otherwise able to conceive) • Ability to give informed consent • Extent: Not described **Exclusion:** • Crohn's disease • Symptoms of active colitis • A modified Baron score at sigmoidoscopy of 2 or 3 • Used enema or suppository therapy for UC in the past 4 weeks • Has started or altered the dose of azathioprine or 6-mercaptopurine in the past 3 months (these drugs were permitted if on a stable dose over that period of time) • Had intolerance to mesalazine • Known HIV infection • Significant renal or hepatic impairment • Or other medical or psychiatric disorder (including alcohol dependence) that in the opinion of the investigator would affect participation in the study • Females if pregnant or lactating **<u>Group 1: 2.4g mesalazine (Asacol) once a day</u>** **Mean age (SD):** 49.5 (15.0) **Sex (m/f):** 53/50 **Extent:** extensive n=31, left sided or sigmoid n=63, proctitis n=9 **Severity of previous relapse:** Not described **Frequency of relapses:** Not described **Current use of immunomodulators:** Only described for Azathioprine or 6-mercaptopurine (see below) **Baseline sigmoidoscopic score:** normal n=79, not normal n=24	N=79 (PPA) Three 800mg mesalazine tablets taken once a day. **Group 2: 800mg mesalazine (Asacol) three times a day (2.4g total)** N=110 randomised/ITT N=94 (complete case population) N=72 (PPA) 800mg mesalazine (Asacol) given three times a day. Total 2.4g/ day. **Concomitant therapy:** None described. See exclusion criteria.	relapse figures from the flow diagram have been used.	**Log p value: 0.211**	Institute for Social Care and Health Research. **Limitations:** Single blind **Additional outcomes:** Multivariate analysis looking at factor affecting the likelihood of relapse Sub-study results looking at adherence. **Notes: Aminosalicylate tolerant population**

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Allocation concealment: Adequate **Blinding:** Single investigator blind. Patients instructed not to reveal their regimen to the research nurse or doctor. **Outcome assessment:** Baron score for sigmoidoscopy. Mayo score for clinical symptoms. **Sample size calculation:** 250 patients were needed, 10% difference between treatment arms, one sided α=5%, power of 80%. **Type of analysis: ITT and PPA** **Compliance rates:** Measured by tablet counts and self-reported adherence. Adherent if they took at least 75% of the expected dose. 95.2% in the OD group and 92.5% in the TDS group were adherent. Unclear if any dropouts/ withdrawals were due to drug related AEs.	**Baseline 5-ASA medication:** Asacol n=78, Pentasa n=14, Balsalazide n=6, other n=5 **Baseline 5-ASA dose frequency:** once n=8, twice n=48, three times n=44. four times n=1, Azathioprine or 6-mercaptopurine use n=11 **Drop outs:** 9 (3 AEs, 2 patient preference, 3 other reasons, 1 lost to follow up) **Group 2: 800mg mesalazine (Asacol) three times a day (2.4g total)** **Mean age (SD):** 50.0 (14.9) **Sex (m/f):** 55/55 **Extent:** extensive n=33, left sided or sigmoid n=54, proctitis n=20 **Severity of previous relapse:** Not described **Frequency of relapses:** Not described **Current use of immunomodulators:** Only described for Azathioprine or 6-mercaptopurine (see below) **Baseline sigmoidoscopic score:** normal n=72, not normal n=38 **Baseline 5-ASA medication:** Asacol n=81, Pentasa n=13, Balsalazide n=9, other n=7 **Baseline 5-ASA dose frequency:** once n=8, twice n=57, three times n=44, Azathioprine or 6-mercaptopurine use n=14 **Drop outs:** 16 (5 patient preference, 7 other reason, 4 lost to follow up) **Definitions** **Relapse:** Symptoms of active disease (bloody diarrhoea or rectal bleeding for 3 days or more). With a sigmoidoscopic appearance of grade 2 or 3 using the modified Baron score. If patients were inadvertently treated for active disease – they were classed as relapsers.				

Table 73: HETZEL1986

Author	Patients	Intervention	Outcome measures	Effect size	Comments
D. J. Hetzel et al Azodisalicylate (Olsalazine) in the treatment of active	**All patients:** **N=30randomised**	**Group 1: Olsalazine 1g b.d.** N=15 randomised	Outcome 1: **Clinical improvement** (a change of at least two grades in	**Week 6** **Group1:**6/15	**Funding:** Pharmacia supplied the olsalazine and gave financial support.

Author	Patients	Intervention	Outcome measures	Effect size	Comments
ulcerative colitis. A placebo controlled clinical trial and assessment of drug disposition. *Journal of Gastroenterology and Hepatology; 1: 257-266. 1986.* **REF ID: HETZEL1986** **Study design and quality:** Double blind RCT, pilot study It is unclear whether the trial was carried out in Australia or not (author's origin) **6 week trial** **Randomisation:** Random number code/unclear **Allocation concealment**: Unclear **Blinding:** Double blind **Outcome assessment:** Patient self assessment (scoring from1-5, very good to very bad). Sigmoidoscopic appearances according to Dick et al, Grade 0-3. **Sample size calculation:** None described. **Type of analysis: ACA** N=2 dropout/ withdrawal due to drug related AEs. N=2 dropouts due to AEs in the	**N=30 ITT** **Drop-outs** (don't complete the study): N=6 (20%) All due to deterioration in diarrhoea. **Inclusion criteria:** Extent: Left sided UC or proctitis (diagnosis by sigmoidoscopy, histology of rectal biopsies and radiological or colonoscopic appearance Severity: Mild to moderate Negative stool culture Rectal corticosteroid or oral sulphasalazine but no other antidiarrhoea medications were permitted up to 7 days prior to the start of the trial. **Exclusion:** Severe colitis Patients receiving oral corticosteroids, azathioprine or other immunosuppressive agents or antibiotics within 4 weeks of the trial Other significant systemic disease Pregnant or potentially fertile women **<u>Group 1: Olsalazine 1g b.d.</u>** **Mean age (SD):**45 (no SD given) **Mean stools per day:**4.3 **Six or more stools per day (moderate severity):** 4 **Treatment in the preceding month:** sulphasalazine n=6 , rectal steroids n=8 **Drop outs:** 2 **<u>Group 2: Placebo</u>** **Mean age (SD):**45 (no SD given) **Mean stools per day:**3.9 **Six or more stools per day (moderate severity):** 3	N=13 (completers) 1g olsalazine twice a day with meals **Total dose: 2g/day** **Group 2: Placebo** N=15 randomised N=11 (completers) Placebo capsules given twice a day with meals **Concomitant therapy:** None. Other therapy was ceased. Patients who deteriorated during the study were eligible to receive the olsalazine openly for 6 weeks in the same closely supervised way.	symptomatic wellbeing to good or very good by week 6)	**Group 2:**2/15	**Limitations:** Unclear randomisation Unclear allocation concealment High dropout rate of 20% No data on extent in the baseline characteristics Unclear if a validated clinical assessment tool Stated to be double blind, no further information given **Additional outcomes:** Sigmoidoscopic improvement Histological improvement Haematological and biochemical tests

Author	Patients	Intervention	Outcome measures	Effect size	Comments
olsalazine group, described as watery diarrhoea. The 4 patients in the placebo group that dropped out due to deterioration in bowel habit were typical of colitis, so not regarded as an AE.	**Treatment in the preceding month:** sulphasalazine n=7, rectal steroids n=6 **Drop outs:** 4 **Extent:** No information given on % proctitis or left sided colitis				

Table 74: HIWATASHI2011

Author	Patients	Intervention	Outcome measures	Effect size	Comments
N. Hiwatashi et al. Clinical trial: effects of an oral preparation of mesalazine at 4g/day on moderately active ulcerative colitis. A phase III parallel-dosing study. *Journal of Gastroenterology; 46: 46-56.2011.* **REF ID: HIWATASHI2011** **Study design and quality:** Double blind RCT Multicentre: 39 medical institutions, Japan **8 week trial** **Randomisation:** Randomly assigned to the two treatment groups in a 1:1 ratio. No further information given. **Allocation concealment**: Unclear	**All patients:** **N=123 randomised** **N=118 FAS** **Drop-outs** (don't complete the study): N=24 (%) (16 in the 2.25g group and 8 in the 4g group discontinued prematurely). >10% difference in missing data between the two treatment arms. **Inclusion criteria:** • 15-64 years of either sex • Diagnosed as having relapsing-remitting UC • Extent: All extents apart from proctitis • Severity: UCDAI score of 6-8 points, moderately active UC **Exclusion:** • Received oral mesalazine > 2.25g/day or oral salazosulfapyridine >4.5g/day or topical rectal therapies within the last 14 days • Taken any corticosteroids (oral, injection, or rectal, except eye drops and inhalants) • Undergone leukocytapheresis within the last 14 days • Taken immunosuppressants within the past 90 days • Taken an infliximab preparation within the past 60 days	**Group 1: 2.25g mesalazine** N=63 randomised N=59 (FAS) N=47 (completers) 2.25g/day of mesalazine (three divided doses) and matching placebo tablets **Group 2: 4g mesalazine (Pentasa)** N=60 randomised N=59 (FAS) N=52 (completers) 4g/day of mesalazine (two divided doses) and matching placebo tablets.	**Outcome 1: Clinical remission** (0-1 in total score) N values calculated from the percentages given in the paper.	**Group1:** 9/59 (15.3%) **Group 2:** 13/59 (22%)	**Funding:** None described. **Limitations:** Unclear method of randomisation and allocation concealment >10% difference in missing data between the two treatment arms. **Additional outcomes:** Mean changes in UCDAI score by severity of disease, attack (first/ relapse)

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Blinding: Double blind. Placebo and mesalazine tablets were identical in size and appearance. **Outcome assessment:** Modified Mayo score, UCDAI score **Sample size calculation:** Planned sample size of 120. No further details given. **Type of analysis: FAS** (full analysis set), population continuing on the study drug for 15 days. **PPA.** **Compliance rates:** Not described. N=2 dropout/ withdrawal due to AEs in the 2.25g group. The SAEs were not counted as a dropout/ withdrawal in the paper	• Taken antidiarrheal drugs within the last 3 days • Participated in another clinical study within the past 6 months • Past history of hypersensitivity to mesalazine preparations or salicylates (except intolerance to salazosulfapyridine) • Severe ADRs after treatment with mesalazine • Nephropathy • Hepatopathy • Malignant neoplasm • Past history of severe nephropathy, hepatopathy, heart disease pulmonary disease, blood disease or pancreatopathy • Pregnant women or women who were suspected to be pregnant or nurse **Group 1: 2.25g mesalazine (Pentasa)** **Sex (m/f):** 33/26 **Mean age (SD):** Not given. Numbers given at 5 year intervals. **Salazosulfapyridine intolerance:** absence n=26, present n=5, unknown n=28 **Past history/ complications:** absent n=16, present n=43 **Extent:** left colitis n=33, enterocolitisi n=26 **UCDAI score at baseline:** 6 n=20, 7 n=20, 8 n=19 **Drop outs:** 16 (13 aggravation of the underlying disease, 2 AEs, 1 drop out) **Group 2: 4g mesalazine (Pentasa)** **Sex (m/f):** 38/21 **Mean age (SD):** Not given. Numbers given at 5 year intervals. **Salazosulfapyridine intolerance:** absence n=25, present n=5, unknown n=29 **Past history/ complications:** absent n=11, present n=48 **Extent:** left colitis n=34, enterocolitisi n=25 **UCDAI score at baseline:** 6 n=19, 7 n=19, 8 n=21 **Drop outs:** 8 (7 aggravation of the underlying disease, 1 wish of the patients)	**Concomitant therapy:** See the exclusion criteria.			

Table 75: HO2004

Reference	Patient characteristics	Predictors & outcome measures	Effect sizes	Comments
G. T. Ho et al. Predicting the outcome of severe ulcerative colitis: development of a novel risk score to aid early selection of patients for second-line medical therapy or surgery. *Alimentary Pharmacology & Therapeutics*; 19: 1079-1087. 2004. **Type of study:** Retrospective cohort study **Setting:** Recruited from gastroenterology unites for two university teaching hospitals and a large district general hospital Edinburgh, Scotland **Follow up period:** The patients hospital admission **Model development:** Univariate screening **Model presentation:** Variables of prognostic significance were categorized and re-entered into a logistic regression model. Integer	**Sample size:** N=1211 admissions N=245 acute flare of UC N=167 eligible patients (fulfilled Truelove & Witts criteria) **<5% missing data?** Not described. **Type of analysis used:** Uni-variate analyses Step wise multiple logistic regression **Appropriate?** Yes **Inclusion criteria:** • Patients admitted for in-patient management of acute UC between January 1995-March 2002 were identified using the regional database of medical/ surgical admissions and respective local hospital discharge databases • Clinical, radiological and histological criteria to confirm UC diagnosis • Severe episode as defined by the Truelove & Witts criteria **Data collection** See inclusion criteria. Case notes were reviewed. **Treatment given**	56 variables were recorded within the first 3 days of medical therapy (demographic, clinical observations, laboratory parameters, x-ray and endoscopic assessments of severity). **Univariate analysis results:** see the table below **Definitions of predictors:** Colonic dilatation: ≥5.5cm diameter of the transverse colon on plain abdominal x-ray. For other definitions see the variables listed in the Effect sizes column. **Routinely measured?** Yes **Outcome and definition:** Response (no colectomy) or non-response to medical therapy (colectomy) with in the period of hospitalisation. **Blinding:** Not reported. **Risk of measurement error:** Low **Risk of inter-observer variability:** Low. Some variability likely measuring colonic dilatation. **Continuous variable analysis:** continuous or categorical- mean stool frequency was continuous and made	**Results** N=60 failed to respond to medical treatment and required colectomy in that admission (40%). 68 in total required colectomy. Two of these patients died post colectomy (pneumonia, arterial thrombosis of the lower limb) 10 patients had colonic dilatation. Colonic dilatation within the 1st 3 days was only used for analysis. 1 patient developed colonic perforation requiring urgent surgery. Median time to surgery (for those with colonic dilatation): 7 days (Inter-quartile range:5-9) Median time to surgery for all patients: 9 days from admission (Inter-quartile range: 7-15 days) **Variables** / **Score** Mean stool frequency <4 — 0 Mean stool frequency >4≤6 — 1 Mean stool frequency >6≤9 — 2 Mean stool frequency >9 — 4	**Source of funding**: None described. **Risk of bias:** • Retrospective cohort • No validation was carried out (done externally in a separate paper) • Unclear if any missing data **Additional outcomes reported:** Response or non-response to medical therapy Colectomy at 60 days Secondary analysis on ciclosporin being considered as a failure of first line medical therapy

Reference	Patient characteristics	Predictors & outcome measures	Effect sizes			Comments
score given to each category of each variable according to its relative contribution in the regression model. Scores were grouped in to low, intermediate and high risk categories. **Model evaluation:** None reported **Model performance:** Calibration- Not reported Discrimination – See Efficacy results.	IV corticosteroids (methylprednisolone 60mg/day or hydrocortisone 400mg/day). 83% had oral 5-ASA, 45% topical therapy, 71% subcutaneous heparin, 13% IV ciclosporin (21 patients on 4mg/kg) and TPN. **Baseline characteristics:** Median age at presentation: 38 years (IQR 27-54yrs) Median duration of admission: non-responders (26 days) and responders (11 days)	into categorical, as was the serum albumin level. Colonic dilation was binary (yes/no). **Key prognostic factors not included?** No.	Colonic dilatation	4		
			Hypoalbuminaemia (<30g/L)	1		
			For predicting non-response to medical therapy with scores ≥4: **Sensitivity:** 85% **Specify:** 75% **Area under the curve :** 0.876 **Area under the curve for colectomy at 60days following presentation:** 0.833 **Ciclosporine treatment was regarded as primary treatment failure:** 0.810 **Colonic dilation were excluded:** 0.807 All patients with a score≥6 failed to respond to medical therapy.			
			Risk	**% of patients**	**Medical failure rates**	
			Low (score 0-1)	42%	11%	
			Intermediate (score 2-3)	34%	45%	
			High (score ≥4)	23%	85%	

Table 76: Univariate analysis statistically significant results (p<0.05)

Variable	Non- responders	Responders	Odds ratio (95% CI)	P- value

Variable	Non- responders	Responders	Odds ratio (95% CI)	P- value
Disease extent (Recto-sigmoid)	3 (5%)	28 (28%)	-	<0.001
Stool frequency >8/day	40 (58.8%)	29 (29.3%)	0.29 (0.15-0.56)	<0.001
Stool frequency Day 1	8.85	6.27	0.80 (0.72-0.89)	<0.001
Stool frequency Day 2	7.39	4.61	0.80 (0.73-0.89)	<0.001
Stool frequency day 3	7.92	4.46	0.79 (0.79-0.87)	<0.001
Mean stool frequency (day 1-3)	8.05 (3.4)	5.2 (2.4)	0.71 (0.62-0.81)	<0.001
Mean temperature (day 1-3)	37.16 (0.52)	37.00 (0.45)	0.51 (0.26-0.98)	0.04
Colonic dilatation	15 (22%)	1 (1%)	0.04 (0.00-0.29)	<0.001
In-patient drug therapy				
5-ASA (800-1200mg/day)	50 (74%)	89 (89%)	3.14 (1.35-7.32)	0.008
Subcutaneous heparin (5000 U/day)	60 (88%)	58 (58%)	0.19 (0.08-0.43)	<0.001
Platelet (x10^9)	461.0 (164.0)	402.5 (133.0)	0.97 (0.95-0.99)	0.01
ESR (mm/h)	50.5 (28.9)	41.0 (24.2)	0.99 (0.97-1.0)	0.04
CRP (mg/L)	6.9 (2.8-19.25)	3.9 (1.5-9.35)	0.98 (0.95-1.01)	0.02
Albumin (g/L)	30.6 (5.0)	34.1 (6.2)	1.10 (1.04-1.17)	0.001

Table 77: Multi-variate analysis statistically significant results (p<0.05)

Variables	Coefficient (S.E.)	P- value	Odds ratio (95% CI)
Mean stool frequency	-0.378 (0.06)	<0.001	0.68 (0.61, 0.78)
Colonic dilatation	-3.548 (1.11)	0.001	0.03 (0.00, 0.20)
Day 1 serum albumin	0.09 (0.03)	0.002	1.10 (1.03, 1.15)
Constant	-	-	-
Mean stool frequency 4≤6/ day	-1.40 (0.73)	0.055	0.25 (0.06, 1.03)
Mean stool frequency 6≤9/ day	-2.20 (0.69)	0.002	0.11 (0.03, 0.43)
Mean stool frequency >9/ day	-4.3 (0.84)	<0.001	0.01 (0.00, 0.07)

Variables	Coefficient (S.E.)	P- value	Odds ratio (95% CI)
Colonic dilatation	-3.8 (1.17)	0.001	0.02 (0.00, 0.22)
Serum albumin <30g/L	-1.24 (0.44)	0.005	0.29 (0.12, 0.69)

(a) It is unclear why colonic dilation is in the results table twice. The other factors may be continuous and categorically presented.

(b) CRP, platelets and ESR implicated in the uni-variate analysis did not achieve statistical significance in the multivariate logistic regression analysis. Additional medical therapies were also not found to be statistically significant in the multivariate analysis apart from the use of TPN. TPN was not included in the modelling because the median time to commencement was 6 days (inter-quartile range 4-7) following the initiation of intravenous corticosteroid therapy. The model is based on the first 3 days.

Table 78: IRELAND1988

Author	Patients	Intervention	Outcome measures	Effect size	Comments
A. Ireland et al. Controlled trial comparing olsalazine and sulphasalazine for the maintenance treatment of ulcerative colitis. *Gut; 29: 835-837. 1988.* **REF ID: IRELAND1988** **Study design and quality:** Double blind, double dummy RCT **6 month trial** **Randomisation:** In blocks of 10. No other information was given. Unclear. **Allocation concealment**: Unclear. Drugs were dispensed by the hospital pharmacy. **Blinding:** Double blind, double dummy **Outcome assessment:** History taken, clinical examination,	**<u>All patients:</u>** **N=164 randomised** **Drop-outs** (don't complete the study): N=30 (18.3%) **Inclusion criteria:** • Male or female aged between 18-75 years • UC in remission • No relapse during the preceding six months **Exclusion:** • Active disease • Hepatic or renal dysfunction • Allergies to sulphonamides or salicylates • If young women, not taking adequate contraceptive precautions • Received corticosteroids, azathioprine or metronidazole during the preceding 6 months **<u>Group 1: 1g Olsalazine</u>** **Mean age (range):** 47 (17-75) **Mean duration of disease:** 10.5 years **SASP on entry:** n=81 **Extent:** proctitis n=37, left sided n=25, total colitis n=20 **Severity of previous relapse:** Not described	**Group 1: 1g Olsalazine** N=82 randomised 500mg of olsalazine twice a day. 250mg capsules of olsalazine were used. Two placebo tablets were also taken twice a day. **Group 2: 2g Sulphasalazine** N=82 randomised 1g sulphasalazine twice a day. 500mg sulphasalazine tablets were used. 2 placebo capsules were also taken twice a day. **Concomitant therapy:** None described. See inclusion/exclusion criteria.	**Outcome 1: Relapse** by 6 months Life table cumulative relapse rate: p=0.1314 Diagram of the life table was shown in the paper. **Outcome 2: Adverse events** Reasons for withdrawal: **Olsalazine:** diarrhoea 10 (6 proctitis, 2 left sided, 2 total colitis), abdo pain 2, indigestion 2, arthralgia 1, itching 1 **SASP:** diarrhoea 3 (2 proctitis, 1 total colitis), indigestion 2, depression 1, rash 1, headache 1, concurrent illness 1	**Group1:** 16/82 **Group 2:** 10/82 **Group1:** 21/82 **Group 2:** 20/82	**Funding:** None described. Helpful advice was given by Pharmacia AB, Sweden. **Limitations:** Unclear method of randomisation and allocation concealment Stated to be double blind, but no description of the blinding was given. **Additional outcomes:** Histological active disease and relapse rate (narrative) **Note:** **Majority of patients were on SASP at entry**

Author	Patients	Intervention	Outcome measures	Effect size	Comments
sigmoidoscopy (0-3 grade according to Truelove & Witts) and rectal biopsy (graded according to Truelove & Richards) taken at entry, 3 and 6 months. **Sample size calculation:** 80% power, 5% significance, 10% drop out rate, 20% difference in relapse rates between the two groups. **Type of analysis: ITT** **Compliance rates:** Not described. N=25 dropout/ withdrawal due to AEs. Not thought to be drug related. 16 in the olsalazine group and 9 in the SASP.	**Frequency of relapses:** Not described **Drop outs:** 19 (3 lost to follow up, 16 due to AEs) **Group 2: 2g Sulphasalazine** **Mean age (range):** 49 (18-75) **Mean duration of disease:** 13.1 years **SASP on entry:** n=81 **Extent:** proctitis n=39, left sided n= 26, total colitis n=17 **Severity of previous relapse:** Not described **Frequency of relapses:** Not described **Drop outs:** 11 (2 lost to follow up, 9 due to AEs) **Definitions** **Remission:** Absence of colitis symptoms together with an absence of inflammation on sigmoidoscopy. **Relapse:** Increased stool frequency with or without blood or mucus and with evidence of inflammation on sigmoidoscopy. Patients were withdrawn if they relapsed or if any side effects occurred which necessitated stopping therapy.				

Table 79: IRVINE2008

Author	Patients	Intervention	Outcome measures	Effect size	Comments
E. J. Irvine et al. The effect of mesalazine therapy on quality of life in patients with mildly and moderately active ulcerative colitis. *Alimentary Pharmacology & Therapeutics; 28: 1278-128. 2008.* **REF ID: IRVINE2008** **Study design and quality:**	**All patients:** **N=687randomised** **N=594 (evaluable at week 3)** **N=576 (evaluable at week 6)** **Drop-outs** (don't complete the study): See the individual studies. The majority of patients with missing IBDQ data had dropped out due to voluntary withdrawal, protocol violation, adverse events, investigator recommendation or lack of treatment effect. The overall	**Group 1: 2.4g mesalamine (Asacol)** N=349 randomised **Group 2: 4.8g mesalamine (Asacol)** N=338 randomised	Outcome 1: **Quality of life** (IBDQ mean change from baseline, (SD))	**ASCEND I** **Group1:**37.3 (36.10) n=154 **Group 2:**45.6 (33.62) n=147 **Mean difference:** -8.30 (-16.18,	**Funding:** Original studies were supported by Procter & Gamble Pharmaceuticals **Limitations:** Both studies had an unclear method of randomisation and allocation concealment One study had no further

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Data from the ASCEND I and II studies see HANAUER2005 & HANAUER2007.	drop outs were similar in both groups. **Inclusion/exclusion criteria:** See original studies. **<u>Group 1: 2.4g mesalamine (Asacol)</u>** **Mean age (SD):** 43.1 (13.82) **Mean baseline UCDAI score:** 6.2 (1.93) **Mean baseline IBDQ score:** 143.3 (35.12) **<u>Group 2: 4.8g mesalamine (Asacol)</u>** **Mean age (SD):** 44.1 (13.27) **Mean baseline UCDAI score:** 6.2 (1.89) **Mean baseline IBDQ score:** 142.3 (35.28) MID calculated by the 0.5xSD of the control group (4.8g) at baseline: 17.64			-0.42) **<u>ASCEND II</u>** **Group1:**38.9 (37.52) n=195 **Group 2:**38.2 (33.13) n=191 **Mean difference:** 0.70 (-6.36, 7.76)	details on double blinding **Additional outcomes:** See original papers.
			Inflammatory Bowel Disease Questionnaire (IBDQ) Four domains: Bowel symptoms (10 items) Systemic symptoms (5 items) Emotional factors (12 items) Social factors (5 items) Score range: 32-224. A higher score indicated a better quality of life. Data for patients missing more than four of 32 questions were not included in the analyses of total score.		

Table 80: ITO2010A

Author	Patients	Intervention	Outcome measures	Effect size	Comments
H. Ito et al. Direct Comparison of Two Different Mesalamine Formulations for the Induction of Remission in Patients with Ulcerative Colitis: A Double-blind, Randomized Study. Inflammatory Bowel Disease; 16 (9): 1567- 1574. 2010. **REF ID:ITO2010A** **Study design and quality:** Double blind, multicentre (53 sites) RCT, Japan **8 week trial** **Randomisation:** Biased coin minimization algorithm was used to balance extent and severity Person independent from the study was in charge of allocation Seven patients were assigned as a block as follows: 2 pts to 2.4g Asacol, 2pts to 3.6g Asacol, 2 pts to Pentasa and 1 pt to placebo Randomization code was sealed and stored until the blind was removed **Allocation concealment**: Adequate. Independent person	**<u>All patients:</u>** **N=229 randomised** **Drop-outs (don't complete the study):** N=47**(20.5%)**(most frequent reason for withdrawal was aggravation of UC) **Inclusion criteria:** 16-64 years old Outpatients Severity: Mild to moderate active UC (UCDAI 3-8 & a bloody stool score of ≥1) **Exclusion:** Severe UC, chronic continuous type UC or acute fulminating type UC Oral mesalamine >2.25g/day, oral salazosulfapyridine >4.5g/day, mesalamine enemas, salazosulfapyridine suppositories, corticosteroids (oral preparations, enemas, suppositories, injections and/or remedies for haemorrhoidal diseases) and /or cytapheresis within 14 days before the start of the investigational drug Any other investigational drug within six months before informed consent History of hypersensitivity to mesalamine or salicylate drugs Severe cardiac disease Severe pulmonary disease and or/ severe haematological diseases Severe hepatopathy, sever nephropathy and/or malignant tumours Pregnant or lactating	Active and placebo tablets split to take them three times a day **Group 1: 2.4g Mesalamine (Asacol)** N=66 N=66 (FAS) N=65 (PPA) Mesalamine 2.4g (delayed pH release, Asacol 400mg tablets) **Group 2: 3.6g mesalamine (Asacol)** N=65 N=64 (FAS) N=62 (PPA) Mesalamine 3.6g (delayed pH release, Asacol 400mg tablets) **Group 3: 2.25g mesalamine (Pentasa)** N=65 N=63 (FAS & PPA) Mesalamine 2.25g (delayed time release, Pentasa 250mg tablets)	Outcome 1: **Clinical remission** (UCDAI≤2 and a bloody stool score of 0 at the final assessment) Outcome 2: **Clinical improvement** (patients with the decrease in UC-DAI by 2 points or more, except patients who experienced a remission). For our analysis this is combined with the remission figures to give a number of all those who had improved. Outcome 3: **Adverse events** Outcome 4: **Serious Adverse events**	Group 1:20/66 Group 2:29/64 Group3:18/63 Group4:3/32 Group 1:30/66 Group 2:41/64 Group3:31/63 Group4:9/32 Group 1: 56/66 Group 2: 53/64 Group3: 55/63 Group4:22/32 Group 1: 2/66 Group 2: 2/64 Group3: 3/63 Group4:0/32	**Funding:** Supported by Zeria Pharmaceutical Co., Ltd **Limitations:** High dropout rate **Additional outcomes:** Superiority of the drugs; decrease in UCDAI Proportion of efficacy Decrease in UCDAI by extent of disease

Author	Patients	Intervention	Outcome measures	Effect size	Comments
was in charge of the random allocation. **Blinding:** Double dummy method, double blind. Code only revealed after the blind was removed. Independent assessment of the mucosa. **Outcome assessment:** UC-DAI (Sutherland et al.) **Sample size calculation:**α=0.05 (two sided) and β=0.1, 54 -55 patients per arm **Type of analysis: FAS and PPA.** Full Analysis Set (FAS): All participants except those who had not taken even one tablet of the investigational drugs, those who did not comply with Good Clinical Practice, those who met exclusion criteria (severe UC, chronic continuous type UC or acute fulminating type UC) and those whose data is missing. Per Protocol Analysis (PPA):Consisted of the FAS except those who did not fulfil the inclusion criteria, those who met the other exclusion criteria, those who received forbidden drugs and those whose drug compliance was less than 75%. **Compliance:** >75% in every patient except for 2 patients. N=3 dropout/ withdrawal due to drug related AEs (A causal relationship to the drug could not be ruled out for one patient	**Group 1: 2.4g mesalamine (Asacol)** **Mean age (SD):**39.4 (12.0) **Extent:** proctitis (n=24), others (n=42) **Episode:** new (n=16), relapse (n=50) **UCDAI mean (SD):** 6.1 (1.6) **Drop outs:** 16 (9 aggravation of UC, 2 AEs, 4 withdrew consent, 1 other) **Group 2: 3.6g mesalamine (Asacol)** **Mean age (SD):**41.6 (10.4) **Extent:** proctitis (n=24), others (n=40) **Episode:** new (n=14), relapse (n=50) **UCDAI mean (SD):** 6.0 (1.6) **Drop outs:** 7 (1 aggravation of UC, 2 AEs, 3 withdrew consent, 1 other) **Group 3: 2.25g mesalamine (Pentasa)** **Mean age (SD):**41.2 (10.1) **Extent:** proctitis (n=25), others (n=38) **Episode:** new (n=8), relapse (n=55) **UCDAI mean (SD):** 6.1 (1.6) **Drop outs:** 14 (7 aggravation of UC, 3 AEs, 3 withdrew consent, 1 other) **Group 2: Placebo** **Mean age (SD):** 35.8 (10.6) **Extent:** proctitis (n=11), others (n=21) **Episode:** new (n=5), relapse (n=27) **UCDAI mean (SD):** 5.9 (1.7) **Drop outs:** 10 (7 aggravation of UC, 1 withdrew consent, 2 other)	**Group 4: Placebo** N=33 N=32 (FAS & PPA) Placebo **Concomitant therapy:** No further information. See inclusion/ exclusion criteria.			

Author	Patients	Intervention	Outcome measures	Effect size	Comments
in the 2.4g Asacol and two patients in the 2.25g Pentasa who withdrew from the study) and 7 withdrawals due to AEs overall					

Table 81: ITO2010B

Author	Patients	Intervention	Outcome measures	Effect size	Comments
H. Ito et al. Direct Comparison of Two Different Mesalamine Formulations for the Maintenance of Remission in Patients with Ulcerative Colitis: A Double-blind, Randomized Study. *Inflammatory Bowel Disease; 16 (9): 1575-1582. 2010.* **REF ID: ITO2010B** **Study design and quality:** Double blind, double dummy RCT Multicentre: 50 centres, Japan **48 week trial** **Randomisation:** A person independent of the study was in charge of the random allocation. The randomization code was sealed and stored until the blind was removed. Treatment assignments were balanced using a biased coin	**<u>All patients:</u>** **N=131 randomised** **N=130 FAS (Good clinical practice violation)** **Drop-outs** (don't complete the study): N=12 (%) This figure excludes relapses. **Inclusion criteria:** • Outpatients • 16-64 years at the time of the informed consent • Quiescent UC defined by an UCDAI of 2 or less and a bloody stool score of 0 • Extent: Not described **Exclusion:** • Corticosteroids (oral preparations, enemas, suppositories, injections and/or remedies for hemorrhoidal disease) and/ or cytopheresis within 14 days before the start of the investigational drugs • Immunosuppressants within 90 days before the start of the investigational drug • Any other investigational drugs within 6 months before informed consent (except the investigational drugs in a study for active UC) • A history of hypersensitivity to mesalamine or salicylates drugs • Severe cardiac disease, pulmonary disease and/or hematological disease	**Group 1: 2.4g mesalazine (Asacol)** N=65 randomised N=65 (FAS) pH dependent release mesalamine formulation, Eudragit-S (Asacol) 400mg tablets. Administered 3 times a day. Total dose 2.4g. **Group 2: 2.4g mesalazine (Pentasa)** N=66 randomised N=65 (FAS) Time dependent release mesalamine formulation with an ethyl cellulose (Pentasa) 250mg tablets. Administered 3 times a day. Total dose 2.4g. **Concomitant therapy:**	**Outcome 1: Relapse** **Log rank p value: 0.79** **Outcome 2: Adverse events** Only those with >10% of the patients suffering the same AE were presented. **Outcome 3: Serious adverse events** The paper does not describe what the SAEs were, but states that one of the Asacol group's SAEs could not have a causal relationship ruled out.	**Group1:** 13/65 **Group 2:** 13/65 **Reported HR (95%CI):** 0.899 (0.41, 1.971) **Group1:** 62/65 **Group 2:** 62/65 **Group1:** 2/65 **Group 2:** 1/65	**Funding:** Some consulting fees and grant support was given by Zeria pharmaceuticals. **Limitations:** Limited baseline characteristics **Additional outcomes:** Mean decrease in UCDAI Absence of bloody stools (HR) **Notes:**

Author	Patients	Intervention	Outcome measures	Effect size	Comments
minimization algorithm (two factors were prior participation in an induction of remission study (same drugs), duration of remission < or >2 years). Balance within each medical center was also taken into consideration. Block randomisation. **Allocation concealment**: Adequate **Blinding:** Double blind. Double dummy. Mucosal appearance was judged by 3 members of the committee blindly. The score had to be the same from every member. **Outcome assessment:** UCDAI. **Sample size calculation:** α=0.05, β-0.1, 60 patients per treatment arm. **Type of analysis: FAS (full analysis set)** included all those except those who had not taken even one tablet of the investigational drug, those who did not comply with Good Clinical Practice and those whose data were missing at the efficacy endpoint. **PPA.** **Compliance rates:** Drug compliance was >75% in every patient. Unclear dropout/ withdrawal due to drug related AEs, n=4 who withdrew due to AEs	• Severe hepatopathy, severe nephropathy and/or a malignant tumors • Pregnant or lactating **Group 1: 2.4g mesalazine (Asacol)** **Mean age (SD):** 43.4 (12.0) **Sex (m/f):** 40/25 **Extent:** Proctitis type n=23, other n=42 **Severity of previous relapse:** not described **Frequency of relapses:** not described **Current use of immunomodulators:** not described **Years of disease duration:** <1 n=5, <2 n=7, <3 n=5, <4 n=5, <5 n=2, ≥5 n=41 **Duration of current remission:** <2 years n=44, ≥2 n=21 **Drop outs:** 6 (1 aggravation of UC (not classed as a relapse), 1 AEs, 3 withdrew consent and 1 other) **Group 2: 2.4g mesalazine (Pentasa)** **Mean age (SD):** 42.6 (10.5) **Sex (m/f):** 41/24 **Extent:** Proctitis type n=27, other n=38 **Severity of previous relapse:** not described **Frequency of relapses:** not described **Current use of immunomodulators:** not described **Years of disease duration:** <1 n=9, <2 n=9, <3 n=7, <4 n=7, <5 n=5, ≥5 n=28 **Duration of current remission:** <2 years n=44, ≥2 n=21 **Drop outs:** 5 (3 AEs, 2 other) **Definitions** **Relapse:** A bloody stool score of 1 or more and UDAI of 3 or more.	See exclusion criteria.			

Author	Patients	Intervention	Outcome measures	Effect size	Comments
(reasons not stated).					

Table 82: JEWELL1974 – induction of remission

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Jewell DP, Truelove SC. Azathioprine in ulcerative colitis: final report on controlled therapeutic trial. British Medical Journal; 14; 4(5945):627-30. 1974. **REF ID: JEWELL1974** **Study design and quality:** **Type of RCT**: Unclear **Multicentre**: No details of number of centres, UK **52 week trial** **Randomisation:** Block randomization. Unclear. **Allocation concealment**: Yes, third person, pharmacist. **Blinding:** unclear **Outcome assessment:** Monthly assessment, symptoms, sigmoidoscopy and biopsy. Sigmoidoscopy graded 0-3. Clinical – Truelove & Witts, histology assessment according to Truelove & Richards.	**<u>All patients:</u>** **N=80 randomized**(an additional 40 patients were recruited to first 40) **N=80 ITT** **Drop-outs** (don't complete the study):10 (failures, don't achieve remission) N=4 (5%) **Inclusion criteria:** Extent: no details (only sigmoidoscopic appearance) Severity: attack of UC, mild, moderate or severe (Truelove and Witts, 1955). **Exclusion:** No details provided **<u>Group 1: Azathioprine (N=40)</u>** **Mean age (SD):** <30 n=7 30+ n=12 40+ n=10 50+ n=6 ≥60 n=5 **Extent:** not reported, only sigmoidoscopic appearance **Severity:** Mild: n=16 Moderate: n=21 Severe: n=3 **M/F:** 21/19 **Drop outs:**2 failures at the end of 4 weeks (there were more in the maintenance of remission section of the trial).	**Group 1: Azathioprine** N=40 randomised N=40 (ITT) N=38 (completers) **Intervention details** 2.5 mg/kg body weight. First 40 patients reduced after 3 months to 1.5-2.0 mg/kg. Second 40 patients maintained at 2.5mg/kg. **Group 2: Placebo** N=40 randomised N=40 (ITT) N=38 (completers) **Intervention details** Dummy tablets were prescribed in equivalent manner to azathioprine. **Concomitant therapy:** All patients were in a frank attack of UC. For	Outcome 1: **Clinical remission** (Not meeting the Truelove & Witts criteria) Outcome 2: **Endoscopic remission** (normal mucosa) **Adverse events:** These were reported for over the 52 weeks trial and not separately for the first 4 week induction of remission section.	**<u>4 weeks (1 month)</u>** **Group 1:** 31/40 **Group 2:** 27/40 **<u>4 weeks (1 month)</u>** **Group 1:** 15/40 **Group 2:** 9/40 **Azathioprine:** Low white blood cell count: N=2 Nausea, abdominal discomfort and diarrhoea n=1 Erythematous rash n=1 **Placebo:** Low white blood cell count : n=1 Hair loss: n=2	**Funding:** Wellcome Foundation **Limitations:** Unclear method of randomisation Unclear blinding Indirect population (7/80) **Additional outcomes:** Histological assessment **Note: patients all were on steroids in addition to treatment. See concomitant therapy.**

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Sample size calculation: Unclear **Type of analysis:** ITT Patients were separated into groups according to their history – first attack, short history (<5 yrs), long history (>5 yrs). **Compliance rates:** N=10 dropout/ withdrawal because they don't achieve remission	**Group 2: Placebo (n=40)** **Mean age (SD):** <30 n=8 30+ n=11 40+ n=10 50+ n=6 ≥60 n=5 **Extent:** not reported, only sigmoidoscopic appearance **Severity:** Mild: n=17 Moderate: n=19 Severe: n=4 **M/F:** 21/19 **Drop outs:**2 failures at the end of 4 weeks (there were more in the maintenance of remission section of the trial). **Definitions** **Remission:** defined by severity of disease using the criteria of Truelove and Witts (1995) **Relapse:** Occurrence of diarrhoea with blood in the motion and with sigmoidoscopic evidence of inflammation **Failures**: failed to go into clinical remission within 6 weeks of corticosteroid treatment.	inpatients they received a standard course of corticosteroids together with general medical measures. Outpatients had oral Prednisolone 5mg four time/day and Prednisolone disodium retention enema nightly. If the response was good after a month's it was reduced. Inpatients: five day intensive course of IV therapy, nil by mouth except water, IV fluids, Prednisolone 40mg daily (IV), 1g tetracycline/day in divided doses, and rectal drip of hydrocortisone hemisuccinate sodium 100mg twice daily. Good clinical response, food and drink resumed and oral Prednisolone 40mg.			

Table 83: JEWELL1974 – maintenance of remission

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Jewell DP, Truelove SC. Azathioprine in ulcerative colitis: final report on controlled therapeutic trial. British Medical	**Induction of remission trial with a maintenance of remission follow up** **All patients:** **N=80 randomized** (an additional 40 patients were recruited to first 40)	**Group 1: Azathioprine** N=40 randomised N=31 entered remission at 1 month	**Outcome 1: Relapse** Unable to calculate the hazard ratio. Figures are those who	**Group 1:** 21/37 **Group 2:** 24/33	**Funding:** Wellcome Foundation

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Journal; 14; 4(5945):627-30. 1974. **REF ID: JEWELL1974** **Study design and quality:** **Type of RCT**: Unclear **Multicentre**: No details of number of centres, UK **52 week trial** **Randomisation:** Block randomization. Unclear. **Allocation concealment**: Yes, third person, pharmacist. **Blinding:** unclear **Outcome assessment:** Monthly assessment, symptoms, sigmoidoscopy and biopsy. Sigmoidoscopy graded 0-3. Clinical – Truelove & Witts, histology assessment according to Truelove & Richards. **Sample size calculation:** Unclear **Type of analysis:** ITT Patients were separated into groups according to their history – first attack, short history (<5 yrs), long history (>5 yrs). **Compliance rates:** Not described.	**N=58 entered remission by 1 month** **N=70 (successfully induced – figure taken from the Cochrane systematic review on Azathioprine)** **Drop-outs** (don't complete the study): N=0 (0%) N=4 (5%) failures at the end of 1 month (induction of remission stage) N=29 (36%) (19 had 3 relapses so were withdrawn from the trial, 10 failures (failed to go into remission) over 1 year) There were no other drop outs reported. **Inclusion criteria for the induction of remission part of the study:** • Extent: no details (only sigmoidoscopic appearance) • Severity: attack of UC, mild, moderate or severe (Truelove and Witts, 1955). **Exclusion:** • No details provided **Baseline characteristics for the induction of remission** **<u>Group 1: Azathioprine (N=40)</u>** **Mean age (SD):** <30 n=7 30+ n=12 40+ n=10 50+ n=6 ≥60 n=5 **Extent:** not reported, only sigmoidoscopic appearance **Severity:** Mild: n=16 Moderate: n=21 Severe: n=3 **M/F:** 21/19 **Drop outs:** 11(2 failures at the end of 4 weeks, in total 3 failures by the end of 1 year. 8 patients had 3 relapses so were withdrawn.)	N=37 successfully induced **Intervention details** 2.5 mg/kg body weight. First 40 patients reduced after 3 months to 1.5-2.0 mg/kg. Second 40 patients maintained at 2.5mg/kg. Maintenance part of the trial the patients were on 2.5mg/kg. **Group 2: Placebo** N=40 randomised N=27 entered remission at 1 month N=33 successfully induced **Intervention details** Dummy tablets were prescribed in equivalent manner to azathioprine. **Concomitant therapy:** All patients were in a frank attack of UC. For inpatients they received a standard course of corticosteroids together with general medical measures. Outpatients had oral Prednisolone	were successfully induced as the denominator. **Outcome 2: Adverse events** These were reported for over the 52 weeks trial **Azathioprine:** Low white blood cell count: N=2 Nausea, abdominal discomfort and diarrhoea n=1 Erythematous rash n=1 **Placebo:** Low white blood cell count : n=1 Hair loss: n=2	**Group 1:** 4/40 **Group 2:** 3/40	**Limitations:** Unclear method of randomisation Unclear blinding Randomised at induction **Additional outcomes:** Remission Histological assessment

Author	Patients	Intervention	Outcome measures	Effect size	Comments
N=0 dropout/ withdrawal due to AEs.	**Group 2: Placebo (n=40)** **Mean age (SD):** <30 n=8 30+ n=11 40+ n=10 50+ n=6 ≥60 n=5 **Extent:** not reported, only sigmoidoscopic appearance **Severity:** Mild: n=17 Moderate: n=19 Severe: n=4 **M/F:** 21/19 **Drop outs:** 18 (2 failures at the end of 4 weeks, in total 7 failures by the end of 1 year. 11 patients had 3 relapses so were withdrawn.) **Definitions** **Remission:** defined by severity of disease using the criteria of Truelove and Witts (1995) **Relapse:** Occurrence of diarrhoea with blood in the motion and with sigmoidoscopic evidence of inflammation **Failures**: failed to go into clinical remission within 6 weeks of corticosteroid treatment.	5mg four time/day and Prednisolone disodium retention enema nightly. If the response was good after a month's it was reduced. Inpatients: five day intensive course of IV therapy, nil by mouth except water, IV fluids, Prednisolone 40mg daily (IV), 1g tetracycline/day in divided doses, and rectal drip of hydrocortisone hemisuccinate sodium 100mg twice daily. Good clinical response, food and drink resumed and oral Prednisolone 40mg.			

Table 84: JIANG2004

Author	Patients	Intervention	Outcome measures	Effect size	Comments
X-L Jiang and H-F Cui Different therapy for different types of ulcerative colitis in China. *World Journal of Gastroenterology; 10 (10):1513-1520.2004.*	**All patients:** **N=42randomised** **Drop-outs** (don't complete the study): N=0 (0%)	**Group 1: Olsalazine(2g)** N=21 randomised Olsalazine sodium capsules (Tianjin Lisheng Pharmaceutical	Outcome 1: **Clinical and endoscopic remission** (subsidence of clinical symptoms with relative normal mucous membrane in colonoscopy)	**Group1:**16/21 **Group 2:**10/21	**Funding:** None described. **Limitations:** Unclear method of randomisation and allocation concealment.

Author	Patients	Intervention	Outcome measures	Effect size	Comments
REF ID: JIANG2004 **Study design and quality:** RCT **8 week trial** **Randomisation:** Randomly divided. **Allocation concealment**: Unclear **Blinding:** Unclear **Outcome assessment:** Colonoscopy: purulent secretion and pseudo polyp were classified into 2 grades. Ulcer, erosion, mucous bleeding, hyperaemic oedema and vascular blurring were classified into grade 0-4 based on severity (0 (none) to 4 (severe)) **Sample size calculation:** Not described. **Type of analysis: ITT** **Compliance rates:** Not described. N=0 dropout/ withdrawal due to drug related AEs.	**Inclusion criteria:** Chronic UC relapsers Extent: no inclusion criteria set. Severity: Unclear **Exclusion:** None described. **Overall the characteristics were:** **Sex:** 19 males, 23 females **Age (Mean):** 32.6 years **UC history (range):** 6 months to 5 years **Unclear extent.** Group 1: Olsalazine Severity: mild n=11, moderate n=8, severe n=2) Group 2: Sulphasalazine 4g Severity: mild n=13, moderate n=7, severe n=1)	Co. Ltd. 250mg) were used twice a day (1.0g/d) **Group 2: Sulphasalazine 4g/day** N=21 randomised Sulphasalazine 1g four times a day **Concomitant therapy:** For patients who could not tolerate diarrhoea of 2-3 times/day, 1-2 pills of Imodium was given daily but not more than 10 days. No other information given.	Outcome 2: **Clinical remission** (defecation 0-2 time/day, no gross blood or microscopic red cells in stool) Outcome 3: **Endoscopic remission** (among the 7 items, 5 or more lowered by a grade after treatment) Outcome 4: **Clinical improvement** (defecation 3-4 times per day with no gross blood in stool but less than 10 RBC per high power microscopic field) Adverse events were reported but it was unclear whether these were the number of events or the number of people who had an event. The results were as follows for olsalazine and sulphasalazine respectively: Abdominal discomfort (3, 15) Heartburn (1,7) Nausea (2,5) Frequency of watery diarrhoea (5,1) Increased ALT (0,1) Decreased WBC (0,1) Skin eruptions (0,2)	**Group1:**15/21 **Group 2:**10/21 **Group1:**11/21 **Group 2:**7/21 **Group1:**20/21 **Group 2:**15/21	Unclear blinding. Limited baseline characteristics. Unclear the extent of the disease. Indirect population: includes patients with severe disease (<10%) **Additional outcomes:** Histological remission and partial remission Endoscopic partial remission

Table 85: KAMM2007

Author	Patients	Intervention	Outcome measures	Effect size	Comments
M. A. Kamm et al. Once-Daily, High-Concentration MMX Mesalamine in Active Ulcerative Colitis. Gastroenterology; 132:66-75. 2007 **REF ID: KAMM2007** **Study design and quality:** Double blind, double-dummy, Phase III multicentre RCT Multicentre: 49 centres in the following countries: Germany, Spain, France, Poland, Hungary, Russia, Israel, Latvia, Lithuania, Estonia **8 week trial** **Randomisation:** centrally via an interactive voice response system. If the assigned treatment group is unavailable at the site on randomization (e.g. delay in medication arrival at the site), patients were allocated to the next treatment in the randomization (forced randomization) **Allocation concealment**: Yes as they were centrally randomised **Blinding:** Double blind (double dummy, no other information	**<u>All patients:</u>** **N=343randomised** (35 forced randomization) **N=341for ITT** (2 patients had +ve stool cultures) N=321 for PPA (N=20 protocol violations) **Drop-outs** (don't complete the study): N=79 (**23%)** (excludes the two removed after randomization for +ve stools). **Inclusion criteria:** ≥18 years Newly diagnosed or relapsing (relapsed ≤6 weeks prior to baseline) Active mild to moderate UC (4-10 on modified UC-DAI) Sigmoidoscopy score ≥1 PGA score≤2 Compatible histology During 3-7 day screening period patient was allowed to continue on a stable dose of mesalamine (≤2.0g/day) if they were on therapy prior to screening. If included in the study then this was withdrawn at baseline **Extent:**> 15cm from anal verge **Exclusion:** Severe UC (PGA score >2) Previously experienced an inadequate or failed response to steroids or	**All patients received 4 tablets and 2 capsules in the morning, 2 capsules at lunch, 2 capsules at dinner, taken with food.** **Group 1: 2.4g mezavant XL mesalamine** N=86 randomised N=84 (2 randomised in error) N=70 (completed the study) Mezavant XL mesalamine 2.4g/day given once daily (1.2g tablets) and placebo capsules/tablets **Group 2: 4.8g mezavant XL mesalamine** N=85 N=72 (completed the study) Mezavant XL mesalamine 4.8g/day given once daily (1.2g tablets) and placebo capsules/tablet	**Outcome 1:clinical and endoscopic remission** (modified UCDAI ≤1 with rectal bleeding and stool frequency of 0, no mucosal friability and ≥1 point reduction in sigmoidoscopy score from baseline) Outcome 2: **Clinical remission** (score of 0 points for stool frequency and rectal bleeding) Outcome 3: **Endoscopic remission** (Modified sigmoidoscopy score of ≤1 (with no mucosal friability) at week 8) Outcome 4: **Clinical improvement** (decrease of ≥3 points from baseline in the total modified UC-DAI score) Outcome 5: **Serious Adverse events**	Group 1: 34/84 Group2:35/85 Group3:28/86 Group4:19/86 Group 1:35/84 Group2:35/85 Group3:29/86 Group4:19/86 Group 1:58/84 Group2:66/85 Group3:53/86 Group4:40/86 Group 1:51/84 Group2:55/85 Group3:48/86 Group4:34/86 Group 1:1/84 Group2:0/85	**Funding:** Supported by Shire Pharmaceuticals **Limitations:** High dropout rate No further details on investigator blinding **Additional outcomes:** Changes in modified UC-DAI score Changes in sigmoidoscopic appearance Changes in rectal bleeding and stool frequency Analysis of treatment failure rate Comparison of the time to withdrawal

Author	Patients	Intervention	Outcome measures	Effect size	Comments
given on investigator blinding) **Outcome assessment:** modified UCDAI (rectal bleeding, stool frequency, mucosal appearance and PGA) **Sample size calculation:** 90% probability of detecting the improvement at the 5% significance level, 85 patients per arm **Type of analysis : ITT**(all patients randomised and received at least one dose of study medication) **and PPA** (all patients in the ITT who were not major protocol violators) Last observation carried forward **(LOCF)** N=4 dropout/ withdrawal due to AEs. None were thought to be drug related.	a mesalamine dose of >2.0g/day Current relapse lasting >6 weeks Relapsed while on maintenance therapy with doses of 5-ASA >2.0g/day Relapsed within 2 weeks of dose reduction from >2.0g/day to <2.0g/day Systemic or rectal steroids within the 4 weeks prior to baseline Immunosuppressant's within the previous 6 weeks Antibiotics within the previous 7 days Repeated treatment (>3 days of use at doses that exceed those available without prescription) with anti-inflammatory drugs within 7 days prior to baseline (with the exception of aspirin of prophylactic aspirin at doses of ≤325mg/day for cardiac disease) Extent only being proctitis (≤15cm from the anus) Previous colonic surgery Crohn's disease Bleeding disorders Active peptic ulcer Immediate or significant risk of toxic megacolon Positive stools for enteric pathogens Hypersensitivity to salicylates or aspirin Moderate to severe renal impairment **<u>Group 1: 2.4g mezavant XL mesalamine</u>** **Mean age (SD):**43.3 (13.30) **Extent:** 70.2% left sided, 8.3% transverse, 21.4% pancolitis **Diagnosis:** 13.1% new **Prior medication:** 2.4% corticosteroids, 1.2% immunomodulators	**Group 3: 2.4g Asacol** N=86 N=70 (completed the study) Delayed release mesalamine (Asacol) 2.4g given in three divided doses (400mg capsules) and placebo tablets **Group 4: Placebo** N=86 N=52 (completed the study) Placebo tablets and capsules **Concomitant therapy:** Patients were not allowed to take alternative UC treatment after the screening period. 13.2% of patients were taking ASAs and similar agents. All apart from 2 patients stopped them on day 1.		Group3:2/86 Group4:2/86	

Author	Patients	Intervention	Outcome measures	Effect size	Comments
	Drop outs:16 (11 due to lack of efficacy, 1 AE/SAEs, 1 patient request and other 3 patients) **Group 2: 4.8g mezavant XL mesalamine** **Mean age (SD):**44.6 (13.13) **Extent:** 78.8% left sided, 4.7% transverse, 16.5% pancolitis **Diagnosis:** 14.1% new **Prior medication:** 1.2% corticosteroids **Drop outs:**13 (11 due to lack of efficacy, 1 protocol violation, 1 patient request) **Group 3: Asacol 2.4g** **Mean age (SD):**41.9 (13.34) **Extent:** 80.2% left sided, 2.3% transverse, 17.4% pancolitis **Diagnosis:** 15.1% new **Prior medication:** 2.3% corticosteroids **Drop outs:**16 (10 due to lack of efficacy, 1 AE/SAEs, 2 patient request, 1 other, 1 protocol violation, 1 lost to follow up) **Group 4: Placebo** **Mean age (SD):**43.2 (14.06) **Extent:** 73.3% left sided, 7.0% transverse, 19.8% pancolitis **Diagnosis:** 11.6% new **Prior medication:** 1.2% corticosteroids **Drop outs:**34 (24 due to lack of efficacy, 2 due to AEs/SAEs, 6 patient request and 2 other) No data given for % mild and % moderate severity, but it is mentioned in the paper that approximately 2/3 of the patients in each arm had moderate severity disease.				

Table 86: KAMM2008

Author	Patients	Intervention	Outcome measures	Effect size	Comments
M. A. Kamm et al. Randomised trial of once- or twice-daily MMX mesalazine for	**All patients:** **N=459 randomised**	**Group 1: mezavant XL once a day (2.4g)** N=225 randomised	**Outcome 1: Relapse** by 12 months (inverse of the proportion of patients who had not	**PPA is used to remove those not meeting the**	**Funding:** Authors had funding or worked for Shire Pharmaceuticals. Statistical

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maintenance of remission in ulcerative colitis. *Gut; 57: 893-902. 2008.* **REF ID: KAMM2008** **Study design and quality:** Open RCT Multicentre: 101 centres, 19 countries (Australia, Czech Republic, Estonia, France, Germany, Hungary, India, Israel, Latvia, Lithuania, Mexico, including Costa Rica, New Zealand, Poland, Romania, Russia, Spain, Ukraine and the USA. **12 month trial** **Randomisation:** Interactive voice recognition system **Allocation concealment**: Adequate. **Blinding:** Open study. **Outcome assessment:** 3 monthly visits. Physical examination, laboratory tests, sigmoidoscopy (only final review), symptoms assessment, PGA (only final review), drug compliance, AE review, concomitant medication review. UCDAI, PGA. **Sample size calculation:** None done as it depended on the number in clinical and	**Drop-outs** (don't complete the study): N=53 (11.5%) **Inclusion criteria:** • Male and female patients • Following the induction of remission after an acute flare of mild to moderate UC • Enrolled directly following up to 8 weeks' treatment for acute disease in the studies by Lichtenstein et al. and Kamm et al, or following a further 8 week extension, study 303. • Clinical and endoscopic remission (UCDAI score of≤1), with rectal bleeding an stool frequency scores of 0, a combined PGA and sigmoidoscopy score of ≤1, no mucosal friability and an additional requirement for a ≥1 point reduction from baseline in sigmoidoscopy score) • **Although not defined in the protocol, some additional patients who were not in strictly defined remission (as above) but deemed by their doctor to be well enough at the end of the parent studies or 8 week extension could enter the randomised maintenance phase of study 303** • Satisfactory medical assessment, with no clinically relevant abnormality other than UC **Exclusion:** • None described. **<u>Group 1: 2.4g mezavant XL mesalazine once a day</u>** **Mean age (SD):** 42.4 (12.1) **Diagnosis:** newly diagnosed n=32, history of UC n=193 **Mean time since diagnosis (SD):** 244.5 (314.1) weeks **Relapses in the last 2 years:** 0-2 n=135, 3-6 n=76, ≥7 n=4, missing n=10 **Extent:** left sided n=175, upper limit in the transverse colon n=14, pancolitis n=36 **Treatment received in parent study:** placebo n=57, mezavant XL 2.4g/day n=68, mezavant XL 4.8g/day n=72, Asacol n=28 **Severity of previous relapse:** Not described **Drop outs:** 26 (AE/SAEs n=11, other n=8, patient request n=2, lost to follow-up n=3, non compliance n=1, protocol violation n=1)	N=219 (efficacy population) 6 patients excluded due to study centre Good Clinical Practice non-compliance. N=171 (PPA) N=182 (completers) 2x 1.2g mezavant XL mesalazine taken once a day. **Group 2: mezavant XL twice a day (2.4g)** N=234 randomised N=232 (efficacy population) 2 patients excluded due to study centre Good Clinical Practice non-compliance. N=191 (PPA) N=195 (completers) 1.2g mezavant XL mesalazine taken twice a day. **Concomitant therapy:** The following were not permitted: Corticosteroids (systemic or rectal), other formulations	relapsed at 12 months) n values are calculated from the percentages who had not relapsed at 12 months figures reported in the paper. **Outcome 2: Adverse events** Most frequent were GI disorders. **Outcome 3: Serious adverse events** 18 patients experienced 22 SAEs. Group 1: 1 patient had abnormal LFTs which were thought to be possibly treatment related. They had a positive test for infectious mononucleosis. 5 due to UC, 1 chronic hepatitis, 1 abnormal liver function test, 1 cerebral infarction, 1 menometrorrhagia, 1 ovarian cyst. Group 2: Due to 1 angina pectoris, 1 pulmonary oedema, 4 due to UC, 1 lung abscess, 2 pneumonia,	**strict inclusion criteria.** **Group1:** 19/171 **Group 2:** 14/191 **Group1:** 88/225 **Group 2:** 86/234 **Group1:** 9/225 **Group 2:** 9/234	analyses performed by Quintiles. **Limitations:** Open study Inclusion of patients not in the strict clinical and endoscopic remission **Additional outcomes:** Separate remission rates for those in who had gone into remission by 8 weeks and those by 16 weeks.

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endoscopic remission from the previous trials. **Type of analysis: Efficacy and PPA** **Compliance rates:** ≥80% of their prescribed study medication. Calculated by pill count. Compliance was 93.3% in group 1, 99.6% in group 2. N=21 dropout/ withdrawal due to AEs.	**Group 2: 2.4g mezavant XL mesalazine twice a day** **Mean age (SD):** 42.6 (13.2) **Diagnosis:** newly diagnosed n=34, history of UC n=200 **Mean time since diagnosis (SD):** 244.5 (314.1) weeks **Relapses in the last 2 years:** 0-2 n=144, 3-6 n=82, ≥7 n=5, missing n=3 **Extent:** left sided n=179, upper limit in the transverse colon n=14, pancolitis n=40 **Treatment received in parent study:** placebo n=61, mezavant XL 2.4g/day n=67, mezavant XL 4.8g/day n=70, Asacol n=36 **Severity of previous relapse:** Not described **Drop outs:** 27 (AE/SAEs n=9, other n=5, patient request n=10, lost to follow-up n=1, protocol violation n=1, death n=1 (due to an electric shock)) **Definitions** **Remission:** Clinical and endoscopic remission (UCDAI score of≤1), with rectal bleeding an stool frequency scores of 0, a combined PGA and sigmoidoscopy score of ≤1, no mucosal friability and an additional requirement for a ≥1 point reduction from baseline in sigmoidoscopy score) **Relapse:** A requirement for alternative treatment for UC, including surgery or an increase in the dose of mezavant XL mesalazine above 2.4g/day.	containing 5-ASA, or immunosuppressants.	1 electric shock, 1 aggravated depression, 1 COPD exacerbation.		

Table 87: KANE2003

Author	Patients	Intervention	Outcome measures	Effect size	Comments
S. Kane et al. A Pilot Feasibility Study of Once Daily Versus Conventional Dosing Mesalamine for Maintenance of Ulcerative Colitis. *Clinical Gastroenterology and Hepatology; 1: 170-173. 2003.* **REF ID: KANE2003**	**All patients:** **N=22 randomised** **Drop-outs** (don't complete the study): N=0 (0%) **Inclusion criteria:** • Documented diagnosis of Ulcerative Colitis • In clinical remission (definition below) for at least 4 months before	Patients took the same dose as before study entry. **Group 1: Once a day mesalamine** N=12 randomised Once a day regimen of mesalamine.	**Outcome 1: Relapse** at 6 months Patient in Group 1 had stopped taking the medication at week 16. Patient in Group 2 took 55% of prescribed regimen and flared after 20 weeks.	**Group1:** 1/12 **Group 2:** 1/10	**Funding:** Supported by a grant from Procter & Gamble Pharmaceuticals and the David and Reva Logan Center for Gastrointestinal Research. **Limitations:** Single blind

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Study design and quality: Pilot RCT United States **6 month trial** **Randomisation:** Random numbers table. **Allocation concealment**: Card in a sealed, opaque envelope given to each patient **Blinding:** Single blind (patients were instructed to follow the dosing instructions on his/her card and not discuss the regimen with their investigators or affiliated personnel. **Outcome assessment:** UCDAI. **Sample size calculation:** Not described. **Type of analysis: ITT** **Compliance rates:** Adherence was calculated using a validated formula. Adherence is >80% of medication taken. 100% for once a day, 70% for >once a day at 3 months and 75% and 70% at 6 months. N=0 dropout/ withdrawal due to drug related AEs.	entry into the study • Receiving mesalamine for maintenance of quiescent disease **Exclusion:** • Documented disease activity in the past 4 months • hospitalisation or steroid therapy for disease activity in the previous 4 months • Use of other immunomodulating drugs to maintain remission • History of other diarrheal illnesses, such as diarrhoea-predominant irritable bowel syndrome and C.Difficile colitis • Using known ant-diarrhoeal drugs **Group 1: Once a day** **Mean age (SD):** 46.2 (13.4) **Mean dose (SD):** 2.5 (0.9) **Time in remission (months):** 10.1 (3.0) **Sex:** male n=2, female n=10 **Extent:** Not described **Severity of previous relapse:** Not described **Frequency of relapses:** Not described **Drop outs:** 0 **Group 2: > once a day** **Mean age (SD):** 37.3 (15.5) **Mean dose (SD):** 2.7 (0.8) **Time in remission (months):** 9.6 (3.7) **Sex:** male n=2, female n=8 **Extent:** Not described **Severity of previous relapse:** Not described **Frequency of relapses:** Not described **Drop outs:** 0 **Definitions** **Remission:** Absence of blood in the stools, urgency or cramping. **Relapse:** >3 on the Harvey-Bradshaw index.	**Group 2: More than once a day mesalamine** N=10 randomised Continued conventional dosing which constituted a twice or three times a day dosing regimen. 3 took mesalamine 3 times a day and 7 took mesalamine twice a day. **Concomitant therapy:** See inclusion/ exclusion criteria. KANE2008 described the mesalamine used in KANE2003 to be Asacol.	Unable to calculate the hazard ratio.		Limited baseline characteristics No extent data at baseline **Additional outcomes:** Patient satisfaction

Table 88: KANE2008

Author	Patients	Intervention	Outcome measures	Effect size	Comments
S. Kane et al. Once daily versus conventional dosing of pH-dependent mesalamine long-term to maintain quiescent ulcerative colitis: Preliminary results from a randomized trial. **REF ID: KANE2008** **Study design and quality:** Single blind RCT **1 year trial** **Randomisation:** Computer generated randomization table assignment **Allocation concealment**: Opaque sealed envelopes **Blinding:** Single blind. Subjects were instructed to conceal their regimen from all research investigators. **Outcome assessment:** 3 monthly telephone contacts. UCDAI. 6 monthly clinic visits. **Sample size calculation:** 15% true difference, 90% power, 53 patients needed. To take account of drop outs 70 per arm. **Type of analysis: ITT**	**All patients:** **N=20 randomised** (recruitment was stopped early because the sponsoring company wanted to proceed with a larger, multicenter study of the once daily long term maintenance) **Drop-outs** (don't complete the study): N=1 (5%) **Inclusion criteria:** • Adult patients over 18 years of age • Documentation of ulcerative colitis by standard criteria • Remission for at least 4 months before study entry • Patients must have been prescribed mesalamine (Asacol®) to maintain quiescent disease **Exclusion:** • Documented disease activity in the last 4 months • Hospitalisation or steroid use for disease activity in the previous 4 months • use of other preparation of 5-aminosalicylates to treat UC • Use of other immunomodulators to induce remission • history of other diarrheal illnesses such as diarrhoea predominant Irritable Bowel Syndrome or C. Difficile colitis • Using known diarrheal drugs • Those found to be taking g<80% of prescribed doses (checked by the pharmacists) **Group 1: Once a day** **Median age (range):** 44 (22-67) **Median length of disease (range):** 6 (2-25) **Extent:** pancolitis n=9, left sided n=2, proctitis n=1 **Average dose at enrolment (range):** 2.4g (1.6-3.2g) **Severity of previous relapse:** Not described. **Frequency of relapses:** Not described. **Drop outs:** 1 (due to death from myocardial infarction)	**All patients took the same dose as they were taking prior to the trial which ranged from 1.6g to 3.2g of mesalamine (Asacol).** **Group 1: Once a day** N=12 randomised Once a day mesalamine (Asacol) **Group 2: More than once a day** N=8 randomised All of the patients in this group previously took their treatment twice a day, so they continued doing so. Mesalamine was Asacol. **Concomitant therapy:** See inclusion/ exclusion criteria.	**Outcome 1: Relapse** by 12 months Unable to calculate the hazard ratio	**Group1:** 6/12 **Group 2:** 5/8	**Funding:** Proctor and Gamble Pharmaceutical grant. **Limitations:** Single blind **Additional outcomes:** Mortality **Notes:** Median time to relapse (range) was 8 months (3-11 months).

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Compliance rates: Monitored by the pharmacists and they used a validated formula. Only 42% were adherent in group 1 and 37.5% in group 2. N=0 dropout/ withdrawal due to drug related AEs.	**Group 2: More than once a day** **Median age (range):** 42 (27-58) **Median length of disease (range):** 6 (3-27) **Extent:** pancolitis n=6, left sided n=2, proctitis n=0 **Average dose at enrolment (range):** 2.4g (1.6-3.2g) **Severity of previous relapse:** Not described. **Frequency of relapses:** Not described. **Drop outs:** 0 **Definitions** **Remission:** Absence of blood in the stools, urgency or cramping. UCDAI score <3. **Relapse:** UCDAI score >3 or an increase of more than 3 points during the preceding time interval.				

Table 89: KIILERICH1992

Author	Patients	Intervention	Outcome measures	Effect size	Comments
S. Kiilerich et al. Prophylactic effects of olsalazine v sulphasalazine during 12 months maintenance treatment of ulcerative colitis. *Gut; 33: 252-255. 1992.* **REF ID: KIILERICH1992** **Study design and quality:** Double blind, double dummy RCT Multicentre: 12 centres, Denmark **12 month trial** **Randomisation:** Computer generated, stratified for each	**All patients:** **N=227 randomised** **N=223 ITT** (they excluded 1 patient due to not fulfilling the inclusion criteria, and 3 patients which were lost to follow up) **N=197 (PPA)** (15 withdrew due to AEs, 2 intercurrent unrelated disease (acute appendicitis and cancer of the colon), 9 non compliance (4 olsalazine, 5 SASP), 1 incomplete case form) **Drop-outs** (don't complete the study): N=30 (13.2%) (See reasons above). <10% difference in missing data between the treatment arms. **Inclusion criteria:** • Medical history of at least two attacks of UC • 18-80 years old • In remission (for the definition see below)	**Group 1: Olsalazine 1g** N=114 randomised N=113 (ITT) N=98 (PPA) 500mg of olsalazine twice a day, taken with meals. Enteric coated. **Group 2: Sulphasalazine 2g** N=112 randomised N=110 (ITT) N=99 (PPA) 1g sulphasalazine twice	**Outcome 1: Relapse** rate (PPA) Life table, cumulative relapse rate, p=0.54 for ITT analysis (so unable to use it to calculate the hazard ratio using the PPA figures. Unclear how many relapses in the ITT analysis). Diagram of the life table is presented in the paper.	**PPA** **Group1:** 46/98 **Group 2:** 42/99	**Funding:** Financial support from Kabi Pharmacia Therapeutics. **Limitations:** Stated to be double blind, double dummy but there is no description of it. **Additional outcomes:** Frequency of relapse comparison (olsalazine and SASP patients combined) in relation to number of active periods Remission

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centre and performed in blocks of four consecutive patients within the centre. **Allocation concealment**: Adequate as central randomisation. **Blinding:** Double blind, double dummy but no further information was given. **Outcome assessment:** Clinical, endoscopic and blood tests at entry, 6 months, 12 months or exit from the study. **Sample size calculation:** 20% relapse rate for SASP. Power 80%, 5% significance, 83 patients per arm. **Type of analysis: ITT and PPA** **Compliance rates:** At each visit the number of tablets consumed was questioned. N=15 dropout/ withdrawal due to AEs. 9 in the olsalazine group (5 diarrhoea, 1 loose stools, 1 abdo pain, 2 constipation) and 6 in the SASP group (2 diarrhoea, 1 urticaria, 1 nausea, 2 dyspepsia).	**Exclusion:** • Hypersensitivity to sulphonamides or salicylates • Pregnant or were planning pregnancy within a year • Received cystostatic or corticosteroid treatment within the last month before entry **NB. Patients who previously were found intolerant of sulphasalazine were excluded.** **<u>Group 1: 1g Olsalazine</u>** **Mean age (range):** 41.4 (20-79) **Mean duration of UC, years (range):** 9.1 (0.3-37) **Extent:** proctitis n=59, proctocolitis n=54 **Number of active periods before entry:** 2 n=25, >2 n=89 **Mean duration of remission, months (range):** 15 (6-321) **SASP on entry:** n=91 **Severity of previous relapse:** Not described **Drop outs:** 15 (9 due to AEs, 6 other reasons (see drop out rate above)) **<u>Group 2: 2g Sulphasalazine</u>** **Mean age (range):** 39.6 (18-75) **Mean duration of UC, years (range):** 8.4 (0.4-38) **Extent:** proctitis n=55, proctocolitis n=57 **Number of active periods before entry:** 2 n=30, >2 n=82 **Mean duration of remission, months (range):** 11 (2-152) **SASP on entry:** n=91 **Severity of previous relapse:** Not described **Drop outs:** 11 (6 due to AEs, 5 other reasons (see drop out rate above)) **<u>Definitions</u>** **Remission:** No visible blood in the stools for more than three days within the last week and/or less than three stools per day for at least four days of the last week and sigmoidoscopy grade 1-2 at admission (no spontaneous bleeding without or with distinct vessels in the mucosa). **Relapse:** Inflammation of the rectal mucosa grade 3-4 on sigmoidoscopy (no distinct vessels in the mucosa, spontaneous bleeding and bleeding by contact with the sigmoidoscope).	a day, taken with meals. **Concomitant therapy:** Not described.			**Notes:** The study describes no relation between relapse frequency and the extent of disease or of a remission period of more or less than three months. No data was provided. **Majority of the patients were on SASP at entry.**

Table 90: KRUIS1995

Author	Patients	Intervention	Outcome measures	Effect size	Comments
W. Kruis et al. Double-blind dose-finding study of olsalazine versus sulphasalazine as maintenance therapy for ulcerative colitis. *European Journal of Gastroenterology and Hepatology; 7 (5): 391-396. 1995.* **REF ID: KRUIS1995** **Study design and quality:** Double blind RCT Multicentre: 15 centres, public hospitals and private practices in Germany, Austria and Switzerland **6 month trial** **Randomisation:** Computer generated randomization in blocks of eight and stratified for each centre. **Allocation concealment**: Unclear **Blinding:** Double blind. Capsules were all similar size, colour and weight. **Outcome assessment:** Recorded abdo pain, frequency and consistency of stools, blood and mucus in stools.	**All patients:** **N=162 randomised** **N=148 (failure rate analysis)** 14 were excluded due to; 5 having active disease at the beginning of the study, 7 with no data recorded after inclusion and 2 in whom remission was not confirmed correctly at entry. **N=109 (PPA)** **Drop-outs** (don't complete the study): N=28 (17.3%) (14 excluded from analysis (see above) and 14 withdrawn (6 due to AEs, 4 lack of compliance, 3 lost to follow-up, 1 myocardial infarction). It is unclear which treatment groups had which withdrawals. >10% difference in missing data between Group2 and Group 4 **Inclusion criteria:** • Diagnosis made in previous active disease episode by endoscopy and histology **Exclusion:** • Infectious disease • Acute ulcerative Colitis • Remission for longer than 12 months • Hypersensitivity to olsalazine, SASP, salicylates or sulphonamides • Existing or planned pregnancy • Chronic intake of corticosteroids, antibiotics or salicylates • Significant disorders other than ulcerative colitis. **Group 1: 0.5g Olsalazine** **Mean age (range):** 41 (20-68) **Duration of UC months (range):** 59 (2-252) **Extent:** proctitis n=2, proctosigmoiditis n=14, left-sided n=19, subtotal/total n=8	The treatment was gradually increased over 5 days: Day 1 & 2: 1 capsule twice daily Days 3 &4: 2 capsules twice daily Day 5 onwards: 2 capsules three times a day **Group 1: 0.5g olsalazine** N=43 randomised N=39 (failure rate analysis) Each capsule contained 83mg of olsalazine. **Group 2: 1.25g olsalazine** N=40 randomised N=35 (failure rate analysis) Each capsule contained 208mg of olsalazine. **Group 3: 2g olsalazine** N=35 randomised N=34 (failure rate	**Outcome 1: Relapse** at 6 months Unable to calculate the hazard ratio. Group 1 results have not been used in the analysis as it is lower than the BNF dose for olsalazine for the maintenance of remission. **Outcome 2: Adverse events** Group 1 results have not been used in the analysis as it is lower than the BNF dose for olsalazine for the maintenance of remission. Group 2: Two due to diarrhoea (both withdrew) and one headache Group 3: 4 due to diarrhoea, 1 heartache/ back pain (patient withdrew), 1 due to loss of libido/ potency Group 4: 2 due to rash/ urticaria (1 patient withdrew), 1 due to	**Failure rate/ author reported analysis** **Group 1:** 9/39 **Group 2:** 13/35 **Group 3:** 5/34 **Group 4:** 11/40 **Failure rate/ author reported analysis** **Group 1:** 2/39 **Group 2:** 3/35 **Group 3:** 6/34 **Group 4:** 4/40	**Funding:** Sponsored by Kabi Pharmacia Therapeutics, Sweden and Germany **Limitations:** Unclear allocation concealment States to be double blind. No information given on physician blinding. >10% difference in missing data between some of the treatment arms **Additional outcomes:** None **Notes:** Differences between all the curves of the treatment groups in the life table (failure rate analysis) were not statistically significant (P=0.11).

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Endoscopic assessment was according to Truelove & Richards. **Sample size calculation:** 35% difference in relapse rates between 0.5 and 2g of olsalazine, 80% power, 5% significance level, 20% drop out rate, 40 patients needed per treatment arm. **Type of analysis: ITT and PPA** **Compliance rates:** 4 patients had poor compliance. It is unclear as to which treatment arm they belonged to. N=6 dropout/ withdrawal due to AEs. It is unclear whether they were drug related. 2 in 0.5g, 2 in 1.25g (due to diarrhoea) and 1 in each of the other treatment groups (rash/urticaria and heartache/back pain)..	**Severity of previous relapse:** mild n=6, moderate n=27, severe n=10 **Previous relapses, n (range):** 4 (0-18) **Duration of remission, weeks (range):** 11(1-52) **Drop outs:** 10(5 patients excluded from failure rate analysis, 5 withdrawals (2 due to AEs)) **Group 2: 1.25g olsalazine** **Mean age (range):** 45 (22-77) **Duration of UC months (range):** 57 (0-300) **Extent:** proctitis n=3, proctosigmoiditis n=19, left-sided n=10, subtotal/total n=8 **Severity of previous relapse:** mild n=3, moderate n=30, severe n=7 **Previous relapses, n (range): 3** (0-10) **Duration of remission, weeks (range):** 13(0-52) **Drop outs:** 9 (5 patients excluded from failure rate analysis,4 withdrawals (2 were AEs)) **Group 3: 2.0g olsalazine** **Mean age (range):** 40 (16-72) **Duration of UC months (range):** 101(1-252) **Extent:** proctitis n=5, proctosigmoiditis n=12, left-sided n=10, subtotal/total n=8 **Severity of previous relapse:** mild n=7, moderate n=22, severe n=6 **Previous relapses, n (range):** 4 (0-18) **Duration of remission, weeks (range):** 14(2-52) **Drop outs:** 5 (2 patients excluded from failure rate analysis, 3 withdrawals (1 due to AEs)) **Group 4: 2g sulphasalazine** **Mean age (range):** 40 (15-76) **Duration of UC months (range):** 46 (3-132) **Extent:** proctitis n=3, proctosigmoiditis n=14, left-sided n=15, subtotal/total n=10 **Severity of previous relapse:** mild n=4, moderate n=32, severe n=6 **Previous relapses, n (range):** 3 (0-10) **Duration of remission, weeks (range):** 14(1-96) **Drop outs:** 4 (2 patients excluded from failure rate analysis, 2 withdrawals (1 due to AEs)) **Definitions** **Remission:** Required normal endoscopic grading. **Relapse:** Patients with a change in their normal endoscopic grading to	analysis) Each capsule contained 333mg of olsalazine. **Group 4: 2g sulphasalazine** N=42 randomised N=40 (failure rate analysis) Each capsule contained 333mg of sulphasalazine. **Concomitant therapy:** None was permitted.	being uncomfortable and 1 due to meteorism. **Relapse at 6 months by extent of disease** Unable to calculate the hazard ratio.	**Failure rate/ author reported analysis** **Proctitis and proctosigmoiditis** **Group 1:** 1/9 **Group 2:** 4/13 **Group 3:** 3/11 **Group 4:** 4/13 **Extended (left sided and more)** **Group 1:** 4/19 **Group 2:** 4/13 **Group 3:** 0/13 **Group 4:** 3/18	

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	at least moderate activity.				

Table 91: KRUIS2001

Author	Patients	Intervention	Outcome measures	Effect size	Comments
W. Kruis et al. Low dose balsalazide (1.5g twice daily) and mesalazine (0.5g three times daily) maintained remission of ulcerative colitis but high dose balsalazide (3.0g twice daily) was superior in preventing relapses. *Gut; 49: 783-789. 2001.* **REF ID: KRUIS2001** **Study design and quality:** Double blind, double dummy RCT Multicentre: 21 centres, Germany **26 week trial** **Randomisation:** Not described. Unclear. **Allocation concealment**: Unclear. **Blinding:** Double blind. No further information given.	**<u>All patients:</u>** **N=133 randomised** **N=132 ITT** (one patient received no treatment) **N=92 completers** **Drop-outs** (don't complete the study): N=42 (31.6%) Excluding insufficient efficacy: N=20 (15%) >10% difference in missing data between treatment arms 2 and 3. **Inclusion criteria:** • Extent: UC involving at least the rectum and sigmoid colon • At least two acute attacks of UC in the medical history • Clinical and endoscopic remission • Aged 18-70 years **Exclusion:** • Proctitis without further extent of the disease • Treatment with oral, IV, or rectal steroids within 14 days prior to visit 1 • Use of antibiotics within 14 days prior to visit 1 except for short term therapy of a defined infection • Immunosuppressive therapy within the last three months • Regular treatment with NSAIDs • Intolerance of 5-ASA	**Group 1: 3g Balsalazide** N=49 randomised N=48 (ITT) N=42 (PPA) 1.5g balsalazide twice a day. Total dose 3g/day. 750mg capsules of balsalazide. Placebo capsules and tablets. Equivalent to 1.05g 5-ASA per day. **Group 2: 6g Balsalazide** N=40 randomised N=40 (ITT) N=38 (PPA) 3.0g balsalazide given twice day. Total dose 6g/day. 750mg capsules of balsalazide. Placebo tablets. Equivalent to 2.10g 5-ASA per day.	**Outcome 1: Relapse** at 26 weeks Log rank test for the time to relapse was p=0.01 for the three groups. A log rank p value was not given for each curve comparison, therefore the HR could not be calculated. **Outcome 2: Adverse events** N values were calculated from the percentages given in the paper.	**Group 1:** 13/48 **Group 2:** 3/40 **Group 3:** 6/44 **Group 1:** 18/48 **Group 2:** 21/40 **Group 3:** 20/44	**Funding:** Supported by Astra Zeneca GmbH, Germany. **Limitations:** >10% difference in missing data for treatment group 2 vs. 3 Unclear method of randomisation and allocation concealment Double blind but no further information was given. **Additional outcomes:** CAI, EI and histological score comparisons Urine data **Notes:** Pairwise contrasts between the two balsalazide doses p=0.003. Not significant between the high dose

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Outcome assessment: CAI and endoscopy assessment according to Rachmilewitz. Histology according to Truelove & Richards. Laboratory and urine assessments. Diary cards. **Sample size calculation:** 25% difference in remission rates, 90% power, 5% significance, 62 patients per arm. **Type of analysis: ITT. Last value extended principle was used for symptom assessment provided the patient had at least one assessment after entry.** **Compliance rates:** Patients were asked to return investigational drugs and the amount of drug remaining at each clinic visit was assessed. N=9 dropout/ withdrawal due to drug related AEs.	**Group 1: 3g Balsalazide** **Mean age (SD):** Not described. **Mean duration of UC symptoms, years (range):** 8.5 (0-36) **Mean time in remission, months (range):** 2.4 (0-10) **Mean No. of previous UC attacks (range):** 6.6 (2-20) **5-ASA use prior to the study:** n=22 **Mean CAI score (range):**1.1 (0-7) **Mean EI score (range):**2.0 (0-8) **Extent:** proctosigmoiditis n=10 , left sided n=19 , subtotal n=9 , total n=10 **Severity of previous relapse:** Not described. **Drop outs:** 21 (3 due to AEs (more than one event per patient; headache, hypertension, malaise, dizziness, abdominal pain, pruritus and skin rash), 1 due to lost to follow up, 13 insufficient efficacy, 4 other) **Group 2: 6g Balsalazide** **Mean age (SD):** Not described. **Mean duration of UC symptoms, years (range):**8.4 (0-29) **Mean time in remission, months (range):**2.4 (0-9) **Mean No. of previous UC attacks (range):**7.7 (2-26) **5-ASA use prior to the study:** n=19 **Mean CAI score (range):** 1.2 (0-4) **Mean EI score (range):**1.9 (0-8) **Extent:** proctosigmoiditis n=12 , left sided n=11 , subtotal n=6 , total n=11 **Severity of previous relapse:** Not described. **Drop outs:** 6 (2 due to AEs (pancreatitis, gingivitis, alopecia and nail disorders), 3 due to insufficient efficacy, 1 due to other) **Group 3: 1.5g Mesalazine** **Mean age (SD):** Not described. **Mean duration of UC symptoms, years (range):**6.7 (0-32) **Mean time in remission, months (range):** 2.3 (0-10) **Mean No. of previous UC attacks (range):** 7.2 (2-20) **5-ASA use prior to the study:** n=23 **Mean CAI score (range):**1.1 (0-5) **Mean EI score (range):**1.6 (0-8) **Extent:** proctosigmoiditis n=12 , left sided n=13 , subtotal n=10 , total n=9 **Severity of previous relapse:** Not described.	**Group 3: 1.5g Mesalazine** N=44 randomised N=44 (ITT) N=40 (PPA) 500mg mesalazine given three times a day. Total dose 1.5g/day. 500mg tablets (Salofalk). Placebo capsules. Equivalent to 1.5g 5-ASA per day. **Concomitant therapy:** No UC medication allowed other than the respective study preparations throughout the trial.			balsalazide and mesalazine group. Conclusions for the PPA time to relapse was said to be the same at the ITT.

Author	Patients	Intervention	Outcome measures	Effect size	Comments
	Drop outs: 15 (4 due to AEs (palpitation, hypotension, tenesmus, nausea, impotence, diarrhoea and alopecia), 1 lost to follow up, 6 insufficient efficacy,4 other) **Definitions** **Clinical remission:** CAI<6 **Endoscopic remission:** EI<4 **Remission of UC:** Both clinical and endoscopic remission **Relapse:** CAI≥6 and EI>4 at completion of the study.				

Table 92: KRUIS2003

Author	Patients	Intervention	Outcome measures	Effect size	Comments
W. Kruis et al. The Optimal Dose of 5-Aminosalicylic Acid in Active Ulcerative Colitis: A Dose-Finding Study With Newly Developed Mesalamine. *Clinical Gastroenterology and Hepatology; 1: 36-43. 2003.* **REF ID: KRUIS2003** Double blind RCT **Study design and quality:** Multicentre (60 hospitals and private practices), Austria, Germany, Hungary and Israel **8 week trial** **Randomisation:** Consecutive assignment to treatment groups by randomization procedure- no further information	**All patients:** **321=randomised** **N=316 ITT**(4 patients were incorrectly diagnosed and 1 patient was included twice) **N=137 (PPA)** **Drop-outs** (don't complete the study): N=80 (24.9%) Of which: N=34 (1.5g treatment group) N=22 (3.0g treatment group) N=24 (4.5g treatment group) **Inclusion criteria:** 18-70 years old Extent: Proctosigmoiditis, left-sided, subtotal/total Severity: Mild to moderate UC (CAI =6-12; EI≥4) ≥1 episode or persistently bloody diarrhoea at least 14 days prior to study start	**Group 1: 1.5g mesalazine pellets (Salofalk)** 104= randomised N=103 (ITT) N=35 (PPA) N=70 (completers) 0.5g mesalamine containing pellets, three times a day (**total1.5g**) Pellets had a Eudragit-L coating to dissolve at a pH>6.0. **Group 2: 3.0g mesalazine pellets (Salofalk)** 108 =randomised N=107 (ITT) N=53 (PPA) N=86 (completers)	Outcome 1: **Clinical remission** (CAI according to Rachmilewitz ≤4) Outcome 2: **Clinical improvement** (CAI decreased by at least 3 points) Outcome 3: **Adverse events** The most frequent adverse event reported in each group was headache. There were 14 SAE's in 12 patients; this includes 7 patients which were hospitalized due to deterioration of UC (it is unclear whether	**Group 1:** 52/103 (50%) **Group 2**:71/107(66%) **Group 3:**58/106(55%) **Group 1:**66/103 **Group 2:**80/107(75%) **Group 3:**70/106(66%) **Group1:**64/102(63%) **Group 2:**66/108(61%) **Group 3:** 63/108(58%)	**Funding:** Supported by Dr. Falk Pharma GmbH, Germany **Limitations:** Unclear method of randomisation and allocation concealment Selective outcome reporting – no data for endoscopic remission High and unclear dropout rate **Additional outcomes:** Probability of not entering remission against the time of treatment Endoscopy improvement Histology improvement

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Allocation concealment: No information on allocation concealment **Blinding:** Double blind Pellets were mixed in with placebo pellets to ensure double blindness. **Outcome assessment:** CAI and EI **Sample size calculation:** Sample size: 1 tailed test, 5% significance and 80% power assuming an 18% difference in remission rates, 105 patients were needed in each arm **Type of analysis: ITT[q] and PPA[r] analysis.** Last observation carried forward was used **Compliance rates:**75 failed to complete study (24% drop out rate) N=27 dropout/ withdrawal due to AEs. It is unclear whether these are drug related. (11 in the 1.5g group, 7 in the 3.0g and 9 in the 4.5g group). The most frequent reason was due	**Exclusion:** Pathogens in the initial microbiologic stool examination Proctitis with an extent of <15cm Pre-treatment with oral/rectal steroids on >3 days in the week before the baseline evaluation Immunosuppressant's in the last 4 weeks before Permanent oral therapy with mesalamine >2g/day in the 2 weeks prior to trial start date Known intolerance to salicylates **<u>Group 1: 1.5g mesalazine pellets (Salofalk)</u>** **Median age (range):** 39 (20-69) **Extent:**57% Proctosigmoiditis, 26% left-sided, 16% subtotal/total, 1% unknown **Duration of disease yrs (SD):** 7.2 (8.1) **CAI mean (SD)**: 7.8 (1.6) **Drop outs:** n=33 (11 due to AEs) **<u>Group 2: 3.0g mesalazine pellets (Salofalk</u>** **Median age (range):**40 (18-75) **Extent:**37% Proctosigmoiditis, 41% left-sided, 21% subtotal/total, 1% unknown **Duration of disease yrs (SD):** 7.7 (7.4) **CAI mean (SD)**: 8.2 (1.7) **Drop outs:** n=21 (7 due to AEs) **<u>Group 3: 4.5g mesalazine pellets (Salofalk)</u>** **Median age (range):**41.5 (19-69) **Extent:**44% Proctosigmoiditis, 33% left-sided, 23% subtotal/total, 0% unknown	1.0g mesalamine containing pellets, three times a day (**total 3.0g**) Pellets had a Eudragit-L coating to dissolve at a pH>6.0. **Group 3: 4.5g mesalazine pellets (Salofalk)** N=109 randomised N=106 (ITT) N=49 (PPA) N=85 (completers) **Intervention details** 1.5g mesalamine containing pellets, three times a day (**total 4.5g**) Pellets had a Eudragit-L coating to dissolve at a pH>6.0. To ensure blindness there was the same number of pellets in each sachets, some were placebo and some were active mesalazine.	there were more). There other SAEs were: elective non intestinal operation (2 patients), deafness, haemolytic anaemia and pneumonia (1 patient each). The paper did not report which treatment groups they belonged to. Endoscopic remission (EI<4) was **stated as an outcome but only the improvement rates were reported** **Life quality Index:** According to Turnbull et al was also reported but this is not a validated index, therefore the data has not been used		Mean time to first response Difference in mean CAI Laboratory assessment

[q] ITT definition: All randomized patients with the exception of 4 incorrectly diagnosed and 1 patient twice included in the study
[r] PPA definition: All patients who did not violate the protocol in a relevant way.

Author	Patients	Intervention	Outcome measures	Effect size	Comments
to deterioration of UC symptoms.	**Duration of disease yrs (SD):** 7.5 (7.8) **CAI mean (SD)**: 8.2 (1.6) **Drop outs:** n=21(9 due to AEs)	**Concomitant therapy:** No concomitant medication to treat UC was allowed.			

Table 93: KRUIS2009

Author	Patients	Intervention	Outcome measures	Effect size	Comments
W. Kruis et al. Once daily versus three times daily mesalazine granules in active ulcerative colitis: a double-blind double-dummy, randomised, non-inferiority trial. *Gut; 58: 233-240. 2009.* **REF ID: KRUIS2009** **Study design and quality:** Double blind, double dummy, Phase III RCT Multicentre: 54 centres in 13 countries; Croatia, Czech Republic, Estonia, Germany, Hungary, Israel, Latvia, Lithuania, Poland, Russia, Slovak Republic, Slovenia and Ukraine **8 week trial** **Randomisation:**1:1 randomisation based on a computer generated scheme **Allocation concealment**:	**<u>All patients:</u>** **N=381randomised** **N=380 ITT/safety** (one patient did not receive study medication so was excluded from the analysis) **N=347(completers)** **N=345 (PPA)** **Drop-outs** (don't complete the study): N=33 (9%) **Inclusion criteria:** 18-75 years old Histologically and endoscopically confirmed diagnosis of established or first attack of ulcerative colitis Extent:>15cm from the anus Severity: CAI>4, EI≥4 (according to Rachmilewitz) **Exclusion:** Crohn's disease Renal or liver insufficiency	**Group 1: 3g mesalazine once a day** N=191 randomised N=174 (completers) N=180 (ACA) 3g of mesalazine (Salofalk granules) given once a day in the morning and 1g of placebo granules given at lunchtime and at night. **Group 2: 1g mesalazine three times a day** N=189 randomised N=173 (completers) N=180 (ACA) 1g of mesalazine (Salofalk granules) and 2g of placebo granules given in the morning and 1g of mesalazine	Outcome 1: **Clinical remission** (CAI≤4)	**Group1:**151/191 (79.1%) (ITT) **Group 2:**143/189 (75.7%) (ITT)	**Funding:** Dr. Falk Pharma. **Limitations:** No further information on double blinding of the physician **Additional outcomes:** Modification of the Disease Activity Index (DAI) remission DAI mucosal healing (DAI≤1) Time to first resolution of clinical symptoms (time from baseline to the day when the patient recorded for the first time in his or her diary to have no more than three bowel movements, all without blood) Physician's Global assessment
			Outcome 2: **Endoscopic remission** (EI<4)	**Group1:**135/191 (71%) (ITT) **Group 2:**132/189 (70%) (ITT)	
			Outcome 3: **Clinical improvement** (decrease in CAI by at least 1 point from baseline to the individual study end) No data was reported. In the text is says that 13-15% had clinical improvement in addition to those in clinical remission. There was no difference between the two groups.		
			Outcome 5: **Adverse**	**Group1:**55/1	

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Adequate. **Blinding:** Double blind. Describes the pathologist to be blinded. **Outcome assessment:** Clinical activity index, endoscopic index **Sample size calculation:**80% power, sample size of 160 in each arm to detect a 15% difference in remission rates. Type 1 error rate of α=0.025. **Type of analysis: ITT and PPA** **LOCF (last observation carried forward)** **Compliance rates:** Checked the medication returned at the follow up visits. No further information described. N=14 dropout/ withdrawal due to AEs (7 people in the once a day group and 7 in the 3 times a day group; with deterioration of UC as the most frequent reason).	Baseline stool positive for bacteria causing bowel disease Immunosuppressant's within 3 months Corticosteroids within 1 month prior to baseline Current relapse that had occurred on >2g/day mesalazine maintenance treatment **<u>Group 1: 3g mesalazine once a day (granules)</u>** **Mean age (SD):**41.8 (14.0) **Diagnosis:** new n=50, established disease n=141 **Extent:** distal (proctosigmoiditis) n= 97, left sided n=55, subtotal-/pancolitis n=39 **Mean CAI (SD):** 121 (63.4) **Mean EI (SD):** 70 (36.6) **Disease severity:** mild (CAI≤8) n=121, moderate (CAI>8) n=70 **Pre-study maintenance medication:** oral 5-ASA n=59, oral sulphasalazine n=26, rectal 5-ASA n=10, immunosuppressant's n=3, oral corticosteroids n=2 **Drop outs:** 17; 6 due to lack of efficacy, 6 protocol violations, 5 for other reasons **<u>Group 2: 1g mesalazine three times a day (granules)(total dose 3g)</u>** **Mean age (SD):**43.3 (13.8) **Diagnosis:** new n=48, established disease n=141 **Extent:** distal (proctosigmoiditis) n= 100, left sided n=40, subtotal-/pancolitis n=49 **Mean CAI (SD):** 7.9 (2.2) **Mean EI (SD):** 7.4 (1.9) **Disease severity:** mild (CAI≤8) n=125, moderate (CAI>8) n=64 **Pre-study maintenance medication:** oral 5-ASA n=53, oral sulphasalazine n=26, rectal 5-ASA n=9, immunosuppressant's n=1, oral corticosteroids n=1 **Drop outs:**16; 7 due to lack of efficacy, 3 protocol violations,1 for adverse events, 5 for other reasons	granules given at lunchtime and at night **Concomitant therapy:** All oral and rectal treatments for ulcerative colitis were to be stopped at baseline. No concomitant medications were allowed (steroids, antibiotics, immunosuppressant's, NSAIDs, other forms of aminosalicylates, loperamide, psyllium-containing drugs or new onset of probiotics.	**events** (most frequently occurring for once a day and three times a day respectively were: headache (9 vs.15), deterioration of UC (8 vs. 10) and nasopharyngitis (6 vs.8)	91 (29%) (ITT) **Group 2:**61/189 (32%) (ITT)	Patient regimen preference
			Outcome 6: **Serious adverse events** Note: None were thought to be drug related. **Group 1:** 3 patients due to deterioration of UC, one patient due to deterioration of UC and an upper respiratory tract infection **Group 2:** 1 patient due to deterioration of UC, one patient due to the development of measles	**Group 1:** 4/191 (ITT) **Group 2:** 2/189(ITT)	
			Outcome 7: **Clinical remission by extent of disease (ITT)**	**<u>Distal disease</u>** **Group 1:** 83/97 (86%) (ITT) **Group 2:** 73/100 (73%) (ITT) **<u>Proximal</u>**	

Author	Patients	Intervention	Outcome measures	Effect size	Comments
				disease **Group 1:** 68/94 (72%)(ITT) **Group 2:** 70/89 (79%)(ITT)	

Table 94: KRUIS2011

Author	Patients	Intervention	Outcome measures	Effect size	Comments
W. Kruis et al. Randomised clinical trial: a comparative dose-finding study of three arms of dual release mesalazine for maintaining remission in ulcerative colitis. *Alimentary Pharmacology and Therapeutics; 33: 313-322. 2011.* **REF ID: KRUIS2011** **Study design and quality:** Double blind, double dummy, Phase III RCT Multicentre: 65 gastroenterology centres, 13 countries(Croatia, Czech Republic, Estonia, Germany, Hungary, Israel, Latvia, Lithuania, Poland, Russia, Slovak Republic, Slovenia, Ukraine)	**All patients:** **N=648 randomised** **N=647 ITT** / safety population N=544 (PPA) (Most frequent protocol deviations that lead to exclusion were intake of study medication for <4 weeks (n=27), last acute episode of UC not ending within 3 months prior to study entry (n=14), CAI not ≤4 at entry (n=13) and >21 days without study medication before the final or withdrawal examination (n=12). The reasons were not significantly different between the three groups. **Drop-outs** (don't complete the study): N=61 (9.4%) <10% difference in missing data between treatment arms. **Inclusion criteria:** • Male and female patients aged 18-75 years • Endoscopically and histologically confirmed diagnosis of UC with mucosal inflammation extending at least 15c, beyond the anal margin during the last active episode • The last active episode had ended within the 3 months prior to	**Group 1: 1.5g mesalazine given as t.d.s.** N=218 randomised N=218 (ITT) N= 185 (PPA) N=169 (completers) 500mg of mesalazine (Salofalk) granules given three times a day. Total dose 1.5g mesalazine/day. Given as two sachets of 0.25g mesalazine mixed with 1.25g placebo in the morning, one sachet of 0.5g mesalazine at noon and in the evening.	**Outcome 1: Relapse** at 1 year Unable to calculate the hazard ratio.	**Group 1:** 29/218 **Group 2:** 44/212 **Group 3:** 17/217	**Funding:** Some of the authors were employees of Dr. Falk Pharma who also funded the study **Limitations:** None. **Additional outcomes:** Clinical remission by baseline endoscopy grade Endoscopic remission at month 12 Number of stools per week Number of bloody stools per week
			Outcome 2: Adverse events Most frequent adverse events were gastrointestinal disorders including deterioration of UC.	**Group 1:** 105/218 **Group 2:** 117/212 **Group 3:** 89/217	
			Outcome 3: Serious adverse events None of the SAEs were thought to be related to	**Group 1:** 6/218 **Group 2:** 7/212 **Group 3:**	

Author	Patients	Intervention	Outcome measures	Effect size	Comments
1 year trial **Randomisation:** Central randomisation in blocks of 3 by means of a computer generated randomisation list. The randomisation list was sealed and held by biostatistical staff of ClinResearch GmbH who was not involved in the study conduct. **Allocation concealment**: Adequate. **Blinding:** Double blind. **Outcome assessment:** Clinical activity index. Endoscopic Index- endoscopy was done at baseline and final visits. Patient diary was used. **Sample size calculation:** 1.5g o.d. versus t.d.s., one sided α=0.025 with a non-inferiority margin of 15%, assuming 60% remission rate in both groups.200 patients per treatment arm with a power of 80%. **Type of analysis: ITT and PPA.** Last observation carried forward for secondary variables. **Compliance rates:** Study medication was checked when it was return and also by monitoring the patient diaries. Compliant if the ratio of the	study entry • They were in remission as defined by CAI≤4 and EI≤3 **Exclusion:** • Crohn's disease • Toxic megacolon • impaired renal function • Serious co-morbidity • Use of immunosuppressants within 3 months prior to study entry • Use of glucocorticosteroids within 1 month prior to study entry **<u>Group 1: 0.5g t.d.s. (1.5g mesalazine/day)</u>** **Mean age (SD):** 43.6 (14.0) **Median disease duration, years (range):** 3.9 (0.2-42.4) **Disease duration ≥5 years:** n=90 **Mean duration of last acute episode, days (95%CI):** 113 [78, 147] **Mean time from start of current remission phase until day 0, days (95% CI):** 67 [36, 97] **Extent:** Not described. **Last acute treatment:** oral mesalazine n=171, rectal mesalazine n=49, oral SASP n=40, oral steroids n=22, rectal steroids n=7, IV steroids n=2, oral budesonide n=5, rectal budesonide n=1, immunosuppressant n=0 **Mean CAI (SD):** 1.2 (1.4) **Mean EI (SD):** 1.6 (1.1) **Severity of previous relapse:** Not described. **Frequency of relapses:** Not described. **Drop outs:** 20 (13 non-cooperation, 4 inclusion/exclusion criteria violation, 3 AEs) **<u>Group 2: 1.5g o.d. mesalazine</u>** **Mean age (SD):** 45.5 (14.2) **Median disease duration, years (range):** 4.2 (0.2-36.6) **Disease duration ≥5 years:** n=100 (47) **Mean duration of last acute episode, days (95%CI):** 80 [71, 89] **Mean time from start of current remission phase until day 0, days (95% CI):** 43 [35, 51] **Extent:** Not described. **Last acute treatment:** oral mesalazine n=164, rectal mesalazine n=61, oral SASP n=45, oral steroids n=13, rectal steroids n=6, IV steroids n=1, oral budesonide n=1, rectal budesonide n=2, immunosuppressant n=0	**Group 2: 1.5g mesalazine o.d.** N=212 randomised N=212 (ITT) N= 182 (PPA) N=151 (completers) 1.5g mesalazine (Salofalk) granules given once a day. Given as two 0.75g sachets of mesalazine mixed with 0.75g placebo in the morning and one 0.5g placebo sachet at noon and placebo sachet in the evening. **Group 3: 3.0g mesalazine o.d.** N=218 randomised N=217 (ITT)- one patient did not take any medication N= 177 (PPA) N=176 (completers) 3.0g of mesalazine (Salofalk) granules given once a day. Given as two 1.5g	the study medication. The reasons were not described in the paper.	8/217	Preference of treatment Renal parameters Trough levels of mesalazine and N-acetyl-mesalazine in plasma at week 2 and week 52 **Notes:**

Author	Patients	Intervention	Outcome measures	Effect size	Comments
number of administered sachets to the schedules number of sachets was >75%.Complaince in all groups was >95%. N=13 dropout/ withdrawal due to AEs.	**Mean CAI (SD):** 1.2 (1.5) **Mean EI (SD):** 1.7 (1.2) **Severity of previous relapse:** Not described. **Frequency of relapses:** Not described. **Drop outs:** 17 (7 patient non-cooperation, 5 inclusion/exclusion criteria violation, 5 AEs) **Group 3: 3.0g mesalazine o.d.** **Mean age (SD):** 45.2 (14.0) **Median disease duration, years (range): 3**.6 (0.1-43.8) **Disease duration ≥5 years:** n=87 (40) **Mean duration of last acute episode, days (95%CI):** 96 [74,117] **Mean time from start of current remission phase until day 0, days (95% CI):** 57 [37, 78] **Extent:** Not described. **Last acute treatment:** oral mesalazine n=161, rectal mesalazine n=58, oral SASP n=42, oral steroids n=19, rectal steroids n=5, IV steroids n=0, oral budesonide n=1, rectal budesonide n=1, immunosuppressant n=1 **Mean CAI (SD):** 1.2 (1.5) **Mean EI (SD):** 1.6 (1.2) **Severity of previous relapse:** Not described. **Frequency of relapses:** Not described. **Drop outs:** 24 (11 patient non- cooperation, 8 inclusion/exclusion criteria, 5 AEs) Differences between the groups: long-standing disease (>5 years) and a shorter interval of remission prior to entry to the study occurred in the 1.5g o.d. group. **Definitions** **Remission:** CAI≤4 and EI≤3 **Clinical relapse:** CAI>4 and an increase of ≥3 from baseline	sachets of mesalazine in the morning, 0.5g placebo sachet at noon and 0.5g placebo sachet in the evening. **Concomitant therapy:** The following was not permitted: steroids, antibiotics, immunosuppressants, NSAIDs, other aminosalicylates treatments, loperamide, psyllium-containing drugs or de novo treatment with probiotics.			

Table 95: LAMET2005/2011

Author	Patients	Intervention	Outcome measures	Effect size	Comments
M. Lamet et al. Efficacy and Safety of	**All patients:** **N=99 randomised**	**Group 1: 1g mesalazine (Salofalk) suppository (once a day)**	**Outcome 1: Clinical remission (DAI<3)**	**Safety population has been**	**Funding:** Supported by Axcan Pharma Inc.

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Mesalamine 1g HS Versus 500mg BID Suppositories in Mild to Moderate Ulcerative Proctitis: A Multicenter Randomized Study. *Inflammatory Bowel Disease; 11 (7): 625-630.2005.* **and** **M. Lamet et al.** A multicentre, Randomized Study to Evaluate the efficacy and Safety of Mesalamine Suppositories 1g at Bedtime and 500mg Twice daily in Patients with Active Mild-to-Moderate Ulcerative Proctitis. *Digestive Diseases and Sciences; 56: 513-522.2011* **REF ID: LAMET2005 & LAMET2011** **Study design and quality:** Partially blinded RCT Multicentre, 18 sites Unclear which country it was based in. **6 week trial** **Randomisation:** Assignment of patients to 1 of 2 treatment groups by a randomization list generated by an automated number programme. Listing for a block of 5 pts were sent to each site with the study	N=97 (safety population- received the medication- unclear which group they were in) **N=87 authors definition ITT** (One patient had abnormal laboratory results, one withdrew consent and 10 did not meet the inclusion/ exclusion criteria). **Drop-outs** (don't complete the study): N=14 (14%) **Inclusion criteria:** • 18-70 years old • Extent: 15cm of the anal margin, not extending above the rectum • Severity: mild or moderate (DAI between 4-11) • Positive for UC proctitis confirmed by endoscopy • No change of smoking habits in the study • Ability to give informed consent • No pathogens, ova or parasites isolated in the patients stool **Exclusion:** • Other confirmed diseases interfering with the measurement of DAI • UC extending beyond the rectum • Chronic use of oral 5-ASA at a dose >4g/day or any form of rectal 5-ASA • Use of any other medication for ulcerative proctitis in the month preceding baseline • Contraindication to use of mesalamine or other related products • Significant impairment of renal or hepatic function • Significant urinary tract obstruction • History of idiopathic pancreatitis • Coagulation disorders or use of anticoagulant drugs (except acetylsalicylic acid at a dose of 325mg/day for cardiovascular disease prevention) • Pregnancy or lactating • Women of child-bearing age not using reliable contraceptives • Other serious medical conditions	N=44 (safety population) N=39 (author defined ITT) 1g 5-ASA/ mesalazine (Salofalk/ Canasa) suppository at bedtime **Group 2: 500mg mesalazine (Salofalk) suppository (twice a day)** N=53 (safety population) N=48 (author defined ITT) 500mg 5-ASA/ mesalazine (Salofalk/ Canasa) suppository, twice a day, in the morning and at bedtime **Concomitant therapy:** See exclusion criteria.		**used as it is the closest to actual ITT figures** **<u>3 weeks</u>** **Group1:** 21/44 **Group 2:** 27/53 **<u>6 weeks</u>** **Group1:** 34/44 **Group 2:** 38/53	**Limitations:** Partially unblinded **Additional outcomes:** Mean DAI scores Mean stool frequency, rectal bleeding, mucosal appearance and general wellbeing.
			Outcome 2: Adverse events Group 1: There were 46 events of which 18 were thought to be drug related (9/44 patients) Group 2: There were 71 events of which 11 were thought to be drug related (9/53)	**Group1:** 24/44 **Group 2:** 30/53	
			A complete response (DAI=0) was also reported but the numbers and percentages reported in the paper did not add up. It wasn't clear whether they were analysed as ITT or PPA, so this has not been included in the analysis.		

Author	Patients	Intervention	Outcome measures	Effect size	Comments
medication. **Allocation concealment**: adequate **Blinding:** Neither physicians or patients were blinded to the treatment. Pathologist, laboratory and statistical analysis were blinded. **Outcome assessment:** Disease Activity Index **Sample size calculation:** Power of 80%, 5% significance level, detect a difference of 1DAI, including drop outs etc. estimated to be 50 per arm. **Type of analysis: Authors definition of ITT** **Last observation carried forward (LOCF) used** **Compliance rates:** Suppository counts were carried out. 96% for 500mg bd group and 97% for the 1g od (this was based on the safety population figures). N=2 dropout/ withdrawal due to drug related AEs.	• Use of any experimental drug within 30 days before enrolment • Presence of *C. Difficile* with toxins A and B **Baseline characteristics** **Group 1: 1g mesalazine (Salofalk) suppository (once a day)** **Sex (m/f):** 14/25 **Mean age (SD):** 39.7 (13.8) **New diagnosis:** yes n=26, no n=13 **Extent:** All proctitis **DAI score:** 4 n=9, 5 n=4, 6 n=9, 7 n=9, 8 n=6, 9 n=2 **Drop outs:** 6 (2 protocol violations, 2 withdrew consent, 1 baseline stool culture positive, 1 met the exclusion criteria) **Group 2: 500mg mesalazine (Salofalk) suppository (twice a day)** **Sex (m/f):** 22/26 **Mean age (SD):** 39.3 (13.5) **New diagnosis:** yes n=31, no n=17 **Extent:** All proctitis **DAI score:** 4 n=6, 5 n=5, 6 n=12, 7 n=9, 8 n=12, 9 n=4 **Drop outs:** 8 (2 due to AEs, 1 lost to follow up, 1 protocol violation, 1 positive for C. Difficile, 1 positive for Gardia Lambia). Unclear why the other two dropped out. It says there were 8 drop outs in this group but only 6 reasons given.				

Table 96: LAURITSEN1986

Author	Patients	Intervention	Outcome measures	Effect size	Comments
K. Lauritsen et al.	**All patients:**	**Group 1: 1g liquid 5-ASA enema (Pentasa)**	**Outcome 1: Clinical remission** (based on a	**Group1:** 7/13	**Funding:** Grants by Sparekassen

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Effects of topical 5-aminosalicylic acid and prednisolone on prostaglandin E2 and leukotriene B4 levels determined by equilibrium in vivo dialysis of rectum in relapsing ulcerative colitis. *Gastroenterology; 91 (4): 837-44. 1986.* **REF ID: LAURITSEN1986** **Study design and quality:** Double blind RCT Denmark **2 or 4 week trial** (withdrew at 2 weeks if achieved remission) **Randomisation:** Block randomisation. No other information given. **Allocation concealment**: Unclear **Blinding:** Double blind. **Outcome assessment:** Binder scores **Sample size calculation:** Not described **Type of analysis: ITT** **Compliance rates:** Not described. N=0 dropout/ withdrawal due	**N=24 randomised/ ITT** **Drop-outs** (don't complete the study): N=1 (4%) Due to condition deterioration (5-ASA group) **Inclusion criteria:** • Extent: localized to sigmoid colon or rectum or both • Severity: symptoms and signs of mild or moderate disease activity (Binder scale) • No drug treatment for UC in preceding month apart from maintenance treatment with sulphasalazine • Capable of inserting enemas • Normal renal and hepatic function **Exclusion:** • Not described **Baseline characteristics** **Group 1: 1g Pentasa liquid enema** **Sex (m/f):** 7/6 **Mean age (range):** 27 (18-55) **Extent:** Not described **Concurrent sulphasalazine therapy:** n=7 **Clinical activity, mild (C_1), moderate (C_2):** 3, 10 **Endoscopic grade, mild (E_1), moderate (E_2), severe (E_3):** 1, 6, 6 **Drop outs:** 1 (deterioration of condition) **Group 2: 25mg Prednisolone liquid enema** **Sex (m/f):** 4/7 **Mean age (range):** 38 (24-66) **Extent:** Not described **Concurrent sulphasalazine therapy:** n=6 **Clinical activity, mild (C_1), moderate (C_2):** 5,6 **Endoscopic grade, mild (E_1), moderate (E_2), severe (E_3):** 2, 8, 1 **Drop outs:** 0	N=13 randomised/ ITT 1000mg enemas (Pentasa) in acidic buffer 100mls, given once a day. **Group 2: 25mg prednisolone liquid enema** N=11 randomised/ ITT 25mg prednisolone in 100mls liquid enema once a day. **Concomitant therapy:** For patients on sulphasalazine (1g b.i.d.) this treatment was unchanged throughout the trial.	diary in which the number of bowel movements and presence or absence of blood) **Outcome 2: Clinical and Endoscopic remission** (Endoscopic remission assessed using Binder 4 point scale, E_0=inactive, clinical activity C_0= inactive) **Outcome 3: Adverse events** 1 patient in each group complained of nausea. The laboratory screening disclosed no significant abnormalities, except for a slight increase in platelet counts and serum concentration of orosomucoid in a few cases.	**Group 2:** 9/11 **Group1:** 3/13 **Group 2:** 8/11 **Group1:** 1/13 **Group 2:** 1/11	Bikuben's Foundation and Jacob og Olga Madsen's Foundation **Limitations:** Unclear method of randomisation and allocation concealment Stated to be double blind but no further information was given. No baseline extent data **Additional outcomes:** Prostagladin and Leukotriene levels.

Author	Patients	Intervention	Outcome measures	Effect size	Comments
to drug related AEs.					

Table 97: LEE1996

Author	Patients	Intervention	Outcome measures	Effect size	Comments
F. I. Lee et al. A randomised trial comparing mesalazine and prednisolone foam enemas in patients with acute distal ulcerative colitis. *Gut; 38: 229-233. 1996.* **REF ID: LEE1996** **Study design and quality:** Single investigator blind RCT Multicentre: United Kingdom **4 week trial** **Randomisation:** Outpatient recruited. Computer generated list prepared by SmithKline Beecham. **Allocation concealment**: Adequate, by an independent 3rd party **Blinding:** Single investigator blind. **Outcome assessment:** Endoscopic grading was done from 1-3. Unclear if it was validated.	**<u>All patients:</u>** **N=334 randomised** **N=295 for analysis** (received ≥11 days of treatment and had no major protocol violations) **Drop-outs** (don't complete the study): N=40 (12%) (unclear how many in each treatment group) **Inclusion criteria:** • ≥18 years attending outpatient clinic • Extent: Not beyond the splenic flexure • Severity: not described • Stated of clinical and sigmoidoscopic relapse **Exclusion:** • Taken oral or rectal corticosteroids or rectal 5-ASA preparations in the month prior to trial entry or required such treatment during the course of the study • Severe allergy or bronchial asthma • Hypersensitivity to corticosteroids or salicylates • Specific cause of their colitis e.g. Crohn's • Clinically significant cardiac, hepatic or renal disease • Pregnant or lactating or not using reliable contraception **<u>Baseline characteristics</u>** **<u>Group 1: 2g mesalazine foam enema</u>** **Sex (m/f):** 76:73 **Mean age (SD):** 44 (13.6)	**Group 1: 2g mesalazine foam enema** N=167 randomised N=149 PPA/ authors analysis 1g mesalazine foam enema, given in two metered applications (total volume 120mls) at night **Group 2: 20mg prednisolone foam enema** N=167 randomised N=146 PPA/ authors analysis 20mg prednisolone foam enema given in one metered application (30mls) at night **Concomitant therapy:** Oral mesalazine or sulphasalazine was allowed if the treatment had been	**Outcome 1: Clinical remission** (≤3 stools/ day with no blood)	**Authors analysis** **<u>4 weeks</u>** **Group1:** 77/149 **Group 2:** 45/146	**Funding:** SmithKline Beecham Pharmaceuticals **Limitations:** Single blind Unclear if endoscopy grading is validated Unclear drop out rate **Additional outcomes:** Global improvement (no definition) Histological remission
			Outcome 2: Endoscopic remission (Grade 1, normal findings including minor abnormalities in vascular patter) at week 4 or withdrawal	**Authors analysis** **<u>4 weeks</u>** **Group1:** 60/149 **Group 2:** 45/146	
			Outcome 3: Adverse events	**Group1:** 57/167 **Group 2:** 43/167	
			Global improvement was also reported but a definition was not given, therefore it has not been included in this review. It was unclear whether those that		

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Sample size calculation: 280 patients were required to complete the study assuming an 80% improvement in prednisolone versus mesalazine **Type of analysis: PPA** **Compliance rates:** Not described N=5 dropout/ withdrawal due to AEs.	**Extent:** proctitis n=14, sigmoiditis n=97, Left sided colitis n=37, not known n=1 **Episode:** new n=21, previous history of UC n=128 **Concomitant oral 5-ASA/ SASP:** n=63 **Drop outs:** unclear (3 AEs (PE, elective prostatectomy, severe abdo pain with rectal discharge), 5 lack of efficacy) **Group 2: 20mg prednisolone foam enema** **Sex (m/f):** 80:66 **Mean age (SD):** 45 (15.0) **Extent:** proctitis n=15, sigmoiditis n=101, Left sided colitis n=27, not known n=3 **Episode:** new n=21, previous history of UC n=125 **Concomitant oral 5-ASA/ SASP:** n=69 **Drop outs:** unclear (2 AEs (PE, eczema round public area and back), 13 lack of efficacy)	stable for one month. Loperamide was allowed as an anti-diarrhoeal agent if clinically indicated.	withdrew due to AEs were classed as SAEs or not. Author had not defined them as this therefore they have not been included in the review.		

Table 98: LEMANN1995

Author	Patients	Intervention	Outcome measures	Effect size	Comments
M. Lémann et al. Comparison of budesonide and 5-aminosalicylic acid enemas in active distal ulcerative colitis. *Alimentary Pharmacology & Therapeutics; 9 (5): 557-62. 1995.* **REF ID: LEMANN1995** **Study design and quality:** Single investigator blind RCT Multicentre, 15 centres, Belgium & France	**All patients:** **N=97 randomised** **N=92 (all patients treated analysis)** **Drop-outs** (don't complete the study): N=18 (18.6%) (excluded from PPA, 5 lost to follow up and 13 protocol violations) **Inclusion criteria:** • Extent: active distal ulcerative colitis or proctitis. Should not exceed splenic flexure • Severity: should have had rectal bleeding the week prior to inclusion and disease state should warrant drug therapy.	**Group 1: 1g mesalazine liquid enema (Pentasa)** N=49 randomised N=47 (all patients treated) N=35 PPA 1g in 100mls mesalazine (Pentasa) liquid enema, given once at night. **Group 2: 2mg budesonide liquid**	**Outcome 1: Clinical remission** (no blood (score 0) and little or no mucus (score 0-1). Judged on a 3 point scale) **Outcome 2: Endoscopic remission** (score of 0 on a four point scale, normal mucosa)	**4 weeks** **Group1:** 28/47 **Group 2:** 17/45 **4 weeks** **Group1:** 6/47 **Group 2:** 6/45	**Funding:** Astra Draco, Sweden **Limitations:** Single blind Unclear method of randomisation and allocation concealment Unclear who dropped out from which treatment group for what reason **Additional outcomes:**

Author	Patients	Intervention	Outcome measures	Effect size	Comments
4 week trial **Randomisation:** No details given. Unclear **Allocation concealment**: No details given. Unclear. **Blinding:** Single investigator blind **Outcome assessment:** Endoscopy was a four point scale (unclear validation). Measurement of clinical symptoms. **Sample size calculation:** 5% significance level, 80% power, 50 patients per group will detect differences of 0.45 and 0.67 in endoscopy and histology scores **Type of analysis:** All patients treated, last observation carried forward, PPA **Compliance rates:** Not described N=0 dropout/ withdrawal due to drug related AEs.	• Stool negative for enteric pathogens • Male or female, 18 years + **Exclusion:** • Received steroids in the last month • Previously treated with 5-ASAs without success and possible hypersensitivity to drug • Liver disease, diabetes • Impaired glucose tolerance • Concomitant disease requiring steroids • Pregnant or breast feeding **Baseline characteristics** **Group 1: 1g mesalazine liquid enema** **Sex (m/f):** 25/24 **Mean age (SD):** 38 (13) **Concurrent therapy:** SASP n=8, mesalazine n=6, olsalazine n=1 **Duration of current exacerbation, mean (SD):** 78 days (78) **Extent:** not described **Drop outs:** unclear **Group 2: 2mg budesonide liquid enema** **Sex (m/f):** 29/19 **Mean age (SD):** 39 (15) **Concurrent therapy:** SASP n=10, mesalazine n=3, olsalazine n=0 **Duration of current exacerbation, mean (SD):** 65 days (65) **Extent:** not described **Drop outs:** unclear	**enema** N=48 randomised N=45 (all patients treated) N= 36 PPA 2mg in 100mls budesonide liquid enema (Entocort), given once at night. **Concomitant therapy:** No information described. Some patients were on oral ASAs.	**Outcome 3: Serious adverse events** Due to bleeding after rectal biopsies and renal colic. Neither were judged to be drug related. **Adverse events:** Two cases of acne were described in the budesonide group in terms of glucocorticosteroids effects. Otherwise adverse events were not really described.	**Group1:** 1/47 **Group 2:** 1/45	Clinical response (no definition) Endoscopic response Histopathology remission and response

Table 99: LENNARDJONES1960

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Lennard- Jones et al.	**All patients** N=37 randomised	**Group 1** N=19 randomised	**Clinical Remission:** Remission of the disease is defined as freedom from	**At 4 weeks, the end of stage 1 of the trial** Group 1=9/19	

Author	Patients	Intervention	Outcome measures	Effect size	Comments
An assessment of prednisone, salazopyrin, and topical hydrocortisone hemisuccinate used as -out-patient treatment for ulcerative colitis Gut, 1960, 1, 217. **REF ID: LENNARDJONES1960** United Kingdom **Duration of follow-up** 3-4 weeks **Study design and quality:** RCT **Randomisation**: odd hospital numbers were allocated to the control group **Allocation concealment**: No information on allocation concealment	**Inclusion criteria:** • Extent: part or • all of the colon distal to the splenic flexure. • Severity: mild • Combination of first attack and relapse **Exclusion criteria**: • none stated **Drop-outs**: None stated	Prednisone was given in a dose of 40 to 60 mg. daily for the first week and then the dose was slowly reduced. **Group 2** N=18 randomised Calcium lactate 1.3g daily	symptoms combined with the finding of an inactive or, rarely, normal mucosa on sigmoidoscopy.	Group 2=3/18	

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Sample size calculation: none **Type of analysis**: ACA for clinical improvement outcome **Compliance rates:** No withdrawals due to drug related AEs.			Adverse effects	Group 1 17/ 51 patients treated with prednisone during the two stages of the trial The symptoms complained of were mooning of the face (n=7), dyspepsia (n=5), acne (n=4), gain in weight (2), palpitations (n=2), flushes (n=1), and syncopal attacks (n=1). Group 2 Two patients treated with calcium lactate developed side-effects, heartburn and "pimples"	

Table 100: LENNARDJONES1960

Author	Patients	Intervention	Outcome measures	Effect size	Comments
J.E Lennard-Jones et al. An assessment of prednisone, salazopyrin, and topical hydrocortisone hemisuccinate used as out-patient treatment for ulcerative colitis.	**All patients:** **N= 60 randomised** **Drop-outs** (don't complete the study): none stated **Inclusion criteria:**	**Group 1: Sulphasalazine (Salazopyrin) 4g** N=20 randomised N=17 (completers)	Outcome 1: **Clinical and endoscopic remission** (freedom from symptoms combined with the finding of an inactive or, rarely, normal mucosa on sigmoidoscopy).	**Group 1:** 2/20 **Group 2:** 9/20	**Funding:** Glaxo supplied the hydrocortisone. Research grant from Board of Governors of the Hammersmith and St Mark's group of hospitals

Author	Patients	Intervention	Outcome measures	Effect size	Comments
REF ID: LENNARDJONES1960 **Study design and quality:** Open RCT Single centre: UK **3-4 week trial (until first assessment),** continued to follow up patients who responded to treatment for 6 months – 2 years. **Randomisation:** blindly drawing a slip from a box containing 60 slips, 20 marked with each treatment **Allocation concealment**: No information given **Blinding:** no blinding **Outcome assessment:** Patients symptoms classified as "no change or worse" or "improved" based on frequency of bowel actions and bleeding. "No symptoms" = normal bowel actions without any bleeding or discharge. Sigmoidoscopy classified as: "Active": oedematous, friable mucosa, no granularity "Moderately active": moist granular, friable mucosa	• Extent: part or all of the colon distal to the splenic flexure. • Severity: mild • Combination of first attack and relapse **Exclusion:** none stated **<u>Group 1: Sulphasalazine (Salazopyrin)</u>** **Mean age (SD):** 38 (16) **Extent:** Not reported **Treated for first attack (%)**: 10/20 (50) **Treated for relapse (%)**: 10/20 (50) **Diarrhoea and bleeding (%):** 11/20 (55) **Bleeding only (%):** 8/20 (40) **Diarrhoea only (%):** 1/20 (5) **Drop outs:** 3 **<u>Group 2: Prednisone</u>** **Mean age (SD):** 44 (14) **Extent:** Not reported **Treated for first attack (%)**: 8/20 (40) **Treated for relapse(%)**: 12/20 (60) **Diarrhoea and bleeding (%):** 13/20 (65) **Bleeding only (%):** 7/20 (35) **Diarrhoea only (%):** 0/20 (0) **Drop outs:** 0 **<u>Group 3: Topical hydrocortisone</u>** **Mean age (SD):** 45 (17) **Extent:** Not reported **Treated for first attack (%)**: 5/20 (25) **Treated for relapse (%)**: 15/20 (75) **Diarrhoea and bleeding(%) :** 13/20 (65) **Bleeding only (%):** 7/20 (35) **Diarrhoea only (%):** 0/20 (0) **Drop outs:** 0	Total dose of 4g daily, no other information given **Group 2: Prednisone** N=20 randomised N=20 (completers) Reducing dose: 60mg od for first week, 45mg od second week and 30mg od for third week. **Group 3: Hydrocortisone enema** N=20 randomised N=16 (completers) 100mg freshly dissolved in 150ml normal saline **Concomitant therapy:** None stated **Note:** if there was a definite or possible improvement the treatment was continued in reduced dosage until remission or apparent maximum benefit was achieved, and it was then slowly withdrawn	Only the data provided at 3-4 weeks has been analysed. The end of the trial data was >12 weeks. Outcome 2: **Adverse events** For prednisone (17/51 patients from both stages of trial, no separate information given): Moon face (n=7), dyspepsia (n=5), acne (n=4), weight gain (n=2), palpitations (n=2), flushes (n=1), syncopal attacks (n=1). For salazopyrin (12/20 patients): nausea (n=4), anorexia (n=3), vomiting (n=2), malaise (n=2), diarrhoea (n=1) and skin rash (n=1). For hydrocortisone (1/20 patients): colic (n=1).		**Limitations:** Inadequate allocation concealment No blinding Technique used for hydrocortisone retention enema difficult for outpatient use in practice, especially when population not selected for ability to perform this treatment **Additional outcomes:** Mean time between start of disease and remission Relapse rate after remission achieved for prednisone group only (19/33 patients over 6 months from remission from both stages of the trial) Clinical improvement (based on frequency of bowel actions and bleeding and improvement in mucosal appearance on sigmoidoscopy). This has not been analysed because the time point is > 12 weeks. **Notes:** Paper contains 2 trials. Oral

Author	Patients	Intervention	Outcome measures	Effect size	Comments
"Inactive": dry, granular, not friable mucosa "Normal": vascular pattern visible throughout **Sample size calculation:** None stated **Type of analysis:** ACA clinical improvement **Compliance rates:** N=7 dropout/ withdrawal due to drug related AEs (3 sulphasalazine, 4 enema not retained).					steroid versus placebo has been extracted separately.

Table 101: LEVINE2002

Author	Patients	Intervention	Outcome measures	Effect size	Comments
D. S. Levine et al. A Randomized, Double Blind, Dose-Response Comparison of Balsalazide (6.75g), Balsalazide (2.25g), and Mesalamine (2.4g) in the Treatment of Active, Mild-to-Moderate Ulcerative Colits. *The American Journal of Gastroenterology; 97 (6): 1398-1407. 2002.* **REF ID: LEVINE2002** **Study design and quality:** Double blind, double dummy	**<u>All patients:</u>** **N=154randomised / ITT/ Safety analysis balsalazide 2.25g,6.75g vs 2.4gmesalamine** **N=147efficacy analysis** (7 protocol violations before screening or during treatment) **Drop-outs** (don't complete the study): N=55 (35.7%) (7 protocol violations, withdrew prematurely (15 mesalamine group, 17 2.25g balsalazide and 16 in the 6.75g balsalazide) **Inclusion criteria:** 18-80 years old	**Group 1: 2.4g Mesalamine (Asacol)** N=51 randomised 2.4g mesalamine (pH 7.0 dependent, delayed release formulation, Asacol) 400mg tablets. Given some active mesalamine tablets and placebo capsules. Total dose: 2.4g/day	For all outcomes, the data was reported as eligible for efficacy		**Funding:** None described. Author is affiliated with AstraZeneca **Limitations:** Unclear method of randomisation and allocation concealment Double blind but no further information given High dropout rate Indirect population
			Outcome 1: **Complete remission (clinical and endoscopic remission)**(normal stool frequency and no blood in stool for 48hrs before visit, PGA score of "quiescent" and a sigmoidoscopy score of mild or normal)	**Group1:**7/36 **Group 2:**8/35	
			Outcome 2: **Clinical improvement**	**Group1:**22/38	

Author	Patients	Intervention	Outcome measures	Effect size	Comments
RCT Multicentre: 15 centres, United States, Puerto Rico **8 week trial** **Randomisation:** No information given. Unclear. **Allocation concealment**: Unclear. **Blinding:** Double blind. **Outcome assessment:** Physician's Global assessment. Sigmoidoscopy scored from normal to severe. **Sample size calculation:** Not described. **Type of analysis: ITT** (ITT definition used in the paper: All patients who were randomized and the last observation carry forward procedure was used for all missing data) **and Efficacy analysis** (EFE (Eligible For Efficacy) definition: All patients receiving at least one dose of medication. The last observation carry forward procedure was used for completing patients with missing data and for missing data from patients terminating early because of adverse	Newly diagnosed or recently relapsed (within 12 weeks) Severity: Mild to moderate UC (confirmed by flexible sigmoidoscopy) No extent restriction given. **Exclusion:** Severe colitis Intolerance of or allergy to salicylates Crohn's disease Hepatic disease Renal disease Evidence of enteric pathogens or parasites Malignancy Used 5-ASA oral products, topical therapies or enemas within the last 7 days Received antibiotics within the last 2 weeks Taken immunosuppressive drugs within the prior 3 months Treated with any investigational drug or device within the prior month Pregnant women Women of child bearing potential not using adequate birth control Patients breast feeding infants **<u>Group 1: 2.4g Mesalamine (Asacol)</u>** **Mean age (SD):**42.8 (2.2)	**Group 2: 6.75g Balsalazide** N=53 randomised 750mg capsules. Given active balsalazide capsules and placebo tablets. 3 capsules and 2 tablets 3 times a day. Total dose: 6.75g/day **Concomitant therapy:** See inclusion/exclusion criteria.	(Improvement by at least one category in the four- category disease activity scale i.e. normal, mild, moderate, severe)	**Group 2:**22/34	(included some patients with severe disease) Unclear validation of sigmoidoscopy scoring Selective outcome reporting. IBDQ listed as a secondary outcome but the results were not reported. **Additional outcomes:** Rectal biopsy score changes Difference in rectal bleeding and in at least one other symptom or sign Sigmoidoscopic score improvement
			Outcome 3: **Adverse events**(ITT) Most frequent were headache (13.7%, 14%, and 11.3%), abdominal pain (2%, 2%, and 9.4%), colitis aggravated (5.9%, 8.0%, and 1.9%), nausea (7.8%, 2%, and 9.4%), vomiting (3%, 10%, and 3.8%) and skin disorders (8%, 6%, and 1.9%); Group 1, 2 &3 respectively.	**Group1:**26/51 **Group 2:** 23/53	
			Outcome 4: **Serious adverse events** (ITT)	**Group1:**2[s]/51 **Group 3:** 1[t]/53	
			Inflammatory Bowel Disease Questionnaire (IBDQ) Specified secondary outcome. No results given in the paper.		

[s] Due to worsening of symptoms
[t] Due to worsening of symptoms

Author	Patients	Intervention	Outcome measures	Effect size	Comments
events, treatment failure or patient request because of worsening symptoms). **Compliance rates:** Not described. N=11 dropout/ withdrawal due to AEs. It is unclear whether these were drug related. (5 in the mesalamine group, 5 2.25g balsalazide and 1 in the 6.75g balsalazide group)	**Episode:** newly diagnosed n=8, relapse n=41 **Extent:**<60cm n=15, >60cm n=34 **Sigmoidoscopic grade:** mild n=0, moderate n=41, severe n=8 **Biopsy grade:** inactive n=3, mild n=7, moderate n=12, severe n=16, severe/erosion n=7 **Physician's Global Assessment:** mild n=4, moderate n=41, **severe n=4** **Drop outs:** 17 (2 protocol violations, 15 patients withdrew prematurely (4 of these were due to treatment failure, 2 SAEs due to worsening of symptoms, 5 AEs in total) **Group 2: 6.75g Balsalazide** **Mean age (SD):**42.3 (1.8) **Episode:** newly diagnosed n=7, relapse n=42 **Extent:**<60cm n=11, >60cm n=38 **Sigmoidoscopic grade:** mild n=2, moderate n=36, severe n=11 **Biopsy grade:** inactive n=7, mild n=4, moderate n=15, severe n=11, severe/erosion n=11 **Physician's Global Assessment:** mild n=7, moderate n=40, severe n=2 **Drop outs:** 20 (4 protocol violations, 16 patients withdrew prematurely (2 of these were due to treatment failure, 1 SAE due to worsening of symptoms)) No significant difference between the ITT and efficacy populations in baseline demographic and disease history and activity characteristics. So only the efficacy population baseline characteristics were presented in the paper (as shown above).				

Table 102: LEVY1981

Author	Patients	Intervention	Outcome measures	Effect size	Comments
N. Levy et al. Ulcerative Colitis in Pregnancy in Israel. *Diseases of the Colon and Rectum; 24: 351-354.1981.* **REF ID: LEVY1981** **Study design and quality:**	**All patients:** Included population • Pregnant women with ulcerative colitis from five hospitals in Israel Excluded population: none described.	**Hospitalized women (n=8) received the following treatment:** **Sulphasalazine +/- Betnesol retention enema, azathioprine and/or prednisolone.**	**Overall** Out of the 60 pregnancies there were 7 spontaneous abortions, 2 therapeutic abortions, 1 premature birth and 50 term deliveries. There was no maternal mortality or severe morbidity. **Active disease/ hospitalised patients**		**Funding:** None described **Limitations:** High risk of bias due to study design

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Retrospective case series study **Israel, five hospitals** **Years studied: 1970-79** **Risk of bias:** High due to study design	**N=31 with 60 pregnancies** <u>Data collection</u> Case records of all the patients were reviewed. All patients were then interviewed. Diagnosis of ulcerative colitis was confirmed by barium enema, proctoscopy and rectal biopsy. <u>Baseline characteristics</u> **Age(years)** 18-20: n=6 21-30: n14 31-40: n=9 41-50: n=2 **Duration of disease prior to first pregnancy** 1-5: n=8 6-10: n=10 11-15: n=10 16-20: n=2 21-25: n=0 >25: n=1 **Ethnic composition of the group** Jewish, born in Israel: n=11 Jewish, born in Arab countries: n=8 Jewish, born in Europe (Ashkenazi): n=11 Arab, born in Israel: n=1		There were eleven patients hospitalized for the deterioration of ulcerative colitis. Eight of them were treated for at least two weeks on the following treatments: Sulphasalazine + Betnesol retention enema (n=2, both trimester 1) Sulphasalazine + azathioprine (n=1, trimester 2) Sulphasalazine (n=1, trimester 2) Sulphasalazine + prednisolone (n=3, trimester 1) Sulphasalazine + prednisolone + azathioprine (n=1). They all received sulphasalazine until delivery (unknown dose). Steroid treatment lasted for >2 months in two patients and for about five months in the other three patients. No special problems arose, no fetal abnormalities found for any of the pregnancies.		**Additional outcomes:** Birth outcomes overall for the case series

Table 103: LICHTENSTEIN2007

Author	Patients	Intervention	Outcome measures	Effect size	Comments
G. R. Lichtenstein et al. Effect of Once- or Twice-Daily MMX Mesalamine (SPD476) for the Induction of Remission of Mild to Moderately Active Ulcerative Colitis. *Clinical Gastroenterology and*	**<u>All patients:</u>** **N=280 randomised**(10 patients underwent forced randomisation, 5 in each mezavant XL group) **N=262 (study's definition of ITT)** **Drop-outs** (don't complete the study):	5 tablets were taken, 4 in the morning and 1 at night. They were to be taken with food. Mezavant XL mesalamine tablets contain 1.2g of the	Outcome 1: **Clinical and endoscopic remission** (modified UCDAI score of ≤1, with a score of 0 for rectal bleeding and stool frequency, and at	**N values were calculated from the % given** **Group1:**26/89 **Group 2:**30/88	**Funding:** Supported by Shire Pharmaceuticals **Limitations:** High dropout rate

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Hepatology; 5: 95-102. 2007. **REF ID: LICHTENSTEIN2007** **Study design and quality:** Phase III double blind RCT Multicentre: 52 centres in; Australia, Costa Rica, the Czech Republic, India, Mexico, New Zealand, Romania, the Ukraine and the USA **8 week trial** **Randomisation:** Randomised centrally via an interactive voice response system. **Allocation concealment**: Paper says ' to ensure that the study was blinded, allocation of active drug and placebo was concealed'. Central randomisation. **Blinding:** Double blind. Identical tablets. **Outcome assessment:** Modified UCDAI (looks at rectal bleeding, stool frequency, mucosal appearance and PGA, each scored from 1-3). Modification	N=79**(28%)** **Inclusion criteria:** Extent:>15cm Severity: Mild to moderate (score of 4-10 on a modified UCDAI), sigmoidoscopy score≥1, PGA≤2 with compatible histology ≥18 years old Newly diagnosed or relapsing (relapsed ≤6weeks before baseline) **Exclusion:** Severe UC (PGA>2) Current relapse lasting > 6weeks. Current relapse while on maintenance treatment with doses of mesalamine >2,0g/day or within 2 weeks of dose reduction from >2.0g/ day to ≤2g/day mesalamine Inadequate/ failed response to steroids or a mesalamine dose of >2.0g/day during relapse Used immunosuppressant's within the previous 6 weeks Used systemic or rectal steroids within the previous 4 weeks Used antibiotics within the previous 7 days Received chronic treatment with anti-inflammatory drugs within the 7 days before baseline (with the exception of aspirin at doses of ≤325mg/day for cardioprotection, which was allowed throughout the study)	active drug. **Group 1: mezavant XL mesalamine 4.8g o.d.** N=94 randomised N=89 (study ITT definition) N=79 (PPA) N=73 (completers) Four 1.2g tablets in the morning, one placebo tablet at night. **Group 2: mezavant XL mesalamine 1.2g b.d.** N=93 randomised N=88 (study ITT definition) N=81 (PPA) N=76 (completers) One 1.2g tablet and three placebo tablets in the morning, 1.2g tablet at night. Total 2.4g/day	least a 1 point reduction in sigmoidoscopy score) Outcome 2: **Clinical remission** (scores of 0 for total stool frequency and total rectal bleeding scores) Outcome 3: **Clinical improvement** (decrease of ≥3 points from baseline in the overall modified UCDAI) Outcome 4: **Adverse events** Most frequent were: worsening UC, flatulence, headache, nausea, diarrhoea and dyspepsia.	**Group 3:** 11/85 **N values were calculated from the % given** **Group1:**29/89 **Group 2:**33/88 **Group 3:** 16/85 **N values were calculated from the % given** **Group1:**53/89 **Group 2:**49/88 **Group 3:** 22/85 **Group 1:** 38/89 **Group 2:** 44/88 **Group 3:**47/85	No information on the double blinding apart from the preparations being identical. **Additional outcomes:** Change in total modified UCDAI score Change in symptoms Change in sigmoidoscopic (mucosal) appearance Time to withdrawal and treatment failures Time to initial clinical remission Laboratory testing Physical examination and vital signs Kaplan Meier curve

Author	Patients	Intervention	Outcome measures	Effect size	Comments
makes sigmoidoscopy score more stringent with friability being present to score ≥2. Symptoms reported via an interactive voice system daily. **Sample size calculation:**255 patients (85 per arm), 90% power, two sided 0.025 significance level. **Type of analysis: ITT** (The study's definition of ITT is that it includes all patients who took at least one dose of the treatment. However 18 patients were also excluded from the analysis from 3 centres who did not stick to Good Clinical Practice (GCP) and there was issues with the accuracy and reliability of the data. It mentions in the study that additional patients were randomized to compensate for this. It is unclear whether these are included in the 280 patients randomised.) **and PPA** **Compliance:** 90% of patients in the safety population took between ≥80% and <120% of the study medication. N=18 dropout/ withdrawal due to AEs (it is unclear which of these were drug related; 11 placebo group, 5 in the 2.4g group and 2 in the 4.8g group). Two SAEs due to pancreatitis were drug related, 1 in each mesalazine group.	Proctitis (≤15cm extent) Previous colonic surgery Crohn's disease Bleeding disorders Active ulcer disease Stools positive for enteric pathogens Moderate or severe renal impairment **Group 1: mezavant XL mesalamine 4.8g o.d.** **Mean age (SD):**40.2 (11.97) **Extent:** left sided n=78 (88.6%), involvement of the transverse n=4 (4.5%), pancolitis n=6 (6.8%) **Severity:** Mild n=38 (43.2%), moderate n=50 (56.8%) **Drop outs:** 21 **Group 2: mezavant XL mesalamine 2.4g b.d.** **Mean age (SD):**41.8 (13.62) **Extent:** left sided n=71 (79.8%), involvement of the transverse n=6 (6.7%), pancolitis n=11 (12.4%) **Severity:** Mild n=35 (39.3%), moderate n=53 (59.6%) **Drop outs:** 17 **Group 3: Placebo** **Mean age (SD):**42.6 (11.68) **Extent:** left sided n=66 (77.6%), involvement of the transverse n=4 (4.7%), pancolitis n=15 (17.6%) **Severity:** Mild n=29 (34.1%), moderate n=55 (64.7%) **Drop outs:** 41	**Group 3: Placebo** N=93 randomised N=85 (study ITT definition) N=52 (completers) N=76 (PPA) 4 placebo tablets in the morning and one at night. **Concomitant therapy:** During the 3-7day screening period patients were permitted to continue on a stable dose of mesalamine (≤2g/day) if they were receiving this treatment at screening. This was then stopped at baseline if they were eligible. Rescue medication was not permitted.	Outcome 5: **Serious Adverse events** **Group 1:** 1 patient had pancreatitis (drug related hypersensitivity), no further information given. **Group 2:** 1 patient had pancreatitis (drug related hypersensitivity), no further information given	**Group 1:** 2/89 **Group 2:** 2/88 **Group 3:** 3/85	

Table 104: LICHTIGER1994

Author	Patients	Intervention	Outcome measures	Effect size	Comments
S. Lichtiger et al. Cyclosporin in severe ulcerative colitis refractory to steroid therapy. *The New England Journal of Medicine; 330 (26):1841-1845. 1994.* **REF ID: LICHTIGER1994** **Study design and quality:** Double blind RCT Two centres, US Up to 14 days of treatment **Randomisation:** Unclear **Allocation concealment**: Unclear **Blinding:** Double blind. Surgeon blinded. **Outcome assessment:** CAI. Surgeon (blinded) assessed the patient daily for colectomy. **Sample size calculation:** Not reported **Type of analysis: ITT** **Compliance rates:** Not described. N=3 dropout/ withdrawal due to drug related AEs.	**<u>All patients:</u>** **N=20 randomised** **N=20 ITT** **Drop-outs** (don't complete the study): N=3 (15%) **Inclusion criteria:** 18-65 yrs old with severe ulcerative colitis. **Eligible if no response to iv corticosteroid therapy (equivalent to a daily dose of 300 mg of hydrocortisone) after seven or more days**. **Patients with a relapse of active disease after a recent hospitalisation, during which they had responded to iv and then oral corticosteroid therapy, were also eligible if they had no response to an additional 60 hours of iv corticosteroid therapy.** All the patients had a score of 10 or higher on a clinical activity index. The criteria of Lockhart-Mummery and Morison were used to establish the diagnosis of ulcerative colitis and to distinguish this form of colitis from Crohn's colitis. All patients had a colonoscopy or barium enema showing the characteristic changes of ulcerative colitis extending at least to the splenic flexure. If a patients' disease had been inactive for more than one year, flexible sigmoidoscopy of the first 30 cm (or less) of the colon was performed to confirm the disease was once again active. Abdominal x-ray films were obtained to establish the approximate extent of colitis and to exclude perforation or megacolon **Exclusion:**	**Group 1: Ciclosporin** N=11 randomised N=11 (ITT) N=8 (completers) Note: Two patients who did not complete therapy were recorded responders. One patient had a grand mal seizure 12 hrs after beginning therapy and is excluded from the available case analysis. Ciclosporin 4 mg/kg of bodyweight per day by continuous infusion for up to 14 days; The dose never exceeded 4 mg/kg per day. **Group 2: Placebo** N=9 randomised N=9 (ITT) N=9 (completers) Placebo **Responders:** In patients who had a response, therapy was changed to 60 mg of oral prednisolone daily and either oral ciclosporin (6 to 8 mg/kg/day) or oral placebo. If the response was maintained for an additional two days the patients was allowed to go home while continuing to take these medications	**Outcome 1: Clinical improvement (Clinical response):** A clinical-activity score of less than 10 on two consecutive days indicated a positive response. Patients whose score did not meet this criteria or whose condition worsened were considered to have no response to treatment. The mean length of time to a response (second consecutive day on which the clinical-activity score was less than 10) was 7 days (range 3 to 14 days)	**0- ≤2 wks** **Ciclosporin:** 9/11 **Placebo:** 0/9	**Funding:** None reported **Limitations:** Unclear method of randomisation and allocation concealment Trial stopped at n=20 after statistically significant resulted was found between the groups **Additional outcomes:** Blood ciclosporin concentrations
			Outcome 2: Colectomy Ciclosporin: One patient elected to undergo surgery before starting oral therapy. One of the non-responders had a grand-mal seizure, the medication was stopped and they underwent a colectomy. Time to surgery not stated but 0-2 weeks implied	**0- ≤ 2 wks** **Ciclosporin:** 3/11 **Placebo:** 4/9	
			Outcome 3: Adverse events No. of patients experiencing one or more adverse events was not stated		

Author	Patients	Intervention	Outcome measures	Effect size	Comments
	If patients had bacterial or parasitic pathogens in their stools, a positive test for C difficile, septicaemia, perforation of the bowel, megacolon, active fungal or viral infection, or uncontrolled hypertension, or if they had taken mercaptopurine, azathioprine, or any investigational drug within the preceding two weeks. Patients were also excluded if they had elevated serum concentrations of hepatic enzymes (more than three times normal), hyperbilirubinemia (levels more than two times normal), renal dysfunction (serum creatinine concentrations more than 33% above the upper limit of normal), or a serum cholesterol concentration of less than 120 mg per decilitre) **<u>Group 1: Ciclosporin</u>** **Mean age (SD):** 34 (range 18 to 60) **Extent:** Universal 8/11, Left-sided 3/11 **Mean duration of parenteral corticosteroid therapy before the study days (range):** 16 (3 to 30) **Concomitant medication before and during the trial – no. of patients (%):**Sulphasalazine or analogue 5/11 Glucocorticoids or mesalamine enemas 4/11 Antibiotics 8/11 Parental nutrition 1/11 **Mean CAI (range):** 13 (10-16) **Drop outs:** 3 due to AEs. **<u>Group 2: Placebo</u>** **Mean age (SD):** 43 (range 20 to 65) **Extent:** Universal 8/11, Left-sided 1/11 **Mean duration of parenteral corticosteroid therapy before the study days (range):** 17 (3 to 36) **Concomitant medication before and during the trial – no. of patients (%)**: Sulphasalazine or analogue 4/9 Glucocorticoids or mesalamine enemas 5/9 Antibiotics 6/9 Parental nutrition 2/9 **Mean CAI (range):** 14 (12-17) **Drop outs:** 0	**Non-responders:** Underwent colectomy or were offered open-label ciclosporin therapy, administered by continuous infusion in a dose of 4 mg/kg/day for a maximum of 14 days (after they had withdrawn from the trial; the treatment code was not broken) **Concomitant therapy:** **All patients received 100 mg of hydrocortisone iv every 8 hrs and hydrocortisone enemas nightly if the drug could be retained.** Patients receiving mesalamine enemas before study entry continued to receive them if the drug could be retained. Likewise, oral sulphasalazine, olsalazine or mesalamine was continued in the same doses in patients already taking these medications. Patients who were already t taking antibiotics continued to receive them if indicated. The patients were treated with loperamide or codeine in an attempt to control diarrhoea; the use of these drugs was accounted for in the clinical-activity score. Antihypertensive drugs were continued or initiated, as indicated. Three patients were receiving total parental nutrition when they entered the study, but it was not initiated in any patients during the study.	**Ciclosporin:** Parasthesias 4/11 Hypertension 4/11 (2 requiring treatment) Nausea and vomiting 1/11 Grand mal seizure 1/11 **Placebo:** Parasthesias 0/9 Hypertension 1/9 Nausea and vomiting 1/9 Grand mal seizure 0/11 **Mortality** was also reported but it was unclear at how many weeks this occurred. On patient in the placebo group had a colectomy due to clinical deterioration and they later died of gram negative sepsis with superimposed cytomegalovirus infection.		

Table 105: LINDGREN1998

Reference	Patient characteristics	Predictors & outcome measures	Effect sizes	Comments
S. C. Lindgren et al. Early predictors of glucocorticosteroids treatment failure in severe and moderately severe attacks of ulcerative colitis. *European Journal of Gastroenterology & Hepatology;* 10 (10): 831-835. 1998. **Type of study: Retrospective cohort** **Setting:** 4 major Swedish hospitals Sweden **Follow up period:** 30 days **Model development:** Derivation study. Development of the Lindgren Index (externally validated in another paper). Univariate analysis followed by discriminant analysis. **Model presentation:** Unclear how they came up with the linear combination equation and multiplier of 0.14. **Model evaluation:**	**Sample size:** N=97 **<5% missing data?** Unclear whether there is 54 patients having missing data on CRP and bowel movements (56%) **Type of analysis used:** Chi- squared, t-tests. Discriminant analysis was used to construct a predictive index. **Appropriate?** Yes **Inclusion criteria:** • Moderate to severe attacks of UC hospitalized in the Gastroenterology Departments in four major Swedish hospitals during 1988-93 • Diagnosis of UC based on established clinical, endoscopic and histopathological criteria • Disease severe enough to warrant treatment with parenteral nutrition and IV glucocorticosteroids at the time of admission • No patient was included more than once **Data collection** From 1988-93. Majority were recruited from the primary catchment area of each hospital. Extent was determined earlier in a quiescent phase by either colonoscopy or double contrast barium examination, or both or by endoscopy at the time of the current exacerbation. **Treatment given**	**Univariate analysis results:** see the table below **Definitions of predictors**: N/A **Routinely measured?** Yes **Outcome and definition:** Colectomy within 30 days from admission (i.e. clinical steroid resistance) Decision to perform colectomy was based on: continuing ill health or deterioration during steroid treatment, intractable bloody diarrhoea, anaemia or malnutrition. **Blinding:** Unclear. **Risk of measurement error:** Low. **Risk of inter-observer variability:** Low. **Continuous variable analysis:** Cut offs were made for the CRP and bowel movement variables. **Key prognostic factors not included?** No	**Results** 30 days after admission, 33 patients had had a colectomy (34%). No significant difference was found between those who had a colectomy and those that didn't for the following: • Sex • Age • Extension of disease • Number of previous exacerbations • Maintenance treatment • Smoking habits Mean duration of disease and steroid treatment prior to admission were significantly different between the two groups. The strongest predictive factors for colectomy were the number of bowel movements, and passage of blood on day 3 of IV steroid treatment, followed by sustained body temperature elevation the day after initiation of treatment and sustained CRP elevation on day 3. **Results of the discriminant analysis (model predictors) showed only CRP and bowel movements to predict the outcome.** **Variables** / **P value** CRP >25 / p=0.012 Bowel movements >4/day / p<0.001	**Source of funding**: None described. **Risk of bias:** • Retrospective cohort • No validation f (done externally in another paper) • Unclear missing data (?56% missing CRP and bowel movement data) **Additional outcomes reported:** None

<table>
<tr><th>Reference</th><th>Patient characteristics</th><th>Predictors & outcome measures</th><th>Effect sizes</th><th>Comments</th></tr>
<tr>
<td>None reported in this study.
Model performance:
Calibration- Not reported
Discrimination – Sensitivity and specificity were able to be calculated although there appears to be missing data. No AUC published.</td>
<td>4-8mg betamethasone twice daily IV with or without simultaneous administration of rectal steroid in enema forma and was unchanged during the 6 year study.
Baseline characteristics:
42 females, 55 males.
Mean age: 47.5years (range 17-90)
Mean duration of disease: 6.2years (range 0-48, median 2)
Extent of disease: 23 distal, 17 extensive, 57 pancolitis
Day of admission:
≥6 bowel movements/ day: n=77
Blood in stools: n=88
Body temperature >37.5◦C: n=28
Smokers n=10, ex-smokers n=22, non-smokers n=57, unknown n=8.</td>
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<table>
<tr><td>No. of bowel movements + 0.14 x CRP>8.0</td><td>p<0.001</td></tr>
<tr><td colspan="2">Cut off – 8 (decided through the results of a chi-squared test)

The paper describes “using this cut off, only 4/25 (16%) with an index value of <8 required colectomy within 30 days, compared with 13/18 (72%) with an index value of >8.0”.
Which only adds up to 43 patients. The sensitivity and specificity figures have been based on this data but note: there is therefore missing data for 54 patients (16 colectomy patients, 38 non surgery patients).
Further on in the text is written “both in combination and used separately these variable had about 75% sensitivity and specificity for prediction of colectomy”.</td></tr>
</table>
<table>
<tr><th>Cut off</th><th>Colectomy</th><th>No colectomy</th><th>Total</th></tr>
<tr><td>>8</td><td>13</td><td>5</td><td>18</td></tr>
<tr><td><8</td><td>4</td><td>21</td><td>25</td></tr>
<tr><td>Total</td><td>17</td><td>26</td><td>43</td></tr>
</table>
Sensitivity: 13/17 (76.5%)
Specificity: 21/26 (80.8%)
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Table 106: LINDGREN2002 – induction of remission

Author	Patients	Intervention	Outcome measures	Effect size	Comments
S. Lindgren et al. Effect of Budesonide Enema on Remission and Relapse Rate in Distal Ulcerative Colitis and Proctitis. *Scandinavian Journal of Gastroenterology; 37(6): 705-710. 2002.* **REF ID: LINDGREN2002** **Study design and quality:** Double blind RCT Multicentre: 15 centres, Sweden **8 week trial** **Randomisation:** Randomized in blocks of 4. No further information was given. **Allocation concealment**: no information was given. **Blinding:** Double blind **Outcome assessment:** Diary cards and endoscopy (unclear validation) **Sample size calculation:** Detect a difference of 0.25 in the remission rates, 50 per group was required, power 80%, with a 0.05 significance level. **Type of analysis: ITT** (1 patient was excluded from the ITT	**<u>All patients:</u>** **N=150 randomised** **N=149 ITT** **Drop-outs** (don't complete the study): N=29 (19%) <10% difference between the treatment arms. **Inclusion criteria:** • ≥18 years old • Extent: distal to the splenic flexure (confirmed colonoscopy or rigid sigmoidoscopy at entry) • Severity: at least hyperaemia, friability and petechie at endoscopy (score of 2 or 3) and passage of blood per rectum during the last week • At least one previous attack • Maintenance treatment with Salazopyrin or 5-ASA products must be discontinued at study entry **Exclusion:** • Colectomy • Need for concomitant glucocorticosteroids treatment • Received steroids in the previous 2 weeks (except contraceptives) • Allergic to corticosteroids • Pregnant or lactating • Possibly interfering hepatic, renal or cardiovascular disease • Any condition associated with poor compliance **<u>Baseline characteristics</u>** Only given overall: **Sex (m/f):** 69/80 **Mean age (range):** 40.5 (18-75 years) No other information was given.	**Group 1: 2mg budesonide liquid enema** N=73 randomised 2mg/100mls budesonide liquid enema once a day in the evening and a placebo enema in the morning. **Group 2: 4mg budesonide liquid enema** N=76 randomised 2mg/100mls budesonide liquid enema twice a day, once in the morning and once in the evening. **Concomitant therapy:** See inclusion/ exclusion criteria. No further information given.	**Outcome 1: Clinical and endoscopic remission** (absence of clinical symptoms [no blood in stools and <3 bowel movements/24hrs] and endoscopic score or 0-1) N values were calculated from the percentages described in the study.	**<u>4 weeks</u>** **Group1:** 24/73 **Group 2:** 31/76 **<u>8 weeks</u>** **Group1:** 37/73 **Group 2:** 41/76	**Funding:** Associated with AstraZeneca R&D, Sweden **Limitations:** Unclear method of randomization and allocation concealment Very limited baseline characteristics Double blind, no further information given Risk of an indirect population (severity of disease) **Additional outcomes:** Adrenal function Follow up relapse data (part 2 of the trial)
			Outcome 2: Adverse events N values were calculated from the percentages described in the study. Most common AEs were flatulence, abdominal pain, fatigue, respiratory infection and nausea. The twice daily regimen had significantly (p=0.001) increased systemic side effects measured as impaired adrenal function.	**Group1:** 48/73 **Group 2:** 54/76	
			Serious adverse events: There were 5 SAEs in 3 patients, but the treatment group and the reasons were not described in the paper.		

Author	Patients	Intervention	Outcome measures	Effect size	Comments
analysis because they did not receive the medication) **LOCF: last observation carried forward method** **Compliance rates:** not described. N=6 dropout/ withdrawal due to AEs.	**Drop outs:** **2mg budesonide enema:** 15 (10 treatment failures, 3 AEs, 2 other) **4mg budesonide enema:** 13 (10 treatment failures, 3 AEs) 1 who discontinues/ was not treated – unclear which group they had been randomised to.				

Table 107: LINDGREN2002

Author	Patients	Intervention	Outcome measures	Effect size	Comments
S. Lindgren et al. Effect of Budesonide Enema on Remission and Relapse Rate in Distal Ulcerative Colitis and Proctitis. *Scandinavian Journal of Gastroenterology; 37 (6): 705-710. 2002.* **REF ID: LINDGREN2002** **Study design and quality:** RCT **6 month trial** **Randomisation:** No details given for Part 2. Part 1 mentions blocked randomisation. Unclear. **Allocation concealment**: Unclear	**<u>All patients:</u>** **N=77 randomised** **N=76 ITT** (one patient never began treatment (budesonide enema)) **Drop-outs** (don't complete the study): N=3 (3.9%) **Patients who were in remission from Part 1 of the trial (double blind, 8 week trial comparing once a day and twice a day budesonide treatment for the induction of remission) were randomized to two arms of maintenance treatment.** **Inclusion criteria for part 1 of the trial:** ≥18 years old Extent: Distal to the splenic flexure (confirmed by colonoscopy or rigid sigmoidoscopy at entry) Severity: At least hyperaemia, friability and petechie at endoscopy (score of 2 or 3) and passage of blood per rectum during the last week	**Group 1: 2mg budesonide liquid enema twice weekly** N=40 randomised N=39 (ITT) N=23 (completers) 3-4 day interval between the enemas each week. **Group 2: Placebo enema twice weekly** N=37 randomised N=37 (ITT) N=22 (completers) 3-4 day interval between the enemas	Outcome 1: **Relapse** at 24 weeks n values were calculated from percentages given in the paper. Outcome 2: **Adverse events** n values were calculated from the % given. Most common AEs were abdominal pain, nausea, flatulence and diarrhoea. Outcome 3: **Serious adverse events** There were five SAEs in 4 people which were thought not to be treatment related. The treatment group the	**Group1:** 16/39 (41%) **Group 2:** 19/37 (51%) **Group1:** 28/39 (72%) **Group 2:** 24/37 (65%)	**Funding:** Associated with AstraZeneca R&D, Sweden (Author). **Limitations:** Unclear method of randomisation and allocation concealment Unclear blinding No baseline characteristics given **Additional outcomes:** Relapse rates at 8 and 16 weeks

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Blinding: Blind pathologist. Part 1 is double blind. Unclear if Part 2 is. **Outcome assessment:** Rigid sigmoidoscopy every 2 months. Endoscopy score 0 (no visible signs of inflammation) to 3. Clinical symptoms recorded twice weekly in the patient's diaries. First and last visit biopsies were taken (score 1-5) **Sample size calculation:** 2/3 of the patients in Part 1 would enter part 2 and be in remission. Relapse rate 40% in part 2.50 per group, 0.05 significance level, power 80%. **Type of analysis: LOCF. ITT and PPA** **Compliance rates:** Not described. N=0 dropout/ withdrawal due to drug related AEs.	At least one previous attack Maintenance treatment with Salazopyrin or 5-ASA products must be discontinued at study entry **Exclusion part 1 of the trial:** Colectomy Need for concomitant glucocorticosteroid treatment Received steroids in the previous 2 weeks (except contraceptives) Allergic to glucocorticosteroids Pregnant or lactating Possibly interfering hepatic, renal or cardiovascular disease Any condition associated with poor compliance **Group 1: 2mg budesonide enema** **No baseline characteristics given.** **Drop outs:** 3 other **Group 2: Placebo enema** **No baseline characteristics given.** **Drop outs:** 0 **Definitions** **Remission:** Absence of clinical symptoms (no blood in stools and <3 bowel movement /24hrs and endoscopic score 0-1. **Relapse:** Presence of clinical symptoms (blood in stools and ≥3 bowel movements/24hrs) or endoscopic score of 2-3.	each week. **Concomitant therapy:** See inclusion/exclusion criteria. No other information given.	patients were in and what the SAE was, was not described.		

Table 108: LOFTBERG1994

Author	Patients	Intervention	Outcome measures	Effect size	Comments
R. Loftberg et al.	**All patients:**	**Group 1: 2.3mg**	**Outcome 1: Endoscopic**	**4 weeks**	**Funding:**

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Budesonide versus prednisolone retention enemas in active distal ulcerative colitis. *Alimentary Pharmacology and Therapeutics; 8: 623-629. 1994.* **REF ID: LOFTBERG1994** **Study design and quality:** Single investigator blind RCT Multicentre: 11 centres, Sweden, Denmark & Norway **8 week trial** **Randomisation:** Randomised separately in blocks of 6 at each centre by a computer programme. **Allocation concealment**: Adequate **Blinding:** Single investigator blind **Outcome assessment:** Endoscopy according to Truelove & Richards. **Sample size calculation:** 80% power including withdrawals, n=100. No significance level quoted. **Type of analysis: ITT** (all those randomised apart from one patient who did not take the medication)	**N=101 randomised** **N=100 ITT** (received the medication) **Drop-outs** (don't complete the study): N=22 (22%) 12 in the budesonide group and 10 in the prednisolone group. <10% difference in drop out rates between treatment arms. **Inclusion criteria:** • Adults, >18 years • Definitive diagnosis: history of diarrhoea and rectal bleeding, endoscopic findings and exclusion of infective cause • Had ≥1 previous attack • Extent: not beyond the splenic flexure (endoscopy verified) • Justification of needing rectal glucocorticosteroids (endoscopy grade>2) • Blood in the stools for preceding week • Severity: not described **Exclusion:** • Use of glucocorticosteroids within the two weeks prior to the start of the study or during the study • Other rectal treatment • Pregnancy or breast feeding **<u>Baseline characteristics</u>** **<u>Group 1: 2.3mg budesonide liquid enema</u>** **Sex (m/f):** 22/23 **Mean age (SD):** 41 (15) **Extent- distance anus-healthy tissue at entry, cm:** 22.1 (13.7) **Drop outs:** 12 (10 treatment failure, 1 misunderstanding, 1 AE) **<u>Group 2: 31.25mg prednisolone liquid enema</u>** **Sex (m/f):** 37/18 **Mean age (SD):** 38 (12)	**Budesonide liquid enema** N=45 randomised 2.3mg budesonide (Entocort) in 115mls liquid enema. Once daily at bedtime. **Group 2: 31.25mg prednisolone liquid enema** N=55 randomised 31.25mg prednisolone disodium phosphate in 125mls liquid enema. Once daily at bedtime. **Concomitant therapy:** Oral sulphasalazine, olsalazine or 5-ASA was allowed to be continued only if it had been taken during the 2 weeks prior to entry and at a constant dose then and during the trial.	**remission** (score of 0) n values were calculated from the percentages given in the paper. Last value extended principle.	**Group1:** 7/45 **Group 2:** 14/55 **<u>8 weeks</u>** **Group1:** 18/45 **Group 2:** 28/55	Grant from Astra Draco AB, Lund, Sweden **Limitations:** Single investigator blind Limited baseline characteristics Risk of indirect population: severity of disease not described **Additional outcomes:** Histological remission Cortisol levels Osteocalcin levels
			Outcome 2: Clinical and endoscopic remission (endoscopic remission and ≤3 stools/day without blood) n values were calculated from the percentages given in the paper. Last value extended principle.	**<u>4 weeks</u>** **Group1:** 7/45 **Group 2:** 13/55 **<u>8 weeks</u>** **Group1:** 16/45 **Group 2:** 26/55	
			No data was given for adverse events, but it was reported that there were slightly more in the budesonide group. Many were GI complaints (mild). Two patients got acne (1 in each group).		

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Compliance rates: Classed as taking 75% of the medication. No patients were assessed as non compliant. N=1 dropout/ withdrawal due to drug related AEs (perianal pain)	**Extent- distance anus-healthy tissue at entry, cm:** 20.2 (13.5) **Drop outs:** 10 (9 treatment failures, 1 misunderstanding) There was a difference in gender ratio- stratification was carried out and found that the difference in gender was no importance in the analysis.				

Table 109: LUDVIGSSON2002

Author	Patients	Intervention	Outcome measures	Effect size	Comments
J. F. Ludvigsson et al. Inflammatory bowel disease in mother or father and neonatal outcome. *Acta Paediatrica, 91: n145-151. 2002.* **REF ID: LUDVIGSSON2002** **Study design and quality:** Cross sectional study **Sweden** **Years studied: October 1997-October 1999** **Risk of bias:** Selection bias: unclear. Some adjustment made for confounders. No description of disease severity. Performance bias: unclear Attrition bias: high risk. Unclear	The study looked at IBD in the mother or father, adjusting for confounders, on the newborn infant. **<u>All patients:</u>** Included population • 21,700 babies born in South East Sweden between October 1997-1999 were invited to join the ABIS (All Babies In Southeast Sweden) study which was a prospective screening programme for the prediction of autoimmune diseases Excluded population • 7 patients could not confirm their diagnosis of Crohn's or UC • 271 twins • Mother infant pairs where the mother had coeliacs disease, lactose intolerance or cow's milk allergy (as they may mimic IBD or be associated with adverse neonatal outcome). Fathers suffering from those diseases and mothers that had IBD were also excluded. This was not applicable for the controls. **N=26 UC mothers**	**Autoimmune controls** Suffered from non diabetic autoimmune disease (Hashimoto's disease/ hypothyreosis, Grave's disease/ hyperthyreosis, Vitamin B_{12} anaemia, SLE/lupus erythematosus, Mb Addision, rheumatoid arthritis) **Mothers with ulcerative colitis** **N=26** **Group 1:** N=4 (took steroids and mesalazine during pregnancy) **Group 2:** N=3 (took steroids	**The only reported outcome for the mothers with UC in relation to medication taken during pregnancy was low birth weight**		**Funding:** Supported by the JDF Wallenberg Foundation, the Swedish Medical Research Council, the Swedish Child Diabetes Foundation (Barndiabetesfonden), Söderbergs Foundation and Novo Nordisk Foundation. **Limitations:** High risk of attrition bias. Unclear risk of selection, performance and detection bias **Additional outcomes:** Birth outcomes by disease (preterm birth, birth weight) **Notes:**
			Outcome: Low birth weight (<2.5kg)	**Group 1:** 1/3 (33%) **Group 2:** 0/4 (0%) **Group 3:** 0/5 (0%) **Group 4:** 0/2 (0%) **Group 5:** 0/1 (0%) **Group 6:** 0/1 (0%) **Group 7:** 0/10 (0%)	
			It is described in the paper that the mothers with ulcerative colitis that used mesalazine during pregnancy "was associated with an even lower birth weight (3121g), as was the use of steroids during pregnancy".		

Author	Patients	Intervention	Outcome measures	Effect size	Comments
dose and duration of therapy Detection bias: unclear. Some patients may have only used a questionnaire, risk of recall bias.	<u>Data collection</u> ABIS study includes information collected from questionnaires. Soon after birth, mothers were given a questionnaire whilst on the maternity ward. Peri-natal questionnaire was 117 questions which were to be answered in hospital or at home. These questions were based on IBD (UC or Crohn's disease). Complementary questionnaire was sent out to all mothers and fathers with IBD to confirm their diagnosis and specify the type of IBD. Mothers were asked about medication during pregnancy. Some diagnoses were validated via telephone or interviewed by the main author. Any uncertainty relating to diagnosis was confirmed by contacting the patient's regular doctor. Disease activity measure: hospitalisation due to IBD during pregnancy **Assumption:** use of medication would reflect the severity of disease <u>Baseline characteristics</u> No baseline characteristics were described.	during pregnancy) **Group 3:** N=5 (took mesalazine during pregnancy) **Group 4:** N=2 (took SASP during pregnancy) **Group 5:** N=1 (took SASP and mesalazine during pregnancy) **Group 6:** N=1 (took olsalazine during pregnancy) **Group 7:** N=10 (took no steroids or 5-ASAs during pregnancy)			Two mothers were hospitalized for UC. No further details given.

Table 110: MANTZARIS1994

Author	Patients	Intervention	Outcome measures	Effect size	Comments
G. J. Mantzaris et al. Intermittent Therapy with High-Dose 5-Aminosalicylic Acid Enemas Maintains Remission in Ulcerative Proctitis and Proctosigmoiditis. *Diseases of the Colon and Rectum; 37(1):58-62.1994.*	**<u>All patients:</u>** **N=38 randomised** **Drop-outs** (don't complete the study): N=0 (0%) **Inclusion criteria:**	**Group 1: Oral mesalazine (1.5g/day)** N=19 randomised 0.5g of mesalazine (Eudragit L coated, Salofalk) three times per day.	Outcome 1: **Relapse**	**Group1:** 13/19 (68%) **Group 2:** 5/19 (26%) **Log rank test: p<0.001**	**Funding:** None described. **Limitations:** Unclear method of randomisation and allocation concealment

Author	Patients	Intervention	Outcome measures	Effect size	Comments
REF ID: MANTZARIS1994 **Study design and quality:** Single blind RCT **2 year trial** **Randomisation:** Not described. Unclear. **Allocation concealment**: Not described. Unclear. **Blinding:** Physician and histopathologist blinded. **Outcome assessment:** Daily recording of clinical symptoms included AEs. Endoscopy graded by Riley et al. from 0(normal) to grade 4. Histology assessed by Friedman et al. and D'Arienzo et al criteria. **Sample size calculation:** None described. **Type of analysis: ITT** **Compliance rates:** 100% in both treatment groups. N=0 dropout/ withdrawal due to drug related AEs.	• Extent: Distal Colitis (proctosigmoiditis or proctitis) which was endoscopically and histologically confirmed • Severity of previous relapse: Mild, moderate or severe • All patients were maintained in full clinical endoscopic and histologic remission on oral SASP or mesalazine and had not been taking steroids for at least two months before study entry **Exclusion:** • None described. **<u>Group 1: Oral mesalazine</u>** **Mean age (range):** 38 (15-69) **Extent:** proctitis n=11, proctosigmoiditis n=8 **Time from previous relapse:** 3-6months n=10, 6-8months n=9 **Severity of previous relapse:** not described by treatment group (see below) **Frequency of relapses:** 0-1 per year n=11, 2-3 per year n=8 **Treatment of previous attacks:** oral SASP/5-ASA n=15/4, and steroid enemas n=4, or 5-ASA enemas n=8 or, oral and rectal steroids n=7 **Drop outs:** 0 **<u>Group 2: Rectal mesalazine</u>** **Mean age (range):** 39 (16-70) **Extent:** proctitis n=10, proctosigmoiditis n=9 **Time from previous relapse:** 3-6months n=12, 6-8months n=7 **Severity of previous relapse:** not described by treatment group (see below) **Frequency of relapses:** 0-1 per year n=12, 2-3 per year n=7 **Treatment of previous attacks:** oral SASP/5-ASA n=14/5, and steroid enemas n=5, or 5-ASA enemas n=6 or, oral and rectal steroids n=8 **Drop outs:** 0 Severity of previous relapse: 1 patient was severe, 22 were moderate and 15 were mild according to the criteria of Truelove & Witts. 9 patients were taking oral mesalazine, and 29 patients were taking oral SASP. After enrolment oral SASP was stopped and patients were randomly assigned to receive either oral mesalazine or the mesalazine enemas. **<u>Definitions</u>**	**Group 2: Intermittent mesalazine enemas (4g/3days)** N=19 randomised 4g of mesalazine enema (Salofalk) every third night. **Concomitant therapy:** See inclusion criteria. No further information was given.		**Of those relapses the severity was:** **<u>Mild</u>** **Group 1: 7/13** **Group 2: 3/5** **<u>Moderate</u>** **Group 1: 5/13** **Group 2: 2/5** **<u>Severe</u>** **Group 1: 1/13** **Group 2: 0/5** When stratified by extent of the lesions, p<0.01	Single blind **Additional outcomes:** Number of relapses in year 1 and 2 separately **Notes:** No treatment related local or systemic side effects were recorded. All patients were previously on SASP or mesalazine prior to study
			Outcome 2: **Colectomy** One patient taking oral mesalazine although had endoscopically and histologically confirmed proctosigmoiditis, developed fulminant colitis with toxic megacolon and underwent an emergency colectomy. It was found in histology that they had universal colitis.	**Group1:** 1/19 **Group 2:** 0/19	

Author	Patients	Intervention	Outcome measures	Effect size	Comments
	Remission: Full clinical, endoscopic and histological remission (indexes not described) **Relapse:** Erythema and loss of vascular pattern were found at endoscopy and if the histology of biopsy specimens taken from these areas showed the presence of acute and chronic inflammatory cell infiltrate.				

Table 111: MANTZARIS2004

Author	Patients	Intervention	Outcome measures	Effect size	Comments
G. J. Mantzaris et al. A Prospective Randomized Observer-Blind 2-Year Trail of Azathioprine Monotherapy versus Azathioprine and Olsalazine for the maintenance of remission of Steroid-Dependent Ulcerative Colitis. *American Journal of Gastroenterology; 99 6): 1122-1128. 2004.* **REF ID: MANTZARIS2004** **Study design and quality:** Single blind RCT Single centre, Greece **2 year trial** **Randomisation:** Not described. **Allocation concealment**: Not described **Blinding:** Single blind.	**<u>All patients:</u>** **N=70 randomised** **Drop-outs** (don't complete the study): N=7 (10%) <10% difference in missing data between the treatment arms **Inclusion criteria:** • Established UC confirmed by colonoscopy and biopsies and a chronic relapsing course for at least 1 year before study entry • **Steroid dependent UC in complete clinical, endoscopic and histologic remission only on oral azathioprine and olsalazine and off steroids for at least 1 month prior to randomisation** • 18 <65 years **Exclusion:** • Active UC (UCDAI>3) • UC maintained in remission on steroids • Evidence of epithelial dysplasia of the colon or any malignancy within 5 years • Existing or intended pregnancy • Breast feeding women • Absence of serum IgG class antibodies to Epstein-Barr virus • Regular use of allopurinol NSAIDs or antibiotics	Adjustment of AZA dose was allowed according to the protocol. If leucopenia, thrombocytopenia, or hepatotoxicity was observed, AZA was discontinued until tests were normalized. Then AZA was introduced at half its dose use at discontinuation. They were then only in the PPA. **Group 1: Azathioprine** N=34 randomised N=25 (completers) 2.2mg/kg of azathioprine per day. **Group 2: Azathioprine & olsalazine** N=36 randomised	**Outcome 1: Relapse** Unable to calculate the hazard ratio. The p value is given for the Kaplan Meier, but the graph includes discontinuations due to adverse events so it cannot be used. **Outcome 2: Mean IBDQ score**	**<u>1 year</u>** **Group1:** 3/34 **Group 2:** 4/36 **<u>2 years</u>** **Group1:** 5/34 **Group 2:** 6/36 **<u>Baseline</u>** **Group1:** 199 (SD 17.25), n=34 **Group 2:** 201 (SD 7.93), n=36) **<u>End of 2 years</u>** **Group1:** 180 (SD 35.1), n=34	**Funding:** None described. **Limitations:** Unclear method of randomisation and allocation concealment Single blind **Additional outcomes:** Sum of the IBDQ scores over the whole time period **Notes:** **There was no difference in the time to relapse of disease (data was not shown).** Severities of the relapses were mild/moderate and controlled by shorter than usual courses of oral steroids.

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Outcome assessment: UCDAI, IBDQ (scored from 32(poor QofL) to 224), sigmoidoscopy and colonoscopy. **Sample size calculation:** 90% power, 50% relapse rate in AZA group reduction of 30% in the combination group, 50 patients per arm. **Type of analysis: ITT and PPA** **Compliance rates:** Counting returned tablets. Non compliant if they had not taken treatment for >4 days in the preceding month. **It was better for the AZA group (97% vs. 87%).** N=7 dropout/ withdrawal due to AEs.	• Heart, pulmonary, liver, or renal failure • Denial of written informed consent **Group 1: Azathioprine** **Mean age (range):** 35 (20-55 years) **Mean disease duration (range):** 4 (2-7 years) **Extent:** total n=11, left sided n=14, sigmoiditis n=9 **Mean prior steroids sessions (range):** 6 (3-10) **Mean time from initiation of induction treatment to cessation of steroids (range):** 15.8 (7.5-19 weeks) **Mean disease remission (range):** 5 (4.5-6.5) weeks **Mean time off steroids (range):** 8.5 (7-9.5) weeks **Mean level of steroid dependency (range):** 12.5 (7.5-20mg) **Severity of previous relapse:** Not described. **Frequency of relapses:** Not described. **Drop outs:** 4 (4 due to AEs) **Group 2: Azathioprine & olsalazine** **Mean age (range):** 33 (21-60 years) **Mean disease duration (range):** 5 (2.5-8 years) **Extent:** total n=12, left sided n=13, sigmoiditis n=11 **Mean prior steroids sessions (range):** 7 (4-10) **Mean time from initiation of induction treatment to cessation of steroids (range):** 15.3 (8-20 weeks) **Mean disease remission (range):** 5.5 (4.5-7) weeks **Mean time off steroids (range):** 8 (6.5-9.5) weeks **Mean level of steroid dependency (range):** 12 (7.5-25mg) **Severity of previous relapse:** Not described. **Frequency of relapses:** Not described. **Drop outs:** 3 (3 due to AEs) **Definitions** **Remission:** Absence of symptoms of colitis in view of a normal sigmoidoscopy with biopsies (UCDAI 0-1). **Relapse:** Development of new symptoms sufficiently severe to warrant treatment with steroids in view of an abnormal sigmoidoscopy (UCDAI>3) **Steroid dependence:** At least two course of oral or IV steroids for exacerbation of colitis within the year preceding randomization, but the disease relapsed anytime the dose of steroids had been reduced to less than 15mg/day.	N=27 (completers) 2.2mg/kg of azathioprine per day and 0.5g olsalazine three times a day (1.5g/day). Olsalazine used was Dipentum. If diarrhoea occurred during the treatment olsalazine was halved for 2-3days. If it then settled the dose was increased over 5-7 days. Azathioprine was Imuran. **Concomitant therapy:** See inclusion/ exclusion criteria.		**Group 2:** 180 (SD 38), n=36	
			Outcome 3: Serious adverse events Group 1: 2 severe diarrhoea, 1 leucopenia Group 2: 1 leucopenia, 1 pancreatitis, 1 transaminemia.	**Group1:** 3/34 **Group 2:** 3/36	
			Adverse events It is unclear whether patients have experienced more than one adverse event, so the data could not be analysed. **Note the leucopenia differences which were significant.** **Group 1: transient leucopenia (5),** respiratory infection (26), urinary infection (1), other infection (3), transient diarrhoea (4), abdominal pain (2), rashes (5), paresthesias (1), other minor events (17) **Group 2: transient leucopenia (12),** respiratory infection (42), urinary infection (2), other infection (6), transient diarrhoea (12), abdominal pain (15), rashes (8), paresthesias (2), other minor events (20)		

Table 112: MARAKHOUSKI2005

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Y. Marakhouski et al. A double-blind dose-escalating trial comparing novel mesalazine pellets with mesalazine tablets in active ulcerative colitis. *Alimentary Pharmacology & Therapeutics; 21: 133-140. 2005.* **REF ID: MARAKHOUSKI2005** **Study design and quality:** Double blind RCT Multicentre: 21 centres, Belarus (1 centre), Russia (6 centres), Czech Republic (8 centres), Slovak Republic (6 centres) **8 week trial** **Randomisation:** Unclear **Allocation concealment**: Unclear **Blinding:** Double blind, double dummy. **Outcome assessment:** CAI and EI **Sample size calculation:**230 patients needed to prove the non-inferiority of the pellets compared with tablets,	**<u>All patients:</u>** **N=233randomised** N=232 (safety population; 1 patient was lost to follow up) **N=229 ITT** **Drop-outs** (don't complete the study): Unclear. Protocol violations: 31 Poor drug compliance (23), 5-ASA pre-treatment with none permitted dosage (5), drug intake <12 days or premature termination because of reason s other than non-efficacy or adverse events (4), baseline CAI<6 (2), dose increase not according to protocol (2), failure to confirm UC (1) **Inclusion criteria:** 18 to 70 years old Extent: ≥15cm beyond the anal margin Severity: Mild to moderately active UC (CAI score of 6-12) and an EI score of ≥4 Diagnosis of active ulcerative colitis required confirmatory endoscopy, histology and negative stool culture **Exclusion:** Use of 5-ASA at a dose higher than 500mg/day on the 7 days prior to baseline Crohn's disease	**Group 1: 1.5-3g mesalazine pellets** **Salofalk** N=115 randomised N=114 (ITT) N=98 (PPA) 0.5g was given in three doses of the mesalazine pellets. The pellets were coated in Eudragit L. Placebo tablets were also given. The pellets were <2mm in size, dissolved at a pH≥6 in the ileocaecal region. **Group 2: 1.5-3g mesalazine tablets** N=118 randomised N=115 (ITT) N=100 (PPA) 0.5g was given in three doses of the mesalazine tablets. The tablets were coated in Eudragit	Outcome 1: **Clinical remission** (CAI≤4) (39% of the patients receiving the pellets had to increase the dose compared to 45% in the tablets group (not statistically significant)	**<u>3 weeks (1.5g/day)</u>** **Group1:**54/114 (47%) **Group 2:**48/115 (42%) **<u>8 weeks (1.5-3.0g)</u>** **Group1:**76/114 (67%) **Group 2:**78/115 (68%)	**Funding:** Dr .Falk Pharma GmbH, Germany. **Limitations:** Unclear method of randomisation and allocation concealment Unclear dropout rate No further description of double blinding **Additional outcomes:** Time to first response Endoscopic improvement Histological improvement PGA
			Outcome 2: **Adverse events** Adverse drug reactions were thought to be in 15 and 11 patients in the pellets and tablet groups respectively.	**Group1:**36/114 **Group 2:**42/118	
			Outcome 3: **Serious adverse events**	**Group1:**0/114 **Group 2:**2[u]/118	

[u] Both due to worsening of disease.

Author	Patients	Intervention	Outcome measures	Effect size	Comments
assuming the difference would be ≤20% (α=2.5%, β=20%) **Type of analysis: ITT and PPA** **Compliance rates:** Not described. N=5 dropout/ withdrawal due to AEs (1 in the pellet group and 4 in the tablet group)	Any prior bowel surgery, except appendectomy Current relapse occurring while patients were on maintenance treatment with 5-ASA >3.5g or sulfasalazine >9g in the week prior to inclusion Toxic megacolon Confirmation of pathogenic micro-organisms and bacterial or viral bowel disease Severe acute episode (CAI>12) Active cancer or a history of colorectal cancer and gastric or duodenal ulcer Oral/rectal steroids on more than 3 days within 1 week before the start of the study Ingestion/ use of immunosuppressant's within 4 weeks prior to the start of the study Ingestion/ use of NSAIDs as permanent treatment, except acetylsalicylic acid ≤100mg/day and paracetamol for analgesic use **Group 1: Mesalazine pellets** **Mean age (SD):**41.9 (No SD given) **Extent:** proctosigmoiditis n=51, left-sided n=45, subtotal n=18 **Mean CAI:** 7.8 **Mean EI:** 7.1 **New diagnosis of UC:** 8.8% **Pre-treatment with oral 5-ASA:** 31% **Pre-treatment with rectal 5-ASA:** 11% **On previous maintenance treatment when relapsed:** 44% **Drop outs:** 1 due to AEs (worsening of UC) **Group 2: Mesalazine tablets** **Mean age (SD):**39.5 (No SD given) **Extent:** proctosigmoiditis n=52, left-sided n=41, subtotal n=22 **Mean CAI:** 7.8 **Mean EI:** 7.4 **New diagnosis of UC:** 8.7%	L. Placebo pellets were also given. In the case of inadequate response to 1.5g 5-ASA/day the daily dose could be increased to 3g 5-ASA not earlier than at the first flow up visit i.e. after about 2 weeks. The dosage was allowed to be increased only once and this increased dosage had to be maintained for the remainder of the study period. **Concomitant therapy:** See inclusion/exclusion criteria.			

Author	Patients	Intervention	Outcome measures	Effect size	Comments
	Pre-treatment with oral 5-ASA: 30% **Pre-treatment with rectal 5-ASA:** 8% **On previous maintenance treatment when relapsed:** 37% **Drop outs:** 4 due to AEs (1 due to worsening of UC, 1 erythematous rash, 1 urticaria and the other due to nausea)				

Table 113: MARTEAU1998

Author	Patients	Intervention	Outcome measures	Effect size	Comments
P. Marteau et al. Use of mesalazine slow release suppositories 1g three times per week to maintain remission of ulcerative proctitis: a randomised double blind placebo controlled multicentre study. *Gut; 42: 195-199.1998.* **REF ID: MARTEAU1998** **Study design and quality:** Double blind RCT Multicentre: 22 centres, France **1 year trial** **Randomisation:** Performed in each centre using sealed envelopes. **Allocation concealment**: Sealed envelopes- unclear whether they were opaque or not.	**<u>All patients:</u>** **N=95 randomised** **Drop-outs** (don't complete the study): N=21 (22.1%) **Inclusion criteria:** Older than 18 years Not pregnant Extent: cryptogenetic proctitis (ulcerative proctitis is described in the text) Experienced at least two episodes of acute proctitis in the year preceding inclusion Clinical remission for less than two weeks at inclusion with an endoscopy score of 0 or 1. **Exclusion:** Cause of proctitis other than ulcerative colitis (infectious, drug induced, radiotherapy, Crohn's disease)	**Group 1: 1g mesalazine (Pentasa) suppositories** N=48 randomised 1g mesalazine (Pentasa) suppositories, three times a week (and not on consecutive days). Total of 13.3g/month. **Group 2: Placebo suppositories** N=47 randomised Placebo suppositories, three times a week. **Concomitant therapy:** See exclusion criteria.	Outcome 1: **Relapse** by 1 year Unable to calculate the hazard ratio. Outcome 2: **Adverse events** Group 1: 4 (anal or rectal pain or difficultly with introducing the suppository), 1 due to asthenia, hypotension and moderate leucopenia at 9 months of treatment (resolved without changing the treatment), 1 due mild hair loss after one month (found not to be significant by the patient and doctor), 1 due to intolerance (anal or rectal burning)	**Group1:** 10/48 **Group 2:** 24/47 **Group1:** 6/48 **Group 2:** 5/47	**Funding:** Ferring SA, France **Limitations:** Unclear method of randomisation. Unsure whether the allocation concealment was sufficient. Mean duration of previous relapse was unbalanced between the two groups. High drop out rate Double blind but then no further information was given. **Additional outcomes:** Reduction of the risk of relapse depending on time

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Blinding: Says double blind, but no further information was described. **Outcome assessment:** Endoscopy scores (0- normal mucosa or etythema to 5 which was deep ulcers) **Sample size calculation:** 93 patients, based on 90% power, type I error of 0.05 to detect a difference of 35% in relapse rate with the log rank test. **Type of analysis: ITT** **Compliance rates:** Not described. N=3 dropout/ withdrawal due to AEs (intolerance).	Pregnancy Hypersensitivity to salicylates Resistance to salicylates during previous acute episode Any other maintenance treatment of ulcerative colitis except previously prescribed oral salicylates provided that the dose was not changed during the whole study period. **<u>Group 1: 1g mesalazine suppositories (intermittent)</u>** **Mean age (SD):** 41.5 (13.5) **Mean extent (SD):** 9.6 cm (6.8) **Severity of previous relapse:** Not described. **Mean no. of episodes in the last year (SD):**2.6 (1.5) **Mean duration of the last episode (SD):** 77 days (68) **Oral treatment (% subjects):** 56.3, n=27 **Endoscopy score of 0:** 50.0% **Drop outs:** 9 (2 lost to follow up, 2 pregnancies, 1 due to intolerance, 4 due to decision of the patient) **<u>Group 2: Placebo suppositories</u>** **Mean age (SD):** 41.2 (11.8) **Mean extent (SD):** 7.6 cm (6.0) **Severity of previous relapse:** Not described. **Mean no. of episodes in the last year (SD):** 3.1 (2.1) **Mean duration of the last episode (SD):** 57 days (63) **Oral treatment (% subjects):** 53.2, n=24 **Endoscopy score of 0:** 44.7% **Drop outs:** 12 (1 lost to follow up, 2 pregnancies, intolerance 2 patients, 7 due to decision of the patient) Clinical parameters were also recorded and were not significantly different between the two treatment groups. **The duration of the episode preceding inclusion was significantly longer in the mesalazine group.** Oral treatment consisted of 5-ASA in 24 and 23 patients of the mesalazine and placebo groups respectively with a daily dose of 1.9 (0.8) g in each group, SASP was 3 and 1 patients in each group respectively. <u>Definitions</u>		Group 2: 4 (anal or rectal pain or difficultly with introducing the suppository), 2 due to intolerance (anal or rectal burning) NB. The above are the number of events, the figures analysed are the number of people with one or more adverse event		intervals Mean time to relapse for both groups for those on oral and not on oral treatment Mean survival without relapse **Notes:** Risk of relapse was not significantly influenced in any group by the endoscopy score at entry (0 or 1) (log rank p=0.26). It was also not influenced by the presence or absence of associated oral treatment (p=0.25).

Author	Patients	Intervention	Outcome measures	Effect size	Comments
	Clinical remission: No rectal bleeding, no mucus in the stools, no diarrhoea, no pain, and no tenesmus. **Relapse:** Occurrence of clinical symptoms with an increase in the endoscopy score ≥1 when compared with the endoscopy score at entry, or occurrence of rectal bleeding more than twice in one day				

Table 114: MARTEAU2005 & CONNOLLY2009B

Author	Patients	Intervention	Outcome measures	Effect size	Comments
P. Marteau et al. Combined oral and enema treatment with Pentasa (mesalazine) is superior to oral therapy alone in patients with extensive mild/moderate active ulcerative colitis: a randomised, double blind, placebo controlled study. *Gut; 54: 960-965. 2005* & **M. P. Connolly et al.** Quality of Life Improvement Attributed to Combination Therapy with Oral and Topical Mesalazine in Mild-to-Moderately Active Ulcerative Colitis. *Digestion; 80: 241-246. 2009.* **REF ID: MARTEAU2005, CONNOLLY2009B** **Study design and quality:** Double blind RCT	**<u>All patients:</u>** **N=127 randomised** **Authors ITT definition:** patients who received the study drug at least once and who had at least one evaluation of efficacy after baseline. **Drop-outs** (don't complete the study): N=21 at 4 weeks (16.5%), <10% difference between the two treatment arms N= 29 at 8 weeks (22.8%) , > 10% difference between the two treatment arms **Inclusion criteria:** • >18 years • Extent: Extensive UC • Severity: active mild/ moderate UC, UCDAI≥3≤8 **Exclusion:** • Infectious colitis • Oral maintenance treatment with >3g sulphasalazine, mesalazine, or 4-ASA within 30 days prior to study • Any immunosuppressive drugs 7 days prior to study • Steroids 7 days prior • Bisulfate, salicylates allergy • Clinically important hepatic, renal, cardiovascular or psychiatric	Oral mesalazine for 8 weeks, the first 4 weeks was in addition to an enema. **Group 1: 4g oral mesalazine and placebo liquid enema** N=56 randomised N=47 (completers at week 4) N=40 (completers at week 8) 2g mesalazine (2 x 1g sachets, Pentasa) given twice a day, and a placebo liquide enema given at night. **Group 2: 4g oral mesalazine and 1g rectal mesalazine liquid enema** N=71 randomised	**Outcome 1: Clinical remission** (UCDAI≤1) MARTEAU2005 **Outcome 2: Clinical improvement** (decrease in UCDAI >2 points) MARTEAU2005	**Author reported ITT analysis** **<u>4 weeks</u>** **Group1:** 16/47 **Group 2:** 25/57 **<u>8 weeks</u>** **Group1:** 20/47 **Group 2:** 37/58 **Author reported ITT analysis** **<u>4 weeks</u>** **Group1:** 29/47 **Group 2:** 51/57	**Funding:** Sponsored by Ferring Pharmaceuticals **Limitations:** Unclear method of randomisation and allocation concealment >10% difference in missing data from the two treatment arms at 8 weeks Stated to be double blind, no further information given **Additional outcomes:** Rectal bleeding Acceptability of combination therapy

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Multicentre: France, UK, Spain, Germany, Netherlands, Sweden **PINCE trial** **4 & 8 week trial** **Randomisation:** Not described. Unclear. **Allocation concealment**: Unclear. **Blinding:** Stated to be double blind. No further information given. **Outcome assessment:** UCDAI. EQ5D. **Sample size calculation:** 30% remission at 4 weeks in group 1, 50% group 2, N=186 **Type of analysis: ITT, PPA** **Compliance rates:** Not described. N=20 dropout/ withdrawal due to AEs. Unclear if these were drug related.	conditions • Pregnancy • Lactation • Inability to follow the protocol **<u>Baseline characteristics</u>** **<u>Group 1: 2g mesalazine (Pentasa) and 1g mesalazine enema (Pentasa)</u>** **Sex (m/f):** 44/27 **Median age (range):** 42 (18-76) **Extent:** All extensive **Duration of UC:** <1 year n=17, 1-10 years n=37, >10 years n=17 **Drop outs by 4 weeks:** 12 (9 AEs, 2 patient decision, 1 other) **Additional drop outs by 8 weeks:** 1 investigator decision **<u>Group 2: 2g mesalazine (Pentasa) and placebo enema</u>** **Sex (m/f):** 32/24 **Median age (range):** 47 (19-79) **Extent:** All extensive **Duration of UC:** <1 year n=8, 1-10 years n=28, >10 years n=20 **Drop outs by 4 weeks:** 9(6 AEs and 3 investigator decision **Additional drop outs by 8 weeks:** 7(5 AEs, 1 patient decision, 1 other)	N=59 (completers at week 4) N=58 (completers at week 8) 2g mesalazine (2 x 1g sachets, Pentasa) given twice a day, and 1g liquid mesalazine (Pentasa) enema given at night. **Concomitant therapy:** See the inclusion/ exclusion criteria.		**<u>8 weeks</u>** **Group1:** 32/47 **Group 2:** 50/58	
			Outcome 3: Quality of Life (EQ5D) SD are in brackets. CONNOLLY2009B	**<u>Baseline scores</u>** **Group1:** 0.762 (0.181) **Group 2:** 0.788 (0.162) **<u>2 week scores</u>** **Group 1:** 0.836 (0.198) **Group 2:** 0.853 (0.159) **<u>4 week scores</u>** **Group 1:** 0.838 (0.203) **Group 2:** 0.906 (0.151) **<u>8 week scores</u>** **Group 1:** 0.862 (0.199) **Group 2:**	

Author	Patients	Intervention	Outcome measures	Effect size	Comments
				0.914 (0.150)	
			Outcome 4: Adverse events MARTEAU2005 Group 1: Most common diarrhoea (4%), headache (4%) and vomiting (3%) Group2: Most common abdominal pain 4%	**At 8 weeks** **Group1:** 28/56 **Group 2:** 24/71	
			Outcome 5: Serious adverse events MARTEAU2005 Due to aggravation of UC symptoms, painful defecation, vomiting, abdominal pain and/or bloody diarrhoea.	**At 8 weeks** **Group1:** 1/56 **Group 2:** 3/71	

Table 115: MATEJIMENEZ2000

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Maté-Jiménez J et al. 6-mercaptopurine or methotrexate added to prednisone induces and maintains remission in steroid-dependent inflammatory bowel disease. Eur J Gastroenterol Hepatol; 12(11):1227-33. 2000 **REF ID: MATEJIMENEZ2000**	**Induction of remission followed by maintenance of remission phase.** **All patients:** **N=34 randomised** (included both UC and CD patients, N=72 – but UC data was presented separately). **N=20 achieved remission and entered the maintenance of remission phase** **Drop-outs** (don't complete the study):	**Group 1: Mercaptopurine (+prednisone)** N=14 randomised N=14 (ITT) N=11 (completed 30 wks and obtained remission)	**Outcome 1: Relapse** Unable to calculate the hazard ratio. Data was available for every 6 weeks. It has been reported at 24, 56	**24 weeks** **Group 1:** 2/11 **Group 2:** 5/7 **Group 3:** 2/2 **56 weeks** **Group 1:** 3/11 **Group 2:** 6/7 **Group 3:** 2/2 **76 weeks** **Group 1:** 4/11 **Group 2:** 6/7	**Funding:** None provided. **Limitations:** Unclear method of randomisation and allocation concealment Unclear blinding

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Study design and quality: **RCT** Single centre Spain **106 week trial** (divided into 2 parts: a study of achieved remission for 30 weeks and maintaining remission for 76 weeks). For the maintaining remission study only patients who achieved remission after stopping prednisone were included. **Randomisation:** All patients were receiving prednisone, were randomly assigned in a 2:2:1 ratio. **Allocation concealment**: Unclear **Blinding:** Unclear **Outcome assessment:** Assessed 2 and 4 weeks after randomization and every 4 weeks thereafter for 30 weeks. For patients who achieved remission: patients were followed up every 6 weeks **Steroid dependent =** 7 or more on the Mayo Clinic Score, or presented more than 2 episodes in last 6 months or	N=14 (41%) (5 withdrawal due to AEs, 9 drop outs due to treatment failure in the induction of remission stage, 26% excluding treatment failures) >10% difference in missing data between the treatment arms during the induction phase **Inclusion criteria:** Steroid dependent IBD (prednisone could not be lowered to 20 mg), Radiological and endoscopic diagnosis of UC Only patients who achieved remission after stopping prednisolone were included. **Extent:** Proctosigmoiditis, Left-sided colon, Subtotal/Total **Severity: Assessed by Mayo clinic score.** **Exclusion:** <15 yrs or >70 yrs; no signed consent; clinically significant cardiac, hepatic or renal disease; ongoing bacterial infection; pregnancy; lactating or no use of reliable contraception; concomitant use of allopurinol, nonsteroidal anti-inflammatory drugs, tetracyclines or phenytoin; extensive previous surgery for CD or likely to need surgery. **<u>Group 1: Mercaptopurine (+prednisone)</u>** **Mean age (SD):** **Extent:** Proctosigmoiditis: N=1 Left-sided colon: N=5 Subtotal/Total: N=8 **Duration of disease**: 3.4 ± 2 yrs **Severity:** Mayo score**:** 9±2 **Drop outs:** N=3 due to side effects **<u>Group 2: Methotrexate (+prednisone) (n=12)</u>** **Mean age (SD):** **Extent:** Proctosigmoiditis: N=1 Left-sided colon: N=4 Subtotal/Total: N=7 **Severity:** Mayo score**:** 9.2±2	**Intervention details** 1.5mg/kg/day mercaptopurine Dose was reduced to 1 mg/kg/day if clinical remission was achieved **Group 2: Methotrexate (+prednisone)** N=12 randomised N=12 (ITT) N=7 (completed 30 wks and obtained remission) **Intervention details** 15mg/wk of methotrexate Dose was reduced to 10 mg/kg/day if clinical remission was achieved **Group 3: 5-ASA (+prednisone)** N=8 randomised N=8 (ITT) N=2 (completed 30 wks and obtained remission) **Intervention details** 3 g/day of 5-ASA. Patients continued with	and 76 weeks, as that was the closest to 6, 12 and 18 months. Figures were calculated from n minus though in remission. Drop outs had occurred in the induction phase. **Outcome 2: Adverse events** These were only reported overall for the UC and Crohn's patients. It was not possible to separate them for analysis.	**Group 3:** 2/2	>10% difference in missing data between treatment arms (induction phase, Gp 1&3, and Gp2&3) Randomised at induction of remission **Additional outcomes:** Number of patients who achieved remission at 0-76 wks, at 6 wk intervals.

Author	Patients	Intervention	Outcome measures	Effect size	Comments
more than 3 in last 12 months. **Mayo Score included** 4 times, each scored 0-3: stool frequency, rectal bleeding, physician's global assessment, and sigmoidoscopy. **Sample size calculation:** Unclear **Type of analysis:** ITT **Compliance rates:** Assessed through diary entries. N=14 dropout/ withdrawal due to drug related AEs.	Duration of disease: 2.9± 2 yrs **Drop outs:** N=5 (3 treatment failure, 2 side effects) **Group 3: 5-ASA (+prednisone) (n=8)** **Mean age (SD):** **Extent:** Proctosigmoiditis: 0 Left-sided colon: 3 Subtotal/Total: 5 **Severity:** Mayo score: 9.5±2 Duration of disease: 2.5 ± 4 yrs **Drop outs:** N=6 (treatment failure) Note: the above drop outs occurred during the induction phase. **Definitions** **Remission** – Mayo Clinic score <7 **Relapse** – Mayo Clinic score of ≥7	this dose if achieved remission **Concomitant therapy:** All patients were receiving an individually adjusted dose of prednisone in order to control symptoms. Highest dose was 1 mg/kg/day. After week 2, prednisone was decreased by 8mg/wk. It was reduced if the condition of the patient remained stable or improved and discontinued if clinical remission was achieved. All other treatments for IBD were stopped for at least 6 months prior to start of study. Only antidiarrhoeal agents were administered and folic acid.			

Table 116: MEYERS1987

Author	Patients	Intervention	Outcome measures	Effect size	Comments
S. Meyers et al. Olsalazine Sodium in the Treatment of Ulcerative Colitis	**All patients:** **N=66randomised**,0.75g,1.5g,3g and placebo	**Group 1: 1.5g Olsalazine** N=16 randomised	Outcome 1: **Therapeutic improvement (clinical improvement)** (Reduction in the global	**Group 1**:4/15 **Group 2**:7/14	**Funding:** None described.

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Among Patients Intolerant of Sulfasalazine. A Prospective, Randomized, Placebo-Controlled, Double-Blind, Dose-Ranging Clinical Trial. *Gastroenterology; 93: 1255-62. 1987.* **REF ID: MEYERS1987** **Study design and quality:** Double blind RCT United States **3 week trial** **Randomisation:** Assignment proceeded in order of entry into the study to achieve a predetermined number of patients within each group. Randomisation scheme supplied by the statistics department of Pharmacia AB. **Allocation concealment**: Unclear **Blinding:** Double blind. Neither the physicians nor the patients were aware of the therapy they received during or at the termination of the study. **Outcome assessment:** Colitis activity was assessed according to the criteria modified from Lennard-Jones et al. Sigmoidoscopic appearance was evaluated according to the	**N=61** (efficacy analysis; evaluated at least once, even if withdrawn before the completion of the 21 days) **Drop-outs** (don't complete the study): N=8 (12%) **Inclusion criteria:** **Note:** Patients were intolerant of sulfasalazine at or below the minimally effective dose of 2g/day. Extent of disease was determined by barium enema or colonoscopy or both within the preceding year. No restriction given. **Exclusion:** Indeterminate or doubt of the diagnosis of ulcerative colitis Colitis in full remission Fulminant colitis activity History of allergy to salicylates Child-bearing age in women not using contraceptive methods Acute cardiopulmonary disease Severe hepatic or renal dysfunction (characterized by serum transaminase or creatinine values two or more times the upper limits of normal) Haematological abnormalities including a platelet count of <150,000mm^3 or a prothrombin time 4s greater than control Chronic infections or other inflammatory disorders Malnutrition indicated by a body weight <75% ideal or serum albumin <435µmol/L (3g/dl) Need for the chronic administration of salicylates or digitalis derivatives	N=15 (efficacy analysis) Four capsules three times a day, mixture of active and placebo capsules to make up the 1.5g daily dose. Each active capsule contained 250mg of olsalazine. **Group 2: 3g Olsalazine** N=15 randomised N=14 (efficacy analysis) Four capsules three times a day, of active capsules. Each active capsule contained 250mg of olsalazine. **Group 3: Placebo** N=20 randomised N=19 (efficacy analysis) Four placebo capsules, three times a day. **Concomitant therapy:** No corticosteroid, immunosuppressive, antibiotic, anticholinergic or antidiarrheal agents were permitted during the study. These agents had to be discontinued	clinical colitis activity that allowed reclassification into a milder category or if there was a lower overall sigmoidoscopic score or both) Outcome 2: **Adverse events** (most common was abdominal pain and upset stomach) The following subgroups were looked at and did not show to influence the response to olsalazine: Extent: proctosigmoiditis vs. left-sided colitis vs. universal colitis Severity: mild vs. moderate vs. severe. Clinical remission was defined but not indicated to be an outcome. No remission data was reported. Definition: no more than two bowel movements per day and no other signs or symptoms of ulcerative colitis	**Group 3:**3/19 All olsalazine including 0.75mg 38/ 46 **Group 4:**16/20	**Limitations:** Unclear allocation concealment Indirect population (includes patient with severe disease) **Additional outcomes:** Mean change in sigmoidoscopy score

Author	Patients	Intervention	Outcome measures	Effect size	Comments
presence of mucosal exudates, texture, erythema and bleeding. Each scored from 0-4, with 0 being normal. **Sample size calculation:** None described. **Type of analysis: ACA** **Compliance rates:** Assessed by pill counts. No description of any patients not being compliant. N=4 dropout/ withdrawal due to AEs (not clear whether drug related). Placebo group: diarrhoea, 0.75g olsalazine due to diarrhoea, 1.5g & 3.0g olsalazine due to a rash(1 patient in each group). Unclear whether the rashes were drug related.	Unable to cooperate fully with the protocol Failed to consume at least 75% of the study medication **Group 1: 0.75g Olsalazine** **Mean age (SD):**41 (18.4), range 12-69 **Extent:** proctosigmoiditis n=8, left-sided colitis n=4, universal colitis n=3. **Severity:** mild n=9, moderate n=5, severe n=1 **Mean sigmoidoscopic score (SD):** 1.7 (1.1), range 0.3-4. **Drop outs:**2 (2 due to diarrhoea or worsening of disease) **Group 2: 1.5g Olsalazine** **Mean age (SD):**38 (17.1), range 20-75 **Extent:** proctosigmoiditis n=11, left-sided colitis n=1, universal colitis n=4. **Severity:** mild n=9, moderate n=5, severe n=2 **Mean sigmoidoscopic score (SD):** 2.1 (1), range 0.3-4. **Drop outs:** 2 (1 due to diarrhoea or worsening of disease, 1 due to a skin rash) **Group 3: 3g Olsalazine** **Mean age (SD):**43 (12.7), range 22-61 **Extent:** proctosigmoiditis n=10, left-sided colitis n=1, universal colitis n=4. **Severity:** mild n=8, moderate n=5, severe n=2 **Mean sigmoidoscopic score (SD):** 1.3 (0.7), range 0.3- 2.3 **Drop outs:** 1 due to a skin rash. **Group 4: Placebo** **Mean age (SD):**39 (13), range 17-69 **Extent:** proctosigmoiditis n=11, left-sided colitis n=5, universal colitis n=4. **Severity:** mild n=10, moderate n=9, severe n=1 **Mean sigmoidoscopic score (SD):** 1.3 (0.9), range 0-3.3 **Drop outs:** 3 (3 due to diarrhoea or worsening of disease) In total there was 8 withdrawals overall. **Note:** Population includes children.	at least 7 days before entry to the study or topical corticosteroids discontinued at least 3 days before entry. All patients were allowed a standard low-residue diet during the study period.			

Table 117: MIGLIOLI1989

Author	Patients	Intervention	Outcome measures	Effect size	Comments
M. Miglioli et al. Oral 5-ASA (Asacol) in mild ulcerative colitis. A randomized double blind dose ranging trial. *Italian Journal of Gastroenterology. 21: Supple: 7-8. 1989.* **REF ID: MIGLIOLI1989** **Study design and quality:** Double blind RCT Symposium article. It has been included as it has been included in the Cochrane systematic review on oral ASAs. Multicentre: 8 centres, Italy **4 week (28 day) trial** **Randomisation:** Not described. The Cochrane review says it was computer generated. **Allocation concealment**: Not described. **Blinding:** Double blind, dummy. Assessments of the colonic appearance were done by the same physician in each center. **Outcome assessment:** Colonic appearance according to the modified criteria of Baron.	**<u>All patients:</u>** **N=73 randomised (48 to two treatment arms)** Only two of the treatment arm doses have been presented as 1.2g is below what is recommended for the induction of remission. **Drop-outs** (don't complete the study): N=6 in the two treatment arms (12.5%). >10% difference in missing data between the two treatment arms. **Inclusion criteria:** • Outpatients • 18-65 years • Extent: >20cm • Severity: mild ulcerative colitis (clinical grading was done according to the criteria modified from Truelove and Witts) **Exclusion:** • None described **<u>Baseline characteristics</u>** No baseline characteristics were described.	**Group 1: 2.4g mesalazine (Asacol)** N=24 randomised N=20 (completers) 400mg tablets of mesalazine (Asacol). Three tablets three times a day (two active, one placebo). **Group 2: 3.6g mesalazine (Asacol)** N=24 randomised N=22 (completers) 400mg tablets of mesalazine (Asacol). Three tablets three times a day (three active). **Concomitant therapy:** Not described.	**Outcome 1: Clinical remission** (no more than 2 bowel movement per day without visible blood in the stool). **Note: figures are taken from the percentages reported in the paper. These differ to the Cochrane reported figures.**	<u>2 weeks</u> **Group1:** 3/24 (12.5%) **Group 2:** 7/24 (29.1%) <u>4weeks</u> **Group1:** 9/24 (37.5%) **Group 2:** 11/24 (45.8%)	**Funding:** Not described. **Limitations:** Unclear method of randomisation (Cochrane reports it to be computer generated) and allocation concealment >10% difference in missing data between the treatment arms No baseline characteristics reported **Additional outcomes:** Endoscopic improvement
			Outcome 2: Clinical improvement (clear decrease in severity of symptoms and signs not satisfying remission criteria) Definition was taken from the Cochrane review as it was not evident in the paper. **Note: figures are taken from the percentages reported in the paper. These differ to the Cochrane reported figures.**	<u>2 weeks</u> **Group1:** 11/24 (45.8%) **Group 2:** 18/24 (74.9%) <u>4 weeks</u> **Group1:** 14/24 (58.3%) **Group 2:** 19/24 (80.8%)	
			Adverse events: They were reported in five patients. They were mild and reversible. It was not stated which treatment groups these people belonged to.		

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Sample size calculation: Not described. **Type of analysis: ITT** **Compliance rates:** Only described as "good". N=0 dropout/ withdrawal due to drug related AEs.					

Table 118: MINER1995

Author	Patients	Intervention	Outcome measures	Effect size	Comments
P. Miner et al. Safety and Efficacy of Controlled-Release Mesalamine for Maintenance of Remission in Ulcerative Colitis. *Digestive Diseases and Sciences; 40 (2): 296-304. 1995.* **REF ID: MINER1995** **Study design and quality:** Double blind RCT Multicentre **12 month trial (48 weeks)** A month was classed as 4 weeks. **Randomisation:** No information was given. **Allocation concealment**: No information was given.	**All patients:** **N=205 randomised** **N=202 (efficacy analysis)** Three patients in the placebo group did not take the medication for at least 5 days. **Drop-outs** (don't complete the study): N =61 (29.8%) >10% difference in missing data between the treatment arms **Inclusion criteria:** • Extent: Pancolitis or left sided colitis • Severity of previous relapse was not described. • 18 years or older • Previously diagnosed UC in remission (Sigmoidoscopic index of <5, mean of <5 stools per day, absence of rectal bleeding) • Female patients of childbearing potential on adequate birth control • Prior use of an immunosuppressive agent or use of oral/rectal steroids required 90 day and 60 day wash outs respectively prior to baseline	**Group 1: Mesalamine 4g** N=103 randomised Controlled release mesalazine 4g/day (Pentasa). Coated in Ethylcellulose to releases throughout the small and large bowel. 1g (250mg capsules) four times a day. **Group 2: Placebo** N=102 randomised N=99 (efficacy analyses as 3 patients did not receive treatment for at least 5 days) Placebo four times a day.	**Outcome 1: Relapse** **Outcome 2: Adverse events** These were only reported as the treatment related AEs and so therefore it has not been included in the data analysis. Most frequent AEs causing withdrawal from the treatment were: **Mesalazine:** Abdominal pain (1 patient) Nausea (1 patient, Hepatitis (1 patient) **Placebo:** Headache (2 patients) Other treatment related events, each for one patient were: melena, abdominal	**Group1:** 35/103 **Group 2:** 56/99 Kaplan Meier life table plot p value ≤0.033	**Funding:** Not described. **Limitations:** Unclear method of randomisation and allocation concealment No information given on the double blinding >10% difference in missing data between the treatment arms **Additional outcomes:** Mean change in sigmoidoscopic score Mean change in rectal bleeding

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Blinding: Double blind, both treatments looked identical. No further information given. **Outcome assessment:** Endoscopy (five categories each scored from 0 (normal) to 3. Maximum score of 15. Histology scored 0 (normal) to 3. Daily diary. **Sample size calculation:** 80% power to detect a 25% difference in recurrence rates between the two treatment groups, α=0.05, two sided. Minimum of 70 patients per arm was needed. **Type of analysis: ITT** (patients who received the randomly assigned treatment for at least five days) **Compliance rates:** Counted retuned unused medication and review of returned empty blister packs. Non compliance in 3 and 4 patients in the mesalamine and placebo groups respectively. N=48 dropout/ withdrawal due to AEs. 2 in the mesalamine and 6 in the placebo group were thought to be drug related.	**Exclusion:** • Pregnant or lactating females • Concomitant therapy with corticosteroids, SASP, other mesalamine formulations, H_2 receptor antagonists, anticholinergics, sucralfate, or chronic antacids was not permitted • Allergy to aspirin, mesalamine or other salicylate compounds **Group 1: 4g Mesalamine** **Mean age (SD):** 39 (11) **Extent:** Left n=75, right n=25 **Prior oral steroid (Y/N):** 42%/58% **Prior rectal therapy within 60 days (Y/N):** 16%/ 84% **Prior rectal therapy within 1 year (Y/N):** 42%/58% **Prior SASP (Y/N):** 85%/15% **Mean baseline sigmoidoscopic index (SD):** 1.7 (1.5) **Mean baseline trips to toilet (SD):** 2.1 (1.1) **Rectal bleeding ≤ 5 days from baseline (Y/N):** 1/99 **Mean biopsy score (SD):** 1.3 (0.6) **Drop outs:** 20 (14 due to AE, 3 due to non compliance, 2 voluntary withdrawal, 1 other) **Group 2: Placebo** **Mean age (SD):** 43 (14) **Extent:** Left n=69, right n=31 **Prior oral steroid (Y/N):** 44%/56% **Prior rectal therapy within 60 days (Y/N):** 14%/ 86% **Prior rectal therapy within 1 year (Y/N):** 28%/72% **Prior SASP (Y/N):** 84%/14% **Mean baseline sigmoidoscopic index (SD):** 1.6 (1.4) **Mean baseline trips to toilet (SD):** 2.1 (1.1) **Rectal bleeding ≤ 5 days from baseline (Y/N):** 3/97 **Mean biopsy score (SD):** 1.3 (0.6) **Drop outs:** 41 ((34 due to AE, 4 due to non compliance, 2 voluntary withdrawal, 1 other) **Definitions** **Relapse:** Three definitions: 1. Sigmoidoscopic index of≥5. And ≥1 of the following: mean of ≥5 trips to the toilet for three of seven continuous days or the presence of rectal bleeding for three of seven continuous days.	**Concomitant therapy:** See inclusion/ exclusion criteria. Loperamide was permitted and was noted in the patient's diary.	pain, dyspepsia, dizziness, vertigo and vision abnormality. The acute hepatitis was thought to be drug related to the mesalamine. An elevated CMV antibody titre was also associated with elevation in liver function tests. It resolved on discontinuation of the mesalamine and darvocet (a concomitant medication) within 30 days. There was no indication of differences in mesalamine effect on maintenance of remission for any of the subgroups (age, gender, disease location, time since last flare, prior oral steroid therapy, prior rectal therapy and previous response to oral steroid, rectal steroid or SASP therapy).		Mean change in biopsy scores Mean change in daily trips to the toilet Remission rates by extent of disease **Note:** Unable to calculate relapse rates by extent of disease as the inverse of remission may include drop outs.

Author	Patients	Intervention	Outcome measures	Effect size	Comments
	2. Sigmoidoscopic index of ≥5 with missing data for trips to the toilet or rectal bleeding at the end of the study or final visit 3. Missing data for the final sigmoidoscopic index and early termination from the trial due to insufficient therapeutic effect. Patients withdrawing due to AEs were not considered to have recurrent UC unless one of the above definitions was met.				

Table 119: MISIEWICZ1965

Author	Patients	Intervention	Outcome measures	Effect size	Comments
J. J. Misiewicz et al. Controlled trial of sulphasalazine in maintenance therapy for ulcerative colitis. *The Lancet; 285: 185-188. 1965.* **REF ID: MISIEWICZ1965** **Study design and quality:** Double blind RCT Great Britain. **12 month trial** **Randomisation:** Not described. Unclear. **Allocation concealment**: Not described. Unclear. **Blinding:** Double blind. Neither the patient nor doctor knew the nature of the treatment given. Identical placebo tablets in size	**<u>All patients:</u>** **N=80 randomised** **N=67 (analysed/completers)** **Drop-outs** (don't complete the study): N=17 (21.25%) >10% difference in missing data between the treatment arms **Inclusion criteria:** • Outpatients who had an attack of proctocolitis in the previous year • Diagnosed on grounds of symptoms, sigmoidoscopic appearance of the rectal mucosa and x-ray • In remission symptomatically and sigmoidoscopically • No restriction regarding length of history and number of previous relapses **Exclusion:** • Radiological evidence of ileal disease or if on sigmoidoscopy their disease was limited to proctitis with a clear upper limit to the mucosal lesion • History of intolerance to SASP	**Group 1: 2g Sulphasalazine** N=42 randomised N=34 (completers) 500mg sulphasalazine taken four times a day. Tablets did not have an enteric coating (Salazopyrin, Pharmacia) **Group 2: Placebo** N=38 randomised N=33 (completers) Placebo tablet taken four times a day. **Concomitant therapy:** Not described.	Outcome 1: **Relapse** by 12 months	**<u>Authors analysis</u>** **Group 1:** 7/34 **Group 2:** 24/33	**Funding:** Pharmacia, Great Britain Ltd supplied the tablets. **Limitations:** Unclear method of randomisation and allocation concealment >10%difference in missing data between the treatment arms Unsure if done completely double blinded Limited baseline characteristics **Additional outcomes:** Haemoglobin and white cell count after treatment
			Only adverse events leading to withdrawal were reported. It is unclear whether patients experienced any others.		

Author	Patients	Intervention	Outcome measures	Effect size	Comments
and colour to the active tablets. **Outcome assessment:** Patients were seen at 2, 3, 6,9,12 months. Symptoms scored as "none" or "present". Sigmoidoscopic assessment according to Baron et al. Side effects not specifically asked about, only documented if the patient complained about them. **Sample size calculation:** None described. **Type of analysis:** Completers analysis (but included those who withdrew to AEs) **Compliance rates:** Patients were asked whether they took the tablets regularly**. 7 in the SASP group did not take the tables regularly**, 5 remained well, 2 relapsed. N=4 dropout/ withdrawal due to drug related AEs (3 in the SASP group, 2 nausea and abdo pain within a few days, and one had side effects after 2 months, and 1 in the placebo group had abdo pain after 2 days)	• Haemoglobin lower than 10g per 100mls • WBC count <5000cells per c.mm. **Group 1: 2g Sulphasalazine** **Mean age:** 47.7 **Extent:** Extensive n=3, left colon n=18, pelvic colon n=9, normal n=2, diverticulosis n=1, no x-ray n=1 **Severity of previous relapse:** Not described. **Frequency of relapses:** Not described **Current use of immunomodulators:** Not described. **Drop outs:** 11 (4 did not attend (2 also had other illness), 2 stopped taking the tablets, 1 thought the tablets were different from sulphasalazine, 1 trial stopped in error, 3 due to AEs) **Group 2: Placebo** **Mean age:** 41.0 **Extent:** Extensive n=5, left colon n=6, pelvic colon n=15, normal n=5, diverticulosis n=1, no x-ray n=1 **Severity of previous relapse:** Not described. **Frequency of relapses:** Not described. **Current use of immunomodulators:** Not described. **Drop outs:** 6 (1 did not attend regularly, 2 stopped taking the tablets, 1 noticed the tablets were different to sulphasalazine, 1 localised proctitis and entered the trial in error, 1 due to AEs) Length of time since last relapse "appears to be the same" in each treatment group. **Definitions** **Remission:** Absence of symptoms. If the patient remained symptom free, the finding of a haemorrhagic mucosa on sigmoidoscopy did not constitute a relapse. **Relapse:** Recurrence of symptoms.				

Table 120: MULDER1988

Author	Patients	Intervention	Outcome measures	Effect size	Comments
C. J. Mulder et al.	**All patients:**	**Group 1: 3g 5-ASA**	**Outcome 1: Clinical improvement**	**4 weeks**	**Funding:**

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Comparison of 5-aminosalicylic acid (3g) and prednisolone phosphate sodium enemas (30mg) in the treatment of distal ulcerative colitis. A prospective, randomized, double blind trial. *Scandinavian Journal of Gastroenterology; 23 (8): 1005-8. 1988.* **REF ID: MULDER1988** **Study design and quality:** Double blind RCT Netherlands **4 week trial** **Randomisation:** No details given. **Allocation concealment**: No details given. **Blinding:** Double blind **Outcome assessment:** Van der Heide scoring system. Unclear whether it is validated. **Sample size calculation:** Not described **Type of analysis: ITT** **Compliance rates:** Not described. N=0 dropout/ withdrawal due to drug related AEs.	**N=29 randomised** **Drop-outs** (don't complete the study): N=2 (6.9%) From 5-ASA due to deterioration **Inclusion criteria:** • Extent: acute relapse or a first attack of idiopathic UC limited to the distal 20cm of the colon • Severity: Mild to moderate • Had not taken corticosteroid medication for at least 1 month prior to trial **Exclusion:** • Chronic UC **Baseline characteristics** **Group 1: 3g 5-ASA liquid enema** **Sex (m/f):** 10/5 **Mean age (range):** 42 (24-63) **Concurrent sulphasalazine therapy:** 14 **Clinical score:** 4.77 +/-1.74 **Endoscopic score:** 8.377 +/- 2.35 **Extent:** not described **Drop outs:** 2 due to deterioration **Group 2: 30mg prednisolone liquid enema** **Sex (m/f):** 10/4 **Mean age (range):** 40 (21-74) **Concurrent sulphasalazine therapy:** 13 **Clinical score:** 5.14 +/-1.35 **Endoscopic score:** 9.00 +/- 2.25 **Extent:** not described **Drop outs:** 0	**liquid enema** N=15 randomised 3g 5-ASA enema once a day. **Group 2: 30mg Prednisolone liquid enema** N=14 randomised 30mg prednisolone liquid enema once a day. **Concomitant therapy:** If the patient was already taking sulphasalazine this treatment was maintained during the trial.	(decrease of ≥2 according to Van der Heide) **Clinical remission** (normalisation of all variables. Includes clinical endoscopic and histologic scores): none of the patients achieved remission as defined above. **Adverse events:** There were no drug related side effects noted.	**Group1:** 11/15 **Group 2:** 11/14	None given. **Limitations:** Unclear method of randomisation and allocation concealment Double blind, no further information given **Additional outcomes:** Endoscopic improvement Histologic improvement Clinical, endoscopic and histologic scores before and after treatment

Table 121: NIELSEN1983

Author	Patients	Intervention/ comparisons	Outcome measures	Effect size	Comments
O. H. Nielsen et al. Pregnancy in Ulcerative Colitis. *Scandinavian Journal of Gastroenterology; 18 (6): 735-742. 1983.* **REF ID: NIELSEN1983** **Study design and quality:** Retrospective cohort study **Denmark** **Years studied: 1968-1979** **Risk of bias:** Selection bias: High risk. Limited baseline characteristics. No adjustments made for confounders. Performance bias: unclear Attrition bias: High risk. Unclear dose and duration of therapy. 2 women had insufficient data/unable to be contacted. Detection bias: unclear	**All patients:** Included population: women <37 years old. Excluded population: • women who had never been pregnant (n=51) • pregnant only before 1 January 1968 or their bowel disease had not started until 6 months after delivery (N=40) • Insufficient data and the women were not able to be contacted (N=2) **N= 97 included women (218 pregnancies of which 173 were included (met inclusion criteria)** Data collection Examination of medical records from a total of 190 fertile women who fulfilled the diagnostic criteria of ulcerative colitis and who during a 12 year period had been treated in the outpatient clinical and/or was admitted to the department. If there was insufficient data recorded, the women were contacted by telephone and/or letter. Baseline characteristics Age at onset of UC (median, range): 24 years (16-36 years) The 97 women had had 1-6 pregnancies each. Delivered 136 children after 173 pregnancies (two were gemellary pregnancies). 88% in remission, 12% active colitis at the start of pregnancy. 87/173 (50%) were in remission the whole way through their pregnancies. No further baseline data was provided.	(a) No treatment (b) Sulphasalazine (for at least 1 month) (c) Systemic (for at least 14 days)/ topical steroids (for at least 7 days) (d) Combinations of the above.	See the table below for the reported outcomes **Authors conclusions:** SASP passes over the placenta but there were no more babies with jaundice born to mothers taking SASP. Mothers receiving corticosteroids did not have an increased frequency of spontaneous abortions, premature children or congenital abnormalities.		**Funding:** Supported by grants from King Christian X's Foundation, P. Carl Pedersen's Foundation and the Danish Medical Research Council. **Limitations:** High risk of selection and attrition bias Unclear risk of performance and detection bias **Additional outcomes:** Overall pregnancy birth outcomes in relation to having UC Activation of UC in different trimesters and birth outcome Disease severity of relapses and birth weight (median and range) Neonatal jaundice (excluded as it was unclear whether it was pathological jaundice only)

Table 122: Birth outcomes

Treatment	Number of pregnancies	Normal live birth	Congenital abnormality	Spontaneous abortion	Stillbirth	Premature birth
No treatment	88	68 (77.3%)	2 (2.3%)	6 (6.8%)	0 (0%)	4 (4.5%)
Sulphasalazine/ salazosulphadimidine	46	31 (67.4%)	1 (2.2%)	8 (17.4%)	0 (0%)	1 (2.2%)
Enema (prednisolone)	7	7 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Systemic corticosteroids	8	7 (87.5%)	0 (0%)	1 (12.5%)	0 (0%)	0 (0%)
SASP + enema	13	12 (92.3%)	0 (0%)	0 (0%)	0 (0%)	1 (9.2%)
SASP + systemic corticosteroids	8	7 (87.5%)	0 (0%)	1 (12.5%)	0 (0%)	1(12.5%)
Enema + systemic corticosteroids	2	2 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
SASP + enema + systemic corticosteroids	1	2 (100%)	0 (0%)	0 (0%)	0 (0%)	2 (100%)

(a) Therapeutic abortion does not include those induced for personal reasons.
(b) Neonatal jaundice: infants developed neonatal hyperbilirubinaemia that required phototherapy
(c) Premature: gestational age under 37 weeks. ***Note: premature births can be classed as normal delivery.***
(d) Congenital abnormalities: Left sided luxatio coxae (n=1), persistent ductus arteriosus, coarcation of the aorta plus left sided coronary hypoplasia (N=1) and bilateral renal aplasia, aplasia of the external genitalia, aplasia of the urinary bladder, bilateral clubfoot, plus polydactylia of the right hand (N=1).
(e) 2/6 premature children in mothers with active disease, 7/111 in the group with inactive disease(live births)
(f) Birth weights were only reported as a median and range, not the number that had a low birth weight
(g) The numbers were not found to add up in the paper. There is one patient not accounted for

Table 123: NILSSON1995

Author	Patients	Intervention	Outcome measures	Effect size	Comments
A. Nilsson et al. Olsalazine versus	**<u>All patients:</u>** **N=329 randomised**	Capsules were taken in the morning and	**Outcome 1: Relapse** (ITT)	**<u>6-18 months</u>** **Group1:**	**Funding:** Financially supported by

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Sulphasalazine for Relapse Prevention in Ulcerative Colitis: A Multicenter Study. *The American Journal of Gastroenterology; 90 (3): 381-387. 1995.* **REF ID: NILSSON1995** **Study design and quality:** Double blind, double dummy RCT Multicentre: 16 centres, Sweden,, Norway and Finland **6-18 months trial** (first entered patients did 18 months, last entered patients did 6 months) **Randomisation:** Unclear. **Allocation concealment**: Unclear **Blinding:** Double blind, double dummy. No further information given. **Outcome assessment:** Endoscopy assessment (scored from 1-4). Measured number of stools, blood, consistency at each clinical visit. Blood tests. **Sample size calculation:** 35% relapse rate for SASP and at most 5% more in the olsalazine group. 80% power, one sided 95% CI, drop out of 15%. Sample size of 150 per treatment group.	**N=322 (efficacy analysis/ ITT)** 7 were considered nonqualified (3 withdrew consent before the study commenced, 2 were diagnosed with Crohn's, 1 got Salmonella type 3 C infection before starting, 1 patient had a grade 3 on sigmoidoscopy at inclusion) **Drop-outs** (don't complete the study): N=50 (15.5 %%) **Inclusion criteria:** • At least two episodes of active colitis during the last 5 years • Remission for the last 3 months before the study (two patients who had been in remission without steroids for 1.2 and 1.5 months were still included in the analysis) • **NB SASP tolerant population** **Exclusion:** • Known allergy to sulphasalazine or 5-ASA or tartrazine • Pregnancy or planned pregnancy during the treatment period • Severe liver or kidney disease **<u>Group 1: Olsalazine 1g</u>** **Mean age (SD):** 41.8 (11.9) **Extent:** proctitis n=37, left sided n=74, subtotal/ Total n=50 **Mean time since diagnosis (yrs) (SD):** 9.2 (7.1) **Mean time in remission (months) (SD):** 12.5 (11.5) **Number of previous attacks:** 2 n=27, 3-5 n=78, 6-10 n=38, >10 n=18 **Severity of previous relapse:** Not described. **Frequency of relapses:** Not described **Drop outs:** 29 (12 for AEs, 17 due to other reasons). Drop outs at 6 months were 14. **<u>Group 2: Sulphasalazine 2g</u>** **Mean age (SD):** 42.4 (12.3) **Extent:** proctitis n=32, left sided n=66, subtotal/ Total n=63 **Mean time since diagnosis (yrs) (SD):** 9.6 (7.7) **Mean time in remission (months) (SD):** 12.2 (10.3) **Number of previous attacks:** 2 n=28, 3-5 n=72, 6-10 n=45, >10 n=16 **Severity of previous relapse:** Not described. **Frequency of relapses:** Not described	evening with a meal. Gradual increase of medication: Days 1 &2: 1 capsule and 1 tablet in the morning Days 3 & 4:1 capsule and 1 tablet twice a day Days 5 & 6:2 capsules and 2 tablets in the morning, 1 capsule and 1 tablet at night From Day 7: Two tablets and two capsules twice a day **Group 1: Olsalazine 1g** N=161 (ITT) Two capsules of olsalazine and two placebo tablets twice a day. Total dose 1g/day. **Group 2: Sulphasalazine 2g** N= 161 (ITT) Two tablets of sulphasalazine and two placebo capsules, taken twice a day. Total dose 2g/day.		59/161 **Group 2:** 55/161 **Log rank test p=0.19** **6 month data (NMA)** **Group1:** 38/161 **Group 2:** 30/161	Pharmacia. **Limitations:** Unclear method of randomisation and allocation concealment No further details given on double blinding **Additional outcomes:** Remission **Notes:** 6-18 month relapse rates by extent of disease (percentages are given, but it is unclear whether it is ITT or PPA to work out the n values). No log rank value given. Olsalazine , SASP Proctitis: 41.9%, 31.0% Left-sided: 53.3%. 40.4% Subtotal/total: 34.2%, 42.6% None were statistically significant. **SASP tolerant population**
			Outcome 2: Adverse events Overall 19 reported diarrhoea in the olsalazine (10 subtotal/total colitis, 8 left sided, 1 proctitis) group versus 3 in the SASP group.	**Group1:** 39/161 **Group 2:** 26/161	
			Outcome 3: Serious adverse event Due to an attack of polyarthritis and fever in connection with a staphylococcal infection in the nose. Rapid improvement was noted after stopping the medication, so it is thought to be probably related to the olsalazine.	**Group1:** 1/161 **Group 2:** 0/161	
			Relapse by extent of disease		

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Type of analysis: ITT (included all patients except those not meeting inclusion criteria. Failure rate includes relapses and withdrawals from treatment) **and PPA** (patients still in remission at the end and those with a relapse were included) **Compliance rates:** Counting remaining pills every 3rd month.85% of the olsalazine, 82% of sulphasalazine returned the remaining drugs for pill counting according to the schedule. Mean compliance was 90.9% and 90.7% respectively. N=20 dropout/ withdrawal due to AEs. 6 in each group in the first 6 months. Overall 12 (5 diarrhoea, 3 other abdo symptoms, 2 skin problems, 1 rheumatic symptoms, 1 impotence) in the olsalazine and 8 (1 diarrhoea, 1 skin, 5 CNS symptoms, 1 rheumatic symptoms) in the SASP.	**Drop outs:** 21 (8 for AEs, 13 due to other reasons). Drop outs at 6 months were 17. 'Other reasons' for drop outs were: noncompliance, consent withdrawal, pregnancy or planned pregnancy, concomitant medication, intercurrent disease, loss to follow up and relapse not confirmed. **Definitions** **Remission:** Grade 1 or 2 on endoscopy and no symptoms indicating relapse, such as diarrhoea or rectal bleeding. **Relapse:** Suspected if there are more than 3 stools a day for more than 5 days and /or visible blood in stool for more than 4 consecutive days. Confirmed by endoscopy - macroscopic changes of grade 3 or 4 in the rectum.	**Concomitant therapy:** No other medication for ulcerative colitis was permitted during the trial.	Unable to calculate the hazard ratio. N values were calculated from the percentages given in the paper but this did not add up to the total number of relapses. As the data was not thought to be accurate the data has not been presented.		

Table 124: NORGARD2003A

Author	Patients	Intervention	Outcome measures	Effect size	Comments
B. Norgard et al. Birth outcome in women exposed to 5-aminosalicylic acid during pregnancy: a Danish	**All patients:** Included population	**Group 1: Early pregnancy** N=42 UC pregnancies Prescribed 5-ASA drugs from	**See the table below for the outcome event rates.** Outcome 1: **Congenital abnormalities** **Early pregnancy group**, one UC patient had a baby with a congenital		**Funding:** None described

Author	Patients	Intervention	Outcome measures	Effect size	Comments
cohort. *Gut; 52: 243-247. 2003.* **REF ID:NORGARD2003A** **Study design and quality:** Retrospective cohort study **Denmark** **Years studied: 1991 to 2000** **Risk of bias:** Selection bias: low risk (note spontaneous abortions not included) Performance bias: unclear Attrition bias: High risk. Unclear dose and duration of therapy. Detection bias: High risk. Risk of misclassification bias with the use of ICD coding and unclear reporting for some congenital abnormalities.	• Women who had a live birth or a still birth after the 28th week of gestation Excluded population • None described **N= unclear** <u>Data collection</u> Data on drug use and outcome data were obtained from the population based registries in North Jutland County. Pharmacies are equipped with computerised accounting systems from which data is then sent to the national health service Birth data taken from the birth registry (maternal age, birth weight, length at birth, [parity, gestational age, sex of the child, stillbirth and smoking status) Congenital abnormality data: County hospital discharge registry. Any doubt on the type of IBD, hospital records were reviewed. Study looked at those who had taken mesalazine or olsalazine. Stratified patients by use of steroids. <u>Baseline characteristics</u> Baseline characteristics were not described separately for the UC patients. Analysis was adjusted for maternal age, parity and smoking status. For birth weight and still birth, it was also adjusted for gestational age.	30 before conception to the end of the first trimester **Group 2: Entire pregnancy** N=65 UC pregnancies Women who had been prescribed 5-ASA drugs during the first to the third trimesters **Group 3: Control group 1** N=19, 418 All pregnant women who had not been prescribed any kind of reimbursed medicine from 3 months before conception to the end of pregnancy **Group 4: Control group2** N=unclear All pregnant women apart from those treated with 5-ASA drugs from three months before conception to the end of pregnancy (allowing for use of other drugs) **Group 5: Control group 3** N=243 Pregnant women treated with 5-ASA drugs outside pregnancy (more than 3 months before or after	abnormality (unclear if the baby had aphakia or atresia of the lacrimal duct). They had only been on 5-ASA and had not had disease activity during the pregnancy. Outcome 2: **<u>Stillbirths</u>** **Entire pregnancy group**, there were three stillbirths. All the women were prescribed 5-ASA. Two were unknown causes (28.6 and 33.6 weeks gestation), the third probably died due to strangulation of the umbilical cord (43 weeks). Outcome 3: **<u>Preterm birth</u>** Group 2: 2 medically induced (increased liver enzymes, severe UC), 4 spontaneous	**Group 2:** 8 (2 were stillbirths) This includes one Crohn's patient's baby	**Limitations:** High risk of attrition and detection bias (ICD coding) Unclear performance bias **Additional outcomes:** Results of the Crohn's patients **Note: Does not look at spontaneous abortions before the 28th week gestation**

Author	Patients	Intervention	Outcome measures	Effect size	Comments
		pregnancy **(IBD control group)**			

Table 125: Birth outcomes for ulcerative colitis patients treated with 5-ASA

Outcome	Events/ total	Reported Odds ratio (adjusted) (95% CI)
Low birth weight (<2.5kg)	3/65 (4.6%)	1.4 (0.4-4.3)
Preterm birth (<37 weeks gestation)	7/65 (10.8%)	2.4 (1.1-5.3)
Stillbirth	3/65 (4.6%)	8.4 (2.0-34.3)
Malformation (different exposure window when examining congenital malformations (exposed in the period 30 days before conception to the end of first trimester)	3/42 (7.1%)	2.1 (0.7-6.9)

(a) Adjusted for mother's age (below 25 years, 25-29 years, and 30 years or more), parity (1 or >1), smoking (yes/no) in a logistic regression model. LBW and stillbirths also for gestational age (32 weeks or less, 33-36 weeks, and 37 weeks or more).

(b) Malformations in the table were all those reported. Overall (Crohn's and UC) there were 4 (2 had not been reported properly, so there is a risk of misclassification bias)

(c) All of the above are calculated from the "entire pregnancy 5-ASA use" apart from the congenital abnormalities which is the "early pregnancy" group.

Table 126: NOTTER2006

Reference	Study description	Findings	Comments
J. Notter & P. Burnard. Preparing for loop ileostomy surgery: Women's accounts from a qualitative study. *International Journal of Nursing Studies. 43 (2): 147-159. 2006.* **REF ID: NOTTER2006** Qualitative study 3 year duration	N= 50 women **Aim of the study:** to explore and describe the perceptions and experiences of women undergoing restorative proctocolectomy. **Data collection:** Semi-structured interviewing. Purposive sampling; maximum variety sampling, selection of a heterogeneous group to identify common experiences, and individual experiences. Interviews were recorded and	**Summary points:** "Where women believed they had been given what they had thought was sufficient (or adequate), information prior to surgery, the reality differed greatly from their expectations". "Surgery appeared much worse" compared to having the illness prior to surgery. It was described as "extremely traumatic and debilitating, with four key issues emerging, pain and shock, body image and sexuality, the loop ileostomy itself and the roles of the general and specialist nurses". 1. Pain and shock General pattern that women found the level of pain was unexpected. Most women had previously experienced severe pain during acute episodes. The women were told the pain would be severe, but they thought they could manage it (references to child birth/ used to pain) but they were shocked/devastated at the level of pain and need for sustained analgesia. Few reported adequate analgesia. 2. Body image and sexuality	**Source of funding:** None described

Reference	Study description	Findings	Comments
	transcribed. **Analysis:** followed principles of descriptive phenomenology. Several stages with bracketing. Each transition was noted and indexed. Re-probing and re-describing for clarification of experiences. Categorisation and theming of data. Perceptions of social phenomena are specific to time, place and context.	Quote from a patient: "he [husband] looked aghast… he went white… I couldn't help I was so weak I cried and that made it worse for him… It's terrible they [families] should be counselled or warned…" Some partners were involved in pre-operative discussions, majority were unprepared for what they saw. The paper describes that none of the partners remembered being offered individual support or counselling at this stage. It was suggested that there is a need for nurses to spend more time with the patient's partners for preparation/ support in the acute phase. "it was awful… they'd explained it but I just wasn't prepared for the mess I saw… all scars and bumps and the ileostomy…" There was a shock seeing their body for the first time and it was described as a thing which they would never recover from. They were said to feel disfigured, less feminine, less of a women. "less of a woman… my husband's wonderful… he really tried but I just knew I wasn't the same… the bag was noisy and it felt odd". The study describes that health care professionals told the patients that they would forget about the bag/ not be a problem, but this was far from the case. Some women did not have such supportive partners; "my husband thinks it is disgusting… we don't mention it… he never saw my stoma I had to keep it covered and he wouldn't talk about it.. the whole subject is taboo… I don't think he touched me at all while I had the ileostomy, and he wouldn't let me keep anything in the bathroom, I had to keep it all out of sight… hidden away". In this particular case neither the patient nor her husband has been offered pre or post surgery counselling. It was also found to be the same (or not remembered to have been offered it) for those who reported real difficulties in coping with the ileostomy. Few women were also aware that a loop or temporary ileostomy was harder to manage/ look worse than end ileostomies. 3. The loop ileostomy Three quarters of the women had experienced some difficulty in coming to terms with the presence of the ileostomy. There was a theme of uncleanliness towards the stoma and feeling of being different (having to kneel in front of a toilet in order to empty the drainable bags). One woman coped relatively well with the stoma and took the equivalence of a baby's changing pack with her so she had everything she could possibly need. The paper describes how the group did not see themselves as toma apaitnets and are likely to reject information that they see as relevant for patients who are keeping the stoma. It was suggested that nurses need to develop special literature for this group. Most of the women felt well supported by the nurses and how to change the appliances, but some found changing the bag hard and humiliating if there were problems with it leaking etc. 4. Roles of the general and specialist stoma care or pouch care nurses Delays in patient care was found to be more likely where there were not stoma care nurses. The specialist nurses were found to recognise the patient's need for help and support. Some patients found the link to a	

Reference	Study description	Findings	Comments
		specialist nurse via the telephone made it possible for them to be discharged home, as they knew they could phone when they needed to. It is described that the lack of privacy was a recurrent theme in the study. Many women thought that they would be feeling well within a few weeks and found it unexpected being debilitated, weak and tired for a longer period of time.	

Table 127: OGATA2006

Author	Patients	Intervention	Outcome measures	Effect size	Comments
H. Ogata et al. A randomised dose finding study of oral tacrolimus (FK506) therapy in refractory ulcerative colitis. *Gut; 55: 1255-1262. 2006.* **REF ID: OGATA2006** **Study design and quality:** Double blind RCT Multicentre: 17 centres, Japan **2 week trial** followed by a 10 week open label extension in which all patients received tacrolimus. **Randomisation:** Not described. **Allocation concealment**: Unclear. **Blinding:** Double blind. Blinding maintained by third party laboratory who carried out the trough level analysis. **Outcome assessment:** Disease activity index.	**<u>All patients:</u>** **N=65randomised** **N=63 safety population** (two patients were not given the drug because they failed to show confirmed visible bloody stools) **N=60 efficacy analysis** (three patients were excluded, two failed to show confirmed visible bloody stools at the start of the study and 1 underwent cytopheresis. **Drop-outs** (don't complete the study): N=12 (18.5%) **Inclusion criteria:** • >15 years • Extent: left sided (except proctosigmoiditis) or pancolitis • Severity: Moderate/ severe active UC, endoscopy score ≥ • All patients were hospitalized • Infectious diarrhoea has been ruled out **Exclusion:** • Known renal or severe hepatic dysfunction • Pregnant women • 3 months previous use of azathioprine, 6-mercaptopurine, ciclosporin or other immunosuppressants • Cytapheresis within 28 days prior to study entry **<u>Baseline characteristics</u>**	Doses adjusted to maintain blood concentrations within specified ranges. Placebo group had pseudo dose adjusted. Blood was collected to determine the trough concentration at 12 or 24 hrs after the initial dose. **Group 1: High trough** N=21 randomised N=19 (completers) Oral tacrolimus 10-15ng/ml level (high trough). Start off taking 0.025mg/kg per day twice daily. **Group 2: Low trough** N=23 randomised N=20 (completers) Oral tacrolimus, 5-	**Outcome 1: Clinical remission** (DAI≤2, with no individual score >1) It is unclear why the denominators are different. Author reported figures have been used in this clinical review.	**Group1:**4/20 **Group 2:**2/19 **Group 3:** 1/17	**Funding:** Astellas pharma Inc. **Limitations:** Unclear method of randomisation and allocation concealment Indirect population (moderate/ severe, and includes some patients who may have chronic active UC) **Additional outcomes:** Partial responders by severity of disease and whether the patients were steroid resistant or dependent Results of the 10 week open label extension
			Outcome 2: Clinical improvement (partial and complete response base on DAI >4 points all categories improved).	**Group1:**13/19 **Group 2:**8/21 **Group 3:** 2/20	
			Outcome 3: Endoscopic remission (mucosal healing, score of 0 or 1)	**Group1:**15/19 **Group 2:**8/18 **Group 3:** 2/16	
			Outcome 3: Serious adverse events Group 1:	**Group1:**1/21 **Group 2:**1/22	

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Sample size calculation:80% improvement (based on previous pilot study), 20% in the placebo group. Two side α=0.025 and power of 90%, 20 patients per treatment group. **Type of analysis: Unclear.** **Compliance rates:** Pills were not counted but there were no identifiable cases of non-compliance. N=2 dropout/ withdrawals thought to be drug related AEs.	**Group 1: High trough** **Sex (m/f):** 9/10 **Mean age (SD):**33.3 (10.3) **Mean disease duration (SD):** 7 yrs (6.3) **Extent:** pancolitis n=12, left sided n=7 **DAI total score:** 6 n=0, 7-9 n=13, 10-12 n=6 **Steroid resistant/dependant:** 5/14 **Previous treatment (within 6 months):** azathioprine n=5, cytapheresis n=4 **Concomitant medication:** prednisolone (≥10mg/day) n=19, 5-ASA n=19 **Drop outs:** 2 (not active UC) **Group 2: Low trough** **Sex (m/f):** 11/10 **Mean age (SD):**31.2 (10.8) **Mean disease duration (SD):** 4.8 yrs (3.5) **Extent:** pancolitis n=14, left sided n=7 **DAI total score:** 6 n=2, 7-9 n=9, 10-12 n=10 **Steroid resistant/dependant:** 5/16 **Previous treatment (within 6 months):** azathioprine n=1, cytapheresis n=4 **Concomitant medication:** prednisolone (≥10mg/day) n=21, 5-ASA n=21 **Drop outs:** 3 (1 lack of efficacy, 2 not active UC) **Group 3: Placebo** **Sex (m/f):** 9/11 **Mean age (SD):**30.0 (6.4) **Mean disease duration (SD):** 6 yrs (3.5) **Extent:** pancolitis n=10, left sided n=10 **DAI total score:** 6 n=1, 7-9 n=8, 10-12 n=11 **Steroid resistant/dependant:** 5/15 **Previous treatment (within 6 months):** azathioprine n=2, cytapheresis n=7 **Concomitant medication:** prednisolone (≥10mg/day) n=20, 5-ASA n=18 **Drop outs:** 7 (6 lack of efficacy, 1 not active UC) **Definitions** **Steroid resistance** defined as unresponsiveness to oral or I.V.	10ng/ml level (low trough). Start off taking 0.025mg/kg per day twice daily. **Group 3: Placebo** N=21 randomised N=14(completers) Placebo. **Concomitant therapy:** Permitted to continue taking drugs containing 5-ASA, or steroids during the study as long as the dosage was not adjusted during the 2 week period prior the start of the study to the end of the trial.	Gastroenteritis Group 2: Sepsis	**Group 3:** 0/20	
			Outcome 4: Adverse events Only reported as minor adverse events and it is unclear whether patients had more than one adverse event, therefore it has not been included in the analysis. Group 1: 9/21 (tremor finger, sleepiness, hot flush, stomach discomfort) Group 2: 3/22 (tremor finger, hot flush) Group 3: 2/20 (sleepiness, headache)		
			Outcome 5 : Clinical and endoscopic remission (complete response, DAI=0) There were no patients with clinical and endoscopic remission in either treatment arms.		

Author	Patients	Intervention	Outcome measures	Effect size	Comments
	corticosteroid therapy (>30mg daily) over at least two weeks. **Steroid dependency** defined as either chronic active UC for >6 months or frequent recurrence (>once a year, or three times or more every two years regardless of intensive medical therapy).				

Table 128: OGATA2012

Author	Patients	Intervention	Outcome measures	Effect size	Comments
H. Ogata et al. Double-Blind, Placebo-Controlled Trial of Oral Tacrolimus (FK506) in the Management of Hospitalized Patients with Steroid-Refractory Ulcerative Colitis. *Inflammatory Bowel Disease; 18 (5): 803-808. 2012.* **REF ID: OGATA2012** **Study design and quality:** **Double blind RCT** Japan, August 2006-February 2008 2 week trial followed by an open trial of 10 weeks **Randomisation:** Performed by the Control Centre (Bellsystem24, a third-party organization independent of study physicians and sponsor). Unclear what method they used to randomize the patients.	**<u>All patients:</u>** **N=62 randomised** **Drop-outs (don't complete the study):** N=0 (0%) **Inclusion criteria:** • Active ulcerative colitis (steroid dependent or steroid resistant) • Extent: All left sided or pancolitis (determined by total colonoscopy • Severity: Moderate to severe UC • Ruled out infectious diarrhoea (stool cultures and C. difficile toxin testing) **Exclusion:** • Known renal or severe hepatic dysfunction • Pregnant women • Taking azathioprine within 3 months prior to entering the study • Cytapheresis within 14 days prior to entry in the study **<u>Group 1: Tacrolimus</u>** Mean age (SD): Not described. Mean total DAI score (SD): 9.8 (1.61) Mean trough concentrations (SD): 12hrs = 1.4 (0.9), 24hrs = 2.2 (1.5), day 7= 9.6 (3.1), day 8= 10.3 (3.1), day 10= 11.6 (3.4), day 14 = 13.0 (4.4) Extent: Not described	**Group 1: Tacrolimus** N=32 randomised Given a dose sufficient enough to achieve and maintain target blood concentrations of 10-15ng/mL. Tacrolimus capsules; 0.5mg or 1mg of FK506. Initiation was at the small dose of 1-2.5mg per time, twice daily. Dose adjustments: proportional calculations of blood trough concentration at steady state and target trough concentration. **Group 2: Placebo** N=30 randomised No details described. **Concomitant therapy:**	Outcome 1: **Clinical remission** (DAI score ≤2) Outcome 2: **Clinical improvement** – clinical response (reduction in DAI of at least 4 points and improvements in all 4 categories; stool frequency, rectal bleeding, mucosal appearance and physician's overall assessment). Outcome 3: **Endoscopic remission** (Mucosal appearance subscore of 0 or 1) Outcome 4: **Adverse events** Most frequent in the tacrolimus group was Numbness (4), headache (4) and	**Group1:**3/32 (9.4%) **Group 2:**0/30 (0%) **Group1:** 16/32 (50%) **Group 2:** 4/30 (13.3%) **Group1:**14/32 (43.8%) **Group 2:**4/30 (13.3%) **Group1:**26/32 (81.3%) **Group 2:**21/30 (70%)	**Funding:** Supported by Astellas Pharma Inc., Japan through financial grants whereby each participating study sit (not individual site investigators) received fixed part reimbursement for every patient enrolled, covering the additional costs of the trial. **Limitations:** Unclear randomisation method and allocation concealment Very limited baseline data No details about the placebo (same look/ taste etc.?) Indirect population (moderate/severe disease) **Additional outcomes:** Clinical remission,

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Allocation concealment: Unclear **Blinding:** Double blind. Blood trough levels were measured by SRL (independent third party) and relayed to the control centre. Patient doses in the placebo group were pseudo adjusted to preserve study blinding. **Outcome assessment:** Disease activity index (DAI) **Sample size calculation:** Assumed clinical response to be 50% in the tacrolimus group and 10% in the placebo group. 31 patients in each treatment arm, two sided alpha of 0.025 and power of 0.9. **Type of analysis: ITT** **Compliance rates:** Questioned by the investigator and it was said that there were no cases of non-compliance. N=0 dropout/ withdrawal due to drug related AEs.	27 patients/32 reached their target trough levels. Drop outs: 0 **Group 2: Placebo** Mean age (SD): Not described. Mean total DAI score (SD): 9.1 (1.05) Extent: Not described Drop outs: 0 **Definitions** Steroid resistant: When the disease failed to respond to a systemic daily dose of 1mg/kg of body weight, or 40mg or more of prednisolone given over at least 7 days, or the equivalent of a daily dose of prednisolone of 30mg or more over at least 2 weeks. Steroid dependent: Patients with active UC in whom attempts to taper steroids had been unsuccessful.	The steroid treatment remained the same from study initiation for 2 weeks, while only those on ≥60mg/day prednisolone were permitted to decrease the dosage during this period. If taking azathioprine at an unchanged dose over the period beginning 3 months prior to the start of the study, they could continue until the end of the trial. 5-ASA was permitted as long as the dose was not changed over the beginning 2 weeks prior to the trial until completion of the study. Nutritional therapy if received was continued. Ciclosporin, biological therapies, 6-mercaptopurine or other immunosuppressants was not permitted.	nausea (4). Most frequent in the placebo group was nausea (3) and headache (3) There were no serious adverse events.		endoscopic remission and clinical improvement figures for patients that reached the desired trough levels Results for the open label extension **Notes:** **Steroid resistant or steroid dependent population**

Table 129: OREN1996

Author	Patients	Intervention	Outcome measures	Effect size	Comments
R. Oren et al.	**All patients:**	**Group 1:**	Outcome 1:	**1 month (analysed**	**Funding:**

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Methotrexate in chronic active ulcerative colitis: a double-blind, randomized, Israeli multicenter trial. *Gastroenterology; 110(5):1416-21. 1996.* **REF ID: OREN1996** **Study design and quality:** **Type of RCT**: Each centre received 4-6 pre-packaged coded sets containing equal number of methotrexate or placebo **Multicentre**: 12 centres **Countries:** Israel **Duration:** 9 months **Randomisation:** Yes **Allocation concealment**: Yes. Performed by a central pharmacy and an unblinded independent observer was the only person who had access to drug code. **Blinding:** Double-blind. **Outcome assessment:** Endoscopic every 3 months. Mayo Clinic scoring system. **Sample size calculation:** Power of this study was to detect a 30% difference between the two groups.	**N=67randomised/ ITT** **Drop-outs** (don't complete the study): **N=19 (28.4%) (over the full 9 months)** **N=13 (19.4%)** (8 drop-outs, 3 treatment failures, 2 side effects) **Inclusion criteria:** **Extent**: Proctitis, left-sided and universal **Severity**: Chronic, active UC. Endoscopically active: Mayo Clinic score of ≥7. Chronicity = steroid therapy ≥7.5 mg/day for at least 4 months preceding 12months. **Exclusion:** age <17 yrs or >75 yrs; no consent; uncooperative or unreliable; not using contraception or breast feeding; alcoholism; disease too mild; allergy or sensitive to test drug; concomitant use of allopurinol, non-steroidal anti-inflammatory drugs, chloramphenicol; cotrixomazole, tetracyclines, and phenytoin; on-going bacterial infection and/or intra-abdominal abscess; chronic liver/kidney disease; recurrent intestinal obstruction; imminent surgery; and disease duration <1 yr. **<u>Group 1: Methotrexate</u>** **Mean age (SD):**38.31± 14.87 **Extent:** Proctitis (7.7%), Left-sided (69.2%), Universal (23.1%) **Other variables:** **Duration of disease**: 7.93±9.30 yrs **Sex (M/F):** 56.5%/43.3% **Drop outs:** N=7 (2 drop-outs, 2 side-effects, 3 treatment failures in 9 months. One of each were in the first 3 months) **<u>Group 2: Placebo</u>** **Mean age (SD):**38.92±15.95 **Extent:** Proctitis (10.3%), Left-sided (65.5%), Universal (24.2%) Other variables: **Duration of disease**: 5.85±5.24 yrs **Sex (M/F):** 48.6%/51.4%	**Methotrexate** N=30 randomised N=30 (ITT) N=23 (completers) **Intervention details** Oral dose on a fixed day/1 x wk in form of 5 tablets of 2.5 mg each (total 12.5mg/wk) **Group 2: Placebo** N=37 randomised N=37 (ITT) N=25 (completers) **Intervention details** Placebo tablets (no other detail provided) **Concomitant therapy:** Immunosuppressives could be used in addition or instead of steroids, but patient had to be off immunosuppressives for ≥3 months at entry to study. **Mesalamine and/or corticosteroids were allowed to at the discretion of the**	**Clinical remission** (data was taken from the Kaplan Meier survival analysis curve in the paper) **Adverse events:** This was not reported overall. Those who withdrew due to AEs in each group were: **Group 1: (at 2 and 5 months, unclear which is when)** Transient leukopenia(n=1) Migraine (n=1) **Group 2(at 0.5 months)** Severe rash (n=1)	**<u>as 4 weeks)</u>** **Group 1:**2/30 (6%) **Group 2:**3/37 (7.5%) **<u>2 months (analysed as 8 weeks)</u>** **Group 1:**2/30 (6%) **Group 2:**6/37(16%) **<u>3 months (analysed as 12 weeks)</u>** **Group 1:**6/30 (20%) **Group 2:**8/37(22%)	Crohn's and Colitis Foundation of America. **Limitations:** High dropout rate (higher in the placebo group) **Additional outcomes:** • Time to remission • No. Of patients with a relapse after first remission • Maintenance of remission • Mean total time of remission of patients entering remission • % total study time in remission **Notes:** PPA was also performed and the same results were found. The Hazard ratio for the time to remission was calculated to be: 0.74 (95%CI 0.36 to 1.49). Out of the 18 patients in remission at 9 months only 8 of these were in remission at 3 months in the placebo arm. 6/14 in the methotrexate arm.

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Type of analysis: ITT **Compliance rates:** N=3 dropout/withdrawal due to AEs, 2 of which were within the first 3 months (1 in each treatment group).	**Drop outs:** N=12 (9 drop-outs, 1 side-effects, 2 treatment failures in 9 months of which 7 drop outs, 1 side effects and 1 treatment failure was in the first 3 months) **Definitions** **Remission:** Mayo Clinic score (including sigmoidoscopy) of≤3, with the condition that the patient was not being administered steroids or a score of ≤2 without sigmoidoscopy results **Relapse:** ≥3 points in Mayo Clinic score (not including sigmoidoscopy) and/or reintroduction of steroids at a dose of ≥300 mg/mo.	**treating physician.** Mesalamine used by: Methotrexate: 66.7% Placebo: 67.6% At start of study: Steroids used by: Methotrexate: 70% Placebo: 73% Metronidazole permitted for perianal disease for <1 m during trial.			

Table 130: OREN1996

Author	Patients	Intervention	Outcome measures	Effect size	Comments
R. Oren et al. Methotrexate in chronic active ulcerative colitis: a double-blind, randomized, Israeli multicenter trial. *Gastroenterology; 110(5):1416-21. 1996.* **REF ID: OREN1996** **Study design and quality:** **Double blind RCT** **Multicentre**: 12 centres **Countries:** Israel	**All patients:** **N=67 randomised** N=32 entered first remission **Drop-outs** (don't complete the study): **N=18 (26.9%)** (11 drop-outs, 3 side effects). There were also 5 treatment failures which have not been included in this figure. >10% difference in missing data between the treatment arms **Inclusion criteria:** **Extent**: Proctitis, left-sided and universal **Severity**: Chronic, active UC. Endoscopically active: Mayo Clinic score of ≥7.	**Group 1: Methotrexate** N=30 randomised N=30 (ITT) N=23 (completers) N=14 (entered first remission) **Intervention details** Oral dose on a fixed day/1 x wk in form of 5 tablets of 2.5 mg each (total 12.5mg/wk)	**Outcome 1: Relapse after first remission** Unable to calculate the hazard ratio	**Group 1:** 9/14 (64.3%) **Group 2:** 8/18 (44.4%)	**Funding:** Crohn's and Colitis Foundation of America. **Limitations:** >10% difference in missing data between the treatment arms (higher in the placebo group) Randomised at induction of remission **Additional outcomes:**
			Adverse events: This was not reported overall. Those who withdrew due to AEs in each group were: **Methotrexate:** Transient leukopenia (n=1) Migraine (n=1)		

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Duration: 9 months **Randomisation:** Yes. : Each centre received 4-6 pre-packaged coded sets containing equal number of methotrexate or placebo **Allocation concealment**: Yes. Performed by a central pharmacy and an unblinded independent observer was the only person who had access to drug code. **Blinding:** Double-blind. Adequate. **Outcome assessment:** Endoscopic every 3 months. Mayo Clinic scoring system. **Sample size calculation:** Power of this study was to detect a 30% difference between the two groups. **Type of analysis:** ITT **Compliance rates:** N=11 dropout/3 withdrawal due to drug related AEs.	Chronicity = steroid therapy ≥7.5 mg/day for at least 4 months preceding 12months. **Exclusion:** age <17 yrs or >75 yrs; no consent; uncooperative or unreliable; not using contraception or breast feeding; alcoholism; disease too mild; allergy or sensitive to test drug; concomitant use of allopurinol, non-steroidal anti-inflammatory drugs, chloramphenicol; cotrixomazole, tetracyclines, and phenytoin; on-going bacterial infection and/or intra-abdominal abscess; chronic liver/kidney disease; recurrent intestinal obstruction; imminent surgery; and disease duration <1 yr. **Group 1: Methotrexate** **Mean age (SD):** 38.31± 14.87 **Extent:** Proctitis (7.7%), Left-sided (69.2%), Universal (23.1%) **Other variables:** **Duration of disease**: 7.93±9.30 yrs **Sex (M/F):** 56.5%/43.3% **Drop outs:** N=7 (2 drop-outs, 2 side-effects, 3 treatment failures) **Group 2: Placebo** **Mean age (SD):** 38.92±15.95 **Extent:** Proctitis (10.3%), Left-sided (65.5%), Universal (24.2%) Other variables: **Duration of disease**: 5.85±5.24 yrs **Sex (M/F):** 48.6%/51.4% **Drop outs:** N=11 (9 drop-outs, 1 side-effects, 1 treatment failure) **Definitions** **Remission:** Mayo Clinic score (including sigmoidoscopy) of≤3, with the condition that the patient was not being administered steroids or a score of ≤2 without sigmoidoscopy results **Relapse:** ≥3 points in Mayo Clinic score (not including sigmoidoscopy) and/or reintroduction of steroids at a dose of ≥300 mg/mo.	**Group 2: Placebo** N=37 randomised N=37 (ITT) N=25 (completers) N=18 (entered first remission) **Intervention details** Placebo tablets (no other detail provided) **Concomitant therapy:** Immunosuppressives could be used in addition or instead of steroids, but patient had to be **off immunosuppressives for ≥3 months at entry to study.** **Mesalamine and/or corticosteroids were allowed to at the discretion of the treating physician.** Mesalamine used by: Methotrexate: 66.7% Placebo: 67.6% At start of study: Steroids used by: Methotrexate: 70% Placebo: 73%	**Placebo** Severe rash (n=1) Time from first remission to first relapse (months) was 2.0 (0.9) for the placebo group and 1.8 (1.1) for the methotrexate group (p value=0.741).		Time from first remission to first relapse % total study time in remission **Notes:** PPA was also performed and the same results were found. The Hazard ratio for the time to remission was calculated to be: 0.74 (95%CI 0.36 to 1.49). Out of the 18 patients in remission at 9 months only 8 of these were in remission at 3 months in the placebo arm. 6/14 in the methotrexate arm.

Author	Patients	Intervention	Outcome measures	Effect size	Comments
		Metronidazole permitted for perianal disease for <1 m during trial.			

Table 131: PAGANELLI2007

Reference	Patient characteristics	Predictors and outcome measures	Effect sizes	Comments
M. Paganelli et al. Inflammation Is the Main Determinant of Low Bone Mineral Density in Pediatric Inflammatory Bowel Disease. *Inflammatory Bowel disease; 13 (4): 416-423. 2007.* **Type of study:** Cross-sectional and prospective cohort **Setting:** Pediatric Gastroenterology and Liver Unit at the University of Rome **Follow up period:** Used data from a previous year and also had biochemical and BMD measurements taken over a week.	**Sample size:** 56 patients; 35 with Crohn's disease and 21 with UC. **<5% missing data?** Unclear. **Type of analysis used:** T-test, Fisher's exact and chi square test. Pearson's or Spearman correlation coefficients of BMAD with different variables. Simple and multiple regression analysis for each variable on BMAD. **Appropriate?** Yes **Inclusion criteria (for UC patients):** • UC diagnosis based on at least 3 of the following: history of diarrhoea and/or blood or mucus in stools, evidence of continuous macroscopic inflammation extending from the rectum to the proximal regions of the colon, histological features typical of UC, and exclusion of CD of the small bowel as the diagnosis through radiology, endoscopy and histology **Exclusion criteria:** • Indeterminate colitis • Another chronic illness known to affect bone mineral status, growth, or pubertal development • Receiving growth hormone, exogenous sexual hormones or antiresorptive drugs such as	**Definitions of Risk factor variables measured:** **Disease activity:** Measured using the Powell Tuck Index for UC patients. Mean of 3 measures of the activity index during the year before enrolment was calculated by a medical chart review. Rachmilewitz endoscopy score was calculated for those who underwent colonoscopy during the 5 months before enrolment. Endoscopy was carried out by the same investigator. **Systemic corticosteroid use:** cumulative and daily dose of corticosteroids (expressed in mg of prednisone) were calculated for the total duration of the disease. **Weight:** expressed as z scores. Single investigator on the same scale and stadiometer. **25-hydroxyvitamin D:** Interval between BMD and biochemical assessments was <7 days. **Outcome and definitions** **Bone mineral density:** BMD of the lumbar vertebrae was obtained by DXA. All scans were performed by the same operator. Device daily calibration. Technical error resulted to be <1%. AreaBMD (aBMD) – sum of bone mineral content of the first 4 lumbar vertebrae divided by the sum of the respective projected areas (grams per square cm). BMD age and sex specific, so aBMD was converted to a z score by Hologic software. Reference data that was published by van der Sluis was used, which was obtained by a Lunar DXA	**Results** • BMAD for children with UC: -1.9 (1.5) • Prevalence of low BMD: 47.6% in UC patients • BMAD was inversely correlated with the mean Powell Tuck index over the year before DXA in patients with UC (r=-0.64, p<0.01) • 25OHD levels: 22.6 ng/mL (16.7) • aBMD (chronological age): -1.5 (1.1) • aBMD (bone age): -1.2 (0) • BMAD (chronological age): -1.9 (1.5) • BMAD was lower in children with UC who had previously been treated with steroids than in children who had never received these drugs (Not statistically significant) **Multiple regression analysis** • The following was the only description of the multiple regression analysis: • Evaluated the contribution of different variables (unclear exactly which ones) • IL-6 and Powell-Tuck Index (mean of 3 evaluations over the year before DXA) were considered for inclusion in the model for children with UC • IL-6 was an independent predictor of BMAD in UC children (R^2= 0.43) • Powell Tuck index was removed from	**Source of funding**: None described. **Risk of bias:** • Limited information reported for the multiple regression analysis • Unclear missing data **Additional outcomes reported:** Other biochemical markers and inflammatory cytokines.

Reference	Patient characteristics	Predictors and outcome measures	Effect sizes	Comments
	bisphosphonates • Total colon resection (UC patients) **Data collection:** Consecutive children with IBD treated in the Pediatric Gastroenterology and Liver Unit at the University of Rome La Sapienza from November 2003-May 2005. **Treatment given:** Not described. **Baseline characteristics: For the UC patients** Sex (m/f): 11/10 Mean age (range): 12.8 (6-19) Pubertal age (Tanner): 1 n=6, 2-3 n=5, 4-5 n=10 Bone age, mean (SD): 13 (3.3) Height (z score), mean (SD): -1.1 (1.3) BMI, mean (SD): -0.3 (1.2) Age at diagnosis, mean (range): 11.5 (5-19) Powell-Tuck Index at enrolment, mean (SD): 7.8 (5.5) Powell-Tuck Index last year, mean (SD): 8.9 (4.5) Corticosteroids (oral prednisone): Cumulative, mean (SD): 2.6 (3.2) g Daily, mean (SD): 11.9 (22.2) mg/d Duration of therapy, mean (SD): 3.2 (2) months Physical activity (hrs/week), mean (SD): 2.2 (2.2)	device. Volumetric density was also estimated by calculating bone mineral apparent density (BMAD) according to Kroger's formula. **Bone age:** Measured in each patient by the method of Greulich and Pyle, and aBMD z score was calculated again using bone age instead of chronological age. **Routinely measured?** Total vitamin D and DEXA scanning are not routinely measured. Weight is routinely measured. **Blinding:** unclear. No information given. **Risk of measurement error:** Unclear. **Risk of inter-observer variability:** Low. Same investigators measured the same tests. **Key prognostic factors not included?** • Ethnicity • Co-prescription of vitamin D • Family history • Diet	the model due to its correlation with IL-6 (r=0.76, p<0.01)	

Table 132: PAOLUZI2005

Author	Patients	Intervention	Outcome measures	Effect size	Comments
O. A. Paoluzi et al. Comparison of two different daily dosages (2.4 vs. 1.2g) of oral mesalazine in a maintenance of remission in ulcerative colitis patients: 1-	**<u>All patients:</u>** **N=156 randomised** **Drop-outs** (don't complete the study): N=16 (10%) (8 in each group)	**Group 1: 1.2g mesalazine** N=76 randomised N=68 (completers) 1.2g mesalazine	**Outcome 1: Relapse** Unable to calculate the hazard ratio.	**<u>At 12 months</u>** **Group1:** 48/76 **Group 2:** 48/80	**Funding:** None described. **Limitations:** Unclear method of randomisation and

Author	Patients	Intervention	Outcome measures	Effect size	Comments
year follow-up study. *Alimentary Pharmacology and Therapeutics; 21: 1111-1119.2005.* **REF ID: PAOLUZI2005** **Study design and quality:** Single blind, open label RCT **12 month trial** **Randomisation:** Unclear **Allocation concealment**: Unclear **Blinding:** Single blind. Medical staff performing the assessment of the clinical, endoscopic and histological activity was blinded. **Outcome assessment:** Clinical symptom assessments and laboratory tests. At the end of each visit disease activity was graded according to Truelove & Witts. Endoscopy was assessed according to Baron et al. Histology was assessed according to Truelove & Richard. **Sample size calculation:** Minimal difference of 20%, α & β error of <5%, 76 patients per arm. **Type of analysis: ITT**	**Inclusion criteria:** • Patients >18 years • Extent: UC >20cm from the anus • Clinical, endoscopic and histological remission • Diagnosis of UC as well as the staging of activity was established on the basis of standard clinical, endoscopic and histological criteria. • Outpatients • Recent disease relapse (within the last 3 months) prior to the study who have been appropriately treated until remission had been achieved • Severity: Activity prior to entry was **mild to moderate** and the treatment consisted in oral and topical mesalazine **Exclusion:** • Steroid dependence • Renal impairment • Pregnancy • Lactation • Established low compliance • Absence of relapse within the 5 years prior to the study **<u>Group 1: 1.2g mesalazine</u>** **Mean age (SD):** 46.9 (11.1) **Disease duration years, range:** 3-27 **Extent:** left sided n=64, diffuse/total n=12 **Severity of previous relapse:** mild to moderate **Frequency of relapses prior to the study:** ≤3 relapses/yr n=36, >3 relapses/year n=40 **Drop outs:** 8 (due to lost to follow up) **<u>Group 2: 2.4g mesalazine</u>** **Mean age (SD):** 47.7 (14.2) **Disease duration years, range:** 4-26 **Extent:** left sided n=56, diffuse/total n=24 **Severity of previous relapse:** mild to moderate **Frequency of relapses prior to the study:** ≤3 relapses/yr n=16, >3 relapses/year n=64	(Asacol). 400mg tablets. One tablet three times a day. **Group 2: 2.4g mesalazine** N=80 randomised N=72 (completers) 2.4g mesalazine (Asacol). 800mg tablets. One tablet three times a day. **Concomitant therapy:** Use of other drugs such as rectal mesalazine or steroids preparations was not permitted during the trial.	**Outcome 2: Relapse by frequency of relapses in the previous year** Unable to calculate the hazard ratio. Within group comparison: There was a significantly greater remission rate in those with ≤3 relapses/year compared to >3 relapses/ year. **Outcome 3: Adverse events** 1patient experienced a side effect of an idiosyncratic manifestation (skin rash) that had previously been treated with SASP, after a few day of mesalazine. **Relapse by extent of disease** Unable to calculate the hazard ratio.	**<u>≤3 relapses/yr</u>** **Group1:** 16/36 **Group 2:** 0/16 **<u>>3 relapses/yr</u>** **Group1:** 32/40 **Group 2:** 48/64 **Group1:** 0/76 **Group 2:** 1/80 **<u>Left sided disease</u>** **Group1:** 40/64 **Group 2:** 32/56 **<u>Diffuse/total disease</u>** **Group1:** 8/12	allocation concealment Single blind, open label **Additional outcomes:** Relapse and remission figures for by age, sex and duration of UC strata. **Notes:** No difference was found when patients were compared according to age, sex, extent and duration of disease.

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Compliance rates: Patient interview to assess adherence. Compliant when the patient took >85% of the drug prescribed for the week (i.e. <3 tablets forgotten per week). Compliance was described as 'good' in both arms. N=1 dropout/ withdrawal due to drug related AEs.	**Drop outs:** 8 (1 due to AE(skin rash) and 7 due to lost to follow up) **Definitions** **Remission:** absence of symptoms and endoscopic/histological changes typical of active UC. **Relapse:** As per the Truelove & Witts criteria.			**Group 2:** 16/24	

Table 133: POKROTNIEKS2000

Author	Patients	Intervention	Outcome measures	Effect size	Comments
J. Pokrotnieks et al. Efficacy and tolerability of mesalazine foam enema (Salofalk foam) for distal ulcerative colitis: a double-blind, randomized, placebo-controlled study. *Alimentary Pharmacology & Therapeutics; 14: 1191-1198.2000.* **REF ID: POKROTNIEKS2000** **Study design and quality:** Double blind, Phase IIb RCT Multicentre: 10 centres, it is unclear what countries the centres were based in **6 week trial** **Randomisation:** Computer	**All patients:** **N=111 randomised/ ITT** **Drop-outs** (don't complete the study): Unclear There were 31 major protocol violators but it is unclear which of these dropped out. 2 patients dropped out due to AEs. **Inclusion criteria:** • Extent: proctitis, proctosigmoiditis or left sided UC (preferably with a disease history of at least 3 months). This was confirmed at baseline a endoscopically, histologically and microbiologically • Left sided colitis patients had to have CAI>4 and EI≥4 • Proctitis and proctosigmoiditis patients had to have a CAI≥3 and EI≥4 • At least occasionally have blood in stools in the week before admission • Severity: mild or moderate UC	**Group 1: 2g mesalazine (Salofalk) foam enema** N=54 randomised/ITT 2g of mesalazine foam enema (Salofalk). Two actuations of foam (each one containing 1g of mesalazine.) in approximately 30mls of foam at night, if possible after defecation. **Group 2: Placebo foam enema** N=57 randomised/ ITT Two actuations of foam in approximately 30mls of foam at night, if	**Outcome 1: Clinical remission** (CAI≤4, associated with a decrease of at least 2 points from baseline) **Outcome 2: Clinical improvement** (investigators global assessment : complete relief, marked or slight improvement, "therapeutic benefit". This outcome was reported as the number of people who had therapeutic benefit and percentages so the total n values have	**ITT** **6 weeks** **Group1:** 35/54 **Group 2:** 23/57 **PPA** **2 weeks** **Group1:** 38/51 **Group 2:** 29/53 **4 weeks** **Group1:** 29/47	**Funding:** Mesalazine and placebo foam enemas and financial help was given by Dr. Falk Pharma GmbH, Germany. **Limitations:** Unclear drop out rate Double blind, no further information given **Additional outcomes:** Histological improvement Clinical remission by disease severity and extent of disease

Author	Patients	Intervention	Outcome measures	Effect size	Comments
generated randomization scheme. Randomised in blocks of four according to the randomization programme. 'Random' based on SAS software. **Allocation concealment**: Adequate **Blinding:** Double blind, no further information was given. **Outcome assessment:** Endoscopic index, clinical activity index. **Sample size calculation:** 80% power with a p value of 0.05 (30% response in mesalazine group). 55 patients were needed per arm. **Type of analysis: ITT and PPA.** LOCF- last observation carried forward for those who left the study early. **Compliance rates:** 89% in the mesalazine arm, 93% in the placebo arm. N=2 dropout/ withdrawal s. Unclear if drug related AEs. 1 patient in the mesalazine group for hallucinations, 1 in the placebo group for diarrhoea and abdominal cramps.	**Exclusion:** • Pathogenic microorganism causing colitis • Pregnant women • Macroscopic lesions not just distal but also proximal to the splenic flexure • Infectious bowel disease • Severe concomitant disease of an acute of chronic nature • Patients requiring systemic corticosteroids or been taking glucocorticosteroids for 1 month • Use of immunosuppressants for 3 months • Use of NSAIDs for 2 weeks • Use of antibiotics • Use of psyllium containing drugs • Use of bile-acid products, Loperamide • Use of other enema or foam products and oral mesalazine, olsalazine or SASP • People in whom mesalazine is contraindicated e.g. renal failure or liver disease • Intolerance of mesalazine and/or 5-ASA releasing drugs • Participation in another clinical study during the preceding 30 days • Alcohol or drug abuse **Baseline characteristics** **Group 1: 2g mesalazine foam enema** **Sex (m/f):** 23/31 **Mean age (range):** 44.1 (19-66) **Proportion of patients with recurrent disease:** n=42 **Extent:** proctitis n=13, proctosigmoiditis n=31, left sided UC n=10 **CAI at baseline:** 6.7 **Endoscopic index at baseline:** 6.9 **Treatment received for current episode:** n=39 **Drop outs:** unclear (1 due to AE) **Group 2: Placebo foam enema** **Sex (m/f):** 26/31 **Mean age (range):** 45.4 (20-69) **Proportion of patients with recurrent disease:** n=42	possible after defecation. **Concomitant therapy:** See the exclusion criteria.	been calculated.	**Group 2:** 25/43 **6 weeks** **Group1:** 35/43 **Group 2:** 26/37	
			Outcome 3: Endoscopic remission (EI≤3)	**ITT** **6 weeks** **Group1:** 26/54 **Group 2:** 17/57	
			Outcome 4: Serious adverse events There were 6 SAEs in 5 patients all for deterioration of UC.	**Group1:** 1/54 **Group 2:** 4/57	
			Outcome 5: Hospitalisations Group 1: due to deterioration of UC Group 2: due to deterioration of UC and one case additionally for decompensation of diabetes mellitus.	**Group1:** 1/54 **Group 2:** 4/57	
			Adverse events: these were not		

Author	Patients	Intervention	Outcome measures	Effect size	Comments
	Extent: proctitis n=20, proctosigmoiditis n=29, left sided UC n=8 **CAI at baseline:** 6.5 **Endoscopic index at baseline:** 6.8 **Treatment received for current episode:** n=42 **Drop outs:** unclear (1 due to AE)		reported as the number of people experiencing an event in each arm so has not been reviewed. 40 patients experienced 78 adverse events, 16 in the mesalazine arm and 52 in the placebo arm.		

Table 134: PORRO1994

Author	Patients	Intervention	Outcome measures	Effect size	Comments
G. B. Porro et al. Comparative trial of methylprednisolone and budesonide enemas in active distal ulcerative colitis. *European Journal of Gastroenterology & Hepatology; 6: 125-130. 1994.* **REF ID: PORRO1994** **Study design and quality:** Single investigator blind RCT Multicentre: 4 centres, Italy **4 week trial** followed by a 4 week open trial **Randomisation:** Central randomisation in blocks of 8. **Allocation concealment**: Adequate **Blinding:** Single investigator blind.	**<u>All patients:</u>** **N=88 randomised/ ITT** **Drop-outs** (don't complete the study): N=8 (%) (3 in the budesonide group, 2 in the methylprednisolone group, 3 unknown which group they were from) **Inclusion criteria:** • ≥18 years old • Extent: distal • Severity: mild to moderate active UC (according to Truelove & Witts) • Rectal bleeding during the week prior to entry • Diagnosis of UC confirmed by histology • Candidates for enema treatment (colonoscopy shows extent not further than the splenic flexure but >15cm from the anus) **Exclusion:** • Patients with concomitant disease requiring oral steroid treatment • Relevant liver disease • Diabetes mellitus • Used steroid enemas during the 2 weeks prior to entry **<u>Baseline characteristics</u>**	**Group 1: 2mg Budesonide liquid enema** N=44 randomised Budesonide 2mg/ 100ml liquid enema. Once daily at bedtime. **Group 2: 20mg Methylprednisolone hemisuccinate liquid enema** N=44 randomised Methylprednisolone hemisuccinate liquid enema 20mg/100ml. Once daily at bedtime. **Concomitant therapy:** Oral sulphasalazine and mesalazine use was permitted if on a constant dose and they had been taking it for the two weeks prior to	**Outcome 1: Hospitalisation** Group 2: due to salmonella infection Clinical and endoscopic remission and clinical improvement figures were presented but due to no definitions being given in the paper, the results will not be included.	**Group1:** 0/44 **Group 2:** 1/44	**Funding:** Supported by a grant from Giuliani SpA, Italy, who also provided the methylprednisolone enemas. Budesonide enemas were provided by Astra Draco. **Limitations:** Single investigator blind **Additional outcomes:** Clinical remission and endoscopic remission (but no definition) Plasma cortisol levels

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Outcome assessment: Hospitalisations. **Sample size calculation:** Difference of 28% in remission rates, 80% power, 5% significance level; 50 patients per treatment arm **Type of analysis: ITT** (all patients treated) **Compliance rates:** Not described N=0 dropout/ withdrawal due to drug related AEs.	**Group 1: 2mg budesonide liquid enema** **Sex (m/f):** 28/16 **Mean age (SD):** 42.6 (15) **Extent:** proctosigmoiditis n=30, left sided colitis n=14 **Oral maintenance treatment:** 5-ASA n=25, SASP n=10 **Clinical grading:** mild n=8, moderate n=36 **Endoscopic grading:** moderate n=24, severe n=20 **Drop outs:** 3 (due to worsening of disease) **Group 2: 20mg methylprednisolone liquid enema** **Sex (m/f):** 33/11 **Mean age (SD):** 43.3 (15) **Extent:** proctosigmoiditis n=28, left sided colitis n=16 **Oral maintenance treatment:** 5-ASA n=20, SASP n=12 **Clinical grading:** mild n=16, moderate n=28 **Endoscopic grading:** moderate n=29, severe n=15 **Drop outs:** 2 (due to respiratory illness, SAE which was a salmonella infection) It is unclear which group the 3 patients who were lost to follow up were in.	entry.			

Table 135: POWELLTUCK1978

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Powell – Tuck et al. A comparison of oral prednisolone given as a single or multiple daily doses for active proctocolitis	All patients N= 45 randomised 5 drop out, 2 data collection inadequate and 3 clinicians unblended. Unclear what	**Group 1** 40mgs prednisolone once a day N=23 randomised **Group 2** 40 mgs prednisolone 10 mgs	**Remission** Activity score = 0	Group 1=3/23 Group 2=5/22	
			Improvement A reduction in score by two or more points	Group 1 =14/23 Group 2=12/22	

Author	Patients	Intervention	Outcome measures	Effect size	Comments
.*Scandinavian Journal of Gastroenterology, 13,833-837* **REF ID: POWELLTUCK1978** United Kingdom **Study design and quality:** single blind RCT Duration of **follow-up:** 2 weeks **Randomisation**: restricted randomisation allocated patients into the two groups according to the patients taking salazopyrin to ensure the same number of people on salazopyrin in each group **Allocation concealment:** No information on allocation concealment **Sample size:** none stated **Type of analysis**: ITT	group **Inclusion** • Active proctocolitis, no proximal limit of disease • Combination of first attack and relapse **Exclusion:** • Steroid or AZT therapy Steroid resistance	four times a day N=22 randomised **Concomitant therapy:** Group 1:16 patients on salazopyrin Group 2:15 patients on salazopyrin	**Side effects** Steroid side effects seen.	Group 1=14/23 Group 2=12/22 Group 1:increased appetite (5).dyspepsia (3),mooning (3),oedema(2),hypokalaemia (2);striae(1), acne (1) Group 2:increased appetite (2).dyspepsia (3),mooning (4),hypertension(4),oedema (2),hypokalaemia(2)acne (2)	

Table 136: POWELLTUCK1986

Author	Patients	Intervention	Outcome measures	Effect size	Comments
J. Powell-Tuck et al.	**All patients:**	**Group 1: 1g mesalazine enema**	**Outcome 1: Endoscopic remission** (non friable	**ITT**	**Funding:** Ferring Pharmaceuticals

Author	Patients	Intervention	Outcome measures	Effect size	Comments
A defence of the small clinical trial: evaluation of three gastrointestinal studies. *British Medical Journal; 292: 599-602. 1986.* **REF ID: POWELLTUCK1986** **Study design and quality:** Double blind RCT Unclear whether it was based in the U.K. **4 week trial** **Randomisation:** No details given. **Allocation concealment**: No details given. **Blinding:** Double blind. **Outcome assessment:** Clinical, sigmoidoscopic and histological assessments were graded from 0-2, with 2 being the most severe. **Sample size calculation:** None described. **Type of analysis: ITT** **Compliance rates:** Not described. N=1 dropout/ withdrawal due to AEs, unclear if drug related.	**N=25 randomised/ ITT** **Drop-outs** (don't complete the study): N=1 (4%) Due to worsening of diarrhoea. **Inclusion criteria:** • Extent: proctosigmoiditis (rectosigmoid, diagnosed clinically, sigmoidoscopically and histologically and shown by barium enema) • Severity: Not described. **Exclusion:** • None described. **<u>Baseline characteristics</u>** **<u>Group 1: 1g mesalazine enema</u>** **Sex (m/f):** 4/8 **Mean age (SD not given):** 49 **Concurrent SASP therapy:** 5 **Extent:** All proctosigmoiditis **Drop outs:** 0 **<u>Group 2: 2g mesalazine enema</u>** **Sex (m/f):** 7/5 **Mean age (SD not given):** 45 **Concurrent SASP therapy:** 3 **Extent:** All proctosigmoiditis **Drop outs:** 1 due to AEs	N=12 randomised 1g/dl 5-ASA (mesalazine) enema at night. Type of mesalazine not specified. **Group 2: 2g mesalazine enema** N=13 randomised 2g/dl 5-ASA (mesalazine) enema at night. Type of mesalazine not specified. **Concomitant therapy:** No other medication apart from sulphasalazine which was continued unaltered.	rectal mucosa- grade 0)	**<u>2 weeks</u>** **Group1:** 7/12 **Group 2:** 4/13 **<u>4 weeks</u>** **Group1:** 9/12 **Group 2:** 6/13	provided the drugs. **Limitations:** Unclear method of randomisation and allocation concealment Limited baseline characteristics Double blind, no further information given **Additional outcomes:** Grading of 0 or not for the following variables at week 2 & 4: Frequency, bleeding, malaise, stool consistency Histological remission **Notes:**
			Outcome 2: Clinical and endoscopic remission (same definition as endoscopic remission plus a score of 0 for all clinical variables; malaise, bowel frequency, stool consistency, rectal bleeding)	**ITT** **<u>2 weeks</u>** **Group1:** 3/12 **Group 2:** 2/13 **<u>4 weeks</u>** **Group1:** 7/12 **Group 2:** 4/13	
			Outcome 3: Adverse events	**Group1:** 0/12 **Group 2:** 1/13	

Table 137: PRANTERA2005

Author	Patients	Intervention	Outcome measures	Effect size	Comments
C. Prantera et al. A New Oral Delivery System for 5-ASA: Preliminary Clinical Findings for MMx. *Inflammatory Bowel Disease; 11: 421-427.2005.* **REF ID: PRANTERA2005** **Study design and quality:** Double blind, double dummy RCT Multicenter: 5 sites, Italy **8 week trial** **Randomisation:** Computer generated randomisation. **Allocation concealment**: Adequate **Blinding:** Double blind, double dummy **Outcome assessment:** Clinical activity index and endoscopic index. **Sample size calculation:** One of convenience. **Type of analysis: ITT, PPA, LOCF** **Compliance rates:** Comparison between what was dispensed and what was recorded to have	**All patients:** **N=79 randomised** (59 recto-sigmoid, 20 left sided disease) N=78 ITT (1 major protocol violation at entry) Authors ITT (all randomized patients who satisfied the inclusion and exclusion criteria) **Drop-outs** (don't complete the study): N=20 (25.3%) >10% difference in missing data between the two treatment arms. **Inclusion criteria:** • >18 years • Extent: left sided UC (≥15cm but no further than the splenic flexure) • Severity: CAI≥6 **Exclusion:** • Infectious colitis • Use of oral or topical steroids/ immunosuppressive agents in the 4 weeks before the study • Bisulfate, salicylates allergy • Clinically important hepatic, renal, cardiovascular or psychiatric conditions • Previous ineffective 5-ASA treatment or refractory SAS treatment • Pregnancy • Lactation • Participation in experimental therapeutic studies in previous 6 months • Inability to follow the protocol **Baseline characteristics** **Group 1: 3.2g mezavant XL mesalazine** **Sex (m/f):** 24/16 **Mean age (SD):** 41.1 (14.4)	**Group 1: 3.6mg mezavant XL mesalazine** N=40 randomised/ ITT 1.2g of mesalazine (mezavant XL) given three times a day plus a placebo enema. **Group 2: 4g liquid mesalazine (Asacol)** N=39 randomised N=38 ITT 4g liquid mesalazine (Asacol) enema plus placebo tablets three times a day. **Concomitant therapy:** No systemic or topical therapy for UC.	**Outcome 1: Clinical remission** (CAI≤4, according to Rachmilewitz) **Outcome 2: Endoscopic remission** (EI≤2) **Outcome 3: Adverse events** None were severe	**ITT** **4 weeks** **Group 1:** 23/40 **Group 2:** 26/38 **8 weeks** **Group1:** 24/40 **Group 2:** 19/38 **Group1:** 18/40 **Group 2:** 14/38 **Group1:** 6/40 **Group 2:** 11/39	**Funding:** None described. **Limitations:** >10% difference in missing data between the two treatment arms. **Additional outcomes:** Clinical improvement is reported but this was not stated as a primary or secondary outcome in the methods, so has not been analysed (post hoc analysis) Histological remission

Author	Patients	Intervention	Outcome measures	Effect size	Comments
been taken in the patient's diaries. 97% for oral tablets and 87.5% for the rectal enema. N= 1 dropout/ withdrawal due to AEs (abdominal and anal pain and headache, enema group)	**Extent:** proctosigmoiditis n=27, left sided colitis n=13 **Mean CAI (range):** 7.75 (6-13) **Mean EI (range):** 6.73 (2-12) **Mean flares in the last year (range):** 1.0 (0-3) **Oral 5-ASA in the last month:** 29 **Drop outs:** 8 (1 pregnancy, 2 consent withdrawn, 5 failure). 20% missing data. **Group 2: 4g rectal mesalazine liquid enema (Asacol)** **Sex (m/f):** 23/16 **Mean age (SD):** 41.3 (12.3) **Extent:** proctosigmoiditis n=32, left sided colitis n=7 **Mean CAI (range):** 7.67 (6-12) **Mean EI (range):** 6.49 (1-11) **Mean flares in the last year (range):** 0.8 (0-4) **Oral 5-ASA in the last month:** 26 **Drop outs:** 12 (1 protocol violation, 2 lost to follow up, 1 consent withdrawn, 7 failure). 31% missing data.				

Table 138: PRANTERA2009

Author	Patients	Intervention	Outcome measures	Effect size	Comments
C. Prantera et al. Clinical trial: ulcerative colitis maintenance treatment with 5-ASA: a 1-year, randomized multicentre study comparing MMX® with Asacol®. *Alimentary Pharmacology and Therapeutics; 30: 908-918. 2009.* **REF ID: PRANTERA2009** **Study design and quality:** Double blind, double dummy RCT	**All patients:** **N=334 randomised** **N=331 ITT** (3 did not take any medication) **N=323 mITT** (reasons for exclusion were relocation to another city or country and withdrawal of informed consent with the first 2 days of the randomization) Modified ITT (mITT): ITT population with the exclusion of patients who either; withdrew from the study for a reason reported by the investigator as clearly independent of treatment or remained in the study for 2 days or less. **N=282 PPA** (17.9% and 12.4% major protocol violations, mezavant XL and Asacol groups respectively)	**Group 1: Mesalazine 2.4g (Asacol)** N=169 (ITT) N=167 (mITT) N=148 (PPA) N= 106 completers Two 800mg tablets in the morning and one 800mg tablet in the evening. **Group 2: Mesalazine 2.4g (mezavant XL)**	**Outcome 1: Relapse** Kaplan Meier p value= 0.48 **Outcome 2: Adverse events** Mainly gastrointestinal disorders. **Outcome 3: Serious adverse events**	**mITT** **Group1:** 50/167 (29.9%) **Group 2:** 39/156 (25%) **Group1:** 99/169 **Group 2:** 92/162 **Group1:** 5/169	**Funding:** Financed by Giuliani S.p.A. An author is also an employee there. **Limitations:** Double blind, double dummy but no details about it was given **Additional outcomes:** Clinical remission based on the patient diary definition

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Multicentre: Italy, Poland and Ukraine **12 month trial** **Randomisation:** Individual computer generated randomization number via an internet based procedure. Equal assignment to the two groups. **Allocation concealment**: Adequate. **Blinding:** Double blind, double dummy, no further details given **Outcome assessment:** 3 monthly clinic reviews or with early withdrawal. Diary card used. Colonoscopy done at 12months/ withdrawal. UCDAI. **Sample size calculation:** 15% higher remission rate for Asacol, 5% significance level, 80% power, 10% drop out rate. 150 patients per treatment arm were needed. **Type of analysis: ITT, mITT, PPA** **Compliance rates:** Checked by tablet counts at each visit. 91.5% took ≥80% of the study medication. N=6 dropout/ withdrawal due to AEs, 3 in each group. 3 were possibly drug related.	**Drop-outs** (don't complete the study): N=28 (8.4%) - 3 did not take any medication, 25 other [see reasons below] <10% difference in missing data between the treatment arms. **Inclusion criteria:** • Male and female aged 18-75 years • Remission of ≥1 month prior to the trial • ≥1 clinically and/or endoscopic relapse in the previous year • Extent: **Left sided UC diagnosis** (rectum to sigmoid colon, or colon up to the splenic flexure). Established by sigmoidoscopy or colonoscopy and confirmed by histology **Exclusion:** • Received oral or topical corticosteroid treatment for ≥1 months • Received immunosuppressant treatment in the last 3 months • Proctitis • Bleeding disorders • Active peptic ulcer • Previous colon surgery • Renal impairment • Malignancy or dysplasia of the colon • Receiving maintenance therapy with 5-ASA doses of >2.4g/day **(note: although this was stated to be an exclusion criteria, patients had >2.4g 5ASA; see baseline characteristics)** • Sensitive to 5-ASA • In the last 12 months, experienced disease activity and were unresponsive to a 12 week course of steroids (steroid refractory) **<u>Group 1: Mesalazine 2.4g (Asacol)</u>** **Mean age (SD):** 44.5 (13.5) **Extent:** left sided n=66, rectum sigmoid n=103 **Mean duration of disease, years (SD):** 6.96 (6.28) **Number of relapses in the last year:** 1 n=143, 2 n=20, ≥3 n=6 **Mean Time in remission, months (SD):** 4.74 (2.99) **5-ASA maintenance therapy dose:** <1.6g n=39, 1.6-<2.4g n=38, ≥2.4g	N=162 (ITT) N=156 (mITT) N=134 (PPA) N=111 completers Two 1.2g tablets in the morning and one placebo tablet in the evening. **Concomitant therapy:** See inclusion/exclusion criteria.	Group 1: One was coded UC, one perianal abscess, one haemorrhoids, one renal colic and the other proteinuria. Group 2: Three were coded as UC, one patient experienced melena, one patient acute pancreatitis and one patient nephrolithiasis.	**Group 2:** 6/162	Clinical and endoscopic remission Time to relapse **Notes:** There was a country effect, with a higher proportion of patients in Poland and Ukraine being in remission at month 12 than patients in Italy. In all analysis, the country effect was statistically significant. Time to relapse: This is shown on a graph. It was not statistically significant (p=0.48), but when the patient diary was included it was (p=0.031).

Author	Patients	Intervention	Outcome measures	Effect size	Comments
	n=71 **UCDAI total score:** 0 n=101, 1 n=67, missing n=1 **Severity of previous relapse:** Not described **Drop outs:** 8 (4 patient request, 3 due to AEs (ankylosing spondylitits, increased pancreatic enzymes without clinical symptoms and epistaxis), 1 protocol violation) **Group 2: Mesalazine 2.4g (mezavant XL)** **Mean age (SD):** 45.4 (14.1) **Extent:** left sided n=70, rectum sigmoid n=92 **Mean duration of disease, years (SD):** 7.02 (6.07) **Number of relapses in the last year:** 1 n=140, 2 n=19, ≥3 n=3 **Mean Time in remission, months (SD):** 5.07 (2.89) **5-ASA maintenance therapy dose:** <1.6g n=27, 1.6-<2.4g n=43, ≥2.4g n=69 **UCDAI total score:** 0 n=88, 1 n=73, missing n=1 **Severity of previous relapse:** Not described **Drop outs:** 17 (8 patient request, 3 due to AEs (prostate cancer, amenorrhoea and melena), 3 lost to follow up, 3 other) **Definitions** **Inclusion criteria remission:** Score of ≤1 on the UC Disease Activity Index, supported by a rectal sigmoidoscopy in the preceding 3 months or colonoscopy in the preceding 6 months. **Clinical remission:** Combined score of ≤1 on the UC-DAI scale , where the combined score was the total of the investigator's assessment of the patient's condition, stool frequency and rectal bleeding (only one of these 3 components could have a value of 1) **Clinical and endoscopic remission:** Clinical remission with a normal mucosal appearance upon endoscopic examination. **Relapse:** UCDAI score >1. Due to lower than expected relapse rates, prior to unblinding the data, the advisory board recommended that patients reporting a dairy card score of >1 for at least 2 consecutive weeks with a rectal bleeding score of ≥1 be classified as clinical relapse at the date of the first day of the week of onset. Kaplan-Meier censoring: patients who did not relapse were censored at the last date of study participation and patient withdrawn were censored at the date of withdrawal.				

Table 139: PRUITT2002

Author	Patients	Intervention	Outcome measures	Effect size	Comments
R. Pruitt et al. Balsalazide Is Superior to Mesalamine in the Time to Improvement of Signs and Symptoms of Acute Mild-to-Moderate Ulcerative Colitis; 97 (12): 3078-3086. 2002. **REF ID: PRUITT2002** **Study design and quality:** Double blind RCT Multicentre: United States **8 week trial** **Randomisation:** Patients were stratified by time since diagnosis and extent of disease. Randomised in a 1:1 ratio, no further details given **Allocation concealment**: Unclear **Blinding:** Double blind. Blind pathologist. **Outcome assessment:** Patient functional assessment (PFA), Physician's global assessment (PGA), sigmoidoscopic assessment (levels not described). **Sample size calculation:** None described.	**All patients:** **N=173randomised** **Drop-outs** (don't complete the study): N=33 described but there are also patients lost to follow up etc. which were not explicit **Inclusion criteria:** 12-80 years old Severity: active mild to moderate ulcerative colitis Extent: at least 12cm of sigmoidoscopically verified disease Relapse (requiring an increase in dose or change in drug therapy) or newly diagnosed Rectal bleeding Patient functional assessment (PFA) score of moderate or severe within the 48hrs prior to screening visit Sigmoidoscopic score of moderate (friable) or severe (spontaneously bleeding) Negative serum pregnancy test for those of child bearing age and practicing a reliable method of contraception Not currently breast feeding **Exclusion:** > 5 relapses of UC in the 2 yrs preceding the screening visit Used oral, rectal or IV steroids within 14 days Used immunosuppressant's within 90 days	**Group 1: 6.75g Balsalazide** N=84 randomised N=73 (ACA) 6.75g Balsalazide/day (Colazal) Given three active capsules and two placebo tablets three times a day Total dose is the equivalent of 2.4g of 5-ASA **Group 2: 2.4g Mesalamine** N=89 randomised N=77 (ACA) 2.4g Mesalamine/ day (delayed release, Asacol) Given two active tablets and three placebo capsules, three times a day Total dose is the equivalent of 2.4g of 5-ASA **Concomitant therapy:** Medications not permitted during the	Outcome 1: **Clinical remission** (PFA score of normal or mild and absence of rectal bleeding) Outcome 2: **Clinical and endoscopic remission** (complete remission-symptomatic remission plus a sigmoidoscopic evaluation score of normal or mild) Outcome 3: **Adverse events** Most common adverse events were headache, nausea, abdominal pain, fever and diarrhoea. 20 patients in the balsalazide group and 24 in the mesalamine group were said to have causally related AEs. Outcome 4: **Serious adverse events**	**Group1:**38/73 (52%) **Group 2:**38/77 (49%) **Assumed ITT analysis. N value calculated from % given.** **Group1:**39/84(46%) **Group 2:**36/89(41%) **Group1:**45/84 (54%) **Group 2:**57/89 (64%) **Group1:**0/84 **Group 2:**2/89 (2)	**Funding:** No funding was described but Salix Pharmaceuticals was an author. **Limitations:** Unclear method of randomisation and allocation concealment Limited baseline characteristics Unclear dropout rate No further information given on double blinding of physician/ patients Unclear scoring system for sigmoidoscopic assessment **Additional outcomes:** Stratum results (newly diagnosed, recently relapsed, extent) for remission Time to symptomatic remission (median) Histology findings Improvement (one severity grade or more) of sigmoidoscopic score, stool frequency, rectal bleeding and PGA shown on graphs.

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Type of analysis: ITT and ACA (All randomized patients that received at least one dose of the study drug. EEP (Efficacy evaluable population): Those who did not have clinically significant protocol violations, met the minimum symptom requirements at baseline, terminated early because of complete remission or treatment failure, or for other reasons but completed either three of four scheduled visits or two scheduled visits plus an unscheduled early termination visit, received at least 70% of the study drug and completed diaries for at least 2 of the 4 days prior to each visit). **Last observation carried forward** **Compliance rates:** Not described. ACA analysis included patients with >70% ingestion of drug treatment. N=9 dropout/ withdrawal due to AEs (3 in the balsalazide and 6 in the mesalamine group). One patient had C. Difficile in the mesalamine group. No other details were given. Unclear if it was drug related.	Used 5-ASA containing agents within 3 days prior to the screening visit History of hypersensitivity or failure to respond to 5-ASA agents Severe Ulcerative Colitis Have an enteric pathogen **ITT baseline characteristics:** **Group 1: 6.75g Balsalazide** **Mean age (SD):**41.6 (13.5) **Extent:**≤40cm n=45, > 40cm n=39 **Drop outs:** 14 (11 treatment failures, 3 adverse events). Unclear how many were administrative (lost to follow up). **Group 2: 2.4g Mesalamine** **Mean age (SD):**40.5 (11.9) **Extent:**≤40cm n=49, > 40cm n=40 **Drop outs:** 19 (13 treatment failures, 6 adverse events). Unclear how many were administrative (lost to follow up). The sigmoidoscopic severity significantly differed at baseline between the two groups (15% versus 28%, balsalazide and mesalamine respectively)	trial were: Other 5-ASA products 4-ASA products Steroids NSAIDs >1 dose/day of chronic low-dose aspirin Immunosuppressant's Antibiotics Laxatives Antidiarrheals Opiates Bile acid binders Topical rectal therapies	No specific definition of clinical improvement given. The PGA improvement is shown graphically. The balsalazide improvement line is higher than the mesalamine and the p value given is 0.013. Strata used were new diagnosis/relapse and extent of disease. Data for each strata was not available for just the extents apart from rectal bleeding.		

Table 140: RAEDLER2004

Author	Patients	Intervention	Outcome measures	Effect size	Comments

Author	Patients	Intervention	Outcome measures	Effect size	Comments
A. Raedler et al. Mesalazine (5-aminosalicylic acid) micropellets show similar efficacy and tolerability to mesalazine tablets in patients with ulcerative colitis – results from a randomized-controlled trial. *Alimentary Pharmacology & Therapeutics; 20: 1353-1363. 2004.* **REF ID: RAEDLER2004** **Study design and quality:** Phase II, double blind RCT Multicentre: 38 European centres **8 week trial** **Randomisation:** No information given. Unclear. **Allocation concealment**: Unclear. **Blinding:** Double dummy technique to ensure blinding. Dispensing investigator, patient, Contract Research Organization, sponsor staff involved in the trial, central laboratory and pathologist were all blinded to the treatment. **Outcome assessment:** CAI and EI according to Rachmilewitz.	**<u>All patients:</u>** **N=362randomised** **N=357 ITT (5 patients had missing post baseline measurements)** **Drop-outs** (don't complete the study): Unclear if all the protocol violators were drop outs. If it is then: N=40 (11%) **Inclusion criteria:** Men and women (18-75 years) Extent:≥12cm proximally Severity: Recurrent mild to moderate UC (CAI_{1-4} of ≥4 and an EI≥4) Diagnosed by clinical appearance, colonoscopy and histology Presence of blood in the stools, stool frequency of >18 stools in the week before treatment initiation Negative microbiological stool culture **Exclusion:** First appearance of ulcerative colitis at baseline Severe UC/ toxic megacolon Radiogenic or drug induced colitis Bacterial enterocolitis Bowel complications such as stenoses, fistulae, perforations or rectal bleedings requiring transfusions Active malignant disease or severe dysplasia confirmed by histological findings	**Group 1: 3g mesalazine micropellets** N=181 randomised N=179 (ITT) N=160 (PPA) 1.5g sachets of micropellets were taken twice daily (morning and evening). Micropellets were emptied onto a spoon and taken with a sufficient amount of liquid (about one glass or 180mls). Placebo tablets. **Group 2: 3g mesalazine tablets** N=181 randomised N=178 (ITT) N=162 (PPA) Two 500mg film coated mesalazine tablets taken three times a day (morning, noon and evening). These were ingested with a glass of liquid (about 180mls). Placebo sachets of micropellets. **Concomitant therapy:**	Outcome 1: **Clinical remission** (CAI_{1-4}≤2) Outcome 2: **Endoscopic remission** (EI≤2) Outcome 3: **Clinical and endoscopic remission** (CAI_{1-7}<4 and EI≤2) Outcome 4: **Adverse events** Headache and nausea were the most frequently reported AEs. Majority were mild. Outcome 5: **Serious adverse events** The SAEs were thought to be related to UC not to the treatment assigned. No further information was given.	**Group1:**120/179 (67%) **Group 2:**112/178 (62.9%) **Group1:**67/179 **Group 2:**71/178 **Group1:**61/179 **Group 2:**59/178 **Group1:**56/181 (30.9%) **Group 2:**43/181 (23.8%) **Group1:**3/181 **Group 2:**6/181	**Funding:** Grant from Merckle. **Limitations:** Unclear method of randomisation and allocation concealment Unclear dropout rate but <20% Limited baseline characteristics **Additional outcomes:** Complete remission (CAI_{1-7}) <4 (NB this does not include any endoscopic findings) Histological evaluation Patient assessment Overall efficacy (assessed by the patients and investigators) Improvement in efficacy (CAI_{1-4})(assessed by the patients)

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Sample size calculation:55% clinical remission rate which is equal in both arms, one sided equivalence limit difference of 20%, α= 2.5%, power 90%, exclusion rate of 25%, 175 patients per treatment arm. **Type of analysis: ITT** (treated with at least one study medication) **and PPA** **Individual last value** **Compliance rates:** Assessed by tablet and sachet counts. Adequate compliance was considered to be 80-120%.96% of the micropellet group and 98% in the tablet group were compliant. N=6 dropout/ withdrawal due to AEs (5 in the micropellet group and 1 in the tablet group)	Clinically relevant haematological endocrine, cardiovascular, hepatic, renal or infectious disease An acute or duodenal ulcer Pathological laboratory values indicating clinically relevant liver or renal disease or severe anaemia History of hypersensitivity to salicylic acid and its derivatives or benzoates or alcohol or drug abuse Received immunosuppressives in the last 90 days, received antibiotics to treat colitis in the last 30 days or glucocorticoids in the last 3 days before enrolment Use of the following concomitant treatments; 5-ASA containing drugs, corticosteroids, fish-oil preparations, immunosuppressives, antibiotics to treat UC, antispasmodics, analgesics, antidiarrhoea agents, anticoagulants, sulphonylureas, probenecid, sulfinpyrazone, spironolactone, furosemide or rifampicin Women who were not postmenopausal or sterilized or not using adequate contraception Pregnant or lactating women. **Group 1: 3.0g mesalazine micropellets** **Age group:** <65 years n=169, ≥65 years n=10 **Concomitant medications: n=56** **Extent:** Not described **Drop outs:** 5 due to AEs, unclear how many more. **Group 2: 3g mesalazine tablets** **Age group:** <65 years n=164, ≥65 years n=14 **Concomitant medications: n=68** **Extent:** Not described **Drop outs:** 1 due to AE, unclear how many more. Mean age was 44 years. The most common concomitant drugs were progestogens and oestrogens in fixed combination (n=29), followed by salicylic acid and derivatives (n=26). Two patients were receiving	See exclusion criteria.			

Author	Patients	Intervention	Outcome measures	Effect size	Comments
	mesalazine (dose not specified).				

Table 141: REEDY2008

Author	Patients	Intervention	Outcome measures	Effect size	Comments
D. Reedy et al. Relapses of Inflammatory Bowel Disease During Pregnancy: In-Hospital Management and Birth Outcomes. *American Journal of Gastroenterology; 103: 1203-1209.2008.* **REF ID: REEDY2008** **Study design and quality:** Retrospective case control study **2 treatment centres, United States** **Years studied: 1989-2001** **Risk of bias:** Patients only age matched Very limited baseline characteristics No controlling for confounders	**<u>All patients: Hospitalized for a disease relapse</u>** Included population • Inflammatory bowel disease pregnant women who were hospitalized for a disease relapse • Controls were age-matched pregnant patients that did not require hospitalisation for inflammatory bowel disease (matched type of IBD) Excluded population • Women with other major medical conditions (severe cardio-respiratory or renal disease and diabetes mellitus) were excluded from the control group **N=11 ulcerative colitis in the case group** (there were also 6 with Crohn's and 1 patient with indeterminate colitis) **N=25 ulcerative colitis in the control group** <u>Data collection</u> All patients were identified from hospital computer databases (using International Classification of Diseases codes). Patients with IBD hospitalized during pregnancy were identified and all charts reviewed to determine how many of these patients were hospitalized for a severe relapse of IBD. Medical records were reviewed and information relating to medical treatment for colitis and clinical response to this treatment was recorded. In addition, where available, data relating to the fetus (gestation period, birth weight, APGAR scores at 1 and 5 min, stillbirth rate, and congenital malformations) and the mother (caesarean section rate, and complications of pregnancy) were recorded. It wasn't always possible to get the obstetric notes due to the patients having care at different institutions.	**All patients were given hydrocortisone.** **Other treatments included:** Sulphasalazine Ciclosporin 5-ASA (oral and enema) Cortenema	See the table below for the outcome results. The data for the control group has not been reported because the paper only reports the overall control group figures (UC, Crohn's and indeterminate colitis). **Authors conclusions:** Higher incidences of preterm birth and low birth weight babies among IBD patients with severe colitis during pregnancy when compared to IBD patients with no relapse. Unclear whether this is related to the severity of the relapse or the medication used to treat the relapse. No increase in the incidence of other adverse outcomes (maternal or fetal death, stillbirths and congenital malformations).		**Funding:** None described **Limitations:** High risk of bias **Additional outcomes:** Results for Crohn's and indeterminate colitis patients as well as the control group overall **Notes:**

Author	Patients	Intervention	Outcome measures	Effect size	Comments
	Definitions **Low birth weight:** <2.5kg **Preterm birth:** Birth before the 37th week gestation **Stillbirths:** Late fetal deaths occurring at or after 28 weeks. **Disease relapse:** continued symptoms of rectal bleeding, cramps, and diarrhoea despite oral corticosteroid treatment. Baseline characteristics **Cases** Age: Range 20-34 years Week of pregnancy when hospitalised: Range 8-31 weeks Disease duration prior to admission (years): Range 1-5 years (some were unknown) Duration of symptoms prior to admission (days): Range 4-60 days Extent of colitis: proctosigmoiditis n=1, pancolitis n=3, unknown n=7 **Controls** Mean age, years (range): 28.9 (19-36) NB this is for all controls, not just the UC ones. No other data was described.				

Table 142: Patient birth outcomes

Patient no:	Medication on admission	Treatment of relapse	Outcome	Medication on discharge	Hospital stay (days)	Gestation period	Birth weight	Pregnancy complication
1	60mg hydrocortisone (oral) Steroid enema Ciproxin 1g/day	219mg hydrocortisone (IV) for 24 days Cefazolin 3g/day SASP 1g t.d.s.	Remission	3g SASP/day	31	35	1,590	None
2	160mg hydrocortisone (oral) 3.5g 5-ASA/day	300mg hydrocortisone (IV) for 6 days 160mg hydrocortisone (oral) for 1 day	Remission	320mg hydrocortisone (oral)	7	33	2,214	ITP
3	240mg hydrocortisone (IV) 1.2g 5-ASA/day	300mg hydrocortisone (IV) for 14 days Cortenema 100mg/day for 18 days	Remission	160mg hydrocortisone (oral) 450mg ciclosporin	18	26	1,080	None

Patient no:	Medication on admission	Treatment of relapse	Outcome	Medication on discharge	Hospital stay (days)	Gestation period	Birth weight	Pregnancy complication
	5-ASA enema 1g Ciproxin	Ciclosporin 220mg (IV) for 8 days Cicosporin 450mg for 4 days		3.2g 5-ASA				
4	200mg hydrocortisone (IV)	300mg hydrocortisone (IV) for 7 days 240mg hydrocortisone (oral) for 1 day Cortenema 100mg for 7 days 5-ASA 2.4g (oral) for 7 days 1g 5-ASA enema for 7 days	Remission	240mg hydrocortisone (oral) Cortenema 100mg 5-ASA 1g enema Cortifoam enema 100mg	6	34	2,722	None
5	180mg hydrocortisone (oral)	300mg hydrocortisone (IV) for 13 days 160mg hydrocortisone (oral) for 1 day Cortenema 200mg Ciclosporin (IV) 220mg for 9 days then 350mg orally for 1 day	Remission		15	N/A	N/A	N/A
6	240mg hydrocortisone (oral) 50mg mercaptopurine	300mg hydrocortisone (IV) for 11 days then 180mg orally for 2 days Ciclosporin 100mg (IV) for 8 days then 250mg orally for 1 day	Remission	120g hydrocortisone (oral) 250mg ciclosporin (oral) 75mg mercaptopurine (oral)	13	N/A	N/A	N/A
7	160mg hydrocortisone (oral) 5-ASA 3.2g	300mg hydrocortisone (IV) for 6 days then 120mg orally for 1 day Cortenema 100mg	Remission	180mg hydrocortisone (oral) 5-ASA 2.4g Cortenema 100mg	5	N/A	N/A	N/A
8	160mg hydrocortisone (oral) 4.8g 5-ASA	220mg hydrocortisone (IV) for 12 days Ciclosporin 220mg (IV) for 5 days	Remission	160mg hydrocortisone (oral) 400mg ciclosporin (oral)	12	39	1,968	None
9	160mg hydrocortisone	200mg hydrocortisone (IV) for 3 days	Colectomy	160mg	10	36	1,700	None

Patient no:	Medication on admission	Treatment of relapse	Outcome	Medication on discharge	Hospital stay (days)	Gestation period	Birth weight	Pregnancy complication
	(oral)			hydrocortisone (oral)				
10	160mg hydrocortisone (oral)	200mg hydrocortisone (IV) for 4 days Ciclosporin 220mg (IV) for 3 days	Remission	160mg hydrocortisone (oral) 500mg ciclosporin (oral)	6	Spontaneous abortion at 15weeks during hospitalisation	-	-
11	160mg hydrocortisone (oral)	200mg hydrocortisone (IV) for 8 days	Colectomy	40mg hydrocortisone (oral)	12	N/A	N/A	N/A

(a) N/A- information not available. No obstetric records were able to be retrieved.
(b) ITP: Immune thrombocytopenic purpura

There were no stillbirths, maternal deaths or congenital malformations recorded in either group of patients.

Table 143: RIIS1973

Author	Patients	Intervention	Outcome measures	Effect size	Comments
P. Riis et al. The Prophylactic Effect of Salazosulphapyridine in Ulcerative Colitis during Long-Term Treatment. *Scandinavian Journal of Gastroenterology; 8 (1): 71-74. 1973.* **REF ID: RIIS1973** **Study design and quality:** Double blind RCT Denmark	**<u>All patients:</u>** **N=50 randomised** **N=49 completers** (one patient was excluded owing to travel abroad) **Drop-outs** (don't complete the study): N=0 (0%) **Inclusion criteria:** • Men and women aged 15-79 years • Diagnosis of UC was made when three of four diagnostic components were present (history, endoscopic appearance, cytological/biopsy findings, radiological appearance)	**Group 1: Sulphasalazine** N=25 (data available) Salazosulphapyridine (Salazopyrin®) tablets. Patients continued with the number of tablets that they had received before the trial period. **Group 2: Placebo** N=24 (data available)	**Outcome 1: Relapse** Unable to calculate the hazard ratio	**Group1:** 6/25 **Group 2:** 7/24 **Median time to relapse:** **Group1:** 93 days **Group 2:** 102 days	**Funding:** supported by the Danish Medical Research Council and Kong Christina X's foundation. Salazopyrin and placebo tablets were provided by Pharmacia AS. **Limitations:** Unclear if allocation concealment was adequate. No baseline characteristics

Author	Patients	Intervention	Outcome measures	Effect size	Comments
6 month trial **Randomisation:** divided into 4 blocks regarding duration of disease and length of remission. Random number table was used. **Allocation concealment**: A set of envelopes containing each patient's code was available in case it should prove imperative to know the nature of the treatment given to a single patient. Unclear if these were opaque. **Blinding:** Double blind. **Outcome assessment:** Unclear. Seen at 3 and 6 months. Based on the relapse definition. **Sample size calculation:** Significance level of 0.1. No further details given. **Type of analysis: ACA** **Compliance rates:** Assessed by tablet counts. 46 patients had a >80% compliance. Those that weren't compliant did not have a relapse. N=0 dropout/ withdrawal due to drug related AEs.	• No symptoms during one year's treatment with SASP only **Exclusion:** • Colectomized patients • Pregnant women **<u>Baseline characteristics</u>** 27 women and 23 men from 17-79 years (median age 42 years) Number of tablets per day: 2/day n=4, 3/day n=6, 4/day n=38, 6/day n=1 **<u>Definitions</u>** **Remission:** Free from symptoms **Relapse:** If rectal bleeding had occurred for >3 successive days or the patients had had more > 3 defecations daily for >5 successive days.	Placebo tablets. Patients continued with the number of tablets that they had received before the trial period. **Concomitant therapy:** Unclear/ no described.			Part of the relapse definition may not be thought of as a relapse? **Additional outcomes:** Relapse by blocks randomised **Notes:** **SASP tolerant population, withdrawal study**

Table 144: RIJK1991

Author	Patients	Intervention	Outcome measures	Effect size	Comments
M. C. M. Rijk and J.H.M. van Tongeren The efficacy and safety of sulphasalazine and olsalazine in patients with active ulcerative colitis. *Gastroenterology; 100: A243. 1991.* **REF ID: RIJK1991** **Study design and quality:** Double blind RCT [Abstract] Multicentre This abstract has been included because it was included in the Cochrane systematic review on oral ASAs for the induction of remission in ulcerative colitis. **6 week trial (patients could continue on for another 6 weeks if no remission had been achieved)** **Randomisation:** Not described. Cochrane described it as centrally randomised. **Allocation concealment**: Not described. Cochrane describe it as adequate. **Blinding:** Double blind. No further information given **Outcome assessment:** Unclear, not described.	**<u>All patients:</u>** **N=55randomised** **Drop-outs** (don't complete the study): N=12 (22%) Due to AE's or increasing severity of disease. **Inclusion criteria:** No severity or extent described. **Exclusion:** None described. **<u>Group 1: 3g Olsalazine</u>** **Drop outs:** 6 **<u>Group 2: 6g Sulphasalazine</u>** **Drop outs:** 6 There was no description of the baseline characteristics given in the abstract.	**Group 1: 3g Olsalazine** N=27 randomised N=21 (completers) No intervention details described. **Group 2: 6g Sulphasalazine** N=28 randomised N=22 (completers) No intervention details described. **Concomitant therapy:** Not described.	Outcome 1: **Clinical and endoscopic remission** (no definition was given, but the Cochrane Systematic review included it as an 'author defined outcome'- assessment based on clinical and endoscopic criteria. Outcome 2: **Adverse events** The paper only describes the adverse events that were minor, so it would underestimate the total number of AEs. It has therefore been excluded from the analysis. **Group1:**6/28 (21.4%) **Group 2:**11/27 (40.7%)	**<u>6 weeks</u>** **Group1:**6/27 (22.2%) **Group 2:**9/28 (32.1%) **<u>12 weeks</u>** **Group 1:**14/26 (53.8%) **Group2:**11/27 (40.7%)	**Funding:** None described. **Limitations:** High dropout rate. Indirect population: may have included severe patients. Unclear baseline characteristics **Additional outcomes:** Endoscopic improvement

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Sample size calculation: Not described. **Type of analysis: ITT** **Compliance rates:** Not described. N=12 dropout/ withdrawal due AEs (unclear if drug related) or increasing severity of disease. 6 in each treatment group.					

Table 145: RIJK1992

Author	Patients	Intervention	Outcome measures	Effect size	Comments
M. C. M. Rijk et al. Relapse-Preventing Effect and Safety of Sulfasalazine and Olsalazine in Patients with Ulcerative Colitis in Remission: A Prospective, Double-blind, Randomized Multicenter Study. *The American Journal of Gastroenterology; 87 (4): 438-442. 1992.* **REF ID: RIJK1992** **Study design and quality:** Double blind RCT Multicentre: 10hospitals, Netherlands **48 week trial**	**<u>All patients:</u>** **N=49 randomised** **N=46 (analysed due to 3 patients being uncooperative)** **Drop-outs** (don't complete the study): N=12 (26%) >10% difference in missing data between the treatment arms **Inclusion criteria:** • Active ulcerative colitis in the past, proven by endoscopy with biopsies and remission for not longer than 2 years • Patients with normal endoscopic appearance but histological signs of inflammation were also included • Recruited from the active UC trial if in remission or met the inclusion criteria but had not participated in the previous trial **Exclusion:**	Indistinguishable capsules. Day 1 & 2: 1/3 of the full dose Days 3 & 4: 2/3 of the full dose Day 5: full dose **Group 1: 2g Olsalazine** N=23 randomised 1g of olsalazine twice a day, taken with meals. In the event of AEs, a reduced dose of 1.5g was allowed. Capsules contain	**Outcome 1: Relapse** by 48 weeks Unable to calculate the hazard ratio. It is stated in the paper that there was no significant difference at any time during the trial between the two treatment groups. The Kaplan Meier curves cross each other. **Outcome 2: Adverse events** Minor AEs were: Group 1: Upper abdo complaints (2), fatigue	**Group1:** 6/23 **Group 2:** 7/23 **Group1:** 9/23 (39.1%) **Group 2:**8/23 (34.8%)	**Funding:** Grant/ financial support and supply of the study drugs from Pharmacia AB, Sweden. **Limitations:** Unclear method of randomisation and allocation concealment Limited baseline characteristics >10% difference in missing data between the treatment arms Double blind but no further information was given

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Randomisation: Randomly assigned. Allocation had a modification of the standardized variance as described by Begg and Iglewicz to insure equal distribution of prognostic factors (duration of disease, sex, age, extent of last exacerbation, attending physician, participation in the active disease trial, time to achieve remission in the trial, medication in that trial). Unclear. **Allocation concealment**: Unclear **Blinding:** Says double blind, no further information was given apart from identical treatments. **Outcome assessment:** History was taken. Endoscopy assessment. Blood tests. **Sample size calculation:** 75 patients per arm. 80% power, 5% significance for a 28% difference in relapse rate between both treatment groups. Due to slow enrolment there were only 46 patients recruited. **Type of analysis:** When a patient dropped out for reasons other than a relapse, they were deducted from the number of patients at risk.	• Uncooperativeness • Colitis had a specific cause (infectious, pseudomembranous, or radiation-induced) • Features of Crohn's disease • Allergy to sulpha drugs or salicylates • Pregnant or desired to become pregnant • Antibiotics or corticosteroids were needed • Presence of a colostomy or ileorectal anastomosis • Two or more liver function tests were abnormal • Signs of cirrhosis of the liver were present • Endogenous creatinine clearance was less than 30ml/min **<u>Group 1: 2g Olsalazine</u>** **Median age (range):** 36 (16-76) **Duration of disease:** <2 yrs n=10, >2 yrs n=13 **Extent of colitis at last exacerbation:** not beyond splenic flexure n=10, beyond splenic flexure n=9, unknown (splenic flexure not reached at endoscopy) n=4 **Severity of previous relapse:** Not described **Frequency of relapses:** Not described **Current use of immunomodulators:** Not described. **Drop outs:** 8 (3 due to loose stools, 4 due to uncooperativeness, 1 shipwrecked) **<u>Group 2: 4g Sulphasalazine</u>** **Median age (range):** 44 (22-78) **Duration of disease:** <2 yrs n=9, >2 yrs n=14 **Extent of colitis at last exacerbation:** not beyond splenic flexure n=9, beyond splenic flexure n=9, unknown (splenic flexure not reached at endoscopy) n=5 **Severity of previous relapse:** Not described **Frequency of relapses:** Not described **Current use of immunomodulators:** Not described. **Drop outs:** 4 (2 due to upper abdominal complaints, 1 due to a rash, 1 due to uncooperativeness) **<u>Definitions</u>** **Remission:** Absence of clinical signs of inflammation i.e. three stools or less per day without blood and a normal mucus membrane on sigmoidoscopy.	167mg of olsalazine. **Group 2: 4g Sulphasalazine** N=23 randomised 2g of SASP twice a day, taken with meals. In the case of AEs a reduced dose of 3g was allowed. Capsules contain 333mg of SASP. **Concomitant therapy:** None described.	(2), loose stools (1), itching (1) Group 2: Upper abdo complaints (3), mild transient rash (1) One patient on SASP developed mild leukopenia. Four patients on SASP and 2 patients on olsalazine's serum haptoglobin levels dropped below the lower limit of normal.		**Additional outcomes:** Relapse free survival at 24 weeks Histological inflammation and relapses Relapse in relation to length of time in remission

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Compliance rates: Mean intake of SASP and olsalazine was 97% and 89% after 24 wks and 90% and 84% after 48 wks. N=6 dropout/ withdrawal due to AEs (3 in each group- see drop outs for further details).	**Relapse:** Blood in stools, with or without diarrhoea and signs of inflammation at endoscopy. Also if at 48 weeks there was endoscopic inflammation but no presence of complaints.				

Table 146: RILEY1988A

Author	Patients	Intervention	Outcome measures	Effect size	Comments
S. A. Riley et al. Comparison of Delayed-Release 5-Aminosalicylic Acid (Mesalazine) and Sulfasalazine as Maintenance Treatment for Patients With Ulcerative Colitis. *Gastroenterology; 94: 1383-9. 1988.* **REF ID: RILEY1988A** **Study design and quality:** Double blind, double dummy RCT Multicentre: 3 centres, United Kingdom **48 week trial** **Randomisation:** Centrally held pharmacy code and medication was pre-packaged to ensure an equal and random allocation at each centre.	**<u>All patients:</u>** **N=100 randomised** **N=92 analysed/ completers** (8 patients were withdrawn; 4 for nonattendance, 2 poor compliance, 1 did not meet the inclusion criteria, 1 patient (SASP group) developed severe ulcerative stomatitis of uncertain aetiology (week 8). **Drop-outs** (don't complete the study): N=8 (8%) <10% difference in missing data between the treatment arms **Inclusion criteria:** • Adult outpatients with chronic UC • Diagnosed on the basis of clinical history and previous sigmoidoscopic and histologic findings • Clinical remission for a minimum period of 1 month before trial entry • Macroscopic appearance of either normal mucosa or only erythema on sigmoidoscopy at the time of trial entry **Each patient had previously taken sulphasalazine maintenance treatment**	On entry to the study patients stopped taking any current SASP maintenance treatment. Varying dose depending on the pre-trial maintenance dose of sulphasalazine. The ratio was 1g SASP to 400mg mesalazine. Patients not taking SASP maintenance treatment at entry were randomized into the lowest dose stratum (2g SASP or 800mg mesalazine/ day). **Group 1: Mesalazine 800mg-1.6g** N=48 completers	**Outcome 1: Relapse** by 48 weeks Unable to calculate the hazard ratio.	**Group1:** 18/48 **Group 2:** 17/44	**Funding:** Supported by Tillots Laboratories **Limitations:** None. **Additional outcomes:** Disease activity indices in those that relapsed and those in remission (stool frequency, sedimentation rate, sigmoidoscopic grade and histological grade) Laboratory variables of those who stayed in remission Mean time to relapse **Notes:**

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Allocation concealment: Adequate as central randomisation. **Blinding:** Double blind, double dummy. One investigator made all the assessments. Independent histopathologists. **Outcome assessment:** Sigmoidoscopy scored from 0-4, histology graded 0-4. Blood and urine laboratory tests. Daily symptom diary. Questioned about 15 side effects at each visit. **Sample size calculation:** None described. **Type of analysis: Completers analysis.** **Compliance rates:** Unused medications were returned at each visit and a tablet count was undertaken. 2 non compliant patients taking SASP (1 stopped the medication, the other took <50%). Otherwise good compliance. N=1 dropout/ withdrawal due to AEs.	**Exclusion:** • Taking other drugs known to have an effect on colitis activity • Received oral or rectal steroids within 1 month of the trial entry • Significant hepatic or renal disease • History of salicylate allergy **Group 1: Mesalazine** **Mean age (SD):** 42.1 (15.5) **Mean disease duration (SD):** 8.1 (5.9) **Extent:** proctitis n=11, proctosigmoiditis n=14, left sided n=13, total colitis n=10 **Mean time from previous relapse (SD):** 12.8 (13.7) **Severity of previous relapse:** Not described. **Frequency of relapses:** more than once/yr n=16, approx once/year n=22, <once/year n=10 **Dose given:** 800mg daily n=39, 1200mg daily n=8, 1600mg daily n=1 **Drop outs:** 2 (unclear which reasons, see drop out section above) **Group 2: Sulphasalazine** **Mean age (SD):** 45.9 (15.6) **Mean disease duration (SD):** 9.2 (9.0) **Extent:** proctitis n=10, proctosigmoiditis n=15, left sided n=10, total colitis n=9 **Mean time from previous relapse (SD):** 15.2 (15.2) **Severity of previous relapse:** Not described. **Frequency of relapses:** more than once/yr n=7, approx once/year n=21, <once/year n=16 **Dose given:** 2g daily n=36, 3g daily n=7, 4g daily n=1 **Drop outs:** 6 (2 non compliant, 1 due to severe ulcerative stomatitis, unclear the other reasons) **Definitions** **Remission:** Absence of blood in the stool **Relapse:** Symptomatic deterioration resulting in a sigmoidoscopy which confirms the macroscopic grading to being worse. Trial medications were then stopped and the patient would be put on oral SASP and appropriate corticosteroids treatment.	Mesalazine (Asacol). Dose range was 800-1600mg per day. Placebo SASP tablets were also given. Medication was split to be given twice daily. **Group 2: Sulphasalazine 2-4g** N=44 completers Enteric coated sulphasalazine (Salazopyrin EN). Dose range was 2-4g per day. Placebo mesalazine tablets were also given. Medication was split to be given twice daily. **Concomitant therapy:** Not described. See inclusion/ exclusion criteria.			Only specific adverse events were reported and lists changes from pre to during the trial e.g. resolution of headaches. No renal impairment found. Biochemical variables showed no consistent changes for either treatment. "Cumulative remission rates did not significantly deviate from one another at any time during the 48 weeks" **Each patient had previously taken sulphasalazine maintenance treatment**

Table 147: RIZZELLO2001

Author	Patients	Intervention	Outcome measures	Effect size	Comments
F. Rizzello et al. Oral Beclomethasone Dipropionate in patients with mild to moderate ulcerative colitis: A dose-finding study **REF ID: RIZZELLO2001** **Italy** **Study design and quality:** Randomised trial - double blind (for steroid dose only), open comparison with 5-ASA. 1.6g/day 5-ASA was used as "placebo" based on Sutherland 1993 which found 5-ASA <2g/day no better than placebo. Multicentre: 3 centres, Italy **4 week trial** **Randomisation:** No information given **Allocation concealment**: No information given **Blinding:** Double blind (for steroid dose only), open comparison with 5-ASA. **Outcome assessment:** Pancolonoscopy graded according to the Baron scale. Histology graded according to	**<u>All patients:</u>** **N=57 randomised** **N=57 ITT** **Drop-outs** (don't complete the study): N=0 **Inclusion criteria:** • Extent: extensive or left sided ulcerative colitis • Severity: mild to moderately severe **Exclusion:** • Severe ulcerative colitis • Remission • Severe hepatic, renal or cardiac insufficiency • Gastroduodenal disease • Diabetes mellitus • Severe hypertension • Senile or postmenopausal osteoporosis • Hypersensitivity to corticosteroids or 5-ASA • Pregnancy or breastfeeding • Systematic or topical corticosteroid, 5-ASA or sulphasalazine in month prior to study **<u>Group 1: Beclomethasone 5mg</u>** **Mean age (SE):** 36.7 (2.4) **Extent:** Left sided (%): 12/19 (63) Extensive(%): 7/19 (37) **Drop outs:** 0 **<u>Group 2: Beclomethasone 10mg</u>** **Mean age (SE):** 41.7 (3.7) **Extent:**	**Group 1: Beclomethasone 5mg/day** N=19 randomised N=19 (completers) 5mg tablet and one placebo tablet od early morning **Group 2: Beclomethasone 10mg/day** N=19 randomised N=19 (completers) 10mg tablet and one placebo tablet od early morning **Concomitant therapy:** No other systematic or topical corticosteroid, 5-ASA or sulphasalazine in month prior to study or during the observation period. Antibiotics permitted (including for "infective or viral complications of the intestinal disease") as were any other drug that did not interfere with the study	Outcome 1: **Remission** (based on histolopathologic analysis of biopsy specimens using Truelove and Richard scale). As this remission definition was histological remission the data has not been analysed as it would underestimate the effect for clinical and endoscopic remission Outcome 2: **Clinical improvement** (reduction of at least 3 points in DAI score from baseline). The n values were calculated from the percentages given in the paper. Outcome 3: **Adverse events**	**Group 1:**3/19 (16.7%) **Group 2:**7/19 (43.7%) **Group 1:** 9/19 (47.4%) **Group 2:** 9/19 (47.4%) **Group 1:**0/19 **Group 2:**2/19 (metrorrhagia and headache)	**Funding:** Chiesi Farmaceutici S.p.A., Italy manufacturers and suppliers Beclomethasone and suppliers 5-ASA (Asacol) **Limitations:** Randomisation method unclear Allocation concealment unclear Compared active dose of steroid to "inactive/ placebo" dose of ASA No blinding for 5-ASA **Additional outcomes:** Mean morning cortisol levels Change in clinical characteristics with treatment

Author	Patients	Intervention	Outcome measures	Effect size	Comments
the Truelove and Richard scale. Clinical symptoms measured using Disease Activity Index (DAI). **Sample size calculation:** 80 patients per arm based on 80% power, p=0.05 for a 40% difference in remission or improvement in steroid arms **Type of analysis:** ITT **Compliance rates:** N=0 dropout/ withdrawal due to drug related AEs.	Left sided (%): 13/19 (68) Extensive(%): 6/19 (32) **Drop outs:** 0	medications.			Statistically significant effects of beclomethasone on haematological values Change in mean biopsy scores **Notes:** Beclomethasone used was pH-dependent, gastroresistant, controlled release oral preparation

Table 148: RIZZELLO2002

Author	Patients	Intervention	Outcome measures	Effect size	Comments
F. Rizzello et al. Oral beclometasone dipropionate in the treatment of active ulcerative colitis: a double-blind placebo-controlled study. *Alimentary Pharmacology and Therapeutics; 16: 1109-1116. 2002.* **REF ID: RIZZELLO2002** **Study design and quality:** Double blind placebo controlled	**<u>All patients:</u>** **N=119 randomised** **N= 119 ITT** **Drop-outs** (don't complete the study): N=14 (11.8%) >10% difference in missing data between the treatment arms. **Inclusion criteria:** • Extent: extensive or left sided ulcerative colitis • Severity: mild to moderately severe (DAI 3-10)	**Group 1: 5-ASA 3.2g/day + Beclometasone 5mg/day** N=58 randomised N=58 (ITT) N=56(completers) 5-ASA (Asacol) 8 x 400mg tablets per day (no information given regarding timing) and 5mg beclometasone od	Outcome 1: **Clinical remission** (DAI score <3) The n values were calculated from the percentages given in the paper. Outcome 2: **Clinical improvement** (responders - reduction of at least 3 points in	**Group1:** 34/58 (58.6%) **Group 2:** 21/61 (34.4%) **Group1:** 44/58 (75.9%)	**Funding:** Chiesi Farmaceutici S.p.A., Italy manufacturers and suppliers of beclometasone and 5-ASA, and performed the statistical analyses. INPHASER S.R.L (Italy) (providers of clinical trial services) for periodic trial monitoring **Limitations:** The difference in proportions missing

Author	Patients	Intervention	Outcome measures	Effect size	Comments
RCT Multicentre: 11 centres, Italy **4 week trial** **Randomisation:** blocks of 4 produced by computer generated randomisation list **Allocation concealment**: adequate **Blinding:** Double blind **Outcome assessment:** Pancolonoscopy graded according to Baron's criteria. Histology graded according to Truelove and Richard's criteria. Clinical symptoms measured using Disease Activity Index (DAI). **Sample size calculation:** 62 patients per arm based on 80% power, p=0.05 for a 25% difference in "response to treatment " (clinical and endoscopic improvement) **Type of analysis:** ITT **Compliance rates:** No patient was considered non compliant. N= 4 dropout/ withdrawal due to drug related AEs. N=10 (1 in Group 1 and 9 in Group2) withdrawal due to clinical worsening (this is in addition to AEs).	• Age ≥18 **Exclusion:** • Severe ulcerative colitis • Remission or newly diagnosed UC • Severe hepatic or renal failure • Gastroduodenal disease • Diabetes mellitus • Heart failure • Severe or moderate hypertension • Neoplastic disease • Psychosis, alcohol or drug abuse • Pregnancy or breastfeeding • Corticosteroid treatment in month prior to study • 5-ASA >3.2g/day or sulphasalazine >2g/day for 2 weeks prior to study **<u>Group 1: 5-ASA + Beclometasone</u>** **Mean age (SD):** 43.1 (14.5) **Extent:** Left sided (%): 38/58 (66) Pancolitis (%): 20/58 (34) **Severity:** Mild (%): 14/58 (24) Moderate (%): 44/58 (76) **Drop outs:** 2 (3.4%) (1 due to AEs, 1 clinical worsening) **<u>Group 2: 5-ASA + placebo</u>** **Mean age (SD):** 44.7 (13.1) **Extent:** Left sided (%): 47/61 (77) Pancolitis (%): 14/61 (23)	early morning **Group 2: 5-ASA 3.2g/day + placebo** N=61 randomised N=61 (ITT) N=49 (completers) 5-ASA (Asacol) 8 x 400mg tablets per day (no information given regarding timing) and matched placebo od early morning **Concomitant therapy:** Not allowed– see exclusion criteria	DAI score from baseline). This is in addition to those in clinical remission. The n values were calculated from the percentages given in the paper. Outcome 3: **Endoscopic remission** (based on Baron's criteria) Outcome 4: **Adverse events**	**Group 2:** 31/61 (50.8%) **Group1:** 18/58 (31.0%) **Group 2:** 10/61 (16.4%) **Group1:** 1/58 (constipation) **Group 2:** 3/61 (facial and abdominal swelling, seizures and pruritus)	between groups is greater than 10% **Additional outcomes:** Morning serum cortisol levels Mean DAI at 4 weeks DAI variables (stool frequency, rectal bleeding, sense of wellbeing and colonoscopy) at 4 weeks compared to baseline Mean ESR at 4 weeks compared to baseline **Notes:** Beclometasone used was pH-dependent, gastroresistant, controlled release oral preparation

Author	Patients	Intervention	Outcome measures	Effect size	Comments
	Severity: Mild (%): 12/61 (20) Moderate (%): 49/61 (80) **Drop outs:** 12 (19.7%) (3 due to AEs, 9 clinical worsening)				

Table 149: ROBINSON1988

Author	Patients	Intervention	Outcome measures	Effect size	Comments
M. Robinson et al. Olsalazine in the treatment of mild to moderate ulcerative colitis. *Gastroenterology; 84: A381. 1988* **REF ID: ROBINSON1988** **Study design and quality:** Double blind RCT [Abstract] Multicentre: 9 centres This abstract has been included because it was included in the Cochrane systematic review on oral ASAs for the induction of remission in ulcerative colitis. **4 week trial** **Randomisation:** Unclear **Allocation concealment**: Cochrane describe it as adequate. In the abstract it is unclear	**<u>All patients:</u>** **N=98randomised** **Drop-outs** (don't complete the study): N=30 (30.6%)14 in the olsalazine group and 16 in the placebo group. This data was taken from the Cochrane review as it was not evident in the abstract. **Inclusion criteria:** Extent: Not described Severity: Mild to moderate **Exclusion:** None described **No baseline characteristics described.**	**Group 1: Olsalazine 3g** N=50 randomised No intervention details were described. **Group 2: Placebo** N=48 randomised No intervention details were described. **Concomitant therapy:** No concomitant medications for ulcerative colitis were permitted.	Outcome 1: Global improvement (no definition given) Although this outcome has no definition, it has been included because it was reported in the Cochrane Systematic review as 'author defined'. The n values were calculated from the percentages given in the paper. No serious adverse events were noted. Diarrhoea occurred in 36% of olsalazine patients	**Group1:**25/50 (49%) **Group 2:**16/48 (33%)	**Funding:** None described **Limitations:** All methods are unclear (randomisation, allocation concealment, baseline characteristics etc.) High dropout rate Unclear scoring of outcomes **Additional outcomes:** Sigmoidoscopic improvement Rectal bleeding

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Blinding: Double blinding, no further information given. **Outcome assessment:** Efficacy was based on diarrhoea, rectal bleeding, mucorhea, sigmoidoscopic score, nausea, abdominal tenderness, tool consistency and global disease severity rating compared to baseline. **Sample size calculation:** None described. **Type of analysis: unclear** **Compliance rates:** not described N=4 dropout/ withdrawals due to AEs (unclear if drug related). This was taken from the Cochrane systematic review as it was not reported in the abstract.3 were in the olsalazine group, 1 in the placebo group.					

Table 150: ROMANO2010

Author	Patients	Intervention	Outcome measures	Effect size	Comments
C. Romano et al. Oral Beclomethasone Dipropionate in Pediatric Active Ulcerative Colitis: A comparison trial with Mesalazine. *Journal of Pediatric Gastroenterology and*	**<u>All patients:</u>** **N=30 randomised** **Drop-outs** (don't complete the study): N=0 **Inclusion criteria:**	**Group 1: 5-ASA 80mg/kg/day** N=15 randomised N=15 (completers)	Outcome 1: **Clinical remission at 4 weeks** (score <10 on PUCAI score)	**Group1:** 5/15 (33.3%) **Group 2:** 12/15 (80%)	**Funding:** None reported. The authors reported no conflicts of interest.
			Outcome 2: **Endoscopic remission at 12 weeks**	**Group1:** 4/15	**Limitations:**

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Nutrition; 50 (4): 385-389. 2010. **REF ID: ROMANO2010** **Study design and quality:** Open label RCT Single centre: Italy **12 month trial (assessed at 4,8 and 12 weeks and at 1 year)** **Randomisation:** "were enrolled with simple randomisation in 2 groups at admission" **Allocation concealment**: Not reported **Blinding:** No blinding **Outcome assessment:** Clinical symptoms measured by Paediatric Ulcerative Colitis Activity Index (PUCAI) score (week 0, 4, 8 and 12) and total colonoscopy and retrograde ileoscopy graded by Baron score on (week 0 and 12). **Sample size calculation:** None stated **Type of analysis:** ITT **Compliance rates:** Not described N=0 dropout/ withdrawal due to drug related AEs.	• Extent: Left sided or pancolitis • Severity: Mild to moderate • Age <18 years • Newly diagnosed or clinical relapse after conventional treatment (defined as maintenance treatment with 5-ASA for at least 3 months after induction of remission with oral steroids of 5-ASA) **Exclusion:** • Severe UC • Extra intestinal manifestations or systemic complications of UC • Exclusively distal involvement (last 12-15cm) • Treatment with immunosuppressors **<u>Group 1: 5-ASA</u>** **Mean age (SD):** 11.5 (1.8) **Extent:** Pancolitis (%): 5/15 (33.3) Left sided (%): 10/15 (66.7) **Duration of disease in months (SD) :** 4 (2) **Newly diagnosed (%):** 10 (66.7) **Drop outs:** 0 **<u>Group 2: Beclomethasone</u>** **Mean age (SD):** 11.5 (1.6) **Extent:** Pancolitis (%): 9/15 (60) Left sided (%): 6/15 (40) **Duration of disease in months (SD) :** 4 (3) **Newly diagnosed (%):** 8 (53.3) **Drop outs:** 0	Oral 5-ASA (Mesalazine, Asacol) 80mg/kg/day **Group 2: Beclomethasone 5mg/day** N=15 randomised N=15 (completers) Oral beclomethasone 5mg/day for 8 weeks followed by maintenance therapy with oral 5-ASA **Concomitant therapy:** Additional enemas with 5-ASA after the first 12 weeks	(Baron score 0-1) Outcome 3: **Adverse events** There were no adverse events reported in either arm. Tolerability was reported to be good.	(26.7%) **Group 2:** 11/15 (73.3%)	Randomisation method used unclear Allocation concealment unclear Open study **Additional outcomes:** Mean PUCAI score at 0,4,8 and 12 weeks Mean Baron score at 0 and 12 weeks Histological remission (absence of crypt abscesses, mucin depletion and inflammatory cell infiltration) at 12 weeks Clinical relapse during 12 months: Group 1: 2/15 (after 8 and 9 months) and Group 2: 5/15 (after 3 to 4 months) ESR, CRP, body weight (percentile) and 8am plasma cortisol levels at baseline and 12 weeks

Table 151: SANDBERGGERTZEN1986

Author	Patients	Intervention	Outcome measures	Effect size	Comments
H. Sandberg-Gertzen et al. Azodisal Sodium in the Treatment of Ulcerative Colitis. A Study of Tolerance and Relapse-Prevention Properties. *Gastroenterology; 90: 1024-1030. 1986.* **REF ID: SANDBERGGERTZEN1986** **Study design and quality:** Double blind RCT, Sweden **6 month trial** **Randomisation:** Allotted at random either to continue on olsalazine or to take an equal number of placebo capsules. Stratification was done for extent of disease and to take account of any relapses in part 1 (induction of remission) of the study. Unclear. **Allocation concealment**: Unclear **Blinding:** Double blind. Biopsies were assessed blindly. **Outcome assessment:** Histology was assessed according to Truelove & Richards. Patients reported and were questioned on side effects. Laboratory tests.	**<u>All patients:</u>** **N=102 randomised** **N=101 completers** (one patient had mental disease and should have been entered into the trial was excluded for non compliance. It is unclear what treatment group they were in) **Drop-outs** (don't complete the study): N=0 (0%) **Inclusion criteria:** • Part two of a study which included patients who after 6 months of medication with olsalazine were in remission and off steroids • Patients were unable to tolerate 2g SASP daily • No ages limits • No extent limit • Women of a fertile age were permitted but they were told to discontinue medication if pregnancy was planned. • If patients were no in remission at the start of the trial they were re-evaluated 2 months later and if they were then in remission they could be entered into the trial. **Exclusion:** • Mental disease where compliance was judged to be unreliable • Patients still on corticosteroids **<u>Group 1: 1g Olsalazine</u>** **Extent:** proctitis n=4, distal UC n=27, extensive or total UC n=21 **<u>Group 2: Placebo</u>** **Extent:** proctitis n=4, distal UC n=24, extensive or total UC n=21 The baseline characteristics are only given for all the patients entering Part 1 of the study and not Part 2. The severity of the previous relapse is given overall but not by treatment group. The severity ranges from Grade 0 to 4.	**Group 1: 1g olsalazine** N=52 randomised 250mg capsules of olsalazine. Given as 500mg twice a day. Total dose 1g/day. **Group 2: Placebo** N=49 randomised Identical placebo capsules. 2 capsules taken twice a day. **Concomitant therapy:** See inclusion/exclusion criteria.	**Outcome 1: Relapse** by 6 months There were two patients who had sigmoidoscopic findings of relapse but no clinical symptoms. These have been excluded from the analysis.	**<u>Overall</u>** **Group1:** 12/52 **Group 2:** 22/49 **By extent of disease:** **<u>Proctitis</u>** **Group1:** 1/4 **Group 2:** 1/4 **<u>Distal UC</u>** **Group1:** 6/27 **Group 2:** 8/24 **<u>Extensive or total UC</u>** **Group1:** 5/21 **Group 2:** 13/21	**Funding:** The treatments and financial support was provided by Pharmacia AB in Sweden. **Limitations:** Unclear method of randomisation and allocation concealment Stated to be double blind, no information given on physician blinding Very limited baseline characteristics **Additional outcomes:** Histology changes. **Note: majority olsalazine tolerant population**

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Sample size calculation: None described. **Type of analysis: ITT** **Compliance rates:** Tested by analysing the serum and urine for the presence of ADS, 5-ASA and acetyl-5-ASA by high performance liquid chromatography. Remaining capsules were counted. Good compliance, no figures given, apart from 1 patient in the olsalazine group. N=0 dropout/ withdrawal due to drug related AEs.	**Definitions** **Remission:** <4 bowel movement per day without visible blood or mucus and with no signs of active disease at sigmoidoscopy. **Relapse:** Occurrence of diarrhoea with macroscopic blood together with the finding of active inflammation on sigmoidoscopy.				

Table 152: SANDBORN2009A

Author	Patients	Intervention	Outcome measures	Effect size	Comments
W. J. Sandborn et al. Delayed-Release Oral Mesalamine 4.8g/day (800mg Tablet) Is Effective for Patients With Moderately Active Ulcerative Colitis. *Gastroenterology; 137: 1934-1943. 2009.* **REF ID: SANDBORN2009A** **Study design and quality:** Double blind, double dummy, Phase III RCT (ASCEND III)	**All patients:** **N=772randomised**(3 patients were not dosed who had been recruited) **Drop-outs** (don't complete the study): N=72 (9.3%) **Inclusion criteria:** 18-75 years old Severity: **Moderately** active UC (PGA=2, ≥1 point in both the stool frequency and rectal bleeding assessment and ≥2 points in the sigmoidoscopy with a +ve friability assessment Extent: >15cm from the anal verge (as confirmed by flexible	**Group 1: 2.4g Mesalamine (Asacol)** N=383 randomised/ITT N=347 (completers) 2.4g/day delayed release mesalamine (Asacol) 400mg tablets 2 x 400mg tablets plus 2 placebo tablets, three times a day	Outcome 1: **Clinical and endoscopic remission** (Complete response [remission] (PGA score = 0 i.e. complete resolution of or normalization of stool frequency, bleeding and sigmoidoscopy with CFT assessment score)) Outcome 2: **Clinical remission** at week 3 and 6 (stool frequency score of 0 and rectal bleeding score of 0)	**Week 6** **Group1:**19/383 (5.0%) **Group 2:**10/389 (2.6%) **Week 3** **Group1:**65/359 (18%) **Group**	**Funding:** Procter and Gamble Pharmaceuticals. Quite a few conflicts of interest with other pharmaceutical companies. **Limitations:** None **Additional outcomes:** Improvement in stool frequency

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Multicentre: 113 centres, Belarus, Canada, Croatia, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, Russian Federation, Serbia and Montenegro, Ukraine, United States (including Puerto Rico) **6 week trial** **Randomisation:** Randomisation: This was done in a 1:1 ratio and locally randomized at each site. Stratified by gender. Telephoned an Interactive Voice Response System for patient randomization and allocation of study medication once the patient was deemed eligible. **Allocation concealment**: Adequate. **Blinding:** Double blind. The treatment that the patient received was not disclosed to the investigator, study-centre personnel, patients, contracted monitors, contracted vendors, or the sponsor (except for selected clinical supplies, bioanalytical, or pharacovigilance personnel). **Outcome assessment:** Physician's Global Assessment. Sigmoidoscopy score from 0-3. It is modified from previous	sigmoidoscopy or colonoscopy) **Exclusion:** UC confined to the rectum Short bowel syndrome Renal or hepatic disease +ve stool sample for *Clostridium difficile*, bacterial pathogens, ova or parasites History of allergy or hypersensitivity to salicylates, aminosalicylates or any component of the delayed-release mesalamine tablets History of HIV infection or AIDS History of alcohol or drug abuse Taking oral 5-ASA containing product >1.6g/day of mesalamine by any route in the last 7 days Taken any corticosteroids (oral, IV, IM or rectal) within the last 30 days Taken immunosuppressive drugs (including azathioprine, 6-mercaptopurine, methotrexate) within the last 90 days Received any antidiarrheal and /or antispasmodic drugs within the previous 3 days Received aspirin (except for cardio-protective reasons, max dose 325mg/day) or other NSAIDs within the last 7 days Used antibiotics (other than topical) or any product containing omega-3 fatty acids within the last 7 days Received infliximab, adalimumab or other biologic treatment of UC within the last 90 days Participated in any drug or device clinical study within the last 30 days Pregnant or lactating women	**Group 2: 4.8g Mesalamine (Asacol)** N=393 recruited N=389 (ITT) N=353(completers) 4.8g/day delayed release mesalamine (Asacol) 800mg tablets 2 x 800mg tablets plus 2 placebo tablets, three times a day **Concomitant therapy:** Prohibited from taking: Aspirin (for non cardio-protective reasons, max 325mg/day) NSAIDs 5-ASA containing compounds Corticosteroids Immunomodulatory drugs Metronidazole Antibiotics (apart from topical) for >10 days throughout the study Antidiarrheal and/or antispasmodics Omega-3 fatty acid products		**2:**91/365 (25%) **<u>Week 6</u>** **Group1:**121/347 (35%) **Group 2:** 152/353 (43%)	Improvement in rectal bleeding PFA improvement PGA improvement Sigmoidoscopy with CFT improvement Subgroup analyses (gender, age, smoking history, extent, duration of UC, previous drug use)
			Outcome 3: **Clinical improvement** (Treatment success/overall improvement (partial response (improvement from baseline in the PGA score and no worsening in any of the 3 component scores) and complete response i.e. those that have improved or gone into remission)	**<u>Week 6</u>** **Group1:**251/383 (65.5%) **Group 2:**273/389 (70.2%)	
			Outcome 3: **Adverse events** Most frequent AEs were headache, UC, nasopharyngitis and nausea, which were similar in both groups.	**Group1:**79/383 (20.6%) **Group 2:**80/389 (20.6%)	
			Outcome 4: **Serious adverse events** **Group 1:** 3 due to UC, 1 lower abdominal pain, 1 enterocolitis and 1 due to gastroenteritis **Group 2:** 1 due to UC, 1 due to drug sensitivity,	**Group1:**6/383 (1.6%) **Group 2:** 4/389 (1.0%)	

Author	Patients	Intervention	Outcome measures	Effect size	Comments
studies to exclude friability from the definition of a score of 1 (mild). It also included a CFT (where the investigators touched the most severely affected area of the sigmoid colon with closed biopsy forceps). UCDAI. **Sample size calculation:**90% power to detect a 3% difference, 306 patients per arm, 0.05 significance **Type of analysis: ITT[v] and PPA[w]** **Compliance rates:** Not described. N=30 dropout/ withdrawal due to AEs (15 patients in each treatment group). Unclear if drug related. Most common reason was due to GI symptoms associated with UC.	**Group 1: 2.4g mesalamine (Asacol)** **Mean age (SD):**42.4 (no SD given) **Extent:** proctosigmoiditis n=183, left-sided n=136, pancolitis n=60 **Prior treatment:** steroids (oral or IV) n=157, immunomodulators n=17, any oral 5-ASA n=323, rectal therapies n=188 **Mean UCDAI (SD):** 7.8 (0.68) **Drop outs:** 36 (15 due to AEs, 1 lost to follow up, 6 lack of treatment effect, 7 unable to meet protocol criteria, 1 protocol violation, 6 voluntary withdrawal) **Group 2: 4.8g mesalamine (Asacol)** **Mean age (SD):**44.1 (no SD given) **Extent:** proctosigmoiditis n=185, left-sided n=138, pancolitis n=61 **Prior treatment:** steroids (oral or IV) n=157, immunomodulators n=16, any oral 5-ASA n=338, rectal therapies n=192 **Mean UCDAI (SD):** 7.8 (0.68) **Drop outs:** 36 (15 due to AEs, 1 investigator discretion, 2 lost to follow up, 6 lack of treatment effect, 5 unable to meet protocol criteria, 7 voluntary withdrawal)	Investigational or marketed drug that might interfere with the drug evaluation.	1 due to colon cancer and 1 due to vasovagal syncope. 60 patients had the CFT edited out and the sigmoidoscopy reread using the definitions used in the infliximab ACT1 and ACT2 trials. These additional outcomes for those 60 patients were: Remission (UCDAI score (Mayo) of ≤2 points with no individual sub score of >1 point) (ITT) 2.4g/day: 19.4% 4.8g/day: 19.5% Patient functional assessment (PFA) remission (PFA score of 0) (ITT) 2.4g/day: 72.3% 4.8g/day: 76.0%		

Table 153: SANDBORN2010

Author	Patients	Intervention	Outcome measures	Effect size	Comments
W. J. Sandborn et al. Once-Daily Dosing of Delayed-Release Oral Mesalamine (400-mg Tablet) Is as Effective as Twice-Daily Dosing for	**All patients:** **N=1027 randomised** (4 did not receive the treatment due to not meeting the inclusion/exclusion criteria, dissatisfied with the randomized regimen and not comfortable with the study) **Drop-outs** (don't complete the study):	**Group 1: Once daily mesalazine (Asacol)** N=514 randomised N=512 (took the treatment)	**Outcome 1: Relapse** Completer's analysis.	**Group1:** 65/445 **Group 2:** 65/443	**Funding:** Funding provided by Procter & Gamble Pharmaceuticals. Quite a few of the authors have declarations of interests

[v] ITT definition: all randomized patients who took ≥1 dose of medication
[w] PPA definition: All patients who had a week 6 outcome and no major protocol violations

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Maintenance of Remission of Ulcerative Colitis. *Gastroenterology; 138: 1286-1296. 2010.* **REF ID: SANDBORN2010** **Study design and quality:** Single blind RCT Multicentre: 193 centres, United States, Puerto Rico and Canada **12 month trial** **Randomisation:** 1:1 ratio. Centrally done via an interactive voice response system. Stratified by prior mesalamine dose within a site. **Allocation concealment**: Adequate **Blinding:** Single investigator blind. **Outcome assessment:** SCCAI scoring. Patient-Defined Remission Index, via an interactive voice response system (yes/no) **Sample size calculation:** 90% power, no difference between treatment arms, 95% 2 sided CI, 10% not analysable, 500 patients per treatment arm. **Type of analysis: ITT, PPA, ACA**	N=135 (13.1%) **Inclusion criteria:** • Male or female patients • 18 years or older • Diagnosis of UC maintained in clinical remission for at least 3 months on Asacol at a stable dose ranging from 1.6 -2.4g/day • Experienced≥1 flare of UC in the previous 18 months **Exclusion:** • History of or current renal or hepatic disease or a history of co-existing acute or chronic organic or uncontrolled functional or mental disease • History of allergy or hypersensitivity to salicylates, aminosalicylates or any component of the Asacol tablet • History of HIV or acquired immune deficiency syndrome • History of alcohol or drug abuse • Received an oral mesalamine containing product at a dose >2.4g/day with the past 3 months • Used rectal mesalamine therapy within 14 days • Taken any corticosteroids (oral, IV, IM or rectal) within the past 90 days • Immunosuppressive drug use (azathioprine, 6-mercaptopurine, methotrexate, cyclosporine) within past 90 days • Received any antidiarrheal and/or antispasmodic drugs with the previous 1 month • Received aspirin (except for cardioprotective indications up to a max dose of 325mg/day) or NSAIDs with the past week • Used antibiotics (other than topical) within 1 month • Received infliximab, adalimumab, certolizumab pegol or other biologic treatment with the past 90 days • Participated in any drug or device clinical study within the past 30 days • Travelled outside the United States and Canada within 2 weeks of the screening visit • Pregnant and/or lactating women	N=445 (completers) 400mg mesalazine tablets. Same dose taken as at baseline (1.6-2.4g/day) **Group 2: Twice a day mesalazine (Asacol)** N=513 randomised N=511 (took the treatment) N=443 (completers) 400mg mesalazine tablets. Same dose taken as at baseline (1.6-2.4g/day) **Concomitant therapy:** Post randomization the following were not permitted: Aspirin (for any indication other than cardioprotective and at a dose no higher than 325mg/day), NSAIDs except for occasional use, other medications containing or metabolized to mesalazine, corticosteroids, immunomodulatory agents, metronidazole, antibiotics (other than		Reported HRs in the paper: **<u>Month 6</u>** **Hazard ratio (95% CI):** 1.17 (0.76, 1.80) **<u>Month 12</u>** **Hazard ratio (95% CI):** 1.01 (0.71, 1.42)	linked to Pharmaceutical companies. **Limitations:** Single blind **Additional outcomes:** Patient defined remission **Notes:** Overall patients preferred to take the medication fewer times a day. Subgroup analysis did not find any differences between the two treatment groups, in particular extent of disease, relapse frequency, prior steroid, SASP, 5-ASA or rectal therapy use, duration of UC, prior maintenance dose, baseline characteristics.
			Outcome 2: Serious adverse events **Group 1:** 25 events. altered state of consciousness (1), appendicitis (2), anal fistula (1), atrial fibrillation (1), Cardiac failure congestive (1), chest pain (1), cholangitis (1), Cholelithiasis (2), clavicle fracture (1), convulsion (1), diverticulitis (1), haemothorax (1), hypertension (1), hyponatremia (1), jaundice cholestatic (1), myocardial infarction (1), renal cancer (1), rib	**Group1:** 18/512 **Group 2:** 9/511	

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Compliance rates: Medication adherence report scale via interactive voice response system, 3 monthly. High adherence rates. N=9 dropout/ withdrawal due to AEs. Once a day: Fatigue (1) and myocardial infarction (1) Twice a day: flatulence (2), abdominal distension (1), cardiomyopathy (1), nausea (1), oesophageal carcinoma (1), plantar fasciitis (1), renal failure (1)	**Group 1: Once a day mesalazine** **Mean age (SD):** 50.4 (14.6) **Extent:** proctosigmoiditis n=108, left-sided colitis n=158, pancolitis n=202 **Prior maintenance dose:** 1.6g n=145, 2.0g n=15, 2.4g n=352 **Prior maintenance regimen:** twice a day n=331, three times a day n=158, once a day n=20, other n=3 **Length of disease history:** <1 n=66, 1-5 n=161, >5-10 n=104, >10 n=180 **Relapse frequency:** >1/mth n=5, 1/6mths n=70, 1/6-12mths n=140, <1/yr n=245, newly diagnosed n=51 **Prior treatment:** steroids (oral or IV) n=117, immunomodulators n=12, biologics n=3, sulfasalazine n=27, rectal therapies n=41 **Total SCCAI scores at baseline:** 0 n=245, 1 n=148, 2 n=116, 3 n=1, 4 n=1 **Severity of previous relapse:** Not described. **Drop outs:** 67 (lost to follow up n=17, AEs n=2, Investigator discretion n=8, unable to meet protocol criteria n=4, protocol violation n=7, voluntary withdrawal n=29) **Group 2: Twice a day mesalazine** **Mean age (SD):** 50.2 (14.8) **Extent:** proctosigmoiditis n=98, left-sided colitis n=186, pancolitis n=190 **Prior maintenance dose:** 1.6g n=145, 2.0g n=5, 2.4g n=361 **Prior maintenance regimen:** twice a day n=304, three times a day n=184, once a day n=17, other n=6 **Length of disease history:** <1 n=61, 1-5 n=150, >5-10 n=135, >10 n=165 **Relapse frequency:** >1/mth n=1, 1/6mths n=84, 1/6-12mths n=149, <1/yr n=233, newly diagnosed n=44 **Prior treatment:** steroids (oral or IV) n=109, immunomodulators n=8, biologics n=0, sulphasalazine n=18, rectal therapies n=44 **Total SCCAI scores at baseline:** 0 n=244, 1 n=178, 2 n=88, 3 n=0, 4 n=0 **Severity of previous relapse:** Not described. **Drop outs:** 68 (lost to follow-up n=23, AEs n=7, Investigator discretion n=14, unable to meet protocol criteria n=1, protocol violation n=9, voluntary withdrawal n=14) **Definitions** **Remission:** Simple Clinical Colitis Activity Index (SCCAI) score of ≤2	topical antibiotics) for >10 days, topical rectal therapies, antidiarrheal and/or antispasmodic medications (except for occasional use) or any investigational or marketed drug that might interfere with the evaluation of the study medication.	fracture (1), spinal compression fracture (1), thrombophlebitis (1), thyroid neoplasm (1), transient ischemic attack (1) and uterine leiomyoma (1). **Group 2**: 14 events: renal failure acute (2), abdominal pain (1), ascites (1), breast cancer (1), cardiomyopathy (1), constipation (1), coronary artery disease (1), deep vein thrombosis (1), dehydration (1), oesophageal carcinoma (1), pulmonary embolism (1), rectal haemorrhage (1), small cell lung cancer metastatic (1) All thought to be doubtfully related to the treatment apart from the renal failure in group 2. **Adverse events** These were only reported for those leading to withdrawal, so the data has not been included in the analysis. **Group1:** 2/512 **Group 2:** 7/511		

Author	Patients	Intervention	Outcome measures	Effect size	Comments
	Relapse: SCCAI score of ≥5 points				

Table 154: SANDBORN2012B

Author	Patients	Intervention	Outcome measures	Effect size	Comments
W. J. Sandborn et al. Once-Daily Budesonide MMX® Extended-Release Tablets Induce Remission in Patients With Mild to Moderate Ulcerative Colitis: Results from the CORE I study. *Gastroenterology; 143: 1218-1226. 2012.* **REF ID: SANDBORN2012B** **Study design and quality:**	**All patients:** **N=510 randomised** **N=489 modified ITT** (20 were excluded due to normal histology at baseline (n=17), major entry criteria violations (3 infectious colitis at study entry) There were four treatment arms: 9mg Budesonide mezavant XL, 6mg Budesonide mezavant XL, 2.4g Asacol and placebo. The two budesonide mezavant XL trial arms have been excluded from this review as it is not currently available in the U.K. **Note:** the 2.4g Asacol arm was a non powered reference arm (active	**Group 1: 2.4g mesalazine (Asacol)** N=127 randomised N=124 (modified ITT) (3 normal histology at entry) N=95 (completers) 2.4g mesalazine (Asacol) per day, given as two 400mg tablets 3	**Outcome 1: Clinical remission** (symptom resolution; score of 0 for both rectal bleeding and stool frequency subscores of the UCDAI) **Outcome 2: Clinical improvement** (≥3 point reduction in the UCDAI score)	**Group1:** 31/124 **Group 2:** 20/121 **Group1:** 42/124 **Group 2:** 30/121	**Funding:** Consulting fees from a long list of pharmaceutical companies. Funding supported by Santarus Inc, and Cosmo Pharmaceuticals SpA. **Limitations:** >10% difference in missing data between the two treatment arms.

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Double blind double dummy Phase 3, RCT Multicentre: 108 centres, North America and India **8 week trial** **Randomisation:** Developed by an external contractor and administered centrally (not within site) via an interactive voice response system. 1:1:1:1 ratio using a block size of 4. As each new patient was randomized, they were given the next available randomisation number which was associated with a study drug. Adequate. **Allocation concealment**: Adequate. **Blinding:** Double blind, double dummy. **Outcome assessment:** UCDAI. **Sample size calculation:** Difference of 20% between at least one budeonside MMX group and placebo at week 8, 110 patients per group, 80% power, α=0.025. Assuming a drop out rate of approx. 10%, 123 patients per group or 492 to be randomized in this study. **Type of analysis: Modified ITT** (patients who received at least one dose of the study drug and	control and internal reference). **Drop-outs** (don't complete the study): N=84 (32.8%) out of the two treatment arms. >10% difference in missing data between the two treatment arms. **Inclusion criteria:** • Adults up to 75 years of age • Severity: active mild to moderate ulcerative colitis for at least 6 months, UCDAI score of 4-10 points • Diagnosis of UC was histologically confirmed from a biopsy specimen obtained at the baseline colonoscopy and read by a blinded central reader • Extent: not proctitis • If taking oral mesalamine or other oral 5ASAs at the screening visits were required to have a wash out of their medication for at least 2 days before randomization **Exclusion:** • Use of oral or rectal corticosteroids within 4 weeks of screening • Use of immunosuppressive agents within 8 weeks of screening • Use of anti-tumor necrosis factor α agents (infliximab, adalimumab) within 3 months of screening • Participation in experimental therapeutic studies in the past 3 months • Diagnosis of severe UC (UCDAI>10 points) • Evidence or history of toxic megacolon • Disease limited to the rectum (proctitis extending from the anal verge up to 15 cm) • Presence of infectious colitis • Presence of severe anaemia, leukopenia or ganulocytopenia • Verified presumed or expected pregnancy or ongoing lactation • Presence of cirrhosis or evident hepatic or renal disease or insufficiency • Presence of severe diseases in other organs and systems • Local or systemic complications or other pathological states requiring therapy with corticosteroids and/or immunosuppressive	times daily. **Group 2: Placebo** N=128 randomised (1 additional patient was assigned to budesonide 6mg but took placebo) N=129 safety population N=121 (modified ITT) (1 infectious colitis at entry, 6 normal histology at entry) N=76 (completers) Intervention details **Concomitant therapy:** Not permitted.	**Outcome 3: Clinical and endoscopic remission** (UCDAI score≤1, with subscores of 0 for both rectal bleeding and stool frequency (based on the 3 days closest to the week 8 visit with nonmissing diary data within a 5 day window closest to the visit [the 5 days did not include any days on which a colonoscopy or the preparation for colonoscopy occurred]), no mucosal friability on colonoscopy and a ≥1 point reduction from baseline in the endoscopic index score).	**Group1:** 15/124 **Group 2:** 9/121	**Additional outcomes:** Endoscopic improvement Endoscopic remission (post hoc analysis, so was not included) Histological remission Results by extent of disease (Post hoc analyses)
			Outcome 4: Adverse events	**Group1:** 80/127 **Group 2:** 81/129	
			Outcome 5: Serious adverse events	**Group1:** 4/127 **Group 2:** 3/129	

Author	Patients	Intervention	Outcome measures	Effect size	Comments
excluded patients with major good clinical practice re-entry criteria violations). **Compliance rates:** N=17 dropout/ withdrawal due to AEs. It is unclear which ones were drug related.	agents • Type 1 diabetes • Glaucoma • Known infection with hepatitis B or C or with human immunodeficiency virus **Baseline characteristics** **Group 1: 2.4g mesalazine (Asacol)** **Median age (range):** 45 (18-72) **Sex (m/f):** 69/55 **Extent:** proctosigmoiditis n=37, left sided colitis n=35, extensive/ pancolitis n=52 **Number of flares in the past 2 years, median (range):** 2 (0-80) **Severity of last flare:** mild n=25, moderate n=81, missing n=18 **Baseline UCDAI score, median (range):** 7 (2-11) missing n=10 **Baseline endoscopic index score, median (range):** 7 (2-11) **Prior mesalamine use:** n=72 **Prior any 5-ASA use:** n=79 **Drop outs:** 32 (3 normal histology at entry, 7 adverse events, 1 protocol violation, 9 consent withdrawn, 2 lost to follow up, 2 investigator decision, 8 treatment failure) **Group 2: Placebo** **Median age (range):** 39 (18-77) **Sex (m/f):** 68/53 **Extent:** proctosigmoiditis n=41, left sided colitis n=34, extensive/ pancolitis n=40, missing n=6 **Number of flares in the past 2 years, median (range):** 2 (0-24) **Severity of last flare:** mild n=30, moderate n=79, missing n=12 **Baseline UCDAI score, median (range):** 7 (1-11) missing n=13 **Baseline endoscopic index score, median (range):** 7 (0-12) **Prior mesalamine use:** n=74 **Prior any 5-ASA use:** n=82 **Drop outs:** 52 (1 infectious colitis at entry, 6 normal histology at entry, 10 adverse events, 2 protocol violations, 10 consent withdrawn, 4 lost to follow up, 2 investigator decision, 14 treatment failure, 3 other)			

Table 155: SCHERL2009

Author	Patients	Intervention	Outcome measures	Effect size	Comments
E. J. Scherl et al. Safety and Efficacy of a New 3.3g b.i.d. Tablet Formulation in Patients With Mild-to-Moderately –Active Ulcerative Colitis: A Multicenter Randomized, Double-Blind, Placebo- Controlled Study. The American Journal of Gastroenterology; 104: 1452-1459. 2009. **REF ID: SCHERL2009** **Study design and quality:** Double blind, Phase III, multicentre (55 sites) RCT United States **8 week trial** **Randomisation:**2:1 ratio. Centralized automated validated interactive voice response system **Allocation concealment**: Adequate **Blinding:** identical tablets, investigator and patient blinded throughout the trial **Outcome assessment:** Modified Mayo disease activity index (MMDAI). Deletion of friability from an endoscopy score of 1.	**<u>All patients:</u>** **N=250 randomised** **N=249 for ITT analysis** (1 patient did not take any medication) **Drop-outs (don't complete the study):** N=95**(38%)**(due to lack of efficacy (27 group 1, 24 group 2), adverse events(15 group 1, 10 group 2), lost to follow up (3 in group 2), other (7 in group 1 and 2 in group 2) and requested (4 in group 1) **Inclusion criteria:** Men and non-pregnant, non-lactating women ≥ 18 years **Severity:** Mild to moderate active UC (score of 6-10 modified Mayo disease activity index) inclusive with a score of ≥2 for rectal bleeding and mucosal appearance **Extent:** ≥20cm from the **rectum** Have not taken ≥6.75g/day of balsalazide or >2.4g/day of mesalamine or equivalent daily dose of any other 5-ASA product in the 2 weeks prior to commencing the study medication **Exclusion:** Worsening or serious complications of UC that failed to improve during chronic (i.e. >7 days) therapy with ≥6.6g/day of balsalazide disodium within 30 days of screening Used chronic immunosuppressive therapy or	**Group 1: 3.3g Balsalazide twice a day (6.6g)** N=167 randomised N=166 (ITT) N=111 (completers) 3.3g of Balsalazide disodium twice a day (1.1g tablets), total 6.6g/day. **Group 2: Placebo** N=83 randomised (& ITT) N=44 (completers) Placebo tablets **Concomitant therapy:** not described. See inclusion/ exclusion criteria.	Outcome 1: **Clinical remission** (score of 0 for rectal bleeding and a combined score of ≤2 for bowel frequency and physician's assessment using the MMDAI subscales at week 8/ end of treatment)	**<u>At week 8/EOT</u>** **Group1:**64/166 (ITT), **Group 2:** 19/83 (ITT),	**Funding:** Funded and supported by Salix Pharmaceuticals. **Limitations:** High dropout rate No baseline extent data **Additional outcomes:** Proportion of patients with improvement (≥ 1 point improvement) from baseline to week 8/EOT in the MMDAI subscale of rectal bleeding, mucosal appearance, bowel frequency, physician's assessment. Mean change from baseline to week8/EOT for the MMDAI score
			Outcome 2: Mucosal healing (endoscopy. Sigmoidoscopy score of 0 or 1) at week 8/EOT**(endoscopic remission)**	**<u>At week 8/EOT</u>** **Group1:**88/166 (ITT), **Group 2:**27/83 (ITT),	
			Outcome 3: Complete remission (MMDAI score of ≤1) at week 8/EOT**(clinical and endoscopic remission)**	**<u>At week 8/EOT</u>** **Group1:**34/166 (ITT), **Group 2:**11/83 (ITT),	
			Outcome 4: **Clinical improvement** (≥3 point improvement from baseline in the total MMDAI score and a ≥1 improvement from baseline in the rectal bleeding subscale of the MMDAI)	**<u>At week 8/EOT</u>** **Group1:**92/166 (ITT), **Group 2:**33/83 (ITT),	
			Outcome 4: **Adverse events** Most frequent AEs	**<u>At week 8/EOT</u>** **Group1:**88/168 ITT	

Author	Patients	Intervention	Outcome measures	Effect size	Comments
The presence of friability is a score of 2 or 3. **Sample size calculation:**80 % power, two sided significance figure of 5%, 2:1 allocation, 150:75 subjects **Type of analysis: ITT** **Compliance:** >88% of patients in the balsalazide or placebo groups were ≥80% compliant. N=25 dropout/ withdrawal due AEs. It is unclear whether these were drug related.	corticosteroids within 30 days of screening Administered intra-rectal aminosalicylates for > 2 consecutive days within 7 days of screening Regularly used NSAIDSs Used cell-depleting therapy Used anti-diarrhoeal therapy during screening and at any time during the study Earlier bowel surgery except appendectomy or cholecystectomy HIV or hepatitis B or C with LFTs outside normal limits Infectious, ischaemic or immunologic diseases involving the GI tract LFT's twice the upper normal limit Clinically significant renal disease Unstable cardiovascular, coagulopathy or pulmonary disease Active malignancy within the last 5 years (apart from BCC, in situ cervical carcinoma that has been excised surgically) Sclerosing cholangitis Positive stools for pathogens Hypersensitivity to salicylates or aspirin Or any condition or circumstance that would prevent completion of the study or interfere with the results (investigator opinion) **Group 1: 6.6g Balsalazide** **Mean age (SD):**43.6 (13.4)		were: headache, nausea, nasopharnygitis, fatigue and constipation	**Group 2:** 47/79 ITT	

Author	Patients	Intervention	Outcome measures	Effect size	Comments
	MMDAI total score, mean (SD):7.8 (1.4) **MMDAI <8 (mild), n (%):** 68 (41.0) **MMDAI≥8 (moderate), n (%):** 98 (59) **Drop outs:** 56 **<u>Group 2: Placebo</u>** **Mean age (SD):**45.4 (13.0) **MMDAI total score, mean (SD): 8.0** (1.4) **MMDAI <8 (mild), n (%):** 26 (31.3) **MMDAI≥8 (moderate), n (%):** 57 (68.7) **Drop outs:** 39 No data on extent of disease given at baseline.				

Table 156: SCHMIDT2009/ 2011

Reference	Patient characteristics	Predictors and outcome measures	Effect sizes	Comments
S. Schmidt et al. Low Bone Mineral Density in Children and Adolescents with Inflammatory Bowel Disease: A Population-Based Study from Western Sweden. *Inflammatory Bowel Disease;* 15 (12): 1844-1850. 2009. **Type of study:** Cross-sectional study And Longitudinal Assessment of Bone Mineral Density in Children and Adolescents With	**Sample size:** N=144 IBD patients N=83 UC patients **<5% missing data?** Not described. **Type of analysis used:** Chi-squared, t-tests, Pearson's correlation and multiple linear regression analysis. BMD was the dependent variable testing the influence of age, gender, BMI, diagnosis, treatment with prednisolone or azathioprine and disease duration. **Appropriate?** Yes **Inclusion criteria:** Age between 6-19 years Previous diagnosis of IBD All children and adolescents with new-onset IBD during the inclusion period	**Definitions of variables measured:** **Bone age:** Radiograph of the left wrist (according to the method of Greulich and Pyle). **Weight, height, age, gender, BMI, disease category** (UC, Crohn's, Indeterminate colitis), **and treatment** (prednisolone, azathioprine). **Prednisolone use:** Recorded if the patient had ever taken prednisolone or not (no regard to daily or cumulative doses). **Routinely measured?** Total vitamin D and DEXA scanning are not routinely measured. Weight is routinely measured. **Outcome and definition:** **Bone Mineral Density:** Dual energy x-ray absorptiometry (DEXA) of the whole body and lumbar spine, applying a Lunar densitometer. Simultaneously body composition was assessed. All patient measurements were done on the same	**<u>At baseline (SCHMIDT2009)</u>** **Results for UC patients** BMD mean z score: -0.8 SD, range-4.4 to +3.7SD, P<0.001. 47% had a decreased BMD with a BMD Z score of the lumbar spine <-1SD, 24.1% ≤ -2 SD The other variables were no presented by diagnosis but were for all IBD patients. **Multiple regression analysis** Male gender and treatment with azathioprine were associated with lower BMD. Age and BMI showed a positive correlation with BMD Neither treatment with prednisolone, disease category, nor disease duration turned out to represent risk factors for lower BMD in this model.	**Source of funding**: Supported by grants from the Frimurare-Barnhusdirrektionen Gothenburg (Sweden) and the Research and Development Centre of the county of Sodra Alvsborg, the Medical Faculty of Gothenburg and West Gothia Region Research Funds. **Risk of bias:** Cross-sectional study Unclear how the patients were recruited No dose/ duration of corticosteroid use Limited information

Reference	Patient characteristics	Predictors and outcome measures	Effect sizes			Comments
Inflammatory Bowel Disease. *Journal of Pediatric Gastroenterology and Nutrition; 55 (%): 511-518. 2012.* **Type of study:** prospective cohort **Setting:** Two Paediatric centres/ hospitals, Sweden **Follow up period:** 2 year period (1 January 2003- 1 January2005) **Reference used:** Reference data was taken from 6 different studies including Caucasian volunteers from 5 different countries (Netherlands, Spain, Finland, Australia and USA) between the ages of 5-19 without any disease or condition known to affect BMD. Total 1135 females, 924 males with DEXA of lumbar spine and 821 females and 673 males with total body scans.	Diagnosis of IBD was made on the basis of the Porto Criteria **Exclusion criteria:** None described. **Data collection:** Unclear. **Treatment given:** Not described. **Baseline characteristics:** These were given overall for all IBD patients and were not separated out for the UC patients. 93 males, 51 females Mean age: 14.2years (range 6-19) Mean disease duration: 41.3 months (range 2-156) Bone age: mean 14.4 years (range 4.6-19) Weight: -0.16 SDS (range -7.8) No patients had ever received bone-protective drugs (calcium, vitamin D, biphosphonates) when they were included in the study.	densitometer. BMD scores were z scores using gender and aged matched paediatric reference data from Lunar. ISCD2007 Paediatric Official Positions: BMD Z score≤-2SD = low BMD **Blinding:** Not described. **Risk of measurement error:** Unclear. **Risk of inter-observer variability:** Unclear. **Key prognostic factors not included?** Ethnicity, Tanner staging, family history, chronic diseases associated with osteoporosis and diet.	**Parameter**	**Regression co-efficient**	**P value**	reported for the multivariate analysis Missing data is not described Some important confounders were not considered **Additional outcomes reported:** Relationship between BMD and gender, age, bone age, BMI, body fat and lean body mass for IBD overall.
			Age	0.63	<0.001	
			BMI	0.56	<0.001	
			Treatment with Azathioprine	-0.20	<0.001	
			Male gender	-0.07	<0.05	
			2 years follow up (SCHMIDT2012) Results from the multivariate analysis: • BMD in the lumbar spine was positively associated with positive changes in height z score (P<0.001) and longer disease duration (P<0.05). • Age had a nonlinear effect • Disease subcategory and treatment with azathioprine or corticosteroids were not significantly associated with a lower change in BMD • Supplementation with vitamin D and calcium didn't significantly affect the change in BMD			

Table 157: SCHROEDER1987

Author	Patients	Intervention	Outcome measures	Effect size	Comments
K. W. Schroeder et al. Coated Oral 5-Aminosalicylic Acid Therapy For Mildly To Moderately Active Ulcerative Colitis. A Randomized Study. *The New England Journal of Medicine; 317(26): 1625-1629. 1987.* **REF ID:SCHROEDER1987** **Study design and quality:** Double blind RCT Single centre. United States. **6 week trial** **Randomisation:** Stratification by extent (left sided and pancolitis) and by previous treatment. After assignment by stratum the patient was randomised by a pharmacist using a randomization sequence developed in the Section of Medical Research Statistics. The paper describes how the patients who were to receive 1.6g/day were entered from only one stratum, stratum 4. No patients were recruited into this stratum for low-dose therapy for several months, so it was subsequently changed to stratum 1. Double-blind status was maintained, but a second randomization scheme for the	**<u>All patients:</u>** **N=88randomised** **N=87 ITT**(one patient dropped out before receiving any treatment. It is not clear which treatment group they are in, so they have been excluded from the ITT analysis) **Drop-outs** (don't complete the study): N=21**(24%)** **Inclusion criteria:** Extent: Not specified. It was determined by flexible proctosigmoidoscoy and double-contrast x-ray films of the colon, complete colonoscopy or both Severity: Mild to moderate Adults UC defined by the usual symptomatic, radiographic and endoscopic criteria. Newly or previously diagnosed disease Patients receiving corticosteroids or sulfasalazine at the time of first contact were required to stop all such therapy at least one week before the start of the study Negative pregnancy test and practice contraception during the trial for women of child bearing potential At least on negative stool examination for ova and parasites and one negative culture for enteric pathogens **Exclusion:** Patients unwilling to stop taking UC drugs that they were currently on	400mg tablets of 5-ASA (Asacol) were used, which dissolves at a pH of 7 or more. It releases the drug in the terminal ileum and colon. Identical looking placebo tablet were used. 12 tablets taken per day (3 pills four times a day) **Group 1: 4.8g mesalamine (Asacol)** N=38 (ITT) N=36 (completers) 3 active tablets, four times a day. **Group 2: 1.6g mesalamine (Asacol)** N=11(ITT) N=8 (completers) 1 active and 2 placebo tablets taken four times a day. **Group 3: Placebo** N=38 (ITT) N=22 (completers)	Outcome 1: **Clinical remission** (complete response: complete resolution of all symptoms (all assessment scores 0; stool frequency, rectal bleeding and PGA)) Outcome 2: **Clinical improvement** (partial response: substantial but incomplete improvement in the assessment scores). The value has then been added to those in remission to give the total number of patients who improved. Outcome 3: **Adverse events** The only reported data for adverse events were the drug related ones. They have not been included in the meta-analysis because it excludes other adverse events that were not thought to be drug related. **Group1:**21/38 (55%) **Group 2:**8/11 (73%) **Group 3:** 23/38 (61%) Most frequently occurring adverse events were: dizziness, light-headedness, faintness (8%, 9%, 8% for 4.8g, 1.6g and placebo respectively), Fever (5%, 0%,	**Group1:**9/38 (24%) **Group 2:**1/11 (9%) **Group 3:** 2/38 (5%) **Group1:**28/38 (74%) **Group 2:**3/11 (27%) **Group 3:** 7/38 (18)	**Funding:** Supported by Tillotts Laboratories, United Kingdom. **Limitations:** Unclear allocation concealment Says double blind, but no further information given. High dropout rate **Additional outcomes:** No response

Author	Patients	Intervention	Outcome measures	Effect size	Comments
1.6g/day dosage that involved more patients for the completion of the study. **Allocation concealment**: Unclear. **Blinding:** Says double blind. No other information was given. **Outcome assessment:** Appears to be the same as the DAI but it has not been called that. Looks at stool frequency, rectal bleeding, flexi proctosigmoidoscopy and PGA, each scored from 0-3, maximum score of 12. **Sample size calculation:**90% Power of detecting a 60% improvement rate in the 4.8g vs. a 20% rate in the placebo. Type 1 error of 5% significance. 32 patients in each group. **Type of analysis: ITT** **Compliance:** 90% of the patients in the safety population took between ≥80% and <120% of the study medication. N=4 dropout/ withdrawal due to drug related AEs (1 in each 5-ASA group for marked worsening of symptoms, increased bloody diarrhoea, one had nausea and vomiting, 2 in the placebo group for urticaria and chest pain)	Known renal or hepatic dysfunction Pregnant women **<u>Group 1: 4.8g mesalamine (Asacol)</u>** **Mean age (SD):**42.5 (13.0) **Extent:** Universal colitis n=10 (26%), left-sided colitis n=28 (74%), rectal sparing n=2 (5%) **Initial mean (SD) assessment score:** **Stool frequency:** 2.29 (0.90) **Rectal bleeding:** 1.82 (0.80) **Flexible proctosigmoidoscopy:** 2.26 (0.64) **PGA:** 1.82 (0.39) **Episode:** Newly diagnosed n=7 (18%) Other variables: **Drop outs:** 2 (5%), (1 due to flare of symptoms, 1 due to adverse reaction) **<u>Group 2: 1.6g mesalamine (Asacol)</u>** **Mean age (SD):**40.3 (11.5) **Extent:** Universal colitis n=0 (0%), left-sided colitis n=11 (100%), rectal sparing n=0 (0%) **Initial mean (SD) assessment score:** **Stool frequency:** 2.00 (0.89) **Rectal bleeding:** 1.64 (1.12) **Flexible proctosigmoidoscopy:** 1.73 (0.65) **PGA:** 1.64 (0.50) **Episode:** Newly diagnosed n=0 (0%) **Drop outs:** 3 (27%), (2 due to no improvement, 1 due to adverse reaction) **<u>Group 3: Placebo</u>** **Mean age (SD):**42.7 (16.0) **Extent:** Universal colitis n=10 (26%), left-sided colitis n=28 (74%), rectal sparing n=3 (8%) **Initial mean (SD) assessment score:** **Stool frequency:** 2.11 (0.95) **Rectal bleeding:** 1.68 (1.09) **Flexible proctosigmoidoscopy:** 2.11 (0.65) **PGA:** 1.76 (0.43) **Episode:** Newly diagnosed n=5 (13%)	3 placebo tablets taken four times a day. **Concomitant therapy:** Corticosteroids, sulfasalazine and any other drugs for colitis were prohibited during the trial.	8%), headache (13%, 18%, 11%), abdominal pain (5%, 9%, 18%), nausea (8%, 9%, 8%), gas (3%, 0%, 8%) and muscle aches (21%, 36%, 11%)		

Author	Patients	Intervention	Outcome measures	Effect size	Comments
	Drop outs:16 (42%), (10 for flare of symptoms, 3 for no improvement, 2 adverse reactions, 1 due to personal reasons) Says no differences in baseline characteristics but group 2 only have patients with left sided disease.				

Table 158: SELBY1985

Author	Patients	Intervention	Outcome measures	Effect size	Comments
W.S. Selby et al. Olsalazine in active ulcerative colitis. *British Medical Journal; 291: 1373- 1375. 1985.* **REF ID: SELBY1985** **Study design and quality:** Unclear blinding RCT United Kingdom **2 week trial** **Randomisation:** Randomly allocated (randomisation being restricted in blocks of four) **Allocation concealment**: Unclear **Blinding:** Unclear. Pathologist was stated to be blind. **Outcome assessment:** Number and consistency of stools and the presence of blood, mucus and abdominal pain were	**<u>All patients:</u>** **N=40randomised** **Drop-outs** (don't complete the study): N=0 (0%) **Inclusion criteria:** Severity: Mild (defined according to Truelove & Witts) Extent: Left sided disease (determined radiographically) **Exclusion:** Receiving corticosteroids (systemically or topically) or immunosuppressive drugs **<u>Group 1: 2g olsalazine</u>** **Mean age (SD):**42 (no SD given, range 19-67) **First attack of UC:** n=4 **Relapse of UC:** n=16 **No. of patients already taking sulphasalazine:** n=13 **Extent:** No data given **Severity:** No data given. **Drop outs:** 0 **<u>Group 2: Placebo</u>** **Mean age (SD):**50 (no SD given, range 15-81)	**Group 1: 2g Olsalazine** N=20 randomised 0.5g of olsalazine capsules (250mg capsules) four times a day. Total dose: 2g **Group 2: Placebo** N=20 randomised Placebo capsules, 2 four times a day. **Concomitant therapy:** Patients taking oral sulphasalazine stopped doing so on entry into the trial.	Outcome 1: **Clinical improvement** (Improvement in the clinical factors listed under outcome assessment was judged to represent a positive response)	**Group1:**13/20 **Group 2:**8/20	**Funding:** Support and supplying materials from Pharmacia. **Limitations:** Unclear method of randomisation, allocation concealment and blinding **Additional outcomes:** Sigmoidoscopic response
			Outcome 2: **Adverse events** **Group 1:** Due to a mild headache (2 patients), light headedness (1patient), increased diarrhoea (2 patients) **Group 2:** Due to nausea	**Group1:**5/20 **Group 2:** 1/20	
			Note: No differences were seen in patients who had not been treated before compared with those who had relapsed while taking sulphasalazine. PAPER?		

Author	Patients	Intervention	Outcome measures	Effect size	Comments
recorded. Sigmoidoscopy was scored according to Dick et al. **Sample size calculation:** None described **Type of analysis: ITT** **Compliance rates:** Not described. N=0 dropout/ withdrawal due to drug related AEs.	**First attack of UC:** n=3 **Relapse of UC:** n=17 **No. of patients already taking sulphasalazine:** n=12 **Extent:** No data given **Severity:** No data given. **Drop outs:**0				

Table 159: SEO2002

Reference	Patient characteristics	Predictors & outcome measures	Effect sizes			Comments
M. Seo et al. Evaluation of the clinical course of acute attacks in patients with ulcerative colitis through the use of an activity index. *Journal of Gastroenterology; 37: 29-34.2002.* **Type of study:** Retrospective cohort **Setting:** Hospital Japan **Follow up period:** Colectomies occurred from day 1 after admission to day 277.	**Sample size:** N=127 (moderate disease in 100, severe in 17 according to Truelove & Witts criteria) Although the majority are classed as moderate disease, they were all hospitalized. **<5% missing data?** Unknown **Type of analysis used:** Chi-squared test, Fishers exact test, unpaired students test. McNemar test. **Appropriate?** Yes **Inclusion criteria:** • Moderate or severe left sided or total ulcerative colitis **Exclusion criteria** • Distal disease where the inflammation did not extend beyond	**Cut off points:** Set between the values of 180 and 210 at intervals of 10. **Definitions of predictors:** Activity index (AI)= 60 x bloody stool + 0.5 x ESR + 13 x bowel movements – 4 x Hb – 15 x albumin +200 **Routinely measured?** Yes **Outcome and definition:** Surgery or no surgery within admission (this is unclear in the paper) **Blinding:** Unclear **Risk of measurement error:** Low **Risk of inter-observer variability:** Low **Continuous variable analysis:** Kept as continuous variables	**Results** 39 of the 127 patients underwent colectomy (27 due to failure of medical therapy, 6 chronic continuous type or difficulty in tapering corticosteroid treatment, 5 massive bleeding, 1 perforation). No deaths were reported.			**Source of funding**: None described. **Risk of bias:** • Retrospective cohort • Unclear whether there was missing data • No validation for use in this population (done externally in another paper) • Partially adequate event: covariate ratio (7-9) **Additional outcomes reported:** Associations with individual clinical parameters.

Reference	Patient characteristics	Predictors & outcome measures	Effect sizes			Comments
Model development/ presentation: Using an Activity Index that has previously been formed for moderate disease and applying it to a severe population. **Model evaluation:** None reported **Model performance:** Calibration- Not reported Discrimination – sensitivity and specificity is reported. AUC is not reported.	the sigmoid-descending colon junction **Data collection** Retrospectively analysed the records of the patients who were admitted between 1980 and 1996. **Treatment given** Majority of patients received systemic corticosteroid therapy apart from 25 patients in the non surgical group who received sulphasalazine. **Baseline characteristics:** Mean age: 32 years (range 12-74 years) Sex: 66 male, 61 female See table below for further details.	**Key prognostic factors not included?** **No**				

Table 160: Baseline characteristics

Characteristic	Non-surgical group N=88	Surgical group N=39	P value
Age (years), mean +/- SD	31.0 +/- 15.3	34.1 +/-14.2	p>0.05
Sex (M/F)	46/42	20/19	p>0.05
Extent of disease (total/ left sided)	65/23	36/3	p<0.05
Disease severity (severe/moderate [Truelove & Witts])	7/81	10/29	p<0.01
Activity index (AI) value, mean +/- SD	200 +/-29	221 +/-29	p<0.01
Systemic administration of steroids	63 (72%)	39 (100%)	p<0.001
Initial dosage of prednisolone (mg), mean +/- SD	51.6 +/- 12.3	55.4 +/- 12.4	p>0.05

Table 161: Comparison of clinical parameters at different time points

	Pre-treatment	1- week medical therapy	2- week medical therapy

Variable	Surgical	Non-surgical	Surgical	Non-surgical	Surgical	Non-surgical
Bloody stool (present/ little or none)	39/0	85/3	35/0*	39/49	33/1*	16/72
Bowel movement score	2.6 +/- 0.6*	2.1 +/- 0.8	2.2 +/-0.8*	1.4 =/-0.7	2.2 +/-0.8*	1.2 +/-0.5
ESR (mm/hr)	35.7 +/- 28.1	31.9 +/- 27.4	29.2 +/-26.8	20.1 +/-19.2	30.3 +/-34.3**	14.4 +/-19.4
Hb (g/dl)	10.5 +/-2.3***	11.4 +/- 2.2	10.7 +/-1.6	11.1+/-2.2	10.7 +/-2.0	11.4 +/-2.0
Albumin (g/dl)	3.2+/-0.7*	3.7 +/-0.6	3.1+/-0.5*	3.7 +/-0.5	3.3+/-0.6*	3.8 +/-0.5
Pulse rate (beats/min)	96.0 +/-20.7**	84.6+/-14.7	87.2+/-17.4**	77.7+/-9.4	89.3+/-12.7**	78.8+/-11.1
Body temperature (◦C)	37.5 +/-0.9	36.7 +/-3.4	37.2 +/-0.6**	36.7 +/-0.4	37.1 +/-0.8**	36.7 +/-0.4

*(a) *p<0.01, **p<0.01, ***p<0.05, surgical versus non-surgical groups*

Table 162: Pre- treatment and after 1 week of treatment predictions

	Pre-treatment predictions		After 1 week of therapy predictions	
Cut off values	PPV for surgical group	NPV for non surgical group	PPV for surgical group	NPV for non surgical group
180	36/105 (34%)	>85%	33/64 (52%)	57/59 (97%)
190	34/88 (39%)	>85%	30/53 (57%)	>90%
200	32/72 (44%)	>85%	26/44 (59%)	>90%
210	23/51 (45%)	60/76 (79%)	17/28 (61%)	>90%

Table 163: Prediction of surgical or non surgical outcome after 2 weeks of medical treatment

Cut off values	PPV for surgical group	NPV for non surgical group	Sensitivity*	Specificity*
180	30/43 (70%)	75/79 (95%)	30/34 (88%)	75/88 (85%)
190	28/38 (74%)	78/ 84 (93%)	28/34 (82%)	78/88 (89%)
200	24/29 (83%)	83/93 (89%)	24/34 (71%)	83/88 (94%)
210	17/21 (81%)	84/101 (83%)	17/34 (50%)	84/88 (95%)

*(a) *These have been calculated from the figures given in the paper*
(b) AI value of 200 was regarded as the cut off value most able to predict colectomy

Table 164: SIDDIQUI2011

Author	Patients	Intervention	Outcome measures	Effect size	Comments
A. A. Siddiqui et al. Effect of Pregnancy on the disease activity in Ulcerative Colitis. *Journal of Postgraduate Medical Institute; 25 (4): 314-7. 2011.* **REF ID: SIDDIQUI2011** **Study design and quality:** Prospective cohort study **Oman, Sultan Qaboos University Hospital** **Years studied:** July 2002-December 2004 **Risk of bias:** Selection bias: High risk. Very limited baseline characteristics. No analysis carried out on out outcomes, so no adjustments done for confounders. Performance bias: unclear Attrition bias: High risk – no dose, compliance or duration of treatment given. Detection bias: High risk. No definitions given for outcomes. Unclear blinding of	<u>All patients:</u> N=60 with ulcerative colitis N=30 pregnancies **Included population** • Diagnosed cases of ulcerative colitis (proven on colonoscopy and biopsy) • Fairly well controlled disease at the time of enrolment **Excluded population:** • Pregnant ladies and any patient of ulcerative colitis with uncontrolled disease • Co-morbid illnesses e.g. hepatitis B & C, autoimmune hepatitis, diabetes mellitus, hypertension etc. <u>Data collection</u> Non probability, convenience sampling. Non-pregnant women were on different modes of contraception including condoms (n=23), intrauterine contraceptive device (n=5), and depot progesterone (n=2). The other patients became pregnant during the study period. At the time of enrolment the following were recorded: history, physical examination, laboratory investigations (FBC, LFTs, CRP, albumin, urea, creatinine) pregnancy test and abdomen US. Enrolment of pregnant women was complete by December 2003. All women were followed up until December 2004. Pregnant women- reviewed monthly Non pregnant women- reviewed every 3 months. All women were in remission at the start of the study. <u>Baseline characteristics</u> All patients (pregnant women) were on mesalamine and folic acid and had fairly well controlled disease.	**Group 1: Pregnant women with UC** N=30 N=24 mild exacerbation (controlled by increasing the dose of mesalamine) N=4 moderate disease exacerbation (required oral steroids) N=2 severe exacerbation (requiring IV steroids followed by oral steroids in the 1st trimester). **Group 2: Non-pregnant women with UC** N=30 N=25 mild exacerbation N=4 moderate disease exacerbation (required oral steroids) N=1 severe exacerbation (requiring IV steroids).	**Results** All patients delivered normally at the time of birth. No growth retardation. No congenital abnormalities.		**Funding:** None. **Limitations:** High risk of bias **Additional outcomes:** Relationship between adverse effect of pregnancy on ulcerative colitis

Author	Patients	Intervention	Outcome measures	Effect size	Comments
investigators to prognostic/ confounding variables and treatment.	Mean age: 25 +/-6 years				

Table 165: SNINSKY1991

Author	Patients	Intervention	Outcome measures	Effect size	Comments
C. A. Sninsky et al. Oral Mesalamine (Asacol) for Mildly to Moderately Active Ulcerative Colitis. A multicenter study. *Annals of Internal Medicine; 115 (5): 350-355. 1991.* **REF ID: SNINSKY1991** **Study design and quality:** Double blind, multicentre (9 sites) RCT, United States **6 week trial** **Randomisation:** Computerised randomization sequences, which were designed to provide equal distribution. No stratification was done on patient characteristics. **Allocation concealment**: Adequate **Blinding:** says double blind but gives no further information	**<u>All patients:</u>** N=158 randomised **Drop-outs (don't complete the study):** N=27**(17%)**excluded from the efficacy analysis (non compliance n=9, ineligibility n=6, voluntary withdrawal n=5, intercurrent illness n=4, loss to follow up n=2 and the use of potentially biasing medication during the study n=1). Unclear how many of them had dropped out or completed the study. In addition to those 27, 22 patients had treatment failure and discontinued treatment (3 in the 1.6g group, 4 in the 2.4g group and 15 in the placebo group) **Inclusion criteria:** 18-75 years of age Severity: Active mild to moderate ulcerative colitis (diagnosis and extent confirmed by endoscopy/barium enema within the last 24 months New or previously diagnosed If on sulfasalazine therapy but still have active signs/ symptoms No extent restriction **Exclusion:**	400mg tablets (resin dissolves at a pH or ≥7, releasing the drug in the terminal ileum and colon) **Group 1: 1.6g Asacol** N=53 randomised N=44 (efficacy analysis, EA) 1.6g mesalamine (5-ASA, Asacol)/ day **Group 2: 2.4g Asacol** N=53 randomised N=43 (efficacy analysis) 2.4g mesalamine (5-ASA, Asacol)/day **Group 3: Placebo** N=52 randomised N=44 (efficacy analysis)	Outcome 1: **Clinical Remission** (complete resolution of all symptoms, with all assessment scores determine to be zero) Outcome 2: **Clinical improvement** (a reduction in the physician's global assessment score and in at least one other component score with no score increased in severity)	**<u>Week 3</u>** **Group1:**1/53 (ITT), 1/44 (EA) **Group 2:**1/53 (ITT), 1/43 (EA) **Group 3:**1/52 (ITT), 1/44 (EA) **<u>Week 6</u>** **Group1:**6/53 (ITT), 6/44 (EA) **Group 2:**6/53 (ITT), 6/43 (EA) **Group 3:**2/52 (ITT), 2/44 (EA) **<u>Week 3</u>** **Group1:**12/53 (ITT), 12/44 (EA) **Group 2:**13/53 (ITT), 13/43 (EA) **Group 3:**3/52 (ITT), 3/44 (EA) **<u>Week 6</u>** **Group1:**13/53 (ITT), 13/44 (EA) **Group 2:**15/53 (ITT), 15/43 (EA) **Group 3:**8/52 (ITT), 8/44 (EA)	**Funding:** Norwich Eaton Pharmaceuticals **Limitations:** Unclear validation of disease activity tool No further information on the double blinding Unclear dropout rate **Additional outcomes:** Maintained condition (no change in PGA) Worsened (increase in any individual score)

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Outcome assessment: Unclear whether it is validated. Looks at PGA, stool frequency, rectal bleeding, sigmoidoscopic findings, and patient's functional assessment. Each scored from 0-3. **Sample size calculation:** None described **Type of analysis: PPA and ITT** N=2 (One patient had a headache, arthralgias, dizziness and nausea. The other patient had worsening of bloody diarrhoea (previous history of a similar reaction to sulfasalazine and 5-ASA enemas.) dropout/ withdrawal due to AEs (both in the mesalamine 2.4 g group). Likely to be drug related as the symptoms resolved to pre study levels after drug withdrawal.	Use of steroids in the last month History or laboratory data suggestive of renal or hepatic dysfunction Allergy/intolerance to aspirin or salicylate containing compounds Positive stool culture **Group 1: 1.6g Asacol** **Mean age (SD):**43.3 (14.4) **Extent:**>40cm N=20, 20-40cm N=25, <20cm N=8 **Episode:** 3.8% newly diagnosed **Drop outs:** unclear **Group 2: 2.4g Asacol** **Mean age (SD):** 43.1 (13.1) **Extent:**>40cm N=24, 20-40cm N=20, <20cm N=9 **Episode**: 9.4% newly diagnosed **Drop outs:** unclear **Group 3: Placebo** **Mean age (SD):**39.2 (13.3) **Extent:**>40cm N=17, 20-40cm N=25, <20cm N=10 **Episode**: 5.8% newly diagnosed: **Drop outs:** unclear Mean assessment scores for each group were similar.	**Concomitant therapy:** Sulfasalazine and topical rectal therapies were discontinued 1 week prior to entry. Corticosteroids, aspirin, NSAIDs, metronidazole, 6-mercaptopurine, azathioprine, cyclosporine, or other investigational drugs were not permitted.	The number of people experiencing adverse events was not reported. There was only the number of events reported. The top three were headache, gas and nausea.		

Table 166: SOOD2000

Author	Patients	Intervention	Outcome measures	Effect size	Comments
A. Sood et al. Role of azathioprine in severe ulcerative colitis: one year,	**83 patients with severe UC were enrolled. 50 of these relapsed within 2 months on corticosteroid withdrawal. They were then randomized into these two groups.**	**Group 1: Azathioprine** N=25 randomised	**Outcome 1: Relapse by 1 year**	**Group1:** 3/25 **Group 2:** 6/25	**Funding:** None described.

Author	Patients	Intervention	Outcome measures	Effect size	Comments
placebo-controlled, randomised trial. *Indian Society of Gastroenterology; 19:14-17. 2000.* **REF ID: SOOD2000** **Study design and quality:** RCT **1 year trial** **Randomisation:** Pseudorandom numbers ranging from 0-1 generated by a scientific calculator. Unclear. **Allocation concealment**: Unclear. **Blinding:** Identical tablets and packaging. Treating Physician was aware of the drug treatment. **Outcome assessment:** Daily symptom diary. Endoscopy according to Baron's criteria. **Sample size calculation:** Not described. **Type of analysis: ITT** **Compliance rates:** Monitored by tablet counts written in the patients diary. Non compliant patients were considered drop outs. N=3 dropout/ withdrawal due to drug related AEs in the	**<u>All patients:</u>** **N=50 randomised** **Drop-outs** (don't complete the study): N=8 (16%) <10% difference in missing data between the treatment arms. **Inclusion criteria:** • Severity: Severe ulcerative colitis on the basis of clinical examination (Truelove & Witts criteria) and endoscopic and histological criteria • Suffered a relapse within two months of corticosteroid withdrawal **Exclusion:** • Pregnancy • Bone marrow suppression • Drug allergy • Liver disease **<u>Group 1: Azathioprine</u>** **Mean age (SD):** 35.2 (11.4) **Mean duration of disease at study entry, years (SD):** 6.7 (4.9) **Extent:** pancolitis n=8, left sided n=12, proctosigmoiditis n=5 **Disease description:** Continuous n=8, episodic n=15, unspecified n=2 **Severity of previous relapse:** All severe. **Frequency of relapses:** Not described. **Current use of immunomodulators:** Not described. **Drop outs:** 5 (2 due to non compliance and violation of treatment protocol, 3 due to AEs) **<u>Group 2: Placebo</u>** **Mean age (SD):** 37.2 (13.2) **Mean duration of disease at study entry, years (SD):** 4.3 (3.4) **Extent:** pancolitis n=8, left sided n=10, proctosigmoiditis n=7 **Disease description:** Continuous n=9, episodic n=14, unspecified n=2 **Severity of previous relapse:** All severe. **Frequency of relapses:** Not described. **Current use of immunomodulators:** Not described.	N=17 in remission (complete and partial) end of the trial Intervention details 6-8g Sulphasalazine, 1mg/kg/day oral prednisolone and 2mg/kg/day of azathioprine. 50mg azathioprine tablets were used. **Group 2: Placebo** N=25 randomised N=16 in remission (complete and partial) end of the trial Intervention details 6-8g Sulphasalazine, 1mg/kg/day oral prednisolone and placebo. Identical tablets to the azathioprine were used for the placebo tablets. **Concomitant therapy:** The corticosteroids were tapered over 12-16 weeks.	**Note:** used authors definition of relapse so partial remission is not included in these figures. **Outcome 2: Adverse events** Azathioprine: 2 due to acute pancreatitis, 1 due to jaundice and increase in transaminases.	**Group1:** 3/25 **Group 2:** 0/25	**Limitations:** Unclear method of randomisation and allocation concealment Patient blinded Significant difference in duration of disease between the two groups at study entry **Additional outcomes:** Remission

Author	Patients	Intervention	Outcome measures	Effect size	Comments
azathioprine group.	**Drop outs:** 3(3 due to non compliance and violation of treatment protocol) **Definitions** **Complete remission:** Clinical improvement with absence of symptoms of active disease (rectal bleeding, bowel frequency) with sigmoidoscopic appearance of grade 0-1 and normal histological pattern. **Partial remission:** Clinical improvement with stool frequency still increased but less than 50% of previous and sigmoidoscopy showing downgrading of severity and granular non friable mucosa (grade 0-22) **Relapse:** Remission followed by worsening of symptoms recognized by the patient as active disease (such as rectal bleeding, loose motions or bowel frequency) with sigmoidoscopic appearance of active colitis.				

Table 167: SOOD2002

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Sood et al. Methylprednisolone acetate versus oral prednisolone in moderately active ulcerative colitis .*Indian journal of gastroenterology, 21,11-13* **REF ID:SOOD2002** **Finland** **Study design and quality:** Open label RCT **Duration of follow-up** 1 ,8 weeks **Randomisation**: using a Casio 82X calculator **Allocation concealment:** No	**All patients** N=40 **Inclusion criteria:** • Newly diagnosed • Moderately active (activity index 150-222) **Exclusion criteria**: • none stated. **Drop outs**:0	**Group 1**:depot IM injection weekly 80mgs Methylprednisolone acetate for 6 weeks N=21 randomised **Group 2**:oral prednisolone 40 mgs od tapering off. N=19 randomised **Concomitant therapy:** sulfasalazine 6g a day	**Outcome 1: Clinical remission** <150 (activity index ,Seo 1992)	<u>Week 1</u> **Group 1:** 18/21 **Group 2**:18/19 <u>Week 8</u> **Group 1**:18/21 **Group 2:** 18/19	
			Outcome 2: Adverse events	**Group 1**: acne (1) **Group2**: 5 Hyperglycaemia (1),moon face(1),acne(3),weight gain(3), hirsutism(1), skin striae (1),	

Author	Patients	Intervention	Outcome measures	Effect size	Comments
details on allocation concealment **Sample size** : none stated **Type of analysis**: ITT					

Table 168: SOOD2002A

Author	Patients	Intervention	Outcome measures	Effect size	Comments
A. Sood et al. The beneficial effect of azathioprine on maintenance of remission in severe ulcerative colitis. *Journal of Gastroenterology; 37:270-274. 2002.* **REF ID: SOOD2002A** **Study design and quality:** Double blind RCT **1 year trial** **Randomisation:** Pseudorandom numbers ranging from 0-1 generated by a scientific calculator. **Allocation concealment**: Unclear **Blinding:** Double blind. Blinded endoscopist. Identical placebo/azathioprine tablets in identical blister packs.	**Induction of remission followed by maintenance of remission.** **<u>All patients:</u>** **N=35 randomised for induction of remission** **Drop-outs** (don't complete the study): N=0 (0%) **Inclusion criteria:** • Newly diagnosed as having ulcerative colitis (based on clinical history, supportive endoscopic appearances and colonic histology as well as failure to isolate known bacterial or protozoal pathogens on stool examination • Extent: Not described. • Severity: Severe disease (Activity index >220) **Exclusion:** • Pregnancy • Lactation • Bone marrow suppression • Drug allergy • Liver disease • Unwillingness to give informed consent according to the Declaration of Helsinki	**Group 1: Azathioprine** N=17 randomised Azathioprine and Sulphasalazine and steroids. 1mg/kg/day corticosteroids 6g/day oral Sulphasalazine & 2.5mg/kg/day azathioprine (50mg tablets) **Group 2: Placebo** N=18 randomised Sulphasalazine, placebo and steroids. 1mg/kg/day	Outcome 1: **Relapse** **Mantel Cox p value: 0.05** **It does not say whether all the patients went into remission specifically in the paper. Assumed that they all did.**	**Group1:** 4/17 **Group 2:** 10/18	**Funding:** None described **Limitations:** Unclear method of randomisation and allocation concealment Randomised at induction **Additional outcomes:** Time to reach remission (significantly different) Laboratory tests Mean disease activity index **Note: Population is newly diagnosed severe UC patients.**
			Adverse events: There were no adverse events reported in either treatment arm.		

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Outcome assessment: Diary. Disease activity index (UCDAI) **Sample size calculation:** None described. **Type of analysis: ITT** **Compliance rates:** Based on diary records of daily intake. Non compliant patients were considered as drop outs. N=0 dropout/ withdrawal due to drug related AEs.	**Group 1: Azathioprine** **Mean age (SD):** 39.59 (14.06) **Mean duration of symptoms at study entry, years (SD):** 0.70 (1.18) **Extent:** pancolitis n=2, left sided n=9, proctosigmoiditis n=6 **Mean activity index (SD):** 248.42 (5.1) **Severity of previous relapse:** All severe. **Frequency of relapses:** Not described. **Current use of immunomodulators:** Not described. **Drop outs:** 0 **Group 2: Placebo** **Mean age (SD):** 34.61 (11.83) **Mean duration of symptoms at study entry, years (SD):** 1.58 (2.37) **Extent:** pancolitis n=5, left sided n=8, proctosigmoiditis n=5 **Mean activity index (SD):** 249.26 (11.9) **Severity of previous relapse:** All severe. **Frequency of relapses:** Not described. **Current use of immunomodulators:** Not described. **Drop outs:** 0 **Definitions** **Complete remission:** Clinical improvement with the absence of symptoms of active disease (rectal bleeding, bowel frequency) with the sigmoidoscopic appearance of grade 0-1 and a normal histological pattern. It was also defined as a score of 150 or lower on the ulcerative colitis disease activity index. **Relapse:** Remission followed by worsening of symptoms, recognized by the patient as active disease (such as loose stools/ bowel frequency or rectal bleeding) with the sigmoidoscopic appearance of active colitis.	corticosteroids 6g/day oral Sulphasalazine & Placebo (identical to the azathioprine tablets) **Concomitant therapy:** The corticosteroid regimen was: 100mg hydrocortisone every 8 hrs for 5 days and then orally at 1mg/kg/day in a tapering schedule i.e. decreasing by 10mg every 10 days to a dose of 20mg/day and then 5mg every 10 days.			

Table 169: SOOD2003

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Sood A et al. Azathioprine versus sulfasalazine in maintenance of	**All patients:** **N=25 randomised** **N=**unclear if ITT or ACA	**Group 1: Oral Azathioprine** N=12 randomised	**Outcome 1: Relapse** Unable to calculate the	**Group 1:** N=5/12 **Group 2:**	**Funding:** none reported.

Author	Patients	Intervention	Outcome measures	Effect size	Comments
remission in severe ulcerative colitis. *Indian J Gastroenterol;22(3):79-81. 2003.* **REF ID: SOOD2003** **Study design and quality:** Randomized open trial 1 centres, India **18 month trial.** Patients were followed up fortnightly during month 1 and monthly thereafter. **Randomisation:** generated pseudorandom numbers ranging from 0-1 using a scientific calculator. Unclear. **Allocation concealment**: Unclear **Blinding:** No, open trial **Outcome assessment:** **Clinical remission:** clinical improvement with absence of symptoms of active disease (rectal bleeding, bowel frequency) with sigmoidoscopic appearance of 0 and normal histological findings, or a score of 150 or lower on the UC colitis disease index (Nitsuro et al 1992) **Endoscopic evaluation:** Baron's criteria: 0=normal mucosa,	**Drop-outs** (don't complete the study): n=2 (Oral Azathioprine group) N=2 (8%) **Inclusion criteria:** • **Extent**: proctosigmoiditis, left-sided and pancolitis. • **Severity:** severe **Exclusion:** • Patients unwilling or unable to give informed consent, unlikely to comply with protocol, on recent immunosuppressive therapy and those with pregnancy, lactation or compromised liver function. **Group 1: Oral Azathioprine** **Mean age (SD):** 35.2 (11.4) **Disease extent:** Proctosigmoiditis: n=2 Left-sided: 6 Pancolitis: 4 Other variables: **Drop outs:** 2 **Male: Female**: 7:5 **Group 2: Sulphasalazine** **Mean age (SD):** 37.2 (13.2) **Disease extent:** Proctosigmoiditis: n=3 Left-sided: 5 Pancolitis: 5 Other variables: **Drop outs:** 0 **Male: Female**: 8:5 **Definitions** **Remission -** Clinical improvement with absence of symptoms of active disease (rectal bleeding, bowel frequency) with sigmoidoscopic appearance of grade 0 and normal histological findings, or as a score of 150 or lower on the ulcerative colitis disease activity index.	N=12 (ITT) N=10 (completers) Intervention details 2.5mg/kg/day of azathioprine in addition to oral corticosteroids in a tapering dosage. **Group 2: Sulphasalazine** N=13 randomised N=13 (ITT) N=13 (completers) Intervention details: 6g/day of Sulphasalazine in addition to oral corticosteroids in a tapering dosage. **Concomitant therapy:** Patients were initially given prednisolone 1mg/kg/day, then reduced by 10mg/kg every fortnight till dose of 20mg/day and 5 mg/day fortnightly thereafter.	hazard ratio because the p value is only given as >0.43. **Outcome 2: Adverse effects**	N=5/13 **Kaplan Meier p value:>0.43** **Group 1:** N=2/12 (acute pancreatitis, 1 bone marrow suppression) **Group 2:** 0/13	**Limitations:** Open trial Unclear method of randomisation and allocation concealment Limited baseline characteristics Randomised at induction of remission **Additional outcomes:** Mean activity index at monthly intervals Survival curves

Author	Patients	Intervention	Outcome measures	Effect size	Comments
1(mild) = hyperaemic mucosa, 2 (moderate) = friability, bleeding to light touch, 3 (severe)=spontaneous bleeding, ulceration and mucopus. **Histology severity grading:** from 0-4 (more severe higher number) **Severe UC =** activity index was more than 220. **Sample size calculation:** unclear **Type of analysis**: unclear **Compliance rates:** N=2 dropout/ withdrawal due to drug related AEs in Azathioprine	**Relapse –** worsening of symptoms(bowel bleeding, increased frequency, loose stools) with sigmoidoscopic evidence of active colitis (granularity, friability, spontaneous bleeding).	<u>For those who relapsed</u> in **Group 1** they were restarted on corticosteroids and sulphasalazine was added. For those who relapsed in **Group 2** were treated with corticosteroids while sulphasalazine was continued.			

Table 170: TARPILA1994

Author	Patients	Intervention	Outcome measures	Effect size	Comments
S. Tarpila et al. Budesonide enema in active haemorrhagic proctitis – a controlled trial against hydrocortisone foam enema. *Alimentary pharmacology and Therapeutics; 8:591-595. 1994.* **REF ID: TARPILA1994** **Study design and quality:**	<u>**All patients:**</u> **N=72 randomised** Two patients were said to be erroneously included (1 refused to co-operate and another did not take the medication as prescribed) **Drop-outs** (don't complete the study): N=1 (1.4%) **Inclusion criteria:**	**Group 1: 2mg Budesonide liquid enema (Entocort)** N=37 randomised/ ITT 2mg/ 100mls budesonide enema (Entocort) once a day at night. **Group 2: 125mg**	**Outcome 1: Endoscopic remission** (score of 0 or 1 after 4 weeks) **Outcome 2: Adverse events**	**Author reported results at 4 weeks** **Group1:** 22/36 **Group 2:** 17/35 **Group1:** 8/37	**Funding:** Budesonide enemas were provided by Astra Draco AB. They also carried out the analysis. **Limitations:** Unclear method of randomisation and allocation concealment

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Single investigator blind RCT Multicentre: 13 centres, Finland and the United Kingdom **4 week trial** **Randomisation:** No details given. **Allocation concealment**: No details given. **Blinding:** Single investigator blind **Outcome assessment:** Sigmoidoscopy scored from 0-3, unclear if validated. Diary cards. **Sample size calculation:** Mean difference of 0.7 (sigmoidoscopy and biopsy score) that had a probability of 80%, assuming a SD of 1 for both. At least 64 patients needed to enter the trial. **Type of analysis: ITT analysis** **Compliance rates:** Not described. N=1 dropout/ withdrawal due to AEs (non drug related).	• 18-75 years • Outpatients of either gender • Extent: Active haemorrhagic proctitis, upper limit had to be visible on rigid sigmoidoscopy • Rectal bleeding in the week prior to entry • Severity: Endoscopic grade of ≥2 **Exclusion:** • Pregnancy • Recent treatment with other trial drugs • Concomitant other steroids necessary • Significant liver disease **<u>Baseline characteristics</u>** **<u>Group 1: 2mg budesonide liquid enema (Entocort)</u>** **Sex (m/f):** 16:21 **Mean age (SD):** 38 (13) **Extent:** All proctitis **Use of other medication:** SASP n=16, 5-ASA n=5 **Drop outs:** 1 due to AE (abdominal pain, diarrhoea and tenesmus. The patient had **severe proctitis** and these symptoms did not improve with the addition of systemic steroids) **<u>Group 2: 125mg hydrocortisone foam enema (Colifoam)</u>** **Sex (m/f):** 17:18 **Mean age (SD):** 42 (13) **Extent:** All proctitis **Use of other medication:** SASP n=16, 5-ASA n=3 **Drop outs:** 0	**hydrocortisone foam enema (Colifoam)** N=35 randomised/ ITT 125mg hydrocortisone actetate in 5mls of foam enema (Colifoam) **Concomitant therapy:** Washout period of 2 weeks for oral or rectal glucocorticosteroids was mandatory. Sulphasalazine and 5-ASA preparations were permitted if the dose was kept constant during the trial.		**Group 2:** 9/35	Single investigator blind Risk of an indirect population (severity of disease) **Additional outcomes:** Endoscopic scores Histology scores Clinical symptoms Quality of life indicators (not validated) Cortisol levels

Table 171: TRALLORI1994

Author	Patients	Intervention	Outcome measures	Effect size	Comments
G. Trallori et al.	**All patients**	Oral dose of 1.2g/day of	**Relapse:**		**Funding**

Author	Patients	Intervention	Outcome measures	Effect size	Comments
5-aminosalicylic acid in pregnancy: clinical report. *Italian Journal of Gastroenterology; 26: 75-78. 1994.* **REF ID: TRALLORI1994** **Study design and quality:** Prospective cohort study **Italy** **Years studied: 1988-1992** **Risk of bias:** Selection bias: Unclear risk. Limited baseline characteristics. No analysis carried out on out outcomes, so no adjustments done for confounders. Performance bias: unclear Attrition bias: low risk Detection bias: unclear	Included population: • Pregnant women in clinical remission from UC • Under treatment with oral, rectal or both 5-ASA treatment • Treatment with 5-ASA was continued throughout the pregnancy Excluded population • None described **N=16 women (19 pregnancies)** <u>Data collection and methods</u> • The women were regularly seen at the outpatient clinic. • They were also enrolled in an epidemiological study of the incidence and prevalence of UC. • UC was diagnosed using clinical, radiological, endoscopic and histological criteria • All patient attended regular clinical check ups (urine analysis and blood pressure every month, alpha fetoprotein, PCR, mucoproteins every 2 months, pelvic ultrasound scans at 3, 6 and 9 months. • Powell Tuck index of the clinical activity of disease was used at the beginning, then every 3 months and during puerperium • Relapse resulted in withdrawal from the trial • Maximum duration of follow up was 12 months (period of the puerperium) <u>Baseline characteristics</u> Age, years (SD): 31.2 (4.5), range 25-35 Disease duration (SD): 7 years (4.0) Disease extent: pancolitis n=9 (two had 2 pregnancies), left sided colitis n=3 (one had 2 pregnancies), proctosigmoiditis n=3	5-ASA (Asacol) Enemas were given twice weekly by clisma containing 4g 5-ASA All patients were initially in remission.	3 women relapsed in the first 3 months and one in the puerperium. 3 had pancolitis and 1 had left sided colitis. The Powell Tuck Indexes were 7, 8, 5 &5. Following treatment was given to induce remission: • 20mg corticosteroids IM per day for 1 month • 1.6g 5-ASA orally After they symptoms had improved: • 1.2g 5-ASA day until the end of pregnancy All patients responded to the therapy.		None described **Limitations:** Unclear selection, performance and detection bias **Additional outcomes:** Relapse free actuarial curve
			Outcome 1: **Normal birth**	Relapsers:3/4 Remission: 13/15	
			Outcome 2: **Spontaneous abortion**	Relapsers:0/4 Remission: 1/15	
			No side effects from the 5-ASA were observed.		

Table 172: TRAVIS1994

Author	Patients	Intervention	Outcome measures	Effect size	Comments
S.P.L. Travis et al. Optimum dose of olsalazine for maintaining remission in ulcerative colitis. *Gut; 35: 1282-1286. 1994.* **REF ID: TRAVIS1994** **Study design and quality:** RCT Multicentre: 2 centres, Oxford or Orebro **12 month trial** **Randomisation:** Random assignment. Unclear **Allocation concealment**: Unclear **Blinding:** Unclear. **Outcome assessment:** Questioning for adverse events. No description of clinical symptom assessments. **Sample size calculation:** 55% relapse in the 0.5g, 36% in the 1.0g and 28% in the 2g group, 80% power, 5% significance, 10% drop out rate, and 60 patients in each group was needed. **Type of analysis: ITT and PPA**	**<u>All patients:</u>** **N=198 randomised** **N=194 ITT** (4 patients withdrew consent or failed to attend after initial visit) **N=155 (PPA)** (17 patients were excluded due to non compliance, concomitant medication or lack of confirmation of remission or relapse by sigmoidoscopy within three weeks of termination of the trial) 22 patients were excluded due to withdrawal for AEs (20) or intercurrent disease (2).It is also mentioned elsewhere in the text that 32 patients withdrew due to AEs, so it is unclear. **Drop-outs** (don't complete the study): Unclear N=49 (24.7%) Unclear drop out rate. Text says 32 premature withdrawals due to adverse events, whereas the flow diagram says 20.17 exclusions described above. **Inclusion criteria:** • Ulcerative colitis in remission for 3 months or more • Diagnosed on standard clinical, endoscopic, histological and radiological criteria • Extent: no restriction **Exclusion:** • None described. **<u>Group 1: 0.5g olsalazine</u>** **Mean age (SD):** 50 (13) **Disease duration (median, range) years:** 13, 1-42 **Remission (median, range) months:** 34, 3-243 **Extent:** proctitis n=11, left sided n=30, subtotal/total n=26 **Previous relapse preventing treatment:** SASP n=47, mesalazine n=6, olsalazine n=10, none n=4 **Sigmoidoscopic grade:** 0 n=44, 1 n=23 **Severity of previous relapse:** Not described. **Frequency of relapses:** Not described.	Two tablets, taken twice daily with food. Active tablets contain 500mg of olsalazine. **Group 1: 0.5g olsalazine** N=67 (ITT) N=53 (PPA) One active tablet and 3 placebo tablets split into two sessions. **Group 2: 1g olsalazine** N=65(ITT) N=56 (PPA) One active tablet and one placebo tablet taken twice a day. **Group 3: 2g olsalazine** N=62 (ITT) N=46 (PPA) Two active tablets taken twice a day. **Concomitant therapy:** None described.	**Outcome 1: Relapse** by 12 months (ITT and PPA) Unable to calculate the hazard ratios (p values given were only for trends and it was thought it would be very inaccurate to read off the small graphs) Group 1 results have not been used in the analysis as it is lower than the BNF dose for olsalazine for the maintenance of remission.	**<u>ITT</u>** **Group 1:** 22/67 **Group 2:** 17/65 **Group 3:** 10/62	**Funding:** Financial support and help with analysing the data by Pharmacia AB, Sweden. **Limitations:** Unclear method of randomisation and allocation concealment Unclear blinding Unclear drop out rate Unclear outcome assessment **Additional outcomes:** Median time in remission before entering the trial for those with subtotal/total disease Duration of remission before the trial and relapse rates (dose appears to be less important in those with longer term remission) **Notes:** ITT life table analysis for remission curves had a p value for trend in proportions of 0.12 and for PPA it was 0.03. For extent of disease, the p values for trend for
			Outcome 2: Adverse events Group 1 results have not been used in the analysis as it is lower than the BNF dose for olsalazine for the maintenance of remission.	**<u>ITT</u>** **Group 1:** 30/67 **Group 2:** 26/65 **Group 3:** 34/62	
			Relapse by 12 months by extent of disease (PPA) Group 1 results have not been used in the analysis as it is lower than the BNF dose for olsalazine for the maintenance of	**<u>PPA</u>** **<u>Proctitis</u>** **Group 1:** 4/8 **Group 2:** 3/8 **Group 3:** 1/10 **<u>Left sided colitis</u>** **Group 1:**	

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Compliance rates: This was assessed by tablet counting and didn't exceed 25% (45 doses) in a 3 month period for any participant. N=20 dropout/ withdrawal due to AEs in the flow diagram. 32 withdrew due to AEs in the text. It is unclear.	**Drop outs:** unclear **Group 2: 1.0g olsalazine** **Mean age (SD):** 46 (123) **Disease duration (median, range) years:** 12, 1-31 **Remission (median, range) months:** 18, 3-253 **Extent:** proctitis n=8, left sided n=33, subtotal/total n=24 **Previous relapse preventing treatment:** SASP n=49, mesalazine n=7, olsalazine n=6, none n=3 **Sigmoidoscopic grade:** 0 n=45, 1 n=20 **Severity of previous relapse:** Not described. **Frequency of relapses:** Not described. **Drop outs:** unclear **Group 3: 2g olsalazine** **Mean age (SD):** 49 (12) **Disease duration (median, range) years:** 13, 1-42 **Remission (median, range) months:** 34 (3-243) **Extent:** proctitis n=11, left sided n=30, subtotal/total n=26 **Previous relapse preventing treatment:** SASP n=47, mesalazine n=6, olsalazine n=10, none n=4 **Sigmoidoscopic grade:** 0 n=44, 1 n=23 **Severity of previous relapse:** Not described. **Frequency of relapses:** Not described. **Drop outs:** unclear **Definitions** **Remission:** No clinical symptoms of active disease and no signs of active inflammation on sigmoidoscopy (grade 0: normal; 1: pink mucosa of quiescent colitis without visible vessels). **Relapse:** Increase in bowel frequency with blood or mucus and evidence of active disease on sigmoidoscopy.		remission.	13/26 **Group 2:** 7/28 **Group 3:** 6/25 **Subtotal/ total colitis** **Group 1:** 4/19 **Group 2:** 7/20 **Group 3:** 3/11	proctitis, left sided UC and subtotal/total colitis were 0.03, 0.06, and 0.37 respectively. Apart from diarrhoea/loose stools, other causes for withdrawal due to adverse events were: upper respiratory symptoms (3), abdominal pain (2), tinnitus (1), nausea (1), back pain (1) and constipation (1).
			Median time to relapse was reported but since more than 50% of patients in all of the treatment groups were still in remission when the trial ended, it can't be used to calculate the hazard ratio. Group 1: 168 days (range 25-378) Group 2: 174 days (range 14-365) Group 3: 191 days (range 50-287)		

Table 173: TRAVIS1996

Reference	Patient characteristics	Predictors & outcome measures	Effect sizes	Comments
S. P.L. Travis et al.	**Sample size:** N=51 episodes in 49 patients	**Univariate analysis results:** see the table below	**Results** 15 patients out of 51 episodes (49 patients) required a colectomy.	**Source of funding**: None described.

Reference	Patient characteristics	Predictors & outcome measures	Effect sizes	Comments
Predicting outcome in severe ulcerative colitis, *Gut;* 38: 905-910. 1996. **Type of study:** Prospective cohort **Setting:** John Radcliffe Hospital Oxford, United Kingdom **Follow up period:** Admission time for episode **Model development:** Univariate and then repeated measures analysis of variance. **Model presentation:** Sensitivity and specificity. **Model evaluation:** None reported. Externally validated in the TURNER2008 paper. **Model performance:** Calibration- Not reported Discrimination – Does not report AUC. Can calculate sensitivity and specificity.	**<5% missing data?** Yes 97% of all potential data was collected. Algorithms that allowed for occasional missing values were used, rather than exclude patients with missing data. **Type of analysis used:** Students unpaired t-test, repeated measures analysis of variance were used to assess differences between outcomes and identify trends. **Appropriate?** Yes **Inclusion criteria:** • Severe ulcerative colitis (Truelove & Witts criteria) • Diagnosis of UC was made on normal clinical, radiological and pathological criteria • Severe episode (passage of ≥6 bloody stools daily with one or more the following criteria: temperature >37.8◦C, pulse >90/min, Hb <10.5g/dl, or ESR >30mm/hr **Data collection** 51 consecutive episodes of severe colitis (Truelove & Witts) affecting 49 patients admitted to the John Radcliffe hospital in Oxford between March 1992-September 1993. **Treatment given** Standard intensive medical therapy for severe colitis. Fluid electrolyte and haemoglobin deficiencies were corrected and hydrocortisone 100mg IV six hourly, rectal hydrocortisone 100mg twice daily. This was continued for five to seven days with oral fluids until it	**Definitions of predictors:** >8 bowel actions on day 3, or with 3-8 bowel actions and a CRP>45mg/l **Routinely measured?** Yes **Outcome and definition:** Colectomy. Indications for colectomy were: failure to respond or frank deterioration during the first few days of intensive medical therapy, continued diarrhoea, abdominal tenderness or a low grade fever after intensive medical therapy, and perforation, increasing colonic dilatation or massive haemorrhage. **Blinding:** Radiologist was blinded to the outcome. **Risk of measurement error:** Low **Risk of inter-observer variability:** Low **Continuous variable analysis:** Set cut offs- CRP>45mg/l and bowel actions to >8 or 3-8. **Key prognostic factors not included?** No	Whether analysed by episode or by patient numbers, repeated measures analysis of variance over the first five days showed that the bowel frequency and CRP were significantly higher ($p<0.00625$) in patients who required colectomy than in those responding partly or completely. 5% significance between colectomy and non-colectomy groups were the following factors: • Mean pulse rate • Haemoglobin • Platelet count • Serum albumin • Orosomucoids The paper describes predicting the outcome on Day 3 to be the following: The simplest rule predicted with 85% success that patients with >8 bowel actions on day 3, or with 3-8 bowel actions and a CRP>45mg/l would need a colectomy on the same admission… four patients who would have been classified as surgical cases did not undergo colectomy that admission but required it in the following months. Three patients underwent colectomy when the rule suggested that they would not. Based on this information the sensitivity and specificity has been calculated based on the number of patients and on the number of episodes, as it was unclear in the text what the rule referred to. **Number of patients =49** **Colectomy** / **No colectomy** / **Total** **Meets rule criteria**: 11 / 4 / 15 **Does not meet rule criteria**: 3 / 31 / 34 **Total**: 14 / 35 / 49	**Risk of bias:** • Partially adequate event: covariate ratio (7-9) • No validation (done externally in another paper) **Additional outcomes reported:** Outcomes in a 12 month follow up period. **Note:** Two patients were later found out to have had Crohn's disease. It is stated in the paper that removing these two did not change the significant variables in the repeated measures analysis of variance.

<table>
<tr><th>Reference</th><th>Patient characteristics</th><th>Predictors & outcome measures</th><th>Effect sizes</th><th>Comments</th></tr>
<tr><td></td><td>was clear that the patient had responded or colectomy was needed. PTN was given to malnourished patients.
Incomplete responders: 4mg/kg/day IV ciclosporin or further IV steroids for up to six days, then converted to oral therapy(ciclosporin 5mg/kg/day and oral steroids), or referred for colectomy.
Baseline characteristics:
26 male, 23 female, age 21-77 years, median 43.
For more detailed baseline characteristics, see the table below.</td><td></td><td>Sensitivity: 78.57%
Specificity: 88.57%
PPV:77.33%
NPV:91.18%
+ve LR:6.88
-ve LR:0.24

Patient episodes =51
<table>
<tr><th></th><th>Colectomy</th><th>No colectomy</th><th>Total</th></tr>
<tr><td>Meets rule criteria</td><td>12</td><td>4</td><td>16</td></tr>
<tr><td>Does not meet rule criteria</td><td>3</td><td>32</td><td>35</td></tr>
<tr><td>Total</td><td>15</td><td>36</td><td>51</td></tr>
</table>
Sensitivity: 80%
Specificity: 88.89%
PPV:75%
NPV:91.43%
+ve LR:7.2
-ve LR:0.225</td><td></td></tr>
</table>

Table 174: Baseline characteristics/ data prior to and on admission

Variable	Responders	Incomplete responders	Colectomy	Overall
Number of episodes	21	15	15	51
Age (SD) years	46.7 (19.2)	47.5 (12.3)	43.2 (15.3)	45.9 (15.3)
First episode (%)	57	7	20	31
Previous remission (range, months)	16 (5-38)	15 (5-240)	9 (3-54)	13 (3-240)
Salicylate therapy(%)	89%	93%	83%	89%
SASP	75%	23%	60%	48%

Variable	Responders	Incomplete responders	Colectomy	Overall
Mesalazine	25%	31%	10%	23%
Olsalazine	0%	46%	30%	29%
Motions/ day (SD)	8 (2)	8 (2)	8 (3)	8 (2)
Pulse rate (SD)	106 (15)	96 (11)	101 (14)	101 (14)
Hb (g/dl) (SD)	12.6 (2.6)	11.3 (2.4)	11.2 (2.0)	11.8 (2.4)
ESR (mm/hr) (SD)	41 (25)	48 (20)	47 (28)	45 (24)
CRP (mg/l) (SD)	43 (38)*	89 (85)	116 (102)	78 (81)
Orosomucoids (mg/dl) (SD)	117 (41)	144 (55)	158 (50)	137 (50)
Truelove & Witts criteria (SD)	2.2 (1.0)	2.1 (0.8)	2.1 (1.3)	2.2 (1.0)
Extent of disease (%)				
Distal	24	20	0	16
Left-sided	19	13	20	18
Extensive	38	13	20	25
Pancolitis	19	54	60	41

Table 175: TURNER2008

Reference	Patient characteristics	Predictors & outcome measures	Effect sizes	Comments
D. Turner et al. Severe paediatric ulcerative colitis: incidence, outcomes and optimal timing for second-line therapy. *Gut;* 57: 331-338. 2008. **Type of study:** Retrospective longitudinal cohort study **Setting:** Single centre, hospital electronic database was searched	**Sample size:** N=114 children identified N=99 eligible admissions (15 excluded due to enteric infections) **<5% missing data?** Not described. Unclear. **Type of analysis used:** Assume ITT as no missing data described. Categorical (Chi- squared, Fishers), continuous (Student t test or Wilcoxon rank sum test). Unadjusted logistic regression, multi-variable regression. ROC curves. **Appropriate?** Yes	**The following indexes were reviewed:** • Travis (Oxford Index) • Lindgren (fulminant colitis index) • Seo • PUCAI (Ho index was unable to be done because colonic dilatation may be age dependent and there is no existing nomogram to standardise colonic width according to age). **Univariate analysis results:** see the	**Results** 42 (42%) required colectomy at short term follow up (2 had tacrolimus or ciclosporin prior). 53 responders: 18 weaned off steroids, 20 steroid dependent, 15 required a colectomy at 1 year follow up. Long term follow up 3 out of the remaining 38 required a colectomy. 4 responded to tacrolimus or ciclosporin of those 1 required a colectomy by 1 year follow up, 1 weaned steroids and 2 were steroid dependent. Of those remaining 3, none required a colectomy at long term follow up.	**Source of funding**: None described. **Risk of bias:** • Retrospective cohort • Partially adequate event: covariate ratio (7-9) • Unclear if missing data • 4 pts failed steroids but did not have a colectomy (indirect,

Reference	Patient characteristics	Predictors & outcome measures	Effect sizes	Comments
Greater Toronto area, Canada **Follow up period:** 1991-2000, short term (on discharge), medium (1 year) and long term (upon transfer to adult care or most recent follow up) **Model development:** Comparing different indexes. Original model is not being formed. **Model presentation:** AUC graphs. **Model evaluation:** None reported. This is evaluating other models formed. **Model performance:** Calibration- Not reported Discrimination – See Efficacy results in the table below.	**Inclusion criteria:** • 2-18 year old children • Admission to Sick Kids for initiation of treatment with IV corticosteroids • Diagnosis confirmed using established clinical endoscopic and histological criteria • First eligible admission (if had multiple admissions) **Exclusion criteria:** • Inter current enteric infection **Data collection** Hospital electronic database was searched for UC related admissions during 1991-2000 using ICD codes for UC. Charts of all the potential patients were retrieved and reviewed. All hospitalised IBD patients (<15 years) were cared for only in Sick Kids for the first 6 years, so it approximated a population cohort. Patients 15years + and all children with post codes indicating residence outside of the GTA, may have constituted a tertiary referral cohort and were excluded from the epidemiological analysis. **Treatment given:** IV corticosteroids therapy was given either as methylprednisolone 1-1.5mg/kg/day, usually up to 60mg daily in two divided doses or equivalent doses of hydrocortisone. 5-ASA was not prescribed. Antibiotics were only given to febrile patients. Second line drugs available were ciclosporin and tacrolimus. **Baseline characteristics:** IV corticosteroids response, failure for the following: Males: 26/53, 21/46 Age: 11.5 (SD 4.1), 11.6 (SD 4.5)	table below. **Definitions of predictors:** See individual index papers. **Routinely measured?** Yes **Outcome and definition:** IV corticosteroid failure (colectomy or second line therapy) by discharge. **Blinding:** Paediatric radiologists were blinded to the clinical and outcome data when reviewing plain abdo radiographs. **Risk of measurement error:** Low. **Risk of inter-observer variability:** Low. **Continuous variable analysis:** Yes then made into categorical variables, see the tables below. **Key prognostic factors not included?** No	The paper describes: The third day of corticosteroid therapy may serve as a screening day to identify non-responders, hence high sensitivity is desired to prepare selected patients for second line therapies. By the fifth day second- line therapy may be executed and thus high specificity is required. The cut offs were chosen to reflect this (apart from Travis which is designed as a fixed dichotomous rule at day 3). See table below. **For the results of the sensitivity, specificity and area under the curve, see the results tables below.**	<10%) **Additional outcomes reported:** None

Reference	Patient characteristics	Predictors & outcome measures	Effect sizes			Comments
	Disease duration: 1.8 (0-13.6), 6.1 (0.2-19) Disease extent: left sided 6/53, 4/46, extensive 47/53, 42/46 Steroid dose (mg/kg/day): 0.94 (0.8-1.4), 1.05 (0.83-1.5) PUCAI at admission: 67 (SD 13.8), 74 (SD9.5) Moderate: 18/53, 7/46 Severe: 35/53, 39/46					

Table 176: Univariate analyses – statistically significant results at Day 3

Variable	IV corticosteroid response (N=53)	IV corticosteroid failure (N=46)	Odds ratio (95% CI)
Nocturnal diarrhoea (episodes/per night)			20.6 (4.9 to 87)
None	25 (47%)	2(4%)	
1-2	28 (53%)	30 (65%)	
>2	0 (0%)	14 (31%)	
Stools per 24h			4.2 (4.3 to 7.7)
0-2	22 (42%)	4 (9%)	
3-5	25 (47%)	14 (30%)	
6-8	5 (9%)	14 (30%)	
>8	1 (2%)	14 (30%)	
Blood in stool			3.5 (1.8 to 7.1)
None or small amount infrequently	10 (19%)	2 (4%)	
Small amount in majority of stools	24 (45%)	10 (22%)	
large amount it the majority of stools	19 (36%)	34 (74%)	
PUCAI score	50 (SD 17)	70 (SD14)	2.2 (1.5 to 3.1)
Seo score	194 (SD34)	226 (SD30)	1.4 (1.2 to 1.6)
Lindgren score	4.2 (SD 2.3)	9.4 (SD4.3)	1.6 (1.3 to 1.9)
Travis score			31 (3.9 to 666)
Positive	0 (0%)	17 (38%)	

Variable	IV corticosteroid response (N=53)	IV corticosteroid failure (N=46)	Odds ratio (95% CI)
Negative	53 (100%)	29 (62%)	
Albumin	33 (SD 5.7)	30 (SD 4.4)	0.53 (0.4 to 0.80)
CRP (mg/dl)	0.71 (SD 0.53)	1.87 (SD 1.57)	6.2 (2.6 to 14.9)
ESR	38 (SD 22)	50 (SD25)	1.3 (1.03 to 1.5)

(a) Non significant variables: temperature (>37.8 degrees), abdominal tenderness, haemoglobin and platelets.
(b) The same variables were statistically significant at day 5.

Table 177: Diagnostic utility of indices on days 3 and 5 of therapy in predicting short-term IV steroid failure

Day and index	Cut-off	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	+ likelihood ratio	- likelihood ratio	Area under the curve
Day 3								
Lindgren	>4	91 (81 to 97)	57 (48 to 62)	65 (58 to 69)	88 (74 to 96)	2.1	0.16	0.85 (0.77 to 0.93)*
Seo	>195	91 (81 to 97)	43 (34 to 48)	59 (52 to 62)	85 (67 to 95)	1.6	0.2	0.77 (0.67 to 0.87)
Lindgren	>8	64 (54 to 70)	92 (83 to 97)	88 (74 to 96)	75 (67 to 79)	8.2	0.4	0.85 (0.77 to 0.93)*
Travis	-	38 (30 to 40)	100 (93 to 100)	88 (74 to 96)	75 (67 to 79)	8.2	0.4	-
Day 5								
Lindgren	>9	36 (27 to 38)	98 (89 to 100)	94 (72 to 100)	60 (55 to 62)	16	0.7	0.87 (0.79 to 0.94)
Seo	>240	27 (18 to 32)	93 (85 to 98)	80 (54 to 95)	56 (51 to 59)	4	0.8	0.78 (0.69 to 0.88)
Travis	-	22 (14 to 24)	100 (91 to 100)	99 (67 to 100)	56 (52 to 56)	10.2	0.8	-

*(a) * it is unclear in the paper whether it uses the cut-off of >4 or >8 in the AUC comparison.*
(b) Unable to calculate Travis AUC due to it being a categorical variable.

Table 178: VAN2003

Author	Patients	Intervention	Outcome measures	Effect size	Comments
G. Van Assche et al. Randomised, double-blind comparison of 4 mg/kg versus 2 mg/kg intravenous cyclosporin in severe ulcerative colitis. *Gastroenterology; 125: 1025-1031. 2003.* **REF ID: VAN2003** **Study design and quality:** Double blind RCT Single centre, Belgium **8 days (primary end point)** **Randomisation:** Not stated **Allocation concealment**: Not stated **Blinding:** Double blind (not for serum creatinine or blood pressure) **Outcome assessment:** CAI. Endoscopy assessment using the Mayo scoring system. **Sample size calculation:** α 0.05 80% power **Type of analysis ITT**	**<u>All patients:</u>** **N=73 randomised** **N=73 ITT** **Drop-outs** (don't complete the study): N=1 (1.37%) **Inclusion criteria:** Patients aged 18 to 70 yrs with an attack of severe ulcerative colitis as defined by a score of 10 or more in the Lichtiger clinical activity index (Lichtiger-modified Truelove and Witts criteria) **Exclusion:** Plain abdominal x-ray was done to exclude toxic megacolon or perforation. A stool culture was obtained including ova/parasites and a specific determination of C difficile toxin. If a microbial or parasitic enteric pathogen was found, patients were not eligible. Other criteria for exclusion included renal insufficiency with a serum creatinine of more than 2 mg/dL, elevation of liver enzymes or bilirubin (< 2 times upper limit of normal), serum cholesterol below 150 mg/dL, uncontrolled hypertension, active viral or bacterial infections, and pregnancy **<u>Group 1: 4 mg/kg</u>** **Mean age (SD):** 39 (14) **Extent:** % pancolitis 42% **Male/female** 21/17 **Mean clinical activity index and DO 13** (range 10 to 17) **Concomitant steroids** 55.2% **Concomitant azathioprine** 21.0% **Drop outs:** 1/38 (anaphylactic reaction immediately after starting the infusion)	**Group 1: 4 mg/kg** N=38 randomised N=38 (ITT) N=37 (completers) Continuous 24-hour infusion of Sandimmune ciclosporin-a; Novartis. From days 1 through day 8, patients were treated with continuous ciclosporin infusions. Dose was changed to achieve blood levels between 250 and 350 ng/mL. On day 8, all responding patients were switched to 8 mg/kg oral ciclosporin and fasted blood levels were maintained between 150 and 300 ng/mL in both groups for 3 months. Non-responding patients were offered to enter an open-phase treatment arm with 4 mg/kg IV ciclosporin for a maximum of 8 additional days. Prophylaxis with sulfamethoxal/trimethoprim 800/160 for the prevention of Pneumocystis pneumonia was started on day 8 and continued until the end of Neural (Novartis) therapy	Outcome 1: **Clinical improvement** (Clinical response) **:** A score of less than 10 on day 8 with a drop of ≥ 3 as compared with baseline	**0- ≤2 weeks** **4 mg/kg:** 32/38 **2 mg/kg:** 30/35	**Funding:** Not reported **Limitations:** Unclear method of randomisation and allocation concealment **Additional outcomes:** Clinical activity index score Median time to response Ciclosporin blood levels
			Outcome 2: **Adverse events** Number of patients experiencing one or more AEs not reported: The adverse events reported were: **4 mg/kg:** Neurological 3/38 Novel cases of hypertension 9/38 Increase serum creatinine (> 10%) 7/38 Fever 3/38 Diabetes mellitus 1/38 Anaphylatic reaction 1/38 **2 mg/kg:** Neurological 2/35 Novel cases of hypertension 3/35 Increase serum creatinine (> 10%) 6/35 Fever 1/35 Diabetes mellitus 0/35		

Author	Patients	Intervention	Outcome measures	Effect size	Comments
N=1 (4 mg) dropout/ withdrawal due to drug related AEs.	**Group 2: 2 mg/kg** **Mean age (SD):** 41 (14) **Extent:** % pancolitis 48% **Male/female** 21/14 **Mean clinical activity index and DO 11** (range 10 to 16) **Concomitant steroids** 60.0% **Concomitant azathioprine** 25.7% **Drop outs:** 0/35	**Group 2: 2 mg/kg** N=35 randomised N=35 (ITT) N=35 (completers) 2 mg/kg ciclosporin to achieve blood levels between 150 and 250 ng/mL. Details as for 4 mg/kg group **Concomitant therapy:** Intravenous corticosteroids were allowed if given prior to enrolment at a stable dose for at least 5 days without clinical response and were kept stable until day 8 of the trial. Patients on oral corticosteroids were eligible if they had been started at least 14 days from inclusion without clinical benefit. Oral corticosteroids were discontinued on day 1, and patients converted to iv steroids. At day 8, patients' conversion to oral steroids was again performed, and steroids were tapered by 5 mg of prednisolone (or equivalent) per week, Azathioprine or 6-mercaptopurine was allowed if they had been started at least 3 months prior to inclusion and the dose had not been changed in the 4 weeks before admission. In those patients, doses were kept stable throughout the study. In all other patients, azathioprine 2.0 to 2.5 mg/kg was initiated at day 8			

Author	Patients	Intervention	Outcome measures	Effect size	Comments
		and continued with regular monitoring for toxicity. Oral mesalamine or sulphasalazine was maintained at stable doses, and rectal mesalamine was also maintained at identical doses for the first 8 days, provided the patient was able to retain the enema. Patients receiving antibiotics at inclusion were continued on the antibiotics if judged clinically necessary, and, during the study, institution of antibiotics was only allowed for intercurrent infections.			

Table 179: VANBODEGRAVEN1996

Author	Patients	Intervention	Outcome measures	Effect size	Comments
A. A. Van Bodegraven et al. Distribution of mesalazine enemas in active and quiescent ulcerative colitis. *Alimentary Pharmacology & Therapeutics; 10: 327-332. 1996.* **REF ID: VANBODEGRAVEN1996** **Study design and quality:** Single blind RCT **12 week trial** **Randomisation:** No details given. Unclear. **Allocation concealment**: Unclear	**<u>All patients:</u>** **N=31 randomised** **N=X ITT** **Drop-outs** (don't complete the study): N=5 (16%) **Inclusion criteria:** • Outpatients • Extent: Not described • Severity: mild/moderate disease, 5-15 points on the Lennard-Jones DAI **Exclusion:** • Bacterial colitis • Inability to retain enemas	**Group 1: 1.5g oral mesalazine and 1g mesalazine liquid enema** N=9 randomised 1.5g mesalazine given orally (500mg x3 Salofalk) and 1g mesalazine (Pentasa) in 100mls liquid enema. **Group 2: 1.5g oral mesalazine and 2g mesalazine liquid enema** N=10 randomised 1.5g mesalazine given	**Outcome 1: Colectomy** **Outcome 2: Adverse events** None reported.	**Group1:** 0/9 **Group 2:** 1/10 **Group 3:** 2/12	**Funding:** Tramedico BV, Weesp, the Netherlands **Limitations:** Single blind Unclear method of randomisation and allocation concealment Limited baseline characteristics **Additional outcomes:** Endoscopic remission (not defined therefore has not been included in the

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Blinding: Single investigator blind **Outcome assessment:** Lennard Jones criteria. **Sample size calculation:** Not described. **Type of analysis: ITT, PPA** **Compliance rates:** Not described. N=0 dropout/ withdrawal due to drug related AEs.	• Previous colon surgery • Hypersensitivity to mesalazine or enema compounds • Use of Loperamide or erythromycin **Baseline characteristics** **Group 1: 1.5g Oral mesalazine and 1g rectal mesalazine** **Sex (m/f):** 5/4 **Mean age (no SD given):** 45 **Endoscopic score, median (range):** 7 (6-11) **Extent:** sigmoid n=5, descending colon n=1, pancolitis n=3 **Drop outs:** 1 (needed IV steroids to obtain remission) **Group 2: 1.5g Oral mesalazine and 2g rectal mesalazine** **Sex (m/f):** 3/7 **Mean age (no SD given):** 40 **Endoscopic score, median (range):** 8 (6-14) **Extent:** sigmoid n=5, descending colon n=3, pancolitis n=2 **Drop outs:** 1 (colectomy due to intractable colitis **Group 3: 1.5g Oral mesalazine and 4g rectal mesalazine** **Sex (m/f):** 6/6 **Mean age (no SD given):** 46 **Endoscopic score, median (range):** 8 (5-12) **Extent:** sigmoid n=4, descending colon n=4, pancolitis n=4 **Drop outs:** 3 (2 colectomies due to progressive colitis and a polyp which proved to be an adenocarcinoma, 1 needed additional steroid therapy)	orally (500mg x3 Salofalk) and 2g mesalazine (Salofalk) in 30mls liquid enema. **Group 3: 1.5g oral mesalazine and 4g mesalazine liquid enema** N=12 randomised 1.5g mesalazine given orally (500mg x3 Salofalk) and 4g mesalazine (Salofalk) in 600mls liquid enema. **Concomitant therapy:** See exclusion criteria. No other information given.			review) Scintigraphic findings

Table 180: VECCHI2001

Author	Patients	Intervention	Outcome measures	Effect size	Comments
M. Vecchi et al. Oral versus combination mesalazine therapy in active ulcerative colitis: a double-blind, double-dummy, randomized multicentre study.	**All patients:** **N=130 randomised** **N=X ITT** **Drop-outs** (don't complete the study):	**Group 1: 2g oral mesalazine (Salofalk) and placebo enema** N=67 randomised 500mg mesalazine	**Outcome 1: Clinical remission** (CAI<4) **Outcome 2: Clinical improvement**	**Group1:** 55/67 **Group 2:** 55/63 **Group1:**	**Funding:** Ravizza Farmaceutici SpA, Muggio, Italy. **Limitations:**

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Alimentary Pharmacology and Therapeutics. 15: 251-256. 2001. **REF ID: VECCHI2001** **Study design and quality:** Double blind, double dummy RCT Multicentre: 15 centres, Italy **6 week trial** **Randomisation:** Carried out in blocks of 4, using a single centralized computer generated randomization list. **Allocation concealment**: Centralised computer allocation. **Blinding:** Double blind, double dummy. Identical appearance of the active drugs and placebo. Codes were in enclosed envelopes which were only opened in the occurrence of a severe AE. **Outcome assessment:** Clinical activity index. Endoscopic index according to Rachmilewitz. **Sample size calculation:** 30% remission in the oral alone group, 65% in the combination group. 65 patients per group. A error of 0.05. **Type of analysis: ITT, PPA**	N=23 (17.7%) <10% difference between the two treatment arms. **Inclusion criteria:** • 18-75 years • Extent: Not proctitis • Severity: Mild to moderate UC, CAI 4-12. **Exclusion:** • Proctitis (colonic involvement <15cm) • Gastrointestinal infection • Current or recent (<30 days) steroid or immunosuppressive treatment • Mesalazine intolerance • Serious concurrent diseases • Pregnancy or lactation **Baseline characteristics** **Group 1: Oral & rectal mesalazine** **Sex (m/f):** 38/25 **Mean age (SD):** 43.5 (13), range 22-77 **Disease duration mean (SD):** 72 (67) **Extent:** proctosigmoiditis n=43, left colon n=17, ascending + transverse n=3 **Mean CAI (SD):** 5.8 (1.4) **Mean EI (SD):** 10.2 (5.0) **Drop outs:** 10 (1 AEs, 6 poor compliance, 3 lack of efficacy) **Group 2: Oral mesalazine & placebo enema** **Sex (m/f):** 38/29 **Mean age (SD):** 43 (14), range 21-74 **Disease duration mean (SD):** 74 (75) **Extent:** proctosigmoiditis n=33, left colon n=17, ascending + transverse n=17 **Mean CAI (SD):** 6.0 (1.8) **Mean EI (SD):** 13.5 (7.6) **Drop outs:** 13 (1 AEs, 10 poor compliance, 2 lack of efficacy)	(Salofalk) tablets, 4 taken twice a day (total 2g/day) and a placebo enema given at bedtime. **Group 2: 2g oral mesalazine and 2g rectal mesalazine (Salofalk)** N=63 randomised 500mg mesalazine (Salofalk) tablets, 4 taken twice a day (total 2g/day) and a 2g/60mls liquid mesalazine (Salofalk) enema given at bedtime. **Concomitant therapy:** See exclusion criteria. No other information given.	(Reduction in CAI of 50% from baseline) **Outcome 3: Endoscopic remission** (EI <4) **Outcome 4: Adverse events**	57/67 **Group 2:** 57/63 **Group1:** 36/62 **Group 2:** 41/58 **Group 1:** 5/67 **Group 2:** 4/63	**Additional outcomes:** Mean time to clinical remission/ improvement Clinical and endoscopic remission (post-hoc analysis, therefore has not been included in the review) Extent of disease (post hoc analysis)

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Compliance rates: No definition given. 16 dropped out because of poor compliance. N=2 dropout/ withdrawal due to AEs, unclear if drug related. 1 in each treatment group (headache & fever, and flu-like syndrome)					

Table 181: WILLIAMS1987

Author	Patients	Intervention	Outcome measures	Effect size	Comments
C. N. Williams et al. Double-Blind, Placebo-Controlled Evaluation of 5-ASA Suppositories in Active Distal Proctitis and Measurement of Extent of Spread Using 99mTc-Labeled 5-ASA Suppositories. *Digestive Diseases and Sciences;32 (12): 71S-75S. 1987.* **REF ID: WILLIAMS1987** **Study design and quality:** Double blind RCT Canada **6 week trial** **Randomisation:** Not described. Unclear. **Allocation concealment**: Not described. Unclear.	**<u>All patients:</u>** **N=27 randomised / ITT** **Drop-outs** (don't complete the study): N=2 (7.4%) (Both were in the placebo group (1 dropped out at 3 weeks, the other tested positive for salmonella) **Inclusion criteria:** • ≥18 years old • Extent: Distal proctitis (≤15cm on sigmoidoscopy) • Severity: Minimum score of 3 derived from two categories in the DAI • Unresponsive to standard therapy (SASP +/- oral prednisone or betamethasone enemas) or newly referred patients **Exclusion:** • Pregnancy • Diverticulitis • Positive stool culture • Taken 4ASA or 5ASA within 48 hrs or rectal steroids within 14 days of entry • Salicylate allergy	**Group 1: 1.5g of 5-ASA suppositories** N=14 randomised/ ITT One 5-ASA suppository (500mg) three times a day. Type of 5-ASA not described. **Group 2: Placebo suppositories** N=13 randomised/ ITT N=11 (completers) One placebo suppository three times a day. **Concomitant therapy:** If the patient was taking	Outcome 1: **Clinical and endoscopic remission** (DAI score of 0) **No adverse events were reported in either group**	**<u>ITT analysis</u>** **<u>Week 3</u>** **Group1:** 5/14 (35.7%) **Group 2:** 0/13 (0%) **<u>Week 6</u>** **Group1:** 11/14 (78.6%) **Group 2:** 1/13 (7.7%)	**Funding:** None described. **Limitations:** Unclear method of randomisation and allocation concealment Double blind, limited information described **Additional outcomes:** Blood test results Mean DAI scores

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Blinding: Stated to be double blind. Drugs dispensed in a double blind fashion. No other details given. **Outcome assessment:** Disease Activity Index **Sample size calculation:** Not described. **Type of analysis: ITT analysis** **Compliance rates:** Not described N=0 dropout/ withdrawal due to drug related AEs.	• Clinically significant liver or kidney dysfunction • History of previous bowel resection **Baseline characteristics** **Group 1: 5-ASA suppositories** **Mean age (SD):** 37.3 (14.5) **Sex M/F:** 8/6 **Extent, mean:** women 9.3cm, men 9.6cm **Concurrent SASP or oral prednisone:** 9 **DAI, mean (SD):** 7.1 (1.8) **Drop outs:** 0 **Group 2: Placebo suppositories** **Mean age (SD):** 42.7 (11.2) **Sex M/F:** 9/4 **Extent, mean:** women 10.5cm, men 9.3cm **Concurrent SASP or oral prednisone:** 6 **DAI, mean (SD):** 7.4 (1.8) **Drop outs:** 2	oral sulphasalazine or prednisone the dose was maintained throughout the trial.			

Table 182: WILLOUGHBY1986

Author	Patients	Intervention	Outcome measures	Effect size	Comments
C. P. Willoughby et al. 5-aminosalicylic acid (Pentasa) in enema form for the treatment of active ulcerative colitis. *Italian Journal of Gastroenterology; 18: 15-17. 1986.* **REF ID: WILLOUGHBY1986** **Study design and quality:**	**All patients:** **N=37 randomised/ ITT** **Drop-outs** (don't complete the study): N=3 (8.1%) Difference between both arms <10%. **Inclusion criteria:** • Extent: All patients had a form of the disease which did not extend beyond the splenic flexure (assessed by sigmoidoscopy and radiology) apart from 4 oxford patients where it extended to the	**Group 1: 1g Pentasa liquid enema** N=19 randomised/ITT N=18 (completers) 1g of 5-ASA (Pentasa) in 100mls liquid enema, given once a day. **Group 2: Placebo**	**Outcome 1: Adverse events** There was also data on a 'response'. This was not included as clinical improvement data because it could have been due to an improvement in either clinical symptoms, grading of sigmoidoscopic or histological appearances and so was not specifically clinical/ symptomatic improvement.	**Group1:** 0/19 **Group 2:** 2/18	**Funding:** Ferring A. S. Denmark supplied the enemas. A representative from Nordic Pharmaceuticals gave help and advice. **Limitations:** Unclear method of randomisation and allocation concealment

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Double blind RCT Multicentre: 2 centres, United Kingdom and Italy **2 week trial** **Randomisation:** Restricted to blocks of 4, to ensure approx. equal arm numbers. No further information was given. **Allocation concealment**: No information given. Unclear. **Blinding:** Double blind. Enemas had the same appearance. **Outcome assessment:** sigmoidoscopy according to Dick et al. Patients symptoms were recorded. **Sample size calculation:** None described. **Type of analysis: Completers analysis** **Compliance rates:** Not described N=0 dropout/ withdrawal due to drug related AEs.	hepatic flexure) • Severity: mild to moderate **Exclusion:** • None described **Baseline characteristics** **Group 1: 1g mesalazine (Pentasa)** **Sex (m/f):** Oxford 8/4, Bologna 2/5 **Mean age (SD):** Oxford 42.0 (12.5), Bologna 39.2 (7.4) **First attacks:** Oxford n=2, Bologna n=0 **No. receiving maintenance SASP:** Oxford n=7, Bologna n=5 **Extent:** Not described **Drop outs:** 1(patient noted discoloration of the enema) **Group 2: Placebo** **Sex (m/f):** Oxford 4/7, Bologna 3/4 **Mean age (SD):** Oxford 48.9 (12.9), Bologna 35.8 (7.1) **First attacks:** Oxford n=1, Bologna n=1 **No. receiving maintenance SASP:** Oxford n=6, Bologna n=3 **Extent:** Not described **Drop outs:** 2(due to rash and polyarthropathy, and diarrhoea and bleeding)	N=18 randomised/ ITT N=16 (completers) Placebo enema (100mls) given once a day. **Concomitant therapy:** No patients were receiving oral or topical corticosteroids. Patients already taking sulphasalazine on entry continued to do so during the trial.			No baseline data on extent or severity Double blind, no further information given **Additional outcomes:** Response **Notes:** Some patients were also on oral SASP.

Table 183: WRIGHT1993

Author	Patients	Intervention	Outcome measures	Effect size	Comments
J. P. Wright et al.	**All patients:**	**Group 1: Olsalazine 2g**	**Outcome 1: Relapse**	**At 12**	**Funding:**

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Olsalazine in Maintenance of Clinical Remission in Patients with Ulcerative Colitis. *Digestive Diseases and Sciences; 38 (10): 1837-1842. 1993* **REF ID: WRIGHT1993** **Study design and quality:** Double blind RCT **12 month trial** **Randomisation:** Stratified into patients with limited colitis (proctitis and left sided colitis) and patients with extensive colitis. Unclear method. **Allocation concealment**: Unclear. **Blinding:** Says double blind but no further information was given. **Outcome assessment:** Clinical activity was assessed by the Harvey Bradshaw Index. Biopsies were reviewed and graded by a single pathologist. Sigmoidoscopy was grade from minimal to severe looking at exudates, erythema, texture and bleeding. **Sample size calculation:** None described. **Type of analysis: ITT**	**N=101 randomised** **Drop-outs** (don't complete the study): Unclear N=17 (17%) <10% difference in missing data between treatment arms **Inclusion criteria:** • Inactive UC diagnosed by the Truelove & Witts criteria • Asymptomatic (formed stool with no blood or mucus) for not less than one week and not more than one month prior to entry into the study. • Extent: no restrictions described **Exclusion:** • <18 years old or >75 years • History of allergy to sulphonamides or salicylates. **<u>Group 1: 2g olsalazine</u>** **Mean age (SD):** 39.8 (14.6) **Extent:** proctitis/ left sided colitis n=39, extensive colitis n=10 **Mean number of months since diagnosis (SD):** 50.4 (68.6) **Mean number of months since last attack (SD):** 2.8 (2.9) **Mean number of months since last symptom (SD):** 0.5 (0.2) **Therapy of last attack:** oral prednisolone n=10, methylprednisolone enemas n=34, both oral and rectal corticosteroids n=5 **Severity of previous relapse:** Not described **Frequency of relapses:** Not described **Drop outs:** 12 (8 drug related diarrhoea. 4 AEs). **<u>Group 2: Placebo</u>** **Mean age (SD):** 44.6 (13.2) **Extent:** proctitis/ left sided colitis n=42, extensive colitis n=10 **Mean number of months since diagnosis (SD):** 54.5 (65.1) **Mean number of months since last attack (SD):** 3.1 (2.9) **Mean number of months since last symptom (SD):** 0.5 (0.2) **Therapy of last attack:** oral prednisolone n=17, methylprednisolone enemas n=28, both oral and rectal corticosteroids n=5 **Severity of previous relapse:** Not described	N=49 randomised 500mg of olsalazine taken four times a day. Total dose of 2g/day. **Group 2: Placebo** N=52 randomised One placebo tablet taken four times a day. **Concomitant therapy:** None described.		**<u>months</u>** **Group1:** 19/49 **Group 2:** 31/52 Life table analysis p=0.024	Supported by Pharmacia Leo Therapeutics AB, Sweden. **Limitations:** Unclear method of randomisation and allocation concealment Double blind but no further information given **Additional outcomes:** Deterioration in rectal mucosa (index changes) Changes in histological assessments. Remission Results for limited and extensive disease **Note:** Median time to relapse **Group1:** 342 days **Group 2:** 100 days The longer remission rate was not significant when the patients were split by disease extent.
			Outcome 2: Adverse events 8 patients in the olsalazine group had drug related diarrhoea, 1 psoriasis flare up, 1 cardiac failure, 1 impotence, and 1 breast fed baby vomited. 1 patient in the placebo group had drug related diarrhoea and 1 patient developed a skin rash.	**Group1:** 12/49 **Group 2:** 2/52	
			Note: Drug related diarrhoea was greater in extensive disease. Extensive disease: n=6/10 olsalazine and n=1/10 placebo group Limited disease: n=2/39 olsalazine and 0/42 placebo		

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Compliance rates: Approximately 88% of the tablets were taken during the trial by both groups. N=9 dropout/ withdrawal due to drug related AEs.	**Frequency of relapses:** Not described **Drop outs:** 5 (1 drug related diarrhoea, 1 lost to follow up, 1 non compliance, 1 protocol exclusion, 1AE). Severity was similar in the two groups at baseline with a score of <2 for the Harvey Bradshaw Index. **Definitions** **Relapse:** Relapse of diarrhoea (with or without blood and mucus) though by the attending physician to warrant introduction of rectal or oral corticosteroids. In view of the expected diarrhoea frequency of approximately 6.3% in patients taking olsalazine, contingency plans were drawn up for these patients: "If an increase in diarrhoea frequency occurred one to two days after treatment was initiated, medication was halved for three days. If the diarrhoea settles to the pre-trial frequency the dose of medication was increased over seven day. If diarrhoea was disabling or persisted despite reduction in dose, and there were no signs on sigmoidoscopy of active UC, the patient was withdrawn and considered to have drug induced diarrhoea."				

Table 184: YOKOYAMA2007

Author	Patients	Intervention	Outcome measures	Effect size	Comments
H. Yokoyama et al. Effect of Weekend 5-Aminosalicylic Acid (Mesalazine) Enema as Maintenance Therapy for Ulcerative Colitis: Results from a Randomized Controlled Study. *Inflammatory Bowel Disease; 13 (9): 1115-1120. 2007.* **REF ID: YOKOYAMA2007** **Study design and quality:**	**All patients:** Production problems with the rectal enema led to slow recruitment. **N=24 randomised** (study stopped after 24 patients enrolled due to interim analysis showing a significant benefit of the weekend 5-ASA group. **N=24 ITT** **Drop-outs** (don't complete the study): N=0 (0%) **Inclusion criteria:**	**Group 1: Oral mesalazine (3g), 2 days rectal mesalazine (1g/day)** N=11 randomised 1g mesalazine (Pentasa) enema once a day at the weekend and 3g oral mesalazine (Pentasa) taken daily.	Outcome 1: **Relapse rates** Stratified analysis could not be done due to the small numbers Covariates- age, sex, CAI score at baseline. Outcome 2: **Adverse events**	**Group1:** 2/11 **Group 2:** 10/13 **Multivariate Hazard ratio** (95% CI): 0.19 (0.04, 0.94)	**Funding:** None described. **Limitations:** Unclear method of randomization Open study **Additional outcomes:** Mean CAI

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Open label RCT 2 centres, Japan **2 year trial which was stopped at a mean 305 days (SD 162)** **Randomisation:** Blind and independent randomization. Block size of 10. Stratified by disease extent, clinical course (relapse rate). No other information given. **Allocation concealment**: Independent third party. Adequate. **Blinding:** No blinding, open. **Outcome assessment:** CAI, laboratory tests. Endoscopy assessment according to Baron et al. **Sample size calculation:** 30% difference in relapse, 0.05 significance with 90% power, 100 patients per arm. **Type of analysis: ITT** **Compliance rates:** Detailed study history during a personal interview as well as a review of the daily medication recorded on the diary cards. N=0 dropout/ withdrawal due to drug related AEs.	• Patients had been induced into a phase of clinical remission • Diagnosis and activity was based on standard clinical endoscopic and histological criteria **Exclusion:** • Patients receiving oral maintenance treatment with sulfasalazine • Severe renal/ hepatic impairment • Malignant disease • Allergy to salicylates • Alcoholism • Drug addiction • Any other disease or condition that might interfere with the study assessments • Participation in another clinical study in the previous 30 days • Women of child-bearing age who were not using an effective method of contraception • Pregnancy • Lactation • Established low compliance for 5-ASA enema as judged by the investigator • Infective colitis • Topical prednisolone • Daily dose of prednisolone >20mg • Use of 5-ASA enemas more than twice a week **<u>Group 1: 3g mesalazine and 1g rectal enema at the weekends</u>** **Mean age (SD):** 36.2 (11.88) **Clinical course:** High relapse rate n=4, low n=4, first attack n=3 **Extent:** total colitis n=4, left sided colitis n=7, proctitis n=0 **Mean CAI (range):** 0.50 (0-2) **Severity of previous relapse:** Not described. **Induction therapy:** prednisolone n=7, 5-ASA enema n=3, ciclosporin n=1 **Drop outs:** 0 **<u>Group 2: 3g mesalazine</u>** **Mean age (SD):** 38.5 (13.91)	**Group 2: Oral mesalazine (3g)** N=13 randomised 3g mesalazine (Pentasa) taken once a day orally. **Concomitant therapy:** If cyclosporine had been used to induce remission the dose was 2-4mg/kg/day for 14 days then a maintenance dose of azathioprine 50mg/day was permitted. Immunosuppressive and antidiarrheal agents continued at the same dosed as before relapse. Medication not permitted in addition to the exclusion criteria were: Antibiotics or any other type of enema In all cases remission was evaluated between 1 week and 1 month after decreasing and/or stopping such medications. Patients fulfilling the entry criteria were enrolled	None were reported in either group to have drug related adverse events.		Mean EI Mean CRP. ESR

Author	Patients	Intervention	Outcome measures	Effect size	Comments
	Clinical course: High relapse rate n=5, low n=5, first attack n=3 **Extent:** total colitis n=6, left sided colitis n=6, proctitis n=1 **Mean CAI (range):** 0.42 (0-2) **Severity of previous relapse:** Not described. **Induction therapy:** prednisolone n=9, 5-ASA enema n=4 **Drop outs:** 0 **Definitions** **Remission:** Absence of symptoms and a score of <4 on the CAI. **Relapse:** Score of 6 or higher on the CAI and >3 in the endoscopic index (EI). Even if the CAI score was lower than 6, the additional use of any medicine was considered a relapse since corticosteroids, antibiotic drugs, immunosuppressive agents, antidiarrhoea agents and also 5-ASA enemas more than twice a week could influence the activity of UC. Patients in whom the dose of corticosteroids could not be decreased were also considered as having relapsed.	within 1 month from the time of remission.			

Table 185: ZINBERG1990

Author	Patients	Intervention	Outcome measures	Effect size	Comments
.J. Zinberg et al. Double-Blind Placebo-Controlled Study of Olsalazine in the Treatment of Ulcerative Colitis. *The American Journal of Gastroenterology; 85 (5): 562-566. 1990.* **REF ID: ZINBERG1990** **Study design and quality:** Double blind RCT It is unclear which country the trial was carried out in (authors origin was the United States) **4 week trial**	**All patients:** **N=15 randomised** **Drop-outs** (don't complete the study): N=6**(40%)** **Inclusion criteria:** Male or female 18-75 years old Newly diagnosed or relapse Extent: disease involvement of 15cm or more above the anal verge, as defined by flexible sigmoidoscopy or colonoscopy Severity: mild to moderate ulcerative colitis with visible blood in the	**Group 1: 3g Olsalazine** N=7 randomised N=5 (completers) 250mg capsules. 12 taken per day; 3 capsules with each meal and 3 at bedtime. Total dose 3g. **Group 2: Placebo** N=8 randomised N=4 (completers) 12 capsules of placebo.	Outcome 1: **Clinical improvement** (assessed in terms of the clinical evaluations) Although there is no specific definition, this study has been included because the Cochrane Systematic review on Oral ASAs included it as an 'author defined' outcome. Outcome 2: **Adverse events** Two patients withdrew due to watery diarrhoea. Five patients had minor side effects which included; transient diarrhoea (3), transient rash (3),	**Group1:**4/7 **Group 2:**2/8	**Funding:** Olsalazine was provided by Pharmacia. They also 'supported in part'. **Limitations:** Inadequate randomisation Unclear allocation concealment Very high dropout rate No detail on double blinding Unclear how valid and accurate the scoring system

Author	Patients	Intervention	Outcome measures	Effect size	Comments
Randomisation: Inadequate- Alternate basis between the drug and placebo. It was carried out by Pharmacia. Patients with a history of SASP intolerance were separately randomised. **Allocation concealment**: Unclear **Blinding:** Double blind. **Outcome assessment:** Endoscopy looked at ulceration, friability, erythema and exudates, each on a 0-3 scale. A patient diary was used to record clinical symptoms. **Sample size calculation:** None described. **Type of analysis: ITT** **Compliance:** Assessed by pill counts. No patient missed more than 3 doses during the study period. N=2 dropout/ withdrawal due to AEs. As it resolved on stopping the olsalazine it could be drug related.	stool **Exclusion:** Use of oral or rectal steroids within 1 week of entry into the study Use of immunosuppressant's within 1 month of entry into the study History of allergy to salicylates History of colorectal cancer Severe cardiac, renal, pulmonary or hematologic disorders **Group 1: 3g Olsalazine** **Mean age (SD):** 37 (no SD given) **Extent:** distal n=5, left sided n=2 **Sulfasalazine intolerant:** n=1 **Mean bowel movements per day:** 4.9 **Mean colonoscopic score:** 7.6 **Drop outs:** 2 due to developing severe watery diarrhoea. **Group 2: Placebo** **Mean age (SD): 56** (no SD given) **Extent:** distal n=6, left sided n=2 **Sulfasalazine intolerant:** n=1 **Mean bowel movements per day:** 4.8 **Mean colonoscopic score:** 6.5 **Drop outs:** 4 due to worsening of UC	3 placebo capsules taken with each meal and at bedtime. They were identical in appearance to the olsalazine tablet. **Concomitant therapy:** 3 days prior to participation SASP, antidiarrheal agents, antispasmodics and anticholinergics were discontinued. Medication that was not permitted included: NSAIDs, salicylates, digitalis derivatives, tranquilizers and antidepressants.	transient flare of acne (2), recurrent anxiety attacks (1). It is unclear which groups these patients were in, so the data could not be analysed.		for the endoscopy **Additional outcomes:** Symptomatic and colonoscopic improvement Mean colonoscopic score at entry and at the end

1.2 Economic evidence tables

Table 186: BRERETON2010

N. Brereton, K. Bodger, M. A. Kamm, P. Hodgkins, S. Yan, and R. Akehurst. A cost-effectiveness analysis of mezavant XL mesalazine compared with mesalazine in the treatment of mild-to-moderate ulcerative colitis from a UK perspective. Journal of Medical Economics 13 (1):148-161, 2010.

N. Brereton, K. Bodger, M. A. Kamm, P. Hodgkins, S. Yan, and R. Akehurst. A cost-effectiveness analysis of mezavant XL mesalazine compared with mesalazine in the treatment of mild-to-moderate ulcerative colitis from a UK perspective. Journal of Medical Economics 13 (1):148-161, 2010.

Study details	Population & interventions	Costs	Health outcomes	Cost effectiveness
Economic analysis: CUA **Study design:** Decision analytic model **Approach to analysis:** Markov model, with 8 week cycles. 8 health states: 1st line ASA, increased ASA dose, prednisolone, 5-ASA failure/severe relapse, surgery, post surgery, remission and death. **Perspective:** UK NHS **Time horizon:** 5 years (lifetime horizon in SA) **Treatment effect duration:** 8 weeks **Discounting:** 3.5% pa for costs and QALYs	**Population:** Patients > 18yrs with newly diagnosed or relapsing active, mild-to-moderate UC. **Cohort settings:** Start age =NR M =NR **Intervention 1:** 2.4 g/day mesalazine increased to 4.8g /day mezavant XL mesalazine (Mezavant) if remission not achieved. **Intervention 2:** 2.4 g/day mezavant XL mesalazine (Mezavant) increased to 4.8g /day mezavant XL mesalazine (Mezavant) if remission not achieved.	**Total costs (mean per patient):** Intvn 1: £5574 Intvn 2: £5582 Incremental (2-1): £8 **Currency & cost year:** UK pounds, cost year unclear. **Cost components incorporated:** Drug costs, out-patient follow-up costs, in-patient costs, surgery costs	**Primary outcome measure:** QALYs (mean per patient) Intvn 1: 3.434 Intvn 2: 3.445 Incremental (2-1): 0.011	**Primary ICER (Intvn 2 vs Intvn 1):** ICER: £749 per QALY gained **Analysis of uncertainty:** PA showed that mezavant XL mesalazine dominated mesalazine on 62% of the occasions and the probability of being cost-effective at a threshold of £20,000 was 74%. SA was conducted to estimate the effect of medication adherence on maintenance of remission. An analysis was also carried out to determine the effect of 5-ASA protection against colorectal cancer. The results are not reported here as maintenance therapy and colorectal cancer are not addressed by this question.
Data sources				
Health outcomes: treatment effect for mesalazine from study by Kamm et al 2007[13] and Kamm et al 2009[12], remission rates for 2nd line corticosteroid from Lennard-jones et al 1960[14]. **Quality-of-life weights:** EQ5D obtained from unpublished studies by Bassi et al 2005[1] and Luces et al 2007[15]. **Cost sources:** BNF, NHS tariff, Department of Health.				
Comments				
Source of funding: Shire Pharmaceuticals **Limitations:** Induction treatments are unlikely to last more than 12 weeks as described by the clinical review protocols. The 5 year time horizon used in this study means that relapse and maintenance therapy have been captured.				
Overall applicability*: Directly applicable **Overall quality**:** Potentially serious limitations				

Abbreviations: CUA = cost-utility analysis; da = deterministic analysis; EQ-5D = Euroqol five dimensions (scale: 0.0 [death] to 1.0 [full health]; <0.0 = worse than death); ICER = incremental cost-effectiveness ratio; NR = not reported; pa = probabilistic analysis; QALYs = quality-adjusted life years

Table 187: BUCKLAND2008

A. Buckland and K. Bodger. The cost-utility of high dose oral mesalazine for moderately active ulcerative colitis. *Aliment.Pharmacol.Ther.* 28(11-12):1287-1296, 2008.

Study details	Population & interventions	Costs	Health outcomes	Cost effectiveness
Economic analysis: CUA **Study design:** Decision analytic model **Approach to analysis:** Decision tree. Patients entering the model received either high dose (HD) or standard dose (SD) mesalazine to induce remission. If induction failed, treatment progressed in the following sequence- outpatient oral steroids, inpatient IV steroids, inpatient IV ciclosporin and surgery. **Perspective:** UK NHS **Time horizon:** 12 weeks **Treatment effect duration:** 6 weeks **Discounting:** N/A	**Population:** Adult patients with moderately active UC (defined by the 'Physician Global Assessment') **Cohort settings:** Start age = NR M = NR **Intervention 1:** SD mesalazine (Asacol MR 2.4 g/day) **Intervention 2:** HD mesalazine (Asacol MR 4.8 g/day)	**Total costs (mean per patient):** Intvn 1: £2474 Intvn 2: £2382 *Incremental* (2-1): -£92 **Currency & cost year:** UK pounds, Cost year unclear. **Cost components incorporated:** Drug costs, investigative costs, in-patient costs, out-patient costs, surgery costs.	**Primary outcome measure:** QALYs (mean per patient) Intvn 1:0.1378 Intvn 2:0.1394 *Incremental (2-1)*:0.0016	**ICER (Intvn 2 vs Intvn 1):** HD mesalazine is less costly and slightly more effect hence it dominates. **Analysis of uncertainty:** All model parameters were varied independently in a one-way sensitivity analysis. Utility scores were changed to upper and lower quartiles based on published EQ-5D scores. Upper and lower values for all other input data were based on 95% confidence intervals or by varying the data +/- 25%. The results were sensitive to the duration of mesalazine treatment. A separate analysis was conducted in which non-responders to 1st line therapy were switched to alternative therapy after 2 weeks (rather than 6 weeks as in the base case). The results showed that HD mesalazine was cost-effective at a threshold of £30,000/QALY. PA was conducted with the results showing that HD mesalazine dominated SD mesalazine in 48% of the simulations. The probability of HD mesalazine being cost-effective at a threshold of £30,000/QALY was 72%.

Data sources

Health outcomes: mesalazine success rates -Hanauer 2005[9]. Other clinical outcomes obtained from Jarnerot 1985[11], Bebb 2004[3], Travis 2004[27], Campbell 2005[4].

Quality-of-life weights: utilities derived from EQ5D obtained from Casellas 2005[6].

Cost sources: BNF, PSSRU 2006. Outpatient costs, investigative costs and surgery costs –Bassi 2004[2].

Comments

Source of funding: Procter and Gamble Pharmaceuticals Ltd, UK **Limitations:** Relative treatment effect was obtained from two studies so unclear if that reflects all evidence in area.

Overall applicability*: Directly applicable **Overall quality**:** Minor limitations

Abbreviations: CUA = cost-utility analysis; ICER = incremental cost-effectiveness ratio; NR = not reported pa = probabilistic analysis; EQ-5D = Euroqol five dimensions (scale: 0.0 [death] to 1.0 [full health]; <0.0 = worse than death)

Table 188: CONNOLLY2009

M. P. Connolly, S. K. Nielsen, C. J. Currie, P. Marteau, C. S. Probert, and S. P. Travis. An economic evaluation comparing concomitant oral and topical mesalazine versus oral mesalazine alone in mild-to-moderately active ulcerative colitis based on results from randomised controlled trial. Journal of Crohn's and colitis 3(3):168-174,2009.

Study details	Population & interventions	Costs	Health outcomes	Cost effectiveness
Economic analysis: CUA **Study design:** Decision analytic model **Approach to analysis:** Markov model with 5 states (active UC, mesalazine-refractory active UC, steroid-refractory UC, infliximab-responsive active UC and remission). A cycle length of 8 weeks was used. Treatment was escalated in the following order- oral and topical mesalazine, tapered course of 40mg oral prednisolone with 20mg prednisolone enema and infliximab. Costs and utilities were driven by response rate. **Perspective:** UK NHS **Time horizon:** 32 weeks (base case) Results from a 16 week abbreviated model (**steroid model**) that excluded infliximab costs and outcomes were reported. No surgical costs/benefits were included in both models to reflect the severity of active disease (mild/moderate).	**Population:** People with mild/moderate exacerbations of extensive UC (UCDAI score 3-8). Patients were steroid-free for 4 weeks prior to enrolment. **Patient characteristics:** See clinical evidence review (Marteau et al. 2005[16]) **Intervention 1:** Oral mesalazine (4g/day) for 8 weeks and placebo for 4 weeks **Intervention 2:** Oral mesalazine (4g/day) for 8 weeks and mesalazine enema (1g/100ml) for 4 weeks **Model inputs** Remission rates: Intervention 1: 0.64 Intervention 2: 0.43 Prednisolone: 0.68 Infliximab: 0.39 GP consultation rates while in remission: 2.2 per year	**Total costs (mean per patient):** Intvn 1: £2390 Intvn 2: £1812 *Incremental* (2-1)*: -£578* **Steroid model** Total costs (mean per patient): Intvn 1: £1399 Intvn 2: £1114 *Incremental* (2-1):- £285 **Currency & cost year:** 2008 UK pounds **Cost components incorporated:** Drug costs - mesalazine (Pentasa-oral and enema), prednisolone (oral and enema) and infliximab. Consultation costs- GP and Gastroenterologist. Clinical tests -stool sample, flexible sigmoidoscopy, C-reactive protein, full blood count, microbiological testing	**Primary outcome measure** QALYs (mean per patient) Intvn 1:0.55 Intvn 2:0.56 *Incremental (2-1):0.01* **Steroid model** QALYs (mean per patient) Intvn 1:0.267 Intvn 2:0.271 *Incremental (2-1):0.003*	Intervention 2 **dominates** intervention 1 **Steroid model** Intervention 2 **dominates** intervention 1 **Analysis of uncertainty** PA was conducted on these parameters: remission with both interventions, probability of success with prednisolone and infliximab, GP consultation rates in remission, utility values for active UC and remission. The combination therapy showed a higher probability of being cost effective over a threshold range of £0-£20,000.

M. P. Connolly, S. K. Nielsen, C. J. Currie, P. Marteau, C. S. Probert, and S. P. Travis. An economic evaluation comparing concomitant oral and topical mesalazine versus oral mesalazine alone in mild-to-moderately active ulcerative colitis based on results from randomised controlled trial. Journal of Crohn's and colitis 3(3):168-174,2009.

Treatment effect duration: 8 weeks **Discounting:** N/A				
Data sources				
Health outcomes: clinical probabilities: mesalazine- Marteau et al. 2005[16], prednisolone- Lennard-Jones et al. 1960[14]. **Quality-of-life weights:** health state Utilities- EQ5D from Poole et al 2008[20] **Resource use:** Travis et al 2008[26], Carter et al 2004[5]. **Cost sources:** costs were obtained from published UK sources **(**BNF,PSSRU 2007, NHS national tariff).				
Comments				
Source of funding: Ferring pharmaceuticals **Limitations:** mesalazine effectiveness from one study so may not reflect all evidence in area.				
Overall applicability: Directly applicable **Overall quality:** Minor limitations				

Abbreviations: CUA = cost-utility analysis; ICER = incremental cost-effectiveness ratio; NR = not reported; pa = probabilistic analysis; EQ-5D = Euroqol five dimensions (scale: 0.0 [death] to 1.0 [full health]; <0.0 = worse than death)

Table 189: CONNOLLY2009A

M. P. Connolly, S. K. Nielsen, C. J. Currie, C. D. Poole, and S. P. Travis. An economic evaluation comparing once daily with twice daily mesalazine for maintaining remission based on results from a randomised controlled clinical trial. *Journal of Crohn's and colitis* 3(1):32-37, 2009.

Study details	Population & interventions	Costs	Health outcomes	Cost effectiveness
Economic analysis: CUA **Study design:** Decision analytic model **Approach to analysis:** 2 health states: remission and active disease. Patients experiencing relapse received treatment in the following order: 1st line - 4g oral and 1g/100ml topical mesalazine, 2nd line – 40mg prednisolone for 4 weeks, 3rd line – Infliximab 5mg/kg at 0,2, and 6 weeks.	**Population:** Patients with mild to moderate ulcerative colitis in remission (UCDAI score of <2) who had experienced a relapse requiring adjustments to their maintenance therapy within the past year. Patients with proctitis (less than or equal to 15cm from the anal verge) **Cohort settings** Start age = NR M = NR **Intervention 1:**	**Total costs (mean per patient):** Intvn 1: £815 Intvn 2: £971 Incremental (2-1): £156 **Currency & cost year:** 2007 UK pounds **Cost components incorporated:** Drug costs, Consultation costs, Diagnostic test costs (sigmoidoscopy, full blood count, c-reactive protein, microbiological tests, electrolytes)	**Primary outcome measure:** QALYs (mean per patient) Intvn 1: 0.935 Intvn 2: 0.931 Incremental (2-1): -0.004	2g OD mesalazine **dominates** 1g BD mesalazine **Analysis of uncertainty:** PA was conducted on these parameters: OD I year relapse rate, BD 1 year relapse rate, compliance OD, compliance BD, clinical consultation rate in relapse period. Probability of 2g OD mesalazine being cost-effective around a £20,000 threshold was 98%.

M. P. Connolly, S. K. Nielsen, C. J. Currie, C. D. Poole, and S. P. Travis. An economic evaluation comparing once daily with twice daily mesalazine for maintaining remission based on results from a randomised controlled clinical trial. *Journal of Crohn's and colitis* 3(1):32-37, 2009.				
Surgery was not included in the model to reflect the UC severity of the trial population. Annual mesalazine treatment costs were adjusted for patient compliance. QALYs were derived by mapping from UCDAI to EQ5D. **Perspective:** UK NHS) **Time horizon:** 1 year **Treatment effect duration:** 1 year **Discounting:** N/A	2g once daily (OD) mesalazine (Pentasa sachet) **Intervention 2:** 1g twice daily (BD) mesalazine (Pentasa sachet)			
Data sources				
Health outcomes: Remission rates for OD and BD mesalazine – Veerman et al 2008[28] **Quality-of-life weights:** UCDAI scores were mapped to EQ5D to derive QALYs. Mapping function based on study by Poole et al 2008.[21] **Cost sources:** Drug costs – BNF, Resource cost – PSSRU, NHS National Tariff. **Resource use:** Bassi et al 2004[2].				
Comments				
Source of funding: Ferring Pharmaceuticals Ltd **Limitations:** Relative treatment effect was obtained from one study, so unclear if that reflects all evidence in this area. Infliximab therapy modelled, however the NICE TA for Infliximab[18] states that it is only an option in patients with severe UC where ciclosporin is contraindicated.				
Overall applicability*: Directly applicable **Overall quality**:** Minor limitations				

Abbreviations: CUA = cost-utility analysis; NR = not reported; pa = probabilistic analysis; EQ-5D = Euroqol five dimensions (scale: 0.0 [death] to 1.0 [full health]; <0.0 = worse than death)

Table 190: DALBASIO1997

G. d'Albasio, F. Pacini, E. Camarri, A. Messori, G. Trallori, A. G. Bonanomi, G. Bardazzi, M. Milla, S. Ferrero, M. Biagini, S. Quaranta, and A. Amorosi. Combined therapy with 5-aminosalicylic acid tablets and enemas for maintaining remission in ulcerative colitis: a randomized double-blind study. *Am.J.Gastroenterol.* 92(7) (7):1143-1147, 1997.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**

G. d'Albasio, F. Pacini, E. Camarri, A. Messori, G. Trallori, A. G. Bonanomi, G. Bardazzi, M. Milla, S. Ferrero, M. Biagini, S. Quaranta, and A. Amorosi. Combined therapy with 5-aminosalicylic acid tablets and enemas for maintaining remission in ulcerative colitis: a randomized double-blind study. *Am.J.Gastroenterol.* 92(7) (7):1143-1147, 1997.

Economic analysis: CCA (NCGC defined) **Study design:** RCT **Approach to analysis:** Within trial analysis **Perspective:** Italian health system **Time horizon:** 12 months **Treatment effect duration:** 12 months **Discounting:** NA	**Population:** Patients (17-65yrs) with UC in remission for a minimum of one month. Remission defined by clinical, histological and endoscopic criteria. **Cohort settings:** Start age = NR M/F =19/17 (Intvn 1) M/F = 20/16 (Intvn 2) **Intervention 1:** 5ASA tablets (1.6g/day) and placebo enemas twice weekly **Intervention 2:** 5ASA tablets (1.6g/day) and 5 ASA enemas (4g/100ml) twice weekly	**Total costs (per patient):** Intvn 1: NR Intvn 2: NR Incremental (2-1): £25 per month which amounts to £30,007 per 100 patients per year and £300.07 per patient **Currency & cost year:** 1995 US dollars (presented here as 1995 UK pounds‡) Cost year unclear **Cost components incorporated:** Drug costs	**Primary outcome measure:** QALYs (mean per patient) Intvn 1: NR Intvn 2: NR **Other outcome measures** Relapses/year : Intvn 1: 13 Intvn 2: 23 Incremental (2-1):10 relapses avoided per 36 patients which works out to approximately 30 relapses avoided per 100 patients/year.	ICER: NR **Other:** £1000.25 per relapse avoided **Analysis of uncertainty:** NR

+Data sources

Health outcomes: Within-trial analysis
Quality-of-life weights: NR
Cost sources: Study by Trallori 1995[25]

Comments

Source of funding: Bracco S.p.A., Milano, Italy **Limitations:** Within-trial analysis so estimate of treatment effects obtained from one source (small RCT). This might not reflect all the evidence in this area.
Limited information provided on resource use. Costs sources and calculations not clearly reported. No sensitivity analysis conducted. Breakdown of drug costs not provided. The study was designed to reflect the management of ulcerative colitis in the Italy therefore resource use may not be applicable to the UK health system. The value of health effects were not expressed in terms of quality-adjusted life years.

Overall applicability*: Partially applicable **Overall quality**:** Very serious limitations

Abbreviations: CCA = cost-consequence analysis; ICER = incremental cost-effectiveness ratio; NR = not reported; ‡ Converted using 1995 Purchasing Power Parities [19]

Table 191: MACKOWIAK2006

J. Mackowiak, I. A two-stage decision analysis to assess the cost of 5-aminosalicylic acid failure and the economics of balsalazide versus mesalamine in the treatment of ulcerative colitis. *Manag.Care Interface* 19(10):39-46, 56, 2006.

J. Mackowiak, I. A two-stage decision analysis to assess the cost of 5-aminosalicylic acid failure and the economics of balsalazide versus mesalamine in the treatment of ulcerative colitis. *Manag.Care Interface* 19(10):39-46, 56, 2006.

Study details	Population & interventions	Costs	Health outcomes	Cost effectiveness
Economic analysis: CEA **Study design:** Decision analysis model (decision tree). **Approach to analysis:** The analysis was conducted in two parts. First, the cost of treatment failure with oral mesalamine was modelled. This incorporated the costs of further treatment (rectal mesalamine, oral steroids, mercaptopurine, azathioprine, IV steroids, cyclosporine, and surgery). The next part of the analysis addressed the cost effectiveness of treatment with either mesalamine or balsalazide. **Perspective:** US health system **Time horizon:** 178 days **Treatment effect duration:** 4 weeks **Discounting:** NA	**Population:** Patients, newly diagnosed, presenting primarily with left-sided UC. **Cohort settings:** Start age = NR **Intervention 1:** Mesalamine delayed tablets (2.4g/day or 4.8g/day) **Intervention 2:** Balsalazide tablets (6.75g/day)	**Total costs (per patient):** Intvn 1: £6,938 Intvn 2: £5,834 Incremental (2-1): -£1,104 **Currency & cost year:** 2006 US dollars (presented here as 2006 UK pounds‡) Cost year unclear **Cost components incorporated:** Drug costs, physician visits, test costs, hospitalisation costs, surgical costs.	**Primary outcome measure:** QALYs (mean per patient): NA **Other outcome measures:** Intvn 1: 78 days without symptoms or steroids (DWSS) Intvn 2: 104 days without symptoms or steroids Incremental (2-1):26 more days without symptoms or steroids	ICER: NR Intvn 1: £88.94/DWSS Intvn 2: £56.09/DWSS Balsalazide **dominates** **Analysis of uncertainty:** SA was conducted but the parameters varied in the analysis were not clearly reported. The remission rate for balsalazide would have to be reduced from 35% to 14% before the two treatment arms result in equal cost effectiveness.

Data sources

Health outcomes: balsalazide remission rates- Green et al[7]; mesalazine remission rates- Schroeder et al[23].

Quality-of-life weights: NA.

J. Mackowiak, I. A two-stage decision analysis to assess the cost of 5-aminosalicylic acid failure and the economics of balsalazide versus mesalamine in the treatment of ulcerative colitis. *Manag.Care Interface* 19(10):39-46, 56, 2006.

Cost sources: drug costs- average wholesale prices, other costs sources not referenced.

Comments

Source of funding: Bracco S.p.A., Milano, Italy **Limitations:** Cost sources not reported, unclear methodology regarding sensitivity analysis, clinical parameters informed by single RCT so this may not capture all the evidence in the area. The cost-effectiveness model was designed to reflect the management of ulcerative colitis in the US therefore resource use may not be applicable to the UK health system. The value of health effects were not expressed in terms of quality-adjusted life years.

Overall applicability*: Partially applicable **Overall quality**:** Potentially serious limitations

Abbreviations: CEA = cost-effectiveness analysis; ICER = incremental cost-effectiveness ratio; NA = not applicable; NR = not reported; SA = sensitivity analysis ǂ Converted using 2006 Purchasing Power Parities[19]

Table 192: PIODI2004

L. P. Piodi, F. M. Ulivieri, L. Cermesoni, and B. M. Cesana. Long-term intermittent treatment with low-dose 5-Aminosalicylic enemas for remission maintenance in ulcerative colitis. *Scand.J.Gastroenterol.* 39(2):154-157, 2004.

Study details	Population & interventions	Costs	Health outcomes	Cost effectiveness
Economic analysis: CCA (NCGC defined) **Study design:** Case control prospective design **Approach to analysis:** **Perspective:** Italian health system **Time horizon:** approximately 6 years (longest follow-up) **Treatment effect duration:** approximately 6 years (longest follow-up) **Discounting:** NA	**Population:** Patients with UC in remission for at least one month. Remission defined as absence of blood and mucus in stools, absence of diarrhoea and no endoscopically detected signs of disease. **Cohort settings:** Start age =NR M =29/42 **Intervention 1:** 5ASA tablets (1.6g/day) **Intervention 2:** 5ASA tablets (1.6g/day) and intermittent 5 ASA enemas (2g/50ml) twice weekly	**Yearly total costs (mean per patient):** Intvn 1: £561 Intvn 2: £747 Incremental (2-1): £186 **Currency & cost year:** 2004 US dollars (presented here as 2004 UK pounds‡) **Cost components incorporated:** Drug costs, proctosigmoidoscopy costs, hospitalisation costs, costs for treating relapses.	**Primary outcome measure:** QALYs (mean per patient) Intvn 1: NR Intvn 2: NR **Other outcome measures** Relapse/year (mean): Intvn 1: 0.46 Intvn 2: 0.26 Incremental (2-1) = 0.20 relapses avoided	**Other outcome measures** £929 per relapse avoided. **Analysis of uncertainty:** NR
Data sources				

L. P. Piodi, F. M. Ulivieri, L. Cermesoni, and B. M. Cesana. Long-term intermittent treatment with low-dose 5-Aminosalicylic enemas for remission maintenance in ulcerative colitis. *Scand.J.Gastroenterol.* 39(2):154-157, 2004.
Health outcomes: Within RCT
Quality-of-life weights: NR
Cost sources: hospitalisations - Italian Public Health Service diagnostic-related group financing system, drug costs - not reported
Comments
Source of funding: NR **Limitations:** Estimate of treatment effects obtained from one source (case control study, small sample size). This might not reflect all the evidence in this area. Costs sources and calculations not clearly reported. No sensitivity analysis conducted. Breakdown of drug costs not provided. The study was designed to reflect the management of ulcerative colitis in the Italy therefore resource use may not be applicable to the UK health system. The value of health effects were not expressed in terms of quality-adjusted life years.
Overall applicability*: Partially applicable **Overall quality**:** Potentially serious limitations

Abbreviations: CCA = cost-consequence analysis: ICER = incremental cost-effectiveness ratio; NR = not reported; ‡ Converted using 2004 Purchasing Power Parities[19]

Table 193: YEN2008

E. F. Yen, S. V. Kane, and U. Ladabaum. Cost-effectiveness of 5-aminosalicylic acid therapy for maintenance of remission in ulcerative colitis. Am.J.Gastroenterol. 103 (12):3094-3105, 2008.

Study details	Population & interventions	Costs	Health outcomes	Cost effectiveness
Economic analysis: CUA **Study design:** Decision analytic model **Approach to analysis:** Markov model. Patients entering the model were either maintained on 5-ASA or not. In the event of a flare, 5-ASA was given and then escalated in the following sequence-oral prednisolone - IV corticosteroids - cyclosporine – Colectomy. Maintenance with mercaptopurine was given following cyclosporine treatment. Infliximab was given following a second flare refractive to IV steroids. Colectomy was carried out	**Population:** People with mild to moderate UC after achieving remission **Cohort settings** Start age = NR M = NR **Intervention 1:** No maintenance 5-ASA. A 4.8g/day dose given after 1st flare and stopped after remission was achieved. **Intervention 2:**	**Total costs (mean per patient):** Intvn 1:£2,089 Intvn 2: £5,027 *Incremental* (2-1)*:* £2,938 **Currency & cost year:** 2004 US dollars (presented here as 2004 UK pounds‡) **Cost components incorporated:** Drug costs, medical care costs, colectomy costs, costs of pouch excision, costs of severe post-colectomy complications.	**Primary outcome measure:** *QALYs (mean per patient)* Intvn 1: 1.75 Intvn 2:1.77 *Incremental (2-1):*0.02 **Other outcome measures (mean):** *Flares of disease per person* Intvn 1: 1.92 flares Intvn 2: 1.38 flares	**Primary ICER (Intvn 2 vs Intvn 1):** ICER: £146,000/QALY **Analysis of uncertainty** One-way sensitivity analysis was undertaken on the all the input parameters. Two input variables that impacted on the ICER was the relative risk of flare on maintenance 5-ASA and cost of 5-ASA. If the cost of 5-ASA was £9/month (sulfasalazine), the ICER would be £10,306/QALY. Two-way sensitivity analysis was undertaken.. The ICER was less than £63,228 in the analysis using a low cost of 5-ASA (£9/month) over a range of values for the relative risk of flare on maintenance 5-ASA. PSA (10,000 simulations) were performed with beta distributions used for probabilities and a log-normal distribution for relative risk. In the base case, the

following infliximab failure. A cycle length of 3 months was applied to remission and outpatient treatment with 5-ASA. Cycle length of 1 month was applied to all other health states. **Perspective:** US healthcare system **Time horizon:** 2 years **Treatment effect duration:** 12 months **Discounting:** Costs: 3%; QALYs:3%	Maintenance 5-ASA (2.4g/day). Dose escalated to 4.8g/day after 1st flare and maintained at 4.8g/day if remission was achieved.			probability that maintenance treatment is cost effective at a threshold of £126,456 is approximately 30%. If a low cost 5-ASA (£9/month) is used, the probability of cost effectiveness at a threshold of £31,614 is 85%.
Data sources				
Health outcomes: Hawkey et al 1997[10], Miner et al 1995[17], Sandberg-Gertzen et al 1986[22], Wright et al 1993[29], the mesalazine study group 1996, Schroeder 1987[23], Hanauer 1993[8], Sutherland et al 1990[24]. **Quality-of-life weights:** utilities derived from various published studies. The utility difference between being in remission with or without maintenance therapy was based on data from a population with Crohn's disease. **Cost sources:** drug costs- Red book, Medical care costs- DRG handbook and Physician Fee Schedule.				
Comments				
Source of funding: Procter and Gamble **Limitations:** 5-ASA clinical probabilities were based on weighted average results from RCTs that assessed different 5-ASAs. The cost-effectiveness model was designed to reflect the management of ulcerative colitis in the US therefore resource use may not be applicable to the UK health system. Some health state utilities were inferred from a Crohn's disease population. The dose of sulfasalazine used in the sensitivity analysis is not specified. This would have an impact on the cost/month and consequently on the ICER.				
Overall applicability*: Partially applicable **Overall quality**:** Minor limitations				

Abbreviations: CUA = cost-utility analysis; CUA = cost-utility analysis; ICER = incremental cost-effectiveness ratio; NR = not reported; pa = probabilistic analysis ‡ *Converted using 2004 Purchasing Power Parities* [19]

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