National Clinical Guideline Centre

Ulcerative colitis

Appendices H-N

Forest plots, ROC curves, NMAs, unit costs, CEAs, research recommendations and author definitions

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.

This document preserves evidence for areas of the guideline that have not been updated in 2019. Black shading indicates text from 2013 replaced by the 2019 update.

Final version

Commissioned by the National Institute for Health and Care Excellence











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Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

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Funding National Institute for Health and Care Excellence

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1 Appendix H: Forest plots and ROC curves

1.1 Induction of remission for a mild to moderate inflammatory exacerbation of ulcerative colitis

Please note that evidence on treatments for inducing remission in people with mild-tomoderate ulcerative colitis was reviewed in 2019. The updated evidence review and full current recommendations can be found on the NICE website.

(Figure 1: Clinical	remission										
	Topical ASA	Placebo	Risk Ratio	(Risk Ratio)							
Study or Subgroup	Events (Total)	Events) (Total) (Weight)	(M-H, Fixed, 95% Cl)	(M-H, Fixed, (95% CI)							
(1.1.2 0≤2 weeks)											
CAMPIERI1990	27 63	7 31 75.1%	(1.90 [0.93, 3.87])	- -							
(CAMPIERI1990A)	8 62	(1) (30) (8.3%)	(7.50 [1.00, 56.44])								
(CAMPIERI1991)	63 66	(1) (27) (12.2%)	(10.36 [1.49, 72.23])								
CAMPIERI1991A	7 18	0 (14) (4.5%)	(11.84 [0.73, 191.17])								
Subtotal (95% CI)	(199)	(102) (100.0%)	(3.84 [2.05, 7.19])	•							
(Total events)	75	9									
(Heterogeneity: Chi ² = 5.82, df = 3 (P = 0.12); l ² = 48%) (Test for overall effect: Z = 4.20 (P < 0.0001))											
(1.1.3 >2≤4 weeks)											
CAMPIERI1990	45 63	(12) (31) (67.5%)	(1.85 [1.15, 2.95])	- <u>∎</u> -							
CAMPIERI1990A	(18) (32)	2 30 8.7%	(8.44 [2.14, 33.32])								
CAMPIERI1991)	58 86	3 27 (19.2%)	6.07 [2.07, 17.82]								
CAMPIERI1991A)	12 (18)	(1) (14) (4.7%)	9.33 [1.37, 63.45]	· · · · · · · · · · · · · · · · · · ·							
Subtotal (95% CI)	(199	(102) (100.0%)	3.58 [2.35, 5.46]	•							
(Total events)	(133)	(18)									
Heterogeneity: $Chi^2 = 1$	1.02, df = 3 (P = 0.	01); $I^2 = 73\%$									
(Test for overall effect: Z	2 = 5.91 (P < 0.000	01)									
(1.1.4 >4 <u>≤6 weeks</u>)											
(POKROTNIEKS2000)	(35) (54)	(23) (57) (100.0%)	(1.61 [1.11, 2.33])								
Subtotal (95% CI)	54	57 (100.0%)	(1.61 [1.11, 2.33]	\bullet							
(Total events)	35	23									
(Heterogeneity: Not appl	licable	_									
Test for overall effect: Z	2 = 2.50 (P = 0.01)										
(1.1.5 >6 <u>≤</u> 8 weeks)											
(HANAUER1998)	(101) (217)	(10) (70) (100.0%)	(3.26 [1.80, 5.88])								
Subtotal (95% Cl)	217	(100.0%)	(3.26 [1.80, 5.88]								
(Total events)	(101)	(10)									
Heterogeneity: Not appl	licable										
(Test for overall effect: Z	2 = 3.92 (P < 0.000										
				(Favours Placebo) (Favours Topical ASA)							
Test for subgroup different	ences: Chi² = 10.6	7, df = 3 (P = 0.01), l² = 71	.9%)								

Figure 2: Clinical remission >2≤4 weeks by extent of disease



(Figure 3:) (Clinical remission >2≤4 weeks, random effects)

	Topical AS	SA) (Placeb	0	Risk Ratio	Risk	Ratio
Study or Subgroup	Events (otal (Events)	Total) (Weight)	M-H, Random, 95% Cl	M-H, Rand	lom, 95% Cl
(1.3.3 >2 <u>≤</u> 4 weeks)						
CAMPIERI1990	45	63 (12)	31 34.4%	(1.85 [1.15, 2.95])		
CAMPIERI1990A	(18)	32 2	30 22.6%	8.44 [2.14, 33.32]		_
CAMPIERI1991	58	86 3	27 26.6%	6.07 [2.07, 17.82]		
CAMPIERI1991A	(12)	18 1	(14) (16.5%)	9.33 [1.37, 63.45]		
Subtotal (95% CI)	(199	(102) (100.0%)	(4.66 [1.64, 13.28])		
(Total events)	(133)	(18)				
(Heterogeneity: Tau ² =	0.77; Chi² = 1	1.02, df = 3 (P =	= 0.01); l² = 73%	6		
(Test for overall effect: 2	Z = 2.88 (P =	0.004)				
					├ ─── ├	+ + +
					0.01 0.1	1) (10) (100)
					Favours Placebo	(Favours Topical ASA)

(Test for subgroup differences: Not applicable

Figure 4: Clinical	improve	ement									
	Topical	ASA	Placeb	0		Risk Ratio	Risk	Ratio			
Study or Subgroup	Events	(Total) (Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fix	ed, 95%			
(1.4.2 0 <u>≤</u> 2 weeks)											
CAMPIERI1990	(50)	63	10	31	20.5%	2.46 [1.45, 4.16]					
CAMPIERI1990A	22	32	6	(30)	9.5%	(3.44 [1.62, 7.30]					
(CAMPIERI1991)	68)	86	(10)	27	(23.2%)	(2.13 [1.29, 3.53])					
CAMPIERI1991A	(15)	18	2	(14)	3.4%)	(5.83 [1.59, 21.40]					
POKROTNIEKS2000	(38)	51	29	53		(1.36 [1.02, 1.83])					
Subtotal (95% CI)		(250)		(155)	(100.0%)	2.12 [1.69, 2.65]					
(Total events)	(193)	(5	(57)								
(Heterogeneity: Chi ² = 12.95, df = 4 (P = 0.01); l ² = 69%)											
(Test for overall effect: Z	. = 6.48 (P -	< 0.0000									
(1.4.3 >2≤4 weeks)											
CAMPIERI1990	54	(63)	(13)	31	(23.9%)	(2.04 [1.33, 3.13])		_			
CAMPIERI1990A	(28)	(32)	10	30		(2.63 [1.56, 4.43])		— —			
CAMPIERI1991	73	(86)	- m	27	23.0%	(2.08 [1.31, 3.31])					
CAMPIERI1991A)	17	18	2	14	(3.1%)	(6.61 [1.82, 23.97])		$ \longrightarrow $			
POKROTNIEKS2000	29	47	25	43	35.8%	(1.06 [0.76, 1.49])	-	-			
Subtotal (95% CI)	—	246	_	145	100.0%	(1.92 [1.56, 2.38]		•			
(Total events)	(201)		61								
(Heterogeneity: Chi ² = 1	6.90, df = 4	(P = 0.0)	02); l² =	76%							
(Test for overall effect: Z	. = 6.09 (P -	< 0.0000 ⁻	1)								
(1.4.4 >4 <u>≤</u> 6 weeks)			_								
(POKROTNIEKS2000)	(35)	43	(26)	37	(100.0%)	(1.16 [0.90, 1.49])					
Subtotal (95% CI)	_	43	_	37	100.0%	(1.16 [0.90, 1.49])					
(Total events)	(35)		(26)								
(Heterogeneity: Not app		0.061									
(Test for overall effect: Z	. = 1.14 (P :	- 0.20)									
(1.4.5 >6≤8 weeks)											
HANAUER1998)	(150)	(217)	(19)	70	(100.0%)	(2.55 [1.72, 3.78])		_ _			
Subtotal (95% CI)		217		70	100.0%	2.55 [1.72, 3.78]		-			
(Total events)	(150)		(19)								
Heterogeneity: Not app	licable										
Test for overall effect: Z	. = 4.65 (P ·	< 0.0000	1)								
							0.2 0.5				
								(Favours Topical ASA)			
Test for subaroup differ	ences: Chi ²	$^{2} = 16.92.$. df = 3 (P = 0.0	$(0007), ^2 =$	82.3%					

Test for subaroup differences: $Chi^2 = 16.92$, df = 3 (P = 0.0007), $I^2 = 82.3\%$

Figure 5: Clinical improvement 0≤2 weeks by extent of disease

rigure J.	ciiiiicai iii	iipi ovei	ment	UZZ W	CERS	DY EALE	int of disease		
		Topical A	SA	Placeb	0		Risk Ratio	Risk	Ratio
Study or Sub	ogroup (Events	Total)	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixe	ed, 95% Cl
(1.5.1 Up to th	ne splenic fl	exure							
CAMPIERI199	91)	68	86	(10)	27	33.2%	2.13 [1.29, 3.53]		
CAMPIERI199	91A)	15	(18)	2	(14)	4.9%	(5.83 [1.59, 21.40])		$ \longrightarrow$
POKROTNIE		38	(51)	(29)	53	61.9%	(1.36 [1.02, 1.83])		
Subtotal (95%	% CI))		155		94	(100.0%)	(1.84 [1.41, 2.39])		•
(Total events)		(121)		(41)					
Heterogeneity	/: Chi² = 7.40), df = 2 (F	P = 0.02	2); l² = 73	%				
Test for overa	all effect: Z =	4.52 (P <	0.0000	1)					
(1.5.2 <20cm)									
CAMPIERI199		50	63	(10)	(31)	68.4%	2.46 [1.45, 4.16]		
CAMPIERI199		22	32	6	30	(31.6%)	3.44 [1.62, 7.30]		
Subtotal (95%	% CI))		95		61	100.0%	2.77 [1.80, 4.26]		
(Total events)		72		(16)					
Heterogeneity									
(Test for overa	all effect: $Z =$	4.64 (P <	0.0000	1)					
								0.1 0.2 0.5	
								(Favours Placebo)	Favours Topical ASA
Test for subar		ces: Chi2	= 2.54	dt = 1 (P)	= 0.11	$1 \frac{12}{12} = 60.6$			

(Figure 6:) (Clinical improvement >2≤4 weeks by extent of disease)



Figure 7: Clinical improvement 0≤2 weeks and >2≤4 weeks , random effects

	(Topical ASA) (Placebo)				Risk Ratio	(Risk Ratio)	
Study or Subgroup	Events	(Total)	Events	(Total)	Weight	M-H, Random, 95% Cl	(M-H, Random, 95% Cl)
(1.7.2 0≤2 weeks)							
(CAMPIERI1990)	(50)	63	10	31	22.5%)	2.46 [1.45, 4.16]	
(CAMPIERI1990A)	22	32	6	30	(17.1%)	(3.44 [1.62, 7.30])	
CAMPIERI1991	68	86	10	27	(23.1%)	2.13 [1.29, 3.53]	
CAMPIERI1991A	(15)	(18)	2	(14)	8.9%	(5.83 [1.59, 21.40])	
(POKROTNIEKS2000)	(38)	51	29	(53)	28.4%)	(1.36 [1.02, 1.83])	
(Subtotal (95% CI))		(250)		(155)	100.0%	(2.30 [1.46, 3.63]	-
Total events	(193)		57				
(Heterogeneity: Tau ² = 0).17; Chi² =	12.95,	df = 4 (P	= 0.01)	; l² = 69%		
Test for overall effect: Z	2 = 3.58 (P	= 0.000	3)				
(1.7.3 2 <u>≤</u> 4 weeks)							
CAMPIERI1990	(54)	63	(13)	(31)	23.0%)	(2.04 [1.33, 3.13])	— — —
CAMPIERI1990A	(28)	(32)	10	(30)	21.0%	(2.63 [1.56, 4.43])	_
CAMPIERI1991	(73)	86	(11)	27	22.2%	(2.08 [1.31, 3.31])	— ∎ —
CAMPIERI1991A	(17)	(18)	2	(14)	9.0%	6.61 [1.82, 23.97]	
(POKROTNIEKS2000)	(29)	47	25	(43)	24.8%	(1.06 [0.76, 1.49])	- - -
Subtotal (95% CI)		246		145	100.0%	2.04 [1.28, 3.25]	-
(Total events)	201		61				
(Heterogeneity: Tau ² = 0).20; Chi² =	16.90,	df = 4 (P	= 0.002	2); l² = 76%	6	
Test for overall effect: Z	. = 3.01 (P	= 0.003)					
							0.1 0.2 0.5 (1) (2) (5 (10)
							(Favours Placebo) (Favours Topical ASA)

(Test for subgroup differences: $Chi^2 = 0.13$ df = 1 (P = 0.72) $l^2 = 0\%$

(Figure 8:) (Endosc	opic rem	ission				
	Topical A	SA (Placebo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	(Total) (E	vents) (To	tal) (Weight	M-H, Fixed, 95% C	(M-H, Fixed, 95% Cl)
(1.8.2 0≤2 weeks)						
CAMPIERI1990A	5	(32)		(30) (33.2%	(4.69 [0.58, 37.84])	
CAMPIERI1991)	27	86	ō	(27) (48.9%)	(8.48 [1.21, 59.49])	_
CAMPIERI1991A	6	(18)	ō	(14) (18.0%	(10.26 [0.63, 168.04])	
Subtotal (95% CI)		136		(71) (100.0%	(7.54 [2.08, 27.36])	
(Total events)	38		2			
(Heterogeneity: Chi ² = 0).26, df = 2 (I	P = 0.88);	$I^2 = 0\%$			
Test for overall effect: 2	Z = 3.07 (P =	: 0.002)				
(1.8.3 >2 <u><</u> 4 weeks)						
(CAMPIERI1990)	36	63	7	(31) (62.3%	(2.53 [1.27, 5.03]	
CAMPIERI1990A	(13)	32	2	(30) (13.7%	6.09 [1.50, 24.78]	
(CAMPIERI1991)	(40)	86	2	(27) (20.2%)	(6.28 [1.62, 24.29])	
CAMPIERI1991A	(10)	(18)	•	(14) (3.7%)		
Subtotal (95% CI)		(199)		02) (100.0%	(4.30 [2.46, 7.50])	
(Total events)	(99)		11			
(Heterogeneity: Chi ² = 3						
Test for overall effect: 2	2 = 5.14 (P <	: 0.00001))			
1.8.4 >4≤6 weeks						
POKROTNIEKS2000	26	(54)	(17)	(57) (100.0%	(1.61 [0.99, 2.62])	
Subtotal (95% CI)	_	54	_	57 100.0%	(1.61 [0.99, 2.62]	\bullet
(Total events)	26		(17)			
Heterogeneity: Not app	olicable					
Test for overall effect: 2	Z = 1.94 (P =	= 0.05)				
(1.8.5 >6 <u>≤</u> 8 weeks)						
(HANAUER1998)	(137)	217	(17)	(70) (100.0%		
Subtotal (95% CI)		217		(70) (100.0%	2.60 [1.70, 3.98]	•
(Total events)	(137)		(17)			
Heterogeneity: Not app	· · · · ·					
(Test for overall effect: 2	Z = 4.40 (P <	: 0.0001)				
						0.01 0.1 (1) (10 (100
	0.110					(Favours Placebo) (Favours Topical ASA)
Test for subaroup difference	rences: Chi ²	= 9.45, dt	= 3 (P = 0	$(0.02), 1^2 = 68$.3%	

Figure 9:) Clinical and endoscopic remission

	Topical ASA		Placebo		Risk Ratio		Risk Rat		Ratio	
		ASA								
Study or Subgroup	Events	(Total)	(Events)	(Total)	(Weight)	M-H, Fixed, 95% C		M-H, Fix	ed, 95% CI	
(1.9.1 >2 <u>≤</u> 4weeks)									L	
WILLIAMS1987	5	(14)	0	13	(100.0%)	(10.27 [0.62, 169.16])		_		
Subtotal (95% CI)		(14)		(13)	100.0%	10.27 [0.62, 169.16]		_		
(Total events)	5		0							
Heterogeneity: Not ap	olicable									
Test for overall effect:	Z = 1.63 (F	P = 0.10								
(1.9.2 >4 <u>≤</u> 6weeks)										
WILLIAMS1987	(11)	(14)	1	(13)	(100.0%)	(10.21 [1.52, 68.49])				
Subtotal (95% CI)		(14)		(13)	100.0%	(10.21 [1.52, 68.49])				
(Total events)	(11)		1							
Heterogeneity: Not ap	plicable)									
(Test for overall effect:	Z = 2.39 (F	P = 0.02								
								<u> </u>	<u> </u>	
							(0.01)	0.1	1 <u>10</u>	(100)
		.:2 0.00	14 ()		 A) 12 A) 12 A) 12 		Favo	ours Placebo	Favours To	pical ASA
Test for subgroup diffe	erences: Cr	$11^2 = 0.00$), at = 1 (I	P = 1.0	0), $I^2 = 0\%$	0				

Figure 10: Adverse events



Figure 11: Serious adverse events

-	(Topical)	ASA	Placebo	3	Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total (Weight)	(M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
(POKROTNIEKS2000)	1	54	4	57 (100.0%)	(0.26 [0.03, 2.29])	
(Total (95% CI))		(54)		57 (100.0%)	0.26 [0.03, 2.29]	
(Total events)	1		4			
(Heterogeneity: Not appl						0.1 0.2 0.5 0 2 5 10
(Test for overall effect: Z	= 1.21 (P =	= 0.23)				avours Topical ASA) (Favours Placebo)

Figure 12: Hospitalisations

	Topical A	SA	Placeb	0	Risk Ratio	(Risk Ratio)
Study or Subgroup	Events	Total) (Events	Total (Weigh	t) (M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
POKROTNIEKS2000	1	54	4	(57) (100.09	0 .26 [0.03, 2.29]	
(Total (95% CI))		54		(57) (100.0°	(0.26 [0.03, 2.29])	
(Total events)			4			
(Heterogeneity: Not appli	cable					
(Test for overall effect: Z	= 1.21 (P = 1	0.23)				avours Topical ASA (Favours Placebo)

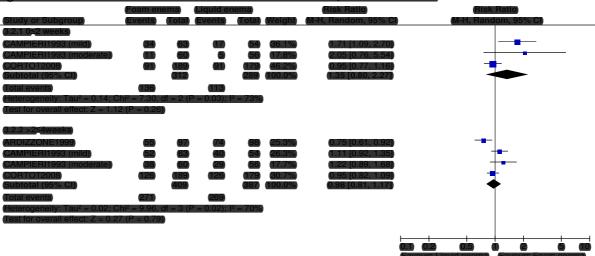
(1.1.1.2) (Preparation comparisons - Foam enema versus liquid enema)

(Figure 13: Clinical remission)

0	-							
	Foam en	ema	Liquid e	nema		Risk Ratio		Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl) (<u>M-H, Fixe</u>	ed, 95% Cl
(3.1.1 0 <u>≤</u> 2 weeks)								
(CAMPIERI1993 (mild))	34	63	(17)	(54)	(15.7%)	(1.71 [1.09, 2.70])		_
CAMPIERI1993 (moderate)		60	5	(56)	4.4%	2.05 [0.76, 5.54]		
CORTOT2008	91	(189)	91	(179)	(79.9%)	(0.95 [0.77, 1.16])	-	-
Subtotal (95% CI)	_	312	_	289	100.0%	(1.12 [0.93, 1.34]	•	•
Total events	(136)		(113)					
Heterogeneity: Chi ² = 7.30, df	= 2 (P = 0,	03); l² =	73%					
Test for overall effect: Z = 1.1	6 (P = 0.25)							
		-						
(3.1.2 >2 <u>≤</u> 4weeks)								
ARDIZZONE1999	(55)	97	74	(98)	26.7%)	0.75 [0.61, 0.92]		
(CAMPIERI1993 (mild))	52	63	40	(54)	(15.6%)	(1.11 [0.92, 1.35])	-	
CAMPIERI1993 (moderate)	38	60	29	56	(10.9%)	(1.22 [0.89, 1.68])	-	
CORTOT2008	126	(189)	126	(179)	46.9%)	(0.95 [0.82, 1.09])	-	ŀ
Subtotal (95% CI)		409		387	100.0%	0.95 [0.86, 1.05]	•	
(Total events)	271		269					
(Heterogeneity: Chi ² = 9.96, df	= 3 (P = 0,	02); l ² =	70%)					
Test for overall effect: Z = 1.03								
		-						
							I I I I I I I I I I I I I I I I I I I	
							0.1 0.2 0.5	0 2 5 10
							(Favours Liquid enema)	(Favours Foam enema)

r subgroup differences: Chi² = 2.26, df = 1 (P = 0.13), l² = 55.7

Figure 14: Clinical remission 0≤2 weeks and >2≤4 weeks, random effects



(Test for subaroup differences: $Chi^2 = 1.30$, df = 1 (P = 0.25), $l^2 = 23.3\%$

Figure 15: Clinical improvement

	(Foam en	ema	Liquid e	nema		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
(3.3.1 0≤2 weeks)							
CAMPIERI1993 (mild))	(54)	63	(39)	(54)	(55.9%)	(1.19 [0.98, 1.44])	+ <mark></mark>
CAMPIERI1993 (moderate)	44	60	32	56	44.1%	(1.28 [0.98, 1.69])	
Subtotal (95% CI)		(123)		(110)	100.0%	(1.23 [1.04, 1.45])	◆
(Total events)	(98)		71				
(Heterogeneity: Chi ² = 0.22, df	= 1 (P = 0.	.64); l² =	= 0%)				
Test for overall effect: $Z = 2.49$) (P = 0.01						
3.3.2 >2≤4weeks	_	_	_	_			
(BIANCONE2007)	(16)	24	17	(24)	(14.8%)	(0.94 [0.64, 1.38])	
(CAMPIERI1993 (mild))	(56) (51)	63	46	(54)	(43.0%)	(1.04 [0.91, 1.20])	
(CAMPIERI1993 (moderate)) (Subtotal (95% CI))	51	(147) (147)	(47)	(134)		$(1.01 \ [0.87, 1.18])$ $(1.02 \ [0.91, 1.13])$	
(Total events)	(123)		(110		100.070		Ť
(Heterogeneity: $Chi^2 = 0.30$, df		86) · 12 -					
Test for overall effect: $Z = 0.28$			- 0 /0/				
	, (0.70						
(3.3.4 >6≤8 weeks)							
BIANCONE2007	(16)	24	(22)	(24)	(100.0%)	(0.73 [0.53, 0.99])	
Subtotal (95% CI)	_	24	_	24	100.0%	0.73 [0.53, 0.99]	
Total events	(16)		(22)				
Heterogeneity: Not applicable							
(Test for overall effect: $Z = 2.03$	B(P = 0.04)						
							(Favours Liquid enema) (Favours Foam enema)
Test for subgroup differences:	$Chi^2 = 9.4$	5 df = 2	P(P = 0.00)	$ 9\rangle ^2 = 7$	78 8%		

Figure 16: Endoscopic remission

	Foam en	ema	Liquid e	nema		Risk Ratio		Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C		M-H, Fixe	d, 95% Cl		
(3.4.1 >2≤4weeks)											
ARDIZZONE1999	(51)	97	67	98	26.4%)	0.77 [0.61, 0.97]					
CAMPIERI1993 (mild))	(41)	63	30	54	(12.8%)	(1.17 [0.87, 1.58])		-	-		
(CAMPIERI1993 (moderate))	23	60	19	56	(7.8%)	(1.13 [0.69, 1.84])			-		
CORTOT2008	(121)	(189)	(130)	(179)	53.0%)	0.88 [0.77, 1.01]		-			
Subtotal (95% CI)		409		(387)	(100.0%)	0.91 [0.81, 1.01]		•			
(Total events)	236		246								
Heterogeneity: Chi ² = 5.70, df	= 3 (P = 0.	13); l² =	47%								
(Test for overall effect: $Z = 1.71$	I (P = 0.09										
										<u> </u>	1
							(0.1) (0.2)	(0.5) (1) (2)	5 10	
		_					Favours Liq	uid enema)	Favours Fo	bam enema	

Figure 17: Clinical and endoscopic remission

	Foam er	nema	Liquid e	nema		Risk Ratio			R	isk R	atio		
Study or Subgroup	Events	Total	Events	(Total)	Weight	(M-H, Fixed, 95% Cl)		(M-H, I	Fixed	, 95% C		
(3.5.1 >2≤4weeks)									_				
ARDIZZONE1999	(48)	97	64	98	(100.0%)	(0.76 [0.59, 0.97])			-	-			
(Subtotal (95% CI))		97		98	100.0%	0.76 [0.59, 0.97]							
(Total events)	48		64										
(Heterogeneity: Not app	licable												
(Test for overall effect: 2	Z = 2.20 (F	P = 0.03											
										_			
							0.1 (0.2)	0.5	Ó	2	(5	
							Eavor	irs iau	id enem	1 a (avours	Foam e	hema
Test for subaroun differ	roncos: No	t applic	ablo				a avoc				arouro	i otani o	Torna

Figure 18: Adverse events

	Foam en	ema	Liquid er	nema		Risk Ratio			Risk	Ratio		
Study or Subgroup	Events	(Total)	Events	(Total)	Weight	(M-H, Fixed, 95% Cl)		M-H, Fixe	ed, 95%	CI	
CAMPIERI1993 (mild)	1	63	1	(54)	(1.7%)	(0.86 [0.05, 13.38])	+		•			
CAMPIERI1993 (moderate)	5	60	2	(56)	(3.3%)	2.33 [0.47, 11.54]					•	\rightarrow
CORTOT2008	(52)	(191)	59	(182)	95.1%)	(0.84 [0.61, 1.15])			_	F		
		_										
(Total (95% CI))		(314)		(292)	(100.0%)	(0.89 [0.66, 1.20])						
(Total events)	58		62									
Heterogeneity: Chi ² = 1.53, df			0%)				0.1	(0.2)	0.5	1 2	6	(10)
(Test for overall effect: $Z = 0.76$	5(P = 0.45)						Fav	ours Foa	m enema	Favour	s Liquid er	iema)

Figure 19: Serious adverse events

	Foam en	ema	Liquid er	nema		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	(Total)	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixe	ed, 95% Cl)	
(CORTOT2008)		(191)	1	(182)	(100.0%)	0.95 [0.06, 15.12]	_			_
Total (95% CI)		(191)		(182)	100.0%	0.95 [0.06, 15.12]	_			-
(Total events)			1							
Heterogeneity: Not app	olicable									(100
Test for overall effect:	Z = 0.03 (P	' = 0.97))				(Favours Fo	am enema)	Favours Liq	uid enema

1.1.1.3 (Preparation comparisons – Suppository versus liquid enema)

Test for subgroup differences: $Chi^2 = 0.21$, df = 1 (P = 0.65), $I^2 = 0\%$

(Figure 20: Clinical remission)

Suppository Liquid enema (Risk Ratio) (Risk Ratio) Study or Subgroup Events (Tota) (Weight) (M-H, Fixed, 95% C) (M-H, Fixed, 95% C) (4.1.1 0<2 weeks) (CAMPIERI1988) (9) (19) (20) (100.0%) (1.18 [0.58, 2.42)) Subtotal (95% CI) (19) (20) (100.0%) (1.18 [0.58, 2.42)) (100.0%) (Total events) (9) (8) (100.0%) (1.18 [0.58, 2.42)) (100.0%)
(4.1.1 0<2 weeks) (CAMPIERI1988) (9) (19) (8) (20) (100.0%) (1.18 [0.58, 2.42]) (Subtotal (95% Cl)) (19) (20) (100.0%) (1.18 [0.58, 2.42])
CAMPIERI1988 (9) (19) (8) (20) (100.0%) (1.18) (0.58) (2.42) Subtotal (95% Cl) (19) (20) (100.0%) (1.18) (0.58) (2.42)
Subtotal (95% CI)) (19) (20) (100.0%) (1.18 [0.58, 2.42])
Total events 9 6
Heterogeneity: Not applicable
(jest for overall effect: Z = 0.46 (P = 0.64)
4.1.2 ≥2≤4 weeks
(CAMPIERI1988) (15) (19) (16) (20) (100.0%) (0.99 [0.72, 1.36)
Subtotal (95% Cl) (19 (20 (100.0%) 0.99 [0.72, 1.36)
Total events (15) (16)
Heterogeneity: Not applicable)
(lest for overall effect: Z = 0.08 (P = 0.94))
(Favours Liquid enema) (Favours Suppository)

igure 21. Clinical Improvement

(Figure 21: Clinical Improver	nent		
Suppository	Liquid enema	Risk Ratio	Risk Ratio
(Study or Subgroup) (Events) (To	tal (Events) (Total (Weight)	(M-H, Fixed, 95% CI)	(M-H, Fixed, 95% CI)
4.2.1 0≤2 weeks			
CAMPIERI1988 (16)	19 (17) (20 (100.0%)	0.99 [0.76, 1.30]	
Subtotal (95% CI)	19 (100.0%)	0.99 [0.76, 1.30]	•
(Total events) (16)	17		
(Heterogeneity: Not applicable)			
Test for overall effect: $Z = 0.07$ (P = 0.	.95)		
4.2.2 >2≤4 weeks			
CAMPIERI1988) (17)	<u>19</u> (18) (20 (100.0%)	(0.99 [0.80, 1.23])	
Subtotal (95% CI)	19 (20) (100.0%)	(0.99 [0.80, 1.23])	—
(Total events) (17)	(18)		
Heterogeneity: Not applicable			
(Test for overall effect: $Z = 0.05$ ($P = 0$.)	96)		
		L	
		0.1	
	0.00 df _ 1 /P _ 0.08) 12 _ 0%	Fav	vours Liquid enema) (Favours Suppository)

(Test for subgroup differences: $Chi^2 = 0.00$, df = 1 (P = 0.98), $I^2 = 0\%$

Figure 22: Endoscopic remission

	Supposit	ory Li	quid er	nema		Risk Ratio		Risk F	latio		
Study or Subgroup	Events	(Total) (Ev	vents	(Total)	Weight	M-H, Fixed, 95% C		M-H, Fixed	d, 95% CI		
(4.3.1 0≤2 weeks)											
CAMPIERI1988	9	(19)	6	(20)	100.0%)	(1.58 [0.70, 3.59])		-+	_		
Subtotal (95% CI)	_	19	_	20 (100.0%)	(1.58 [0.70, 3.59])					
(Total events)	9		6								
(Heterogeneity: Not app	olicable										
(Test for overall effect:)	Z = 1.09 (P :	= 0.28)									
(4.3.2 >2 <u>≤</u> 4 weeks)								L	_		
CAMPIERI1988	(14)	19	13	20 (100.0%)	(1.13 [0.75, 1.72])			_		
Subtotal (95% CI)		19		20 (100.0%	(1.13 [0.75, 1.72]					
(Total events)	(14)		13								
(Heterogeneity: Not app	olicable										
(Test for overall effect:	Z = 0.59 (P =	= 0.56)									
									_		+
							Favours Liquid	enema)	Favours Sup		,
To at fam and surrous all fa			£ 4 (D	0 40)	12 00()		, avours Liquiu	ononia	i avouis oup	pository	

Test for subgroup differences: $Chi^2 = 0.50$, df = 1 (P = 0.48), $l^2 = 0^6$

1.1.1.4 (Dose comparisons)

Figure 23: Clinical remission – 1g versus 1.5g

	(Topical AS	6A 1g	Topical ASA	1.5g		Risk Ratio	Risk Ratio
Study or Subgroup	Events	(Total)	Events	(Total)	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
(5.1.1 0 <mark>≤2 weeks</mark>)							
(CAMPIERI1990)	(13)	(32)	(14)	(31)	(100.0%)	0.90 [0.51, 1.59]	
Subtotal (95% CI)	_	32	—	31	100.0%	0.90 [0.51, 1.59]	
Total events	(13)		14				
(Heterogeneity: Not app	olicable)						
(Test for overall effect: 2	Z = 0.36 (P =	0.72)					
(5.1.2 >2 <u>≤</u> 4 weeks)							
(CAMPIERI1990)	22	(32)	23	31	(100.0%)	(0.93 [0.68, 1.27])	
Subtotal (95% CI)		32		31	100.0%	0.93 [0.68, 1.27]	•
(Total events)	22		23				
(Heterogeneity: Not app	licable						
(Test for overall effect: 2	Z = 0.48 (P =	0.63)					
Test for subgroup diffe	rences: Chi ²	= 0.01. d	f = 1 (P = 0.93	3). $ ^2 = 0$	%		(Favours Higher dose) (Favours Lower dos

Figure 24: Clinical remission – 1g versus 2g

	(Topical AS	A 1g	Topical A	SA 2q	Risk Ratio	Risk Ratio
Study or Subgroup	Events	(Total)	Events	(Total) (Weight)	(M-H, Fixed, 95% C	(M-H, Fixed, 95% CI)
(5.2.1 0≤2 weeks)						
(CAMPIERI1991)	9	27	(1)	(30) (100.0%)	(0.91 [0.45, 1.85])	
(Subtotal (95% CI)		27		30 (100.0%)	0.91 [0.45, 1.85])	
(Total events)	9		(1)			
(Heterogeneity: Not app	plicable					
Test for overall effect:	Z = 0.26 (P =	0.79)				
(5.2.2 >2 <u><</u> 4 weeks)						
CAMPIERI1991	(17)	27	20	(30) (100.0%)	(0.94 [0.64, 1.39])	
Subtotal (95% CI)		27	_	30 (100.0%)	(0.94 [0.64, 1.39])	
(Total events)	(17)		20			
(Heterogeneity: Not app						
(Test for overall effect:	Z = 0.29 (P =	(0.77)				
(5.2.3 >6≦8 weeks)						
(HANAUER1998)	(34)	70	(35)		(0.94 [0.67, 1.33])	
Subtotal (95% CI)	04	73 73	00	(71) (<u>100.0%</u>) (71) (100.0%)	0.94 [0.67, 1.33]	
(Total events)	34		(35)			Ť
(Heterogeneity: Not app						
(Test for overall effect:		(0, 74)				
Test for subgroup diffe	ronooc Chi2	_0.01 df	_ 2 (D _ 1	00) $12 - 00/)$		(Favours Higher dose) (Favours Lower dose)

Figure 25: Clinical remission – 1g versus 4g

	Topical AS	SA 1g	Topical A	SA 4g		(Risk Ratio)	(Risk Ratio)
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
(5.3.1 0 <u>≤</u> 2 weeks)							
(CAMPIERI1991)	9	27	(13)	29	(100.0%)	0.74 [0.38, 1.45]	
Subtotal (95% CI)		27		29	(100.0%)	0.74 [0.38, 1.45]	
(Total events)	9		(13)				
Heterogeneity: Not app	olicable						
(Test for overall effect: 2	Z = 0.87 (P =	0.39)					
(5.3.2 >2 <u>≤</u> 4 weeks)							
CAMPIERI1991	17	27	21	29	(100.0%)	0.87 [0.60, 1.25]	
Subtotal (95% CI)		27		(29)	(100.0%)	0.87 [0.60, 1.25]	
(Total events)	17		21				
(Heterogeneity: Not app							
Test for overall effect: 2	Z = 0.75 <u>(</u> P =	0.45)					
(5.3.3 >6≤8 weeks)							
	_		_	_			
(HANAUER1998) (Subtotal (95% CI))	(34)	(73) (73)	(32)	73	(100.0%)	(1.06 [0.74, 1.52]) (1.06 [0.74, 1.52])	
	-	13	_	13	100.0 /0	(1.00 [0.74, 1.32])	—
(Total events)	(34)		32				
(Heterogeneity: Not app		0.740					
(Test for overall effect: 2	z = 0.33 (P =	0.74)					
Test for ordenue differ		1 00 4			00/		(Favours Higher dose) (Favours Lower dose)
(Test for subaroup diffe	rences: Chi ²	= 1.09. 0	a = 2 (P = 0)	$(58), 1^2 =$	0%		

Figure 26: Clinical remission – 2g versus 4g

	Topical AS	6A 2g	(Topical A	SA 4g	Risk Ratio	(Risk Ratio)
Study or Subgroup	Events	Total	Events	(Total) (Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
(5.4.1 0 <u>≤</u> 2 weeks)						
CAMPIERI1991	(11)	30	(13)	(29) (100.0%	(0.82 [0.44, 1.52])	
(Subtotal (95% CI))		30		(29) (100.0%	0.82 [0.44, 1.52]	
(Total events)	11		(13)			
(Heterogeneity: Not app	olicable					
(Test for overall effect:)	Z = 0.64 (P =	0.53)				
(5.4.2 >2 <u>≤</u> 4 weeks)						
(CAMPIERI1991)	20	(30)	(21)	(29) (100.0%		
Subtotal (95% CI)		(30)		(29) (100.0%	0.92 [0.66, 1.29]	\bullet
(Total events)	20		21			
(Heterogeneity: Not app						
Test for overall effect:	Z = 0.48 (P =	0.63)				
(5.4.0. (50 meetre)						
(5.4.3 >6 <u>≤</u> 8 weeks)						
(HANAUER1998)	(35)	71	(32)	73 (100.0%		
Subtotal (95% CI)	_	71	_	(73) (100.0%	(1.12 [0.79, 1.60])	
(Total events)	(35)		(32)			
(Heterogeneity: Not app						
Test for overall effect:	Z = 0.66 (P =	0.51)				
Tact for subgroup diffo		4 05 -				Favours Higher dose) (Favours Lower dose)

Figure 27: Clinical improvement – 1g versus 1.5g

st for subgroup differences: $Chi^2 = 0.00$, df = 1 (P = 0.97), $I^2 = 0\%$

	Topical AS	A 1g	Topical ASA	1.5g		Risk Ratio	Risk Ratio
Study or Subgroup	Events	(Total)	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
(5.5.1 0 <u>≤</u> 2 weeks)							
CAMPIERI1990	(24)	(32)	26	31	(100.0%)	(0.89 [0.69, 1.15])	
(Subtotal (95% CI))		(32)		31	100.0%	0.89 [0.69, 1.15])	•
(Total events)	(24)		26				
(Heterogeneity: Not app	licable						
(Test for overall effect: 2	Z = 0.87 (P =	0.39))					
(5.5.2 >2 <u><</u> 4 weeks)							
CAMPIERI1990	26	(32)	28	31	100.0%	0.90 [0.73, 1.10]	
(Subtotal (95% CI))		32		31	(100.0%)	(0.90 [0.73, 1.10])	-
(Total events)	26		28				
Heterogeneity: Not app							
(Test for overall effect: 2	Z = 1.02 (P = 1)	0.31))					
	01.10	0.00					Favours Higher dose (Favours Lower dose)

Figure 28: Clinical improvement – 1g versus 2g

	(Topical AS	A 10	Topical AS	SA 20	Risk Ratio	Risk Ratio
Study or Subgroup	(Events)	Total	Events	(Total) (Weight)	(M-H, Fixed, 95% C	
(5.6.1 0≤2 weeks)	Liteine	Total		Total (Treight)		
CAMPIERI1991	21	27	(23)	(30) (100.0%)	(1.01 [0.77, 1.35])	
(Subtotal (95% CI))		27		(30) (100.0%)	(1.01 [0.77, 1.35])	
(Total events)	(21)	_	23			
Heterogeneity: Not app	olicable		_			
(Test for overall effect: 2	Z = 0.10 (P =	0.92)				
(5.6.2 >2≦4 weeks)						
CAMPIERI1991	23	27	25	30 (100.0%)	(1.02 [0.82, 1.28]	
Subtotal (95% CI)		27		(30) (100.0%)	(1.02 [0.82, 1.28])	•
(Total events)	23		25			
(Heterogeneity: Not app						
(Test for overall effect: 2	Z = 0.19 (P =	0.85)				
(5.6.3 >6≤8 weeks)						
(HANAUER1998)	(49)	73	(46)	(71) (100.0%)	(1.04 [0.82, 1.31])	
Subtotal (95% CI)	43	73	40	71 (100.0%)	(1.04 [0.82, 1.31])	
(Total events)	(49)	_	(46)			T
(Heterogeneity: Not app						
(Test for overall effect: 2		0.77)				
						(0.1) (0.2) (0.5) (1) (2) (5) (10) (Favours Higher dose) (Favours Lower dose)
(Test for subaroup diffe	rences: Chi2	= 0.01. df	[•] = 2 (P = 0.	99), $l^2 = 0\%$		a around higher according to a construction according

Figure 29: Clinical improvement – 1g versus 4g

	(Topical AS	SA 1g	Topical A	SA 4g)	_	Risk Ratio	Risk Ratio
Study or Subgroup	(Events)	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl)
(5.7.1 0≤2 weeks)							
CAMPIERI1991	21	(27)	24	(29)	(100.0%)	(0.94 [0.72, 1.22])	
Subtotal (95% CI)		27		29	100.0%	0.94 [0.72, 1.22]	\bullet
(Total events)	21		24				
(Heterogeneity: Not app	olicable						
Test for overall effect: 2	Z = 0.47 (P =	0.64)					
(5.7.2 >2 <u>≤</u> 4 weeks)							
CAMPIERI1991	(23)	27	25	29	(100.0%)	0.99 [0.80, 1.22]	
Subtotal (95% CI)		27		(29)	(100.0%)	0.99 [0.80, 1.22]	\bullet
(Total events)	23		25				
(Heterogeneity: Not app	-						
(Test for overall effect: 2	<u>Z = 0.11 (P =</u>	0.91)					
(5.7.3 >6≤8 weeks)							
(HANAUER1998)	(49)	(73)	65	(73)	(100.0%)	(0.89 [0.72, 1.10])	
Subtotal (95% CI)		73		73	(100.0%)	0.89 [0.72, 1.10]	→
(Total events)	49	_	(55)	_			
Heterogeneity: Not app	licable						
Test for overall effect: 2		0.27)					
							(0.1) (0.2) (0.5) (1) (2) (5) (10) (Favours Higher dose) Favours Lower dose)
(Test for subaroup diffe	rences: Chi ² :	= 0.46, c	lf = 2 (P = 0	.79), l² =	: 0%)		avours higher doser (Favours Lower doser

Figure 30: Clinical improvement – 2g versus 4g

	Topical AS		Topical AS	SA 4q)	Risk Ratio	Risk Ratio
Study or Subgroup	Events	(Total)	Events	(Total) (Weight	M-H, Fixed, 95% C	I) (M-H, Fixed, 95% Cl)
(5.8.1 0 <mark>≤</mark> 2 weeks)						
CAMPIERI1991	23	30	24	29 (100.0%)	0.93 [0.72, 1.20]	
Subtotal (95% CI)		(30)		(29) (100.0%	(0.93 [0.72, 1.20]	•
Total events	23		24			
Heterogeneity: Not app						
(Test for overall effect: 2	Z = 0.58 (P =	0.56)				
5.8.2 >2≤4 weeks						
	-	-		00 (100 00/		
(CAMPIERI1991) (Subtotal (95% CI))	25	<u>30</u> 30	20	(29) (100.0%) (29) (100.0%)		
(Total events)	25		25	25 1100.070	0.01 [0.10, 1.20]	Ŧ
(Heterogeneity: Not app	الحصالة		20			
(Test for overall effect: 2	-	0.76)				
		00)				
(5.8.3 >6≦8 weeks						
(HANAUER1998)	46	71	55	73 (100.0%	0.86 [0.69, 1.07]	i i i i i i i i i i i i i i i i i i i
Subtotal (95% CI)		(71)		73 (100.0%	0.86 [0.69, 1.07]	◆
(Total events)	(46)		55			
(Heterogeneity: Not app	olicable					
(Test for overall effect: 2	Z = 1.37 (P =	0.17)				
						0.1 0.2 0.5 0 2 5 10
Toot for subgroup diffe		0 57 - 10		75) 12 00()		(Favours Higher dose) (Favours Lower dose)

Figure 31: Endoscopic remission – 1g versus 1.5g

	(Topical AS	SA 1a	Topical AS	A 1.5a		Risk Ratio		Risk I	Batio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C			d, 95% Cl		
(5.9.2 >2≤4 weeks)	Licino	Total	Liono	Total	Troight	un 11, 1 1xcd, 00 /0 0		, III I, I KO	u, oo /o o.		
CAMPIERI1990			47		(100.00/)				_		
(Subtotal (95% CI)	(19)	(32)			100.0%	(1.08 [0.70, 1.66] (1.08 [0.70, 1.66]					
	-	52	-	31	100.0 /0	(1.00 [0.70, 1.00]					
(Total events)	(19)										
(Heterogeneity: Not app											
(Test for overall effect: 2	Z = 0.36 (P =	: 0.72)									
							(Favours Hid		Envoured	_ower dos	
							ravours mig	gner dose	ravoursi	_ower dos	e

(Test for subgroup differences: Not applicable)

Figure 32: Endoscopic remission – 1g versus 2g)

	(Topical A	SA 1g	(Topical A	SA 2g		Risk Ratio	Risk Ratio
Study or Subgroup	Events	(Total)	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% CI
(5.10.1 0 <mark>≤2weeks</mark>)							
CAMPIERI1991	7	27	9	(30)	68.9%	(0.86 [0.37, 2.00])	
POWELLTUCK1986	0	12	4	(13)	(31.1%)	(1.90 [0.74, 4.88])	
Subtotal (95% CI)		39		43	100.0%	(1.18 [0.64, 2.20]	
(Total events)	(14)		(13)				
(Heterogeneity: Chi ² = 1	l.49, df = 1 (l	[•] = 0.22);	; l² = 33%)				
(Test for overall effect: 2	Z = 0.54 (P =	0.59)					
<u>5.10.2 >2≤4 weeks</u>							<u> </u>
CAMPIERI1991	(12)	27	(13)	(30)	68.1%)	(1.03 [0.57, 1.85])	
POWELLTUCK1986	9	(12)	6	(13)	(31.9%)	(1.63 [0.83, 3.18])	
(Subtotal (95% CI))		39		43	100.0%	(1.22 [0.78, 1.89])	
(Total events)	(21)		(19)				
(Heterogeneity: Chi ² = 1			$ ^2 = 4\%$				
(Test for overall effect: 2	∠ = 0.87 (P =	0.39)					
(5.10.3 >6≤8 weeks)							
(HANAUER1998)	(43)			74	100.00/	(0.91 [0.70, 1.18])	
(Subtotal (95% CI)	45	(73) (73)	(46)		(100.0%)	(0.91 [0.70, 1.18])	
(Total events)	43		46	_			
(Heterogeneity: Not app			40				
(Test for overall effect: 2		0.47)					
rost for overall effect. 2	<u> </u>	0.47					
Test for subgroup differ	ronoog Chi2	_ 1 57 d	f _ 0 (P _ 0	46) 2-	0.0/		(Favours Higher dose) (Favours Lower dose)

(Test for subgroup differences: $Chi^2 = 1.57$, df = 2 (P = 0.46), $I^2 = 0\%$

Figure 33: Endoscopic remission – 1g versus 4g

0	(Topical AS	A 1a	Topical AS	A 4m		Risk Ratio	Risk Ratio
Study or Subgroup	(Events)	Total	Events		Weight	M-H, Fixed, 95% C	
(5.11.1 0≤2 weeks)							
(CAMPIERI1991)		27	(1)	29	(100.0%)	(0.68 [0.31, 1.51])	
Subtotal (95% CI)		27		29	(100.0%)	0.68 [0.31, 1.51]	
(Total events)			(11)				
(Heterogeneity: Not app							
(Test for overall effect: 2	Z = 0.94 (P = 1)	0.34))					
(5.11.2 >2≤4 weeks)							
(CAMPIERI1991)	(12)	27)	(15)	20	(100.0%)	(0.86 [0.50, 1.49])	
Subtotal (95% CI)		27		29	(100.0%)	0.86 [0.50, 1.49]	
(Total events)	(12)	_	(15)	_			-
(Heterogeneity: Not app	licable		_				
Test for overall effect: Z	Z = 0.54 (P =	0.59)					
(5.11.3 >6 <u>≤</u> 8 weeks)							
(HANAUER1998)	(43)	73	48	73	(100.0%)	(0.90 [0.70, 1.15])	
Subtotal (95% CI)	_	73	-	73	(100.0%)	(0.90 [0.70, 1.15])	
(Total events)			48				
(Heterogeneity: Not app (Test for overall effect: 2		0 30)					
Host for overall effect. 2	0.05 (1" =	0.00					
							(C.1) (C.2) (C.5) (1) (2) (5) (10) (Favours Higher dose) (Favours Lower dose)
Test for subgroup differ	rences: Chi² =	= 0.41, df	= 2 (P = 0.	81), l² =	0%)		avours higher doser (ravours Lower doser

Figure 34: Endoscopic remission – 2g versus 4g

	(Topical AS	SA 2g	Topical A	SA 4g	Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	(Total) (Weight)	M-H, Fixed, 95% C	I) (M-H, Fixed, 95% CI)
(5.12.1 0≤2 weeks)						
CAMPIERI1991	9	30	(11)	(29) (100.0%)	(0.79 [0.39, 1.62])	
Subtotal (95% CI)		30		29 (100.0%)	0.79 [0.39, 1.62]	
(Total events)	9		(11)			
(Heterogeneity: Not app	olicable)					
Test for overall effect:	Z = 0.64 (P =	0.52)				
(5.12.2 >2≤4 weeks)						_
CAMPIERI1991	(13)	<u>30</u> 30	(15)	(29) (100.0%)	(0.84 [0.49, 1.44])	
Subtotal (95% CI)	_	30	_	(29) (100.0%)	0.84 [0.49, 1.44]	
(Total events)	(13)		(15)			
(Heterogeneity: Not app		0.50				
Test for overall effect:	Z = 0.64 (P =	0.52)				
(5.12.3 >6≤8 weeks)						
(HANAUER1998)	46	71	48	(73) (100.0%)	(0.99 [0.78, 1.25]	
Subtotal (95% CI)		71		73 (100.0%)	(0.99 [0.78, 1.25])	➡
(Total events)	(46)	_	(48)			
Heterogeneity: Not app	olicable		_			
Test for overall effect:		0.90)				
						(0.1) (0.2) (0.5) (1) (2) (5) (10) (Favours Higher dose) (Favours Lower dose)
(Test for subaroup diffe	rences: Chi ²	= 0.55, df	⁻ = 2 (P = 0	1.76 , $l^2 = 0\%$		arours rights accor (arours cower accor

Figure 35: Clinical and endoscopic remission – 1g versus 2g

	(Topical AS)	A 1g) (Topical AS	6A 2g	Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	(Total) (Weight)	(M-H, Fixed, 95% C	M-H, Fixed, 95% CI
(5.13.1 0 <u>≤</u> 2 weeks)						
POWELLTUCK1986	3	(12)	2	(13) (100.0%)	(1.63 [0.33, 8.11])	
(Subtotal (95% Cl))		12		(13) (100.0%)	(1.63 [0.33, 8.11])	
(Total events)	3		2			
Heterogeneity: Not app	licable					
(Test for overall effect: Z	. = 0.59 (P = 0).55))				
(5.13.2 >2 <u>≤</u> 4 weeks)						
POWELLTUCK1986	7	(12)	4	(13) (100.0%)	(1.90 [0.74, 4.88])	
Subtotal (95% CI)		(12)		(13) (100.0%)	(1.90 [0.74, 4.88])	
(Total events)	7		4			
(Heterogeneity: Not app	licable					
(Test for overall effect: Z	2 = 1.33 (P = 0).18))				
(Teet few enderwerden differ						(Favours Higher dose) (Favours Lower dose)

Test for subgroup differences: $Chi^2 = 0.03$, df = 1 (P = 0.87), $I^2 = 0\%$

Figure 36: Adverse events

	Lower do	ose) (Higher	dose		Risk Ratio	Risk Ratio
Study or Subgroup	Events	(Total) (Events)	(Total)	Weight	(M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
5.15.1 1g versus 1.5g						
CAMPIERI1990	1	32 0	31	26.0%	(2.91 [0.12, 68.81])	
Subtotal (95% CI)		32	(31)	26.0%)	2.91 [0.12, 68.81]	
(Total events)	1	0				
(Heterogeneity: Not app	licable					
(Test for overall effect: Z	. = 0.66 (P	= 0.51)				
5.15.2 1g versus 2g						
POWELLTUCK1986	0	12 1	(13)	74.0%	0.36 [0.02, 8.05]	
Subtotal (95% CI)		12	(13)	74.0%	0.36 [0.02, 8.05]	
(Total events)	0	•				
(Heterogeneity: Not app	licable					
(Test for overall effect: Z	. = 0.65 (P	= 0.52))				
(Total (95% CI))		44	44	100.0%	(1.02 [0.15, 7.15])	
(Total events)	1					
(Heterogeneity: Chi ² = 0	.85, df = 1	$(P = 0.36); I^2 = 0$	1%			
Test for overall effect: Z	. = 0.02 (P	= 0.98)				(Favours Lower dose) (Favours Higher dose)
Test for subgroup differ	ences: Chi ^a	² = 0.85, df = 1 (P = 0.36	5), l² = 0%)		

(1.1.1.5) (Regimen comparison – once versus twice a day)

Figure 37: Clinical remission

	Once a day	(Twice a	day	Risk Ratio	(Risk Ratio)
Study or Subgroup	Events (To	tal) (Events)	(Total) (Weight)	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
6.1.1 >2<4weeks					<u> </u>
LAMET2005	21	44 27	(53) (100.0%)	0.94 [0.62, 1.41]	
Subtotal (95% CI)	(44	53 (100.0%)	0.94 [0.62, 1.41]	\bullet
(Total events)	21	27			
(Heterogeneity: Not ap	plicable				
Test for overall effect:	Z = 0.31 (P = 0	0.75)			
6.1.2 >6<8 weeks					
LAMET2005	34	44 38	53 (100.0%)	(1.08 [0.85, 1.36])	
(Subtotal (95% CI)	(44	53 (100.0%)	(1.08 [0.85, 1.36])	•
(Total events)	34	38			
Heterogeneity: Not ap	plicable				
(Test for overall effect:	Z = 0.63 (P = 0.63)	0.53)			
					(Favours Twice a day) (Favours Once a day)
Test for subgroup diffe	erences: Chi² =	0.34, df = 1 (P = 0.56), l² = 0%		

Figure 38: Adverse events

	Once a day (Twice			day		Risk Ratio	Risk Ratio						
Study or Subgroup	Events	(Total)	Events	(Total) (Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI						
LAMET2005	24	44	30	53 (1	100.0%	0.96 [0.67, 1.38]							
(Total (95% Cl))		44		53 (1	100.0%)	0.96 [0.67, 1.38]	\bullet						
(Total events)	24		30										
(Heterogeneity: Not ap	olicable												
Test for overall effect:	Z = 0.20 (F	° = 0.84)					(Favours Once a day) (Favours Twice a day						

1.1.1.6 (Regimen and dose comparison – once a day (1g) versus three times a day (1.5g)



Figure 40: Clinical improvement



Figure 41: Endoscopic remission

	Once a da	iy (1g)	3 times a day	r (1.5g))	(Risk Ratio)	e	isk Ratio			
Study or Subgroup	Events	(Total)	Events	(Total) (Weight)	M-H, Fixed, 95% CI	(M-H, I	Fixed, 95%	o CI		
(7.3.1 >4⊴6 weeks)										
(ANDUS2010)	(153)	201	(164)	(207) (100.0%)	(0.96 [0.87, 1.07])					
(Subtotal (95% CI))		201		207 (100.0%)	0.96 [0.87, 1.07]		•			
Total events	153		(164)							
Heterogeneity: Not app	licable									
Test for overall effect: 2	L = 0.75 (P =	= 0.45)								
						05		2	6	10

0 E

(Test for subgroup differences: Not applicable

Figure 42: Adverse events

	Once a da	y (1g)	3 times a da	y (1.5g))	Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
ANDUS2010	68	(201)	43	207 (100.0%)	0.91 [0.62, 1.35]	
(Total (95% CI))		201		(207) (100.0%)	0.91 [0.62, 1.35]	-
(Total events)	38		(43)			
(Heterogeneity: Not app	olicable					
(Test for overall effect:)	Z = 0.47 (P =	0.64)				Favours Once a day - 10 Favours SOnce a day -1 50

Figure 43: Serious adverse events

	Once a day	y (1g))	3 times a day	/ (1.5g))	(Risk Ratio)	Risk Ratio
Study or Subgroup	Events	Total	Events	Total (Weight)	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
ANDUS2010		201		207) (100.0%)	(1.03 [0.06, 16.35])	
(Total (95% CI))		201		(207) (100.0%)	(1.03 [0.06, 16.35])	
(Total events)			•			
(Heterogeneity: Not ap	plicable					
(Test for overall effect:	Z = 0.02 (P =	0.98))				Eavours Once a day - 10 Eavours Once a day -150

Figure 44: Hospitalisations



1.1.2) (Topical corticosteroids)

Figure 45: Endose	copic rem	ission (>	>4≤6w	eeks		
	(Topical St	eroid	Placebo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	(Total) (Ev	vents) (To	otal) (Weight)	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
HANAUER1998A	(46)	(114)	9	57 (100.0%)	2.56 [1.35, 4.85]	
(Total (95% CI))		(114)		(57) (100.0%)	(2.56 [1.35, 4.85])	
(Total events)	(46)		9			
(Heterogeneity: Not app	olicable					
(Test for overall effect:	Z = 2.87 (P =	0.004)				(Favours Placebo) (Favours Topical steroic)

Figure 46: Clinical and endoscopic remission (>4≤6weeks)

	Topical St	eroid	Placeb	0		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	1	M-H, Fixe	ed, 95% Cl	
HANAUER1998A	26	(114)	2	(57)	(100.0%)	6.50 [1.60, 26.43]				
(Total (95% CI))		(114)		57	(100.0%)	6.50 [1.60, 26.43]				
(Total events)	26		2							
Heterogeneity: Not app							001 (100
(Test for overall effect: 2	Z = 2.62 (P =	= 0.009)					Eavou	rs Placebo	Eavours T	opical steroid

Figure 47: Serious adverse events 100.0% 1 0.2 0.5 2

1.1.2.1

Preparation comparison - Foam versus liquid enema

Figure 48: Clinica	l remissio	on (>2≤4w	eeks		
	Foam enem	na) (Liquid e	nema	Risk Ratio	Risk Ratio
Study or Subgroup	Events (T	otal Events	Total (Weight)	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
GROSS2006	(151)	265) (174)	(268) (100.0%)	0.88 [0.77, 1.01]	
(Total (95% CI))		265	(268) (100.0%)	0.88 [0.77, 1.01]	\bullet
(Total events)	(151)	(174)			
Heterogeneity: Not app	olicable				
Test for overall effect:	Z = 1.87 (P = (0.06))			Favours Liquid enema) Favours Foam enema

Figure 49: Clinical improvement (>2≤4weeks)

	Foam enema Liquid enema					Risk Ratio	(Risk Ratio						
Study or Subgroup	Events	(Total)	Events	Total	Weight	(M-H, Fixed, 95% Cl			M-H, Fi	xed,	95% CI		
GROSS2006	(177)	(210)	205	239	(100.0%)	(0.98 [0.91, 1.06])							
(Total (95% CI)		210		239	(100.0%)	(0.98 [0.91, 1.06])				•			
(Total events)	(177)		205										
Heterogeneity: Not ap	plicable								05				10
Test for overall effect:	Z = 0.44 (P	= 0.66)					Favo	urs Liqu	uid enema) 6	avours I	Foam en	ema

Figure 50: Endoscopic remission (>2≤4weeks)

	(Foam enema) (Liquid enema)				Risk Ratio	Risk Ratio							
Study or Subgroup	Events	(Total)	Events	Total	Weight	(M-H, Fixed, 95% CI)		(M-H, F	ixed,	95% CI		
GROSS2006	(106)	204)	(127)	234	(100.0%)	(0 .96 [0.80, 1.14])							
(Total (95% CI)		204		234	(100.0%)	0.96 [0.80, 1.14]				+			
Total events	(106)		(127)										
(Heterogeneity: Not ap	plicable								05				
(Test for overall effect:	Z = 0.48 (P	' = 0.63)					Eavo	urs Lia	uid enem:		avours E	oam en	ema

Figure 51: Adverse events

	Foam en	ema) (l	_iquid en	ema		Risk Ratio		Risk	Ratio		
Study or Subgroup	Events	(Total) (Events	(Total)	Weight	(M-H, Fixed, 95% CI)	1	M-H, Fixe	ed, 95% CI)		
GROSS2006	86	267	87	268	(100.0%)	(0.99 [0.78, 1.27])		-	-		
(Total (95% CI)		267		268	100.0%	0.99 [0.78, 1.27]		•			
(Total events)	86		87								
(Heterogeneity: Not ap								05 0	2	6	10
Test for overall effect:	Z = 0.06 (P	= 0.95)					(Favours F	oam enema	Favours L	iquid enem	a

Figure 52: Serious adverse events

	(Foam enema) Liquid enema					(Risk Ratio)			sk Ratio			
Study or Subgroup	Events	(Total)	Events	Total	Weight	(M-H, Fixed, 95% CI		<u>(M-H, Fix</u>	ed, 95% Cl)		
GROSS2006	2	267	4	268	(100.0%)	(0 .50 [0.09, 2.72])	•					
(Total (95% CI)		267		268	100.0%	0.50 [0.09, 2.72]						
Total events	2		4									
(Heterogeneity: Not app		0 40					0.1 0.2	0.5		5 10		
(Test for overall effect:	Z = 0.80 (P	= 0.42)	,				Favours	Foam enema	Favours L	Liquid enema		

1.1.2.2 Dose comparison – Budesonide

Figure 53: Endoscopic remission (>4≤6weeks) Cower dose Risk Ratio Risk Ratio Study or Subgroup Events (otal Weight M-H, Fixed, 95% C) (7.2.3 2mg versus 8mg budesonide (HANAUER1998A) (19 C1 (00, 100.0%) 0.78 [0.49, 1.24) Gubtotal (95% CI) 54 (60, 100.0%) 0.78 [0.49, 1.24) (Total events) (19 27 (Heterogeneity: Not applicable (Test for overall effect: Z = 1.05 (P = 0.29)) (Test for subgroup differences: Not applicable

Figure 54: Clinical and endoscopic remission

(inguic 34. cillica			111351011		
	Lower dos	se) (Higher d	lose	Risk Ratio	Risk Ratio
Study or Subgroup	Events (T	otal (Events)	(Total) (Weight)	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
(7.4.1 >2 <u>≤</u> 4 weeks (2m	ıg vs 4mg bu	udesonide)			
LINDGREN2002	(24)	73 31	(76) (100.0%)	0.81 [0.53, 1.23]	
Subtotal (95% CI)		73	(76) (100.0%)	0.81 [0.53, 1.23]	
Total events	(24)	31			
(Heterogeneity: Not app	olicable				
Test for overall effect:	Z = 0.99 (P =	0.32)			
7 4 0 . Acc wools for					
(7.4.2 >4≦6 weeks (2m	-	-			
(HANAUER1998A)	(10)	54 (16)	60 (100.0%)	(0.69 [0.35, 1.40])	
Subtotal (95% CI)		(54)	60 (100.0%)	0.69 [0.35, 1.40]	
(Total events)	(10)	(16)			
(Heterogeneity: Not app	olicable				
(Test for overall effect:	Z = 1.02 (P =	0.31)			
7 4 0 6 20 mm also (0m					
(7.4.3 >6 <u>≤</u> 8 weeks (2m	ig vs 4mg of	budesonide)			
(LINDGREN2002)	37	(73) (41)	76 (100.0%)	0.94 [0.69, 1.28]	
(Subtotal (95% CI))		73	(76) (100.0%)	0.94 [0.69, 1.28]	
(Total events)	(37)	(41)			
Heterogeneity: Not app	olicable				
Test for overall effect:	Z = 0.40 (P =	0.69)			
					0.1 0.2 0.5 (1 2 5 (1)
Test for subgroup diffe	roncos: Chi2	-0.76 df -2.0			Favours Higher dose) (Favours Lower dose)

Figure 55: Adverse events

	Lower d	ose	Higher d	dose		Risk Ratio		Risk F	Ratio	
Study or Subgroup	Events	(Total)	Events	(Total)	Weight	M-H, Fixed, 95% Cl		M-H, Fixed	d, 95% CI	
(7.5.3 2mg versus 4mg	g budeson	ide								
LINDGREN2002	48	(73)	(54)	(76)	(100.0%)	(0.93 [0.74, 1.15])			-	
(Subtotal (95% CI))		73		(76)	100.0%	0.93 [0.74, 1.15]		•	•	
Total events	(48)		(54)							
Heterogeneity: Not app	olicable									
(Test for overall effect: 2	Z = 0.69 (P	= 0.49								
							0.1 0.2	0.5 1	2	5 10
(Test for subgroup diffs							Favours Lo	wer dose	Favours Hi	gher dose

(Test for subgroup differences: Not applicable)

(Figure 56: Serious adverse events)

	Lower do	ose (ligher d	dose		Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	(Total) (E	vents	(Total)	Weight	M-H, Fixed, 95% CI		M-H, Fixe	ed, 95% Cl)
7.6.2 2mg versus 8mg	budesoni	de								
(HANAUER1998A)	0	54	3	60	100.0%	0.16 [0.01, 3.00]	•	_		
(Subtotal (95% CI))		(54)		60	(100.0%)	0.16 [0.01, 3.00]				
Total events	0		3							
Heterogeneity: Not app	licable									
Test for overall effect: Z	. = 1.23 (P	= 0.22)								
							0.01			100
Tast for subgroup diffor							Favours I	_ower dose	Favours H	ligher dose)

(Test for subgroup differences: Not applicable)

(1.1.3) (Interclass comparison)

(1.1.3.1) (Budesonide foam enema versus hydrocortisone foam enema)

Figure 57: Clinical remission (>6≤8 weeks)

	Budesonide foam	enema) (H	lydrocortisone foam	n enema		Risk Ratio	Ris	k Ratio		
Study or Subgroup	Events	Total	Events	(Total) (W	eight	M-H, Fixed, 95% C	l) M-H, Fiz	xed, 95% Cl		
BARMEIR2003	64	(120)	67	(128) (10	0.0%)	(1.02 [0.81, 1.29])	-	-		
(Total (95% CI))		(120)		(128) (10	00.0%)	(1.02 [0.81, 1.29])		◆		
(Total events)	64		67							
(Heterogeneity: Not app	licable									-
Test for overall effect: 2	Z = 0.16 (P = 0.88))					(Favours Hydrocortisone	(Favours B	udesonid	

(Figure 58: Adverse events)

	Budesonide foam	enema) (H	lydrocortisone foam	n enema	Risk Ratio		Risk Ratio		
Study or Subgroup	Events	Total	Events	(Total) (Weight)	M-H, Fixed, 95% Cl	(M-	H, Fixed, 95%	C	
BARMEIR2003	36	(120)	60	(128) (100.0%)	0.77 [0.54, 1.09]				
(Total (95% CI))		(120)		(128) (100.0%)	0.77 [0.54, 1.09]		◆		
(Total events)	36		50						
(Heterogeneity: Not appli	cable								40
Test for overall effect: Z	= 1.48 (P = 0.14))					(Favours Budes	nide) (Favou	rs Hydrocor	rtisone

(Figure 59: Serious adverse events)

	Budesonide foam	enema (Hy	drocortisone foam	n enema	Risk Ratio	Risk	Ratio
Study or Subgroup	Events	Total	Events	Total (Weight)	(M-H, Fixed, 95% CI)	M-H, Fix	ed, 95% Cl)
BARMEIR2003	0	(120)		(128) (100.0%)	0.27 [0.03, 2.35]		
(Total (95% CI))		(120)		(128) (100.0%)	(0.27 [0.03, 2.35])		
(Total events)			4				
(Heterogeneity: Not app	licable						
(Test for overall effect: Z	Z = 1.19 (P = 0.23))				1	Favours Budesonide	(Favours Hydrocortisone)

1.1.3.2 (Budesonide liquid enema versus prednisolone liquid enema)

Figure 60: Endoscopic remission – Fixed effects (Eudesonide enema) (Eisk Fatio) (Eisk Fatio) (Study or Subgroup) (Events) (Tota) (Weigh) (H-H, Fixed, 95% C) (A.1.1 >2-54 weeks DANIELSSON1987/ (16) (31) (8) (33) (8.3.1%) (2.13 [1.06, 4.26)) (10.027, 1.38) VALUE SSON1987/ (16) (31) (8) (33) (8.1%) (1.19 [0.72, 1.38)) (1.19 [0.72, 1.38)) VALUE SSON1987/ (16) (23) (22) (19 [0.72, 1.38)) (19 [0.72, 1.38)) Colspan="2">(Interrogeneity: Chi? = 5.26, df = 1 (P = 0.02); I? = 81%) Test for overall effect: Z = 0.67 (P = 0.50) (10.02%) (0.79 [0.50, 1.22)) (11.22) (11.22) (13) (25) (25) (100.02%) (0.79 [0.50, 1.22)) (10.02%)

or subaroup differ

Figure 61: Endoscopic remission – random effects



Figure 62. Clinical and endosconic remission

inguic oz. cini	cai ana che	10300							
	Budesonide ei	nema	Prednisolone	enema		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	(Total) (Weight	M-H, Fixed, 95% C) (M-F	l, Fixed, 95% Cl	
(4.3.1 >2 <u>≤</u> 4 weeks									
LOFTBERG1994	7	45	13	55 (1	100.0%)	0.66 [0.29, 1.51]			
Subtotal (95% CI)		45		55 (100.0%)	0.66 [0.29, 1.51]			
(Total events)	7		13						
Heterogeneity: Not app	olicable								
(Test for overall effect:	Z = 0.99 (P = 0.3)	2))							
		_							
(4.3.2 >6≦8 weeks)								_	
LOFTBERG1994	(16)	(45)	26	55 (1	100.0%)	(0.75 [0.46, 1.22])	_		
Subtotal (95% CI)		(45)		(55) (1	100.0%)	0.75 [0.46, 1.22]	-		
(Total events)	(16)		26						
(Heterogeneity: Not app	olicable								
(Test for overall effect: 2	Z = 1.16 (P = 0.2	5))							
Tast for subgroup diffo	roncos: $Chi^2 = 0$	17 df_1	(P_070) 2_	00/			Favours Predniso	ravours E	udesonide

1.1.3.3 Budesonide liquid enema versus methylprednisolone liquid enema

Figure 63: Hospitalisations

	Budesonide e	nema M	lethylprednisolone	enema	Risk Ra	atio		Risk	Ratio		
Study or Subgroup	Events	Total	Events	(Total) (Wei	ght) (M-H, Fixe	d, 95% CI)		M-H, Fixe	ed, 95% CI		
PORRO1994	0	44	•	(44) (100.	0% (0.33 [0.	01, 7.97] 🗲					
(Total (95% CI))		44		(44) (100.	0%) (0.33 [0.	01, 7.97]					
(Total events)	0										
(Heterogeneity: Not app	olicable										
(Test for overall effect:)	Z = 0.68 (P = 0.5	0)				Ea.	vours Bud	esonide	Eavours M	ethvinre	d

Note: (Methylprednisolone is the type of prednisolone used in this study)

(1.1.4) (Interclass and preparation comparison)

(1.1.4.1) (Budesonide liquid enema versus hydrocortisone foam enema)

Figure 64: Endoscopic remission (>2≤4weeks)

	Budesonide liquid	enema (F	hydrocortisone foam	n enema)		Risk Ratio	(Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fix	ed, 95% CI	
(TARPILA1994)	22	(36)	17	35	(100.0%)	(1.26 [0.82, 1.93])	-		
(Total (95% CI))		66		65	(100.0%)	(1.26 [0.82, 1.93]	-		
(Total events)	22		(17)						
Heterogeneity: Not appli	cable								
(Test for overall effect: Z	= 1.05 (P = 0.29))						avours Hydrocortisone	(Favours Bud	lesonide

(Figure 65: Adverse events)

	Budesonide liquid	enema (Hy	ydrocortisone foan	n enema	Risk Ratio	Ris	k Ratio	
Study or Subgroup	Events	Total	Events	Total Weight	M-H, Fixed, 95% CI	M-H, Fi	xed, 95% Cl	
(TARPILA1994)	6	67	•	(35) (100.0%)	(0.84 [0.37, 1.93])			
Total (95% CI)		37		35 (100.0%)	0.84 [0.37, 1.93]			
(Total events)	8		9					
(Heterogeneity: Not ap	olicable				ł			
Test for overall effect:	Z = 0.41 (P = 0.68))					(Favours Budesonide	Favours Hy	drocortisone

(1.1.5) (Topical aminosalicylates versus topical corticosteroids)

Figure 66: Clinical remission

	(Topical /	ASAs	(Topical Ste	riods		Risk Ratio	(Risk Ratio)
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	(M-H, Fixed, 95% Cl)
(1.1.2 0)≤2 weeks							
BINDER1987	27	(56)	(19)	61	(74.5%)	(1.55 [0.98, 2.46])	t <mark>ene</mark> t
FARUP1995	(11)	41	6	38	(25.5%)	(1.70 [0.70, 4.14])	+
Subtotal (95% CI)		97		99	100.0%	(1.59 [1.05, 2.40])	•
(Total events)	38		25				
(Heterogeneity: Chi ² = (0.03, df = 1	(P = 0.8)	35); l² = 0%)				
(Test for overall effect:	Z = 2.19 (P	' = 0.03)					
(1.1.3 >2)≤4 weeks)							
(FARUP1995)					0 00/	(1.21 [0.68, 2.15])	
(FRIEDMAN1986A)	(17)	(41)	(13)	(<u>38</u>) (9)	(8.9%) (0.7%)	(4.00 [0.55, 29.17])	
(HARTMAN2010)	78	(101)	66	(104)	(42.8%)	(1.22 [1.02, 1.46])	
(LAURITSEN1986)		(13)	9		(6.4%)	$(0.66 \ [0.37, 1.17])$	_ _
(LEE1996)		(149)	45	(146)	(29.9%)	(1.68 [1.26, 2.24])	-
(LEMANN1995)	28	47	17	(45)	(11.4%)	(1.58 [1.01, 2.46])	
(Subtotal (95% CI))		360		353	(100.0%)	(1.38 [1.19, 1.59])	♦
(Total events)	211		(151)				
Heterogeneity: Chi ² =	11.59, df =	5 (P = 0	$.04$; $l^2 = 57\%$				
(Test for overall effect:	Z = 4.37 (P	' < 0.000	01))	-			
(1.1.4 >6 <u>≤</u> 8 weeks)							<u> </u>
HARTMAN2010	82	(106)	65	(101)	(100.0%)	(1.20 [1.01, 1.44])	
Subtotal (95% CI)		(106)		(101)	(100.0%)	(1.20 [1.01, 1.44])	•
(Total events)	82		65				
(Heterogeneity: Not app	plicable						
Test for overall effect:	Z = 2.03 (P	' = 0.04)					
							Favours Steriods) (Favours ASAs)
(Test for subaroup diffe	erences: Ch	i ² = 2.16	5, df = 2 (P = 1	0.34), l²	= 7.5%)		

Risk Ratio ß k Ratio 1 <u>66</u> 9 101 (13 45 17 $(0.04): |^2 = 5$ 0.1 Ó (10

4 weeks. rand

r subgroup differences. Not applicable

Figure 68: Clinical improvement



Figure 69: Clinical improvement >2≤4 weeks, random effects

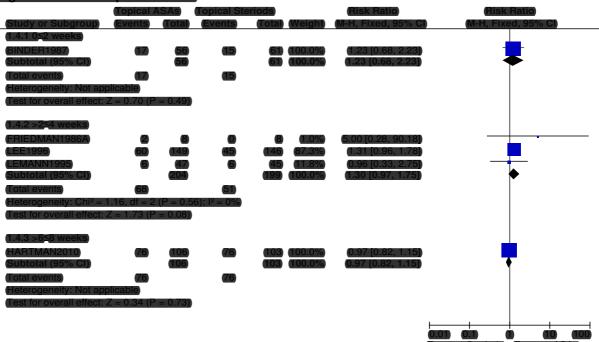
	(Topical /	ASAs	Topical Ste	riods		Risk Ratio	Risk	Ratio	
Study or Subgroup	Events	(Total)	Events	(Total)	Weight	M-H, Random, 95% C	l) (M-H, Rand	dom, 95% Cl)	
(1.11.2 >2)≤4 weeks									
FRIEDMAN1986A	7	9	2	9	41.9%	(3.50 [0.98, 12.48])		—	
MULDER1988	(11)	15	(11)	14	58.1%	0.93 [0.62, 1.41]	-	-	
(Subtotal (95% CI))		24		23	100.0%	(1.62 [0.37, 7.06])			
(Total events)	(18)		(13)						
(Heterogeneity: Tau ² =)		,	f = 1 (P = 0.0)	03); l² = 8	30%)				
(Test for overall effect: 2	Z = 0.65 (P	(= 0.52)							
							1 1		
							0.02 0.1)	1 10 50	
Toot for subgroup diffe							Favours Steriods	Favours ASAs	

Figure 70: Quality of life



(Test for subgroup differences: $Chi^2 = 0.00$, df = 1 (P = 0.99), $I^2 = 0\%$

Figure 71: Endoscopic remission



(Test for subgroup differences: $Chi^2 = 3.11$, df = 2 (P = 0.21), $I^2 = 35.7\%$)

Figure 72: Clinical and endoscopic remission

	(Topical A	ASAs	Topical Ste	riods		Risk Ratio	Risk Ra	itio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed,	95% CI
(1.5.1 0 <u>≤</u> 2 weeks)							_	
BINDER1987	(15)	(56)	(12)	61	(100.0%)	(1.36 [0.70, 2.65])		<u> </u>
Subtotal (95% CI)		56		61	(100.0%)	(1.36 [0.70, 2.65])		
(Total events)	15		(12)					
(Heterogeneity: Not ap	plicable							
(Test for overall effect:	Z = 0.91 (P	= 0.36)						
(1.5.2 >2 <u>≤</u> 4 weeks)								
LAURITSEN1986	3	(13)	8	(11)	(100.0%)	0.32 [0.11, 0.91]		
Subtotal (95% CI)		(13)		(11)	100.0%	0.32 [0.11, 0.91]		
(Total events)	3		8					
(Heterogeneity: Not ap	plicable							
Test for overall effect:	Z = 2.13 (P	= 0.03)						
							(Favours Steriods) (F	avours ASAs
Test for subaroup diffe	erences: Ch	$i^2 = 5.22$.	df = 1 (P = 1)	$0.02)$, $ ^2$:	= 80.9%)			

Figure 73: Adverse events

	(Topical A	ASAs	Topical Ste	eriods		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
BINDER1987	13	61	6	62	6.4%	(2.20 [0.89, 5.42])	
(FARUP1995)	6	41	6	38	6.7%	(0.93 [0.33, 2.63])	
FRIEDMAN1986A	1	9		9	(1.1%)	(1.00 [0.07, 13.64])	
HARTMAN2010	(31)	(119)	(36)	(118)	(38.7%)	0.85 [0.57, 1.28]	
LAURITSEN1986	1	(13)	1	(11)	(1.2%)	0.85 [0.06, 12.01]	
(LEE1996)	57	(167	43	(167	46.0%	(1.33 [0.95, 1.85])	–
		_					
(Total (95% CI))		410		(405)	(100.0%)	(1.16 [0.92, 1.48])	₹
(Total events)	(109)		(93)				
(Heterogeneity: Chi ² = 4			-2); l² = 0%)				
(Test for overall effect:)	Z = 1.25 (P	= 0.21)					(Favours ASAs) Favours Steriods

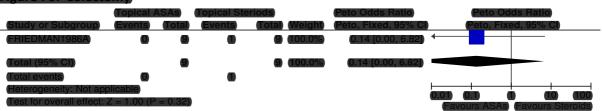
Figure 74: Serious adverse events

-	(Topical A	ASAs	Topical Ste	eriods		Risk Ratio	(Risk F	Ratio
Study or Subgroup	Events	Total	Events	(Total)	Weight	M-H, Fixed, 95% Cl	M-H, Fixed	d, 95% Cl
HARTMAN2010	2	(119)		(118)	49.6%	(1.98 [0.18, 21.58])		
(LEMANN1995)		47		(45)	(50.4%)	(0.96 [0.06, 14.85])	e	
								-
(Total (95% CI))		(166		163	(100.0%)	(1.47 [0.25, 8.63])		
(Total events)	3		2					
Heterogeneity: Chi ² = 0	(Heterogeneity: Chi ² = 0.15, df = 1 (P = 0.69); l ² = 0%)							
(Test for overall effect:	Z = 0.42 (P	= 0.67)					(Favours ASAs)	Favours Steroids

Figure 75: Hospitalisations

	(Topical A	SAs	Topical Ste	eriods		Risk Ratio	(Risk F	latio
Study or Subgroup	Events	(Total)	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixe	d, 95% CI
FRIEDMAN1986A	1	9		9	33.2%	(1.00 [0.07, 13.64])		
(HARTMAN2010)		(119)	2	(118)	66.8%	(0.50 [0.05, 5.39])		
								_
(Total (95% CI)		(128)		(127)	(100.0%)	0.66 [0.12, 3.79]		
(Total events)	2		3					
(Heterogeneity: Chi ² = 0.15, df = 1 (P = 0.70); l ² = 0%								
Test for overall effect: 2	Z = 0.46 (P	= 0.64))					Favours ASAs	Favours Steroids





(1.1.6) Oral aminosalicylates

(1.1.6.1) (Oral aminosalicylates versus placebo)

Figure 77: Clinical remission

Gludy or Subgroup Events flotal Wreigh M-H. Erked, 95% C3 (M-H. Erked, 95% C3 Gluds Standard Gluds 0 62 000059 0.951(0.09, 10.57) Gluds Velkweeks 0 62 000059 0.951(0.09, 10.57) Gluds Velkweeks 0 62 0.00059 0.951(0.09, 10.57) Gluds Velk 0 0 62 0.00059 0.951(0.09, 10.57) Gluds Velk 0 0 0 0.951(0.09, 10.57) 0.951(0.09, 10.57) Gluds Velk 0 0 0.9 0.9 0.951(0.09, 10.57) Gluds Velk 0 0.9 0.9 0.9 0.9 0.9 Gluds Velk 0 0.9 0.9 0.9 0.9 0.9 0.9 Gluds Velk 0 0.9 <th></th> <th>Oral ASA</th> <th>Placebo</th> <th>Risk Ratio</th> <th>Risk Ratio</th>		Oral ASA	Placebo	Risk Ratio	Risk Ratio
SNINSKY1199 0 0.00 0.02 0.02 10.057 Subtrate 0.00 0.00 0.02 0.00 10.057 Cotatevents 0 0 0.00 0.02 0.00 10.057 Cotatevents 0 0.00 0.00 0.00 0.00 0.00 0.00 Cotatevents 0.00			il) (Events) (Total)	Weight) (M-H, Fixed, 95% Cl)	(M-H, Fixed, 95% Cl)
Gubronal (95% CI) 005 52 (000%) 094 (0.09 10.57) (Gala events) 0 0 0 Heterogeneity: Not applicable (11.2.54weeks ~5 weeks) 638 (0.00.15.66) (11.2.54weeks ~5 weeks) GGHISOEDER19820 10 49 0 45.653 638 (0.00.15.66) GMISTOEDER19820 10 49 0 630 (65.93) 633 (12.0.9.43) Gubroal (5% CI) 155 9 00.0058 6.37 (12.0.9.43) (11.2.5 weeks) Gubroal (5% CI) 155 9 00.0058 6.37 (12.0.9.43) (11.2.9.9.43) Gata events 22 0 (11.3.5 Weeks) (11.2.9.9.43) (11.2.9.9.43) Gubroal (10.5% CI) 0.132 0.132 0.129 (12.4.133) (11.2.9.9.43) Gubroal (10.6% CI) 0.132 0.129 (12.9.115.2.50) (11.2.50) (11.2.50) Gubroal (10.5% CI) 0.1020 0.129 (10.0058 (13.9.115.3.2.33) (11.1.5.3.02) (11.1.5.3.02) Gubroal (10.5% CI) 0.1020 0.129 (10.0058 (13.9.115.3.2.33) (13.110.59.2.09) (13.110.59.2.09) (13.110.59.2.09) (13.110.59.2.09) (13.110.59.	(1.1.1 >2 weeks)≤4 week	(S)			
Cotal events 0 0 Heterogeneity: Not applicable 0 0 Heterogeneity: Not applicable 0 0 Cotal events 0 0 SchilbGEDERIBER 0 0 0 SchilbGEDERIBER 0 0 0 0 SchilbGEDERIBER 0 0 0 0 0 SchilbGEDERIBER 0.07. cft = 1 (F = 0.79): F = 0.59 0 0.00.058 0.37 (11.20, 9.43) Heterogeneity: ChF = 0.07. cft = 1 (F = 0.79): F = 0.59 0 0.00.058 0.37 (11.20, 9.43) 0 Heterogeneity: ChF = 0.07. cft = 1 (F = 0.79): F = 0.59 0 0.00.058 0.37 (11.20, 9.43) 0 Heterogeneity: ChF = 0.07. cft = 1 (F = 0.79): F = 0.59 0 0.00.058 0.37 (11.20, 9.43) 0 (Coll events) 0.07. cft = 1 (F = 0.79): F = 0.59 0.00.059 <td< td=""><td></td><td></td><td></td><td></td><td></td></td<>					
(titerogeneity: Notapplicable) (1.2.5-4weeks < G weeks)	Subtotal (95% CI)	100	5 5 (100.0% (0.98 [0.09, 10.57])	
(fest for overall effect; Z = 0.02; (P = 0.99) (1.12 > 44weeks) < 55 weeks	(Total events)	2	1		
III.2 = Aweeks < 6 weeks					
SCHHOEDEH1987 10 49 0 68 45.579 6.88 (0.90, 16.65) Subtotal (9555Cl) (15) 40 (100, 02) 6.37 (120, 9.43) 6.67 (120, 9.43) Total events 62 64 40 (100, 02) (137, 1120, 9.43) 6.67 (120, 9.43) Total events 62 63 62 64.45% (120, 9.43) 6.67 (120, 9.43) Total events 62 63 6.67 (120, 9.43) 6.67 (120, 9.43) 6.67 (120, 9.43) (Tata events 63 100, 02, 93 6.67 (120, 120, 9.43) 6.77 (110, 150, 120, 9.43) (Tata events 63 62 64.45% 6.70 (112, 120, 9.43) 6.70 (112, 120, 9.43) (Tata events 63 63 6.70 (112, 110, 9.10, 100, 100, 100, 100, 100, 100, 100,	(Test for overall effect: Z	= 0.02 (P = 0.9	19]		
SCHHOEDEH1987 10 49 0 68 45.579 6.88 (0.90, 16.65) Subtotal (9555Cl) (15) 40 (100, 02) 6.37 (120, 9.43) 6.67 (120, 9.43) Total events 62 64 40 (100, 02) (137, 1120, 9.43) 6.67 (120, 9.43) Total events 62 63 62 64.45% (120, 9.43) 6.67 (120, 9.43) Total events 62 63 6.67 (120, 9.43) 6.67 (120, 9.43) 6.67 (120, 9.43) (Tata events 63 100, 02, 93 6.67 (120, 120, 9.43) 6.77 (110, 150, 120, 9.43) (Tata events 63 62 64.45% 6.70 (112, 120, 9.43) 6.70 (112, 120, 9.43) (Tata events 63 63 6.70 (112, 110, 9.10, 100, 100, 100, 100, 100, 100, 100,	A 1 0 . Awarka Cowark	-			
ShillixSKY199) 12 005 0 22 0 Subtotal (955°CI) 155 0 0 00000% 6.37 (1.20, 9.43) Icatal events 22 0 0 0 0.29% 0.37 (1.20, 9.43) Icatal events 0.07, off = 1 (P = 0.79); H = 0% 0.02 0 0.029% 0.37 (1.20, 9.43) Icatal events 65 192 10 00 0.29% 0.39 (1.32, 4.33)					
Subtotal (95% C) (155) (100.05% (137 (120, 9.43)) Total events (22 (100.05% (137 (120, 9.43)) Total events (22 (100.05%) (137 (120, 9.43)) Total events (23 (110, 100, 100, 100, 100, 100, 100, 100					
Iotal events 22 0 Heterogeneity: ChiP = 0.07, df = 1 (P = 0.79); P = 0%) Test for overall effect: Z = 2.31 (P = 0.02) 1.1.3 > 56weeks/<8 weeks					
(Heterogeneity: Chi² = 0.07, di = 1 (P = 0.79); l² = 0%) (Test for overall effect: Z = 2.31 (P = 0.02)) (1.1.3 >6weeks) (HANAUER1993) 65 (192) (1) (1020) 66 (193) (1) (1020) 67 (193) (1) (2010A) 67 (193) (1) (1020) 62 (177) (1) (1020) 62 (177) (1) (1021) 63 (129) (1) (101) (121) (1) (211) (131) (2) (211) (151) (3) (124, 11.06) (4) (163) (16) (5) (121) (151) (2) (21) (7.5%) (151) (3) (2) (100,0%) (139) (3) (2) (100,0%) (139) (3) (2) (100,0%) (139) (114 events) (37) (3) (100,0%) (111) (114 events) (27) (125) (21) (111) (111) (0.59, 2.08) (111) (111) (0.59, 2.08) (111) (111) (0.59, 2.08) (111) (111) (0.59, 2.08) (111) (111) (0.59, 2.08) (111) (114				100.078) (5.57 [1.20, 9.45]	
Test tor overall effect: Z = 2.31 (P = 0.02) 11.3 > 56 weeks (HANAUEH1993) 55 192 11 90 12.979 2.39 [1.32, 4.33) 1102010A 67 193 3 62 4.493 3.70 [1.15, 2.69] KAMAUEH1993 52 177 15 65 18.753 1.86 [1.15, 3.02] KAM207 62 177 15 65 18.753 1.86 [1.15, 3.02] SANDBORN2012B 61 124 20 121 17.553 1.51 [0.91, 2.50] SCHERL2009 64 68 1.893 1.89 [1.53, 2.33] + Total events 679 68 (1.68 [1.09, 2.61]) + Test for overall effect: Z = 5.87 (P < 0.00001)		_	-		
11.3 > 6weeks ≤8 weeks HANAUER1993 65 192 11 90 12.9% 2.39 1.32,4333 (IC2010A) 62 193 6 32 4.4% 3.70 11.24,110.61 (KAMM2007) 69 255 19 80 24.6% 1.76 1.15,269 LICHIENSTEIN2007 62 177 15 85 18.7% 1.86 1.15,3.02) SANUBORN2012B 61 124 20 121 17.5% 1.51 1.91 2.50) SCHERL2009 64 166 19 83 21.9% 1.68 1.09,2.61) Subtotal (95% CI) 1107 497 0.00.0% 1.89 1.53,2.33) + Total events 379 88 - - - - Heterogeneity: Chi² = 3.16, ci = 5 (P = 0.68); P = 0.75) - - - - - 11.4 >8 weeks - - 110.59, 2.08) - - - - (Total events) 27 12 - - - -					
HANAUER1993 66 192 11 60 12.9% 2.39 [1.32, 4.33] (TC2010A) 67 193 6 62 4.4% 6.70 [1.15, 2.69] (LCHTENSTEIN2007) 62 177 16 65 18.7% 1.86 [1.15, 3.02] SANDBORN2012B 61 0.24 20 121 17.5% 1.51 [0.91, 2.50] SCHERL2009 64 0.66 19 63 21.9% 1.68 [1.09, 2.61] Subtotal (95% CI) (1107) 497 (00.0%) (1.89 [1.53, 2.03) + Heterogeneity: Chi ² = 3.16, df = 5 (P = 0.68); P = 0.7% 111 [0.59, 2.08] + + Total events 67 183 12 90 (00.0%) 1.11 [0.59, 2.08] Subtotal (95% CI) 183 12 90 (00.0%) 1.11 [0.59, 2.08] + HANAUER1996 27 183 12 90 (00.0%) 1.11 [0.59, 2.08] + Ital events 27 12 90 (00.0%) 1.11 [0.59, 2.08] + + Ital events 27 12 12	(Test for overall effect: Z	= 2.31 (P = 0.0	(2)		
HANAUER1993 66 192 11 60 12.9% 2.39 [1.32, 4.33] (TC2010A) 67 193 6 62 4.4% 6.70 [1.15, 2.69] (LCHTENSTEIN2007) 62 177 16 65 18.7% 1.86 [1.15, 3.02] SANDBORN2012B 61 0.24 20 121 17.5% 1.51 [0.91, 2.50] SCHERL2009 64 0.66 19 63 21.9% 1.68 [1.09, 2.61] Subtotal (95% CI) (1107) 497 (00.0%) (1.89 [1.53, 2.03) + Heterogeneity: Chi ² = 3.16, df = 5 (P = 0.68); P = 0.7% 111 [0.59, 2.08] + + Total events 67 183 12 90 (00.0%) 1.11 [0.59, 2.08] Subtotal (95% CI) 183 12 90 (00.0%) 1.11 [0.59, 2.08] + HANAUER1996 27 183 12 90 (00.0%) 1.11 [0.59, 2.08] + Ital events 27 12 90 (00.0%) 1.11 [0.59, 2.08] + + Ital events 27 12 12	/1.1.3 >6weeksi≤8 week	5			
(TO2010A) 67 193 6 62 4.4% 6.70 [1.24, 11.06] (KAMM2007) 99 255 19 66 24.6% 1.76 [1.15, 2.69] LICHTENSTEIN2007 62 177 16 65 18.7% 1.86 [1.15, 3.02] SANDBORN2012B 61 124 20 121 17.5% 1.51 [0.91, 2.50] SCHERL2009 64 165 19 63 21.9% 1.68 [1.09, 2.61] Subtotal (95% CI) 1107 497 100.0% 1.89 [1.53, 2.33] • Total events 379 68 • • • Heterogeneity: Chi² = 3.16, dt = 5 (P = 0.68); l² = 0% • • • Test for overall effect: Z = 5.87 (P < 0.00001)					
(KAMM2007) 99 255 19 66 24.6% 1.76 [1.15, 2.69] LICHTENSTEIN2007) 62 177 16 65 18.7% 1.86 [1.15, 3.02] SANDBORN2012B G1 124 20 121 17.5% 1.51 [0.91, 2.50] SCHERL2009 64 166 19 63 21.9% 1.68 [1.09, 2.61] Subtotal (95% CI) 1107 (497 100.0% 1.89 [1.53, 2.33] • Total events 679 68 Heterogeneity: Chi² = 3.16, df = 5 (P = 0.68); l² = 0% 1.11 [0.59, 2.08] • Test for overall effect: Z = 5.87 (P < 0.00001)					
LICHTENSTEIN2007 62 177 16 85 18.7% 1.86 1.15, 3.02) SANDBORN2012B 61 124 20 021 17.5% 1.51 0.91, 2.50) SCHERL2009 64 165 19 83 21.9% 1.68 1.09, 2.61) Subtotal (95% CI) (1107) 497 100.0% 1.89 1.53, 2.33) + Iotal events 379 88 - - - - Ital events 62 12 90 100.0% 1.11 [0.59, 2.08) - Ital events 62 12 - - - - - Ital events 62 12 - - - - -					- - -
SANDBORN2012B G1 024 20 121 07.5% 0.51 0.91, 2.50) SCHERL2009 G4 066 19 83 21.9% 0.68 1.09, 2.61) Subtotal (95% Cl) 0107 097 100.0% 1.89 1.53, 2.33) Iotal events 379 88 Heterogeneity: Chi² = 3.16, di = 5 (P = 0.68); l² = 0% 1.89 1.53, 2.33) Iotal events 379 88 Heterogeneity: Chi² = 3.16, di = 5 (P = 0.68); l² = 0% 1.11 0.59, 2.08) Ital >8 weeks 90 100.0% 0.11 0.59, 2.08) HANAUER1996 62 083 90 100.0% 0.11 0.59, 2.08) Subtotal (95% Cl) 083 90 100.0% 0.11 0.59, 2.08) 1.11 0.59, 2.08) Iotal events 62 02 010 00 00 00 00 60 Heterogeneity: Not applicable Icst for overall effect: Z = 0.31 (P = 0.75) Image: Color of the col					- - -
SCHERL2009 64 166 19 83 21.9% 1.68 11.09, 2.61) Subtotal (95% Cl) (107) 497 100.0% 1.89 1.53, 2.33) Total events 379 88 Heterogeneity: Chi ² = 3.16, df = 5 (P = 0.68); l ² = 0% Test for overall effect: Z = 5.87 (P < 0.00001)					+
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(Heterogeneity: Chi² = 3.16, df = 5 (P = 0.68); l² = 0% (Test for overall effect: Z = 5.87 (P < 0.00001))					•
(Iest for overall effect: Z = 5.87 (P < 0.00001))	(Total events)	(379)	(88)		
(1.1.4 >8 weeks) (HANAUER1996) (27) (83) (12) (90) (100.0%) (1.11 (0.59, 2.08)) Subtotal (95% Cl) (183) (90) (100.0%) (1.11 (0.59, 2.08)) Total events (27) (12) Heterogeneity: Not applicable (12) Test for overall effect: Z = 0.31 (P = 0.75)) (12) Guide field of the second sec	Heterogeneity: Chi ² = 3. ⁻	16, df = 5 (P =	0.68); l² = 0%)		
(HANAUER1996) (27) (83) (12) (90) (100.0%) (1.11 [0.59, 2.08]) Subtotal (95% Cl) (183) (90) (100.0%) (1.11 [0.59, 2.08]) (Total events) (27) (12) (Heterogeneity: Not applicable) (12) (12) (Test for overall effect: Z = 0.31 (P = 0.75)) (12) (10) (10) (10) (Favours Placebo) (10) (10) (10) (10) (10) (10)	Test for overall effect: Z	= 5.87 (P < 0.0	0001)		
(HANAUER1996) (27) (83) (12) (90) (100.0%) (1.11 (0.59, 2.08)) Subtotal (95% CI) (183) (90) (100.0%) (1.11 (0.59, 2.08)) (Total events) (27) (12) (Heterogeneity: Not applicable) (12) (12) (Test for overall effect: Z = 0.31 (P = 0.75)) (12) (10) (10) (12) (12) (12) (12) (12) (12) (12) (12) (12) (12) (12) (12) (12) (12) (12) (12) (12) (12) (12) (12) (12) (12) (12) (12) (12) (12) (12) (12) (12) (12) (12) (12) (12) (12) (12) (12) (12) (12) (12) (12) (12) (12) (12) (12) (12) (12) (12) (12) (12) (12) (13) (12) (12) (12) (12) (
Subtotal (95% CI) 183 90 100.0% 1.11 [0.59, 2.08] (Total events) 27 12 (Heterogeneity: Not applicable) (Test for overall effect: Z = 0.31 (P = 0.75)) (D.02 0.1 0 60 (Favours Placebo) (Favours Oral ASA)	(1.1.4 >8 weeks)				<u> </u>
Itelerogeneity: Not applicable Itelerogeneity: Not applicable (Test for overall effect: Z = 0.31 (P = 0.75)) Itelerogeneity: Not applicable Image:			;		
(Heterogeneity: Not applicable) (Test for overall effect: Z = 0.31 (P = 0.75)) 0.02 0.1 0 00 50 (Favours Placebo) Favours Oral ASA	Subtotal (95% CI)	(18:	3 90 (100.0% (1.11 [0.59, 2.08])	-
(Test for overall effect: Z = 0.31 (P = 0.75)) 0.02 0.1 0 00 50 (Favours Placebo) Favours Oral ASA	Total events	27	(12)		
0.02 0.1 0 00 50 (Favours Placebo) (Favours Oral ASA)	Heterogeneity: Not appli	cable			
(Favours Placebo) (Favours Oral ASA)	Test for overall effect: Z	= 0.31 (P = 0.7	[5]		
(Favours Placebo) (Favours Oral ASA)					
(Favours Placebo) (Favours Oral ASA)					0.02 0.1 (1) (10 50
(Test for subgroup differences: $Chi^2 = 4.13$, $df = 3$ (P = 0.25), $l^2 = 27.3\%$)					

Test for subgroup differences: $Chi^2 = 4.13$, df = 3 (P = 0.25), $l^2 = 27.3\%$

Figure 78: Clinical i	mprove	ment					
	Oral A	SA	Placeb	0		Risk Ratio	Risk Ratio
Study or Subgroup	Events	(Total) (Events	Total	Weight	(M-H, Fixed, 95% Cl	(M-H, Fixed, 95% Cl
(1.2.1 >2 weeks)≤4 weel	KS						
(DICK1964)	(14)	(18)	9	(23)	(18.9%)	(1.99 [1.13, 3.50])	
MEYERS1987	—	29	3	19	(8.7%)	2.40 [0.77, 7.50]	+
ROBINSON1988	25	50	(16)	48	(39.1%)	(1.50 [0.92, 2.44])	+=-
(SELBY1985)	13	20	8	20	19.2%	(1.63 [0.87, 3.04])	+
SNINSKY1991	25	(106)	3	52	9.6%	(4.09 [1.29, 12.92]	_
ZINBERG1990	4	7	2	8	4.5%	(2.29 [0.59, 8.91])	
Subtotal (95% Cl)	_	230	_	170	100.0%	(1.98 [1.46, 2.68])	•
(Total events)	92		41				
Heterogeneity: Chi ² = 3.	31, df = 5	(P = 0.6)	5); l ² = 0	%			
Test for overall effect: Z	= 4.40 (P	< 0.000	1)				
(1.2.2 >4 weeks)≦6 weel	KS						
(HETZEL1986)	6	(15)	2	(15)	9.7%	(3.00 [0.72, 12.55])	
SCHROEDER1987	31	49	7	38	38.2%	(3.43 [1.70, 6.93]	
SNINSKY1991	28	(106)	8	(52)	(52.1%)	(1.72 [0.84, 3.50])	+
Subtotal (95% CI)		170		105	100.0%	(2.50 [1.57, 3.98])	\bullet
Total events	65		(17)				
(Heterogeneity: Chi ² = 1.	92, df = 2	(P = 0.3)	8); l² = 0	%			
(Test for overall effect: Z	= 3.85 (P	= 0.000	1)				
(1.2.3 >6 weeks)≤8 weel	(S)						
HANAUER1993	(157	(192)	(49)	(90)	28.1%	(1.50 [1.23, 1.84])	•
(ITO2010A)	(102)	(193)	9	(32)	6.5%	(1.88 [1.06, 3.32])	
KAMM2007	(154)	(255)	34	(86)	(21.4%)	(1.53 [1.15, 2.02])	-
LICHTENSTEIN2007	(102)	(177)	22	(85)	(12.5%)	(2.23 [1.52, 3.26])	
SANDBORN2012B	42	(124)	30	(121)	12.8%	(1.37 [0.92, 2.03])	1
SCHERL2009	92	(166)	(33)	83	(18.6%)	(1.39 [1.03, 1.88])	
Subtotal (95% CI)		(1107)		(497)	(100.0%)	(1.59 [1.40, 1.80])	▼
(Total events)	649		(177)	_			
Heterogeneity: Chi ² = 5.				%			
(Test for overall effect: Z	= 7.09 (P	< 0.000	01))				
							(Favours Placebo) (Favours Oral AS)
(Test for subgroup differe	ences: Chi	$^{2} = 4.70$, df = 2 (I	P = 0.1	$10), 1^2 = 57$.5%)	

Figure 79: Endoscopic remission

	Oral ASA	Placebo	Risk Ratio	Risk Ratio
Study or Subgroup	Events (Total)	Events (Total) (Weigh	t) (M-H, Fixed, 95% Cl)	M-H, Fixed, 95% Cl
(1.3.2 >6 weeks)≤8 we	eks			
HANAUER1993	(89) (192)	28 90 28 .5%	(1.49 [1.06, 2.10])	
KAMM2007	(177) (255)	40 86 44.7%	(1.49 [1.17, 1.90])	-
SCHERL2009	88 (166)	27 83 26.9 %	(1.63 [1.16, 2.29]	
Subtotal (95% CI)	613	(259) (100.0%	6 (1.53 [1.29, 1.82])	•
(Total events)	354	95		
Heterogeneity: Chi ² =	0.19, df = 2 (P = 0	0.91); l² = 0%)		
Test for overall effect:	Z = 4.84 (P < 0.00	0001)		
1.3.3 >8 weeks				
HANAUER1996	73 (183)	(31) (90) (100.0%		
Subtotal (95% CI)	(183)	(90) (100.0%	6 (1.16 [0.83, 1.62])	₹
(Total events)	(73)	31		
(Heterogeneity: Not ap				
(Test for overall effect:	Z = 0.86 (P = 0.3)	9)		
			1	
			0.0	
				vours Placebo) (Favours Oral ASA)
Lest for subaroup diffe	erences: Chi ² = 2.0	08. df = 1 (P = 0.15). l² =	51.9%	

Figure 80: Clinical and endoscopic remission

	Oral AS	SA)	Placeb	00		Risk Ratio	(Risk I	Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixe	d, 95% Cl
(1.4.2 >6 weeks)≤8 week	S							
KAMM2007	97	255	(19)	86	42.4%	(1.72 [1.12, 2.64])		-
LICHTENSTEIN2007	56	177	11	85	22.2%	2.44 [1.35, 4.42]		
(SANDBORN2012B)	(15)	(124)	9	121	(13.6%)	(1.63 [0.74, 3.57])	-	•
SCHERL2009	34	166	(11)	(83)	21.9%)	(1.55 [0.83, 2.89])	+	• •
(Subtotal (95% CI))		722		375	(100.0%)	(1.83 [1.38, 2.43]		•
Total events	202		50					
(Heterogeneity: Chi ² = 1.3				%				
(Test for overall effect: Z	= 4.19 (P <	< 0.00	01))					
							0.01 (0.1) (1) (10) (100)
							Favours Placebo	Favours Oral ASA
(Test for subgroup differe	nces: Not	applic	able					

Figure 81: Adverse events

	Oral AS	A	Placeb	0		Risk Ratio	Risk Ratio	
Study or Subgroup	Events)	Fotal) (Events	Total	Weight	(M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl	
DICK1964	8	21	2	(23)	0.6%	(4.38 [1.05, 18.35])		
FEURLE1989	12	52	9	(53)	2.9%	(1.36 [0.63, 2.95])		
HANAUER1993	(34)	(192)	(20)	(90)	(8.9%)	(0.80 [0.49, 1.30])		
(ITO2010A)	(164)	(193)	22	(32)	(12.3%)	(1.24 [0.97, 1.57])	+	
LICHTENSTEIN2007	82	(177)	47	(85)	20.7%	0.84 [0.65, 1.07]		
MEYERS1987	38	(46)	(16)	(20)	7.3%	(1.03 [0.80, 1.33]	+	
SANDBORN2012B	80	(127)	81	(129)	26.2%	(1.00 [0.83, 1.21]	• •	
SCHERL2009	88	(168)	47	(79)	20.8%	0.88 [0.70, 1.11]	-	
SELBY1985	5	20	1	(20)	0.3%	5.00 [0.64, 39.06]		
(Total (95% CI)		996		(<u>531</u>)	100.0%	(1.00 [0.90, 1.11])	•	
(Total events)	(511)		245					
(Heterogeneity: Chi ² = 14	(Heterogeneity: Chi² = 14.00, df = 8 (P = 0.08); l² = 43%)							(100)
(Test for overall effect: Z	= 0.00 (P =	= 1.00)))				(Favours Oral ASA) (Favours Pla	

Figure 82: Serious adverse events

	Oral ASA	Placebo		Risk Ratio	Risk Ratio		
Study or Subgroup	Events (Total) (Events) (Total)	Weight	(M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI		
HANAUER1993	(14) (192) 590	38.5%	(1.31 [0.49, 3.53])			
(ITO2010A)	7 (193) 0 32	(4.8%)	(2.55 [0.15, 43.62])			
KAMM2007	3 (255) 2 86	(16.9%)	(0.51 [0.09, 2.98])			
LICHTENSTEIN2007	4 (177) 3 85	22.9%	0.64 [0.15, 2.80]			
SANDBORN2012B	4 127) 3 (129)	(16.8%)	(1.35 [0.31, 5.93])			
(Total (95% Cl))	944	422	(100.0%)	(1.09 [0.58, 2.06]	-		
(Total events)	(32)	(13)					
(Heterogeneity: Chi ² = 1.78, df = 4 (P = 0.78); l ² = 0%)							
Test for overall effect: Z	= 0.26 (P = 0.7)	9)			(0.01) (0.1) (1) (10) (100) (Favours Oral ASA) (Favours Placebo)		

(1.1.7) (Oral aminosalicylate versus oral aminosalicylate: dose comparison)

(1.1.7.1) (Mesalazine (Pentasa)

Figure 83: Clinical remission

Figure 65. Chilical ren	111551011				
Lo	w dose) (H	ligh dose		Risk Ratio	(Risk Ratio)
Study or Subgroup (Eve	ents) (Total) (Ev	vents) (Total)	Weight	(M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
2.1.1 2g versus 4g Pentasa					
HANAUER1993	28 97	28 95	68.5%)	(0.98 [0.63, 1.52])	—— <mark>—</mark> ——
Subtotal (95% CI)	97	(95)	68.5%	0.98 [0.63, 1.52]	\bullet
Total events	28	28			
Heterogeneity: Not applicab	le				
(Test for overall effect: $Z = 0$.)	.09 (P = 0.93))				
2.1.2 2.25g versus 4g Pent	asa				
HIWATASHI2011	9 <u>59</u>	(13) (59)	31.5%	(0.69 [0.32, 1.49])	
(Subtotal (95% CI)	(59)	(59)	(31.5%)	0.69 [0.32, 1.49]	
(Total events)	9	(13)			
(Heterogeneity: Not applicab	le				
(Test for overall effect: $Z = 0$.)	.94 (P = 0.35))				
(Total (95% CI))	(156)	(154)	(100.0%)	(0.89 [0.61, 1.30])	
(Total events)	(37)	41			
(Heterogeneity: $Chi^2 = 0.59$, (); $I^2 = 0\%$			
Test for overall effect: $Z = 0$.				_	(Favours Higher dose) (Favours Lower dose)
(Test for subgroup difference	es: Chi² = 0.59,	df = 1 (P = 0.4)	44), l² = 0%		

Data reported at 8 weeks.

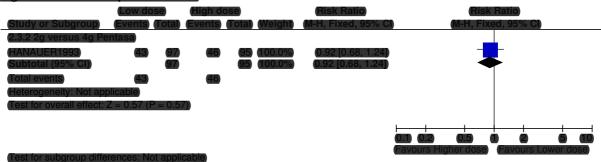
Figure 84: Clinical improvement

	Low dose	High dose		Risk Ratio	Risk Ratio
Study or Subgroup	Events (Total	Events (Total	Weight	M-H, Fixed, 95% C	(M-H, Fixed, 95% CI)
2.2.1 2g versus 4g Pe	entasa				
HANAUER1993	(7) (97)	80 95	64.2%	(0.94 [0.82, 1.08])	
Subtotal (95% CI)	97	95	64.2%	0.94 [0.82, 1.08]	◆
(Total events)	77	80			
Heterogeneity: Not app	olicable				
(Test for overall effect:)	Z = 0.87 (P = 0.3	9))			
2.2.2 2.25g versus 4g	Pentasa				
HIWATASHI2011	27 59	45 59	35.8%	0.60 [0.44, 0.82]	
Subtotal (95% CI)	(59)	59	(35.8%)	0.60 [0.44, 0.82]	\bullet
(Total events)	27	(45)			
Heterogeneity: Not app	olicable				
(Test for overall effect:)	Z = 3.21 (P = 0.0	01)			
(Total (95% CI))	(156)	(154	100.0%	0.82 [0.72, 0.94]	\bullet
(Total events)	(104)	(125)			
Heterogeneity: Chi ² = 8	8.02, df = 1 (P =)	0.005); l² = 88%)			
(Test for overall effect: 2	Z = 2.93 (P = 0.0	03)			(Favours Higher dose) (Favours Lower dose)
Tost for subgroup diffo	roncos: $Chi^2 = 6$	80 df = 1 (P = 0)		Q5 20/	a avoid o higher according to avoid a cower accord

(Test for subgroup differences: $Chi^2 = 6.80$, df = 1 (P = 0.009), $I^2 = 85.3\%$

Data reported at 8 weeks.)

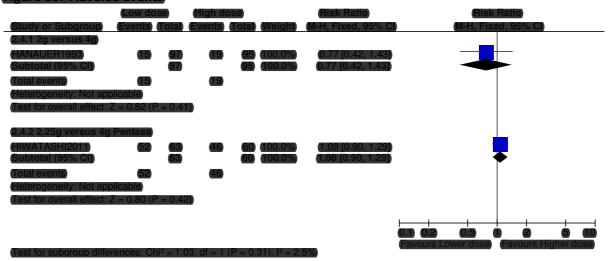
Figure 85: Endoscopic remission



(rest for subgroup differences. Not ap

Data reported at 8 weeks.

Figure 86: Adverse events



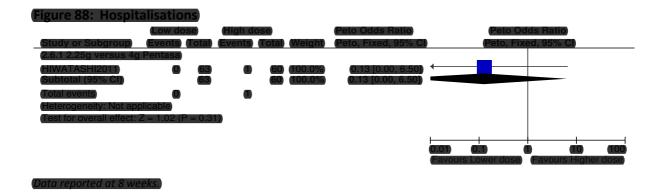
Data reported at 8 weeks.

Figure 87: Serious adverse events

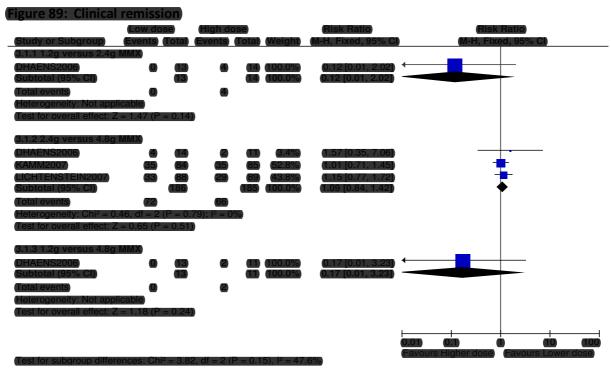
Low	dose	High do	ose		Risk Ratio		Risk	Ratio	
Study or Subgroup (Event	s (Total)	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fix	ed, 95% CI	
(2.5.1 2g versus 4g)								I	
(HANAUER1993) (1)	0 97	4	95	100.0%	(2.45 [0.80, 7.54])				
Subtotal (95% CI)	97		95	100.0%	2.45 [0.80, 7.54]				
(Total events)	0	4							
(Heterogeneity: Not applicable)									
(Test for overall effect: $Z = 1.56$	6 (P = 0.1	2))							
	_								
2.5.2 2.25g versus 4g Pentas	a								
HIWATASHI2011	0 63	2	60	(100.0%)	0.19 [0.01, 3.89]	•			
(Subtotal (95% CI))	63		60	(100.0%)	0.19 [0.01, 3.89]				
(Total events)	0	2							
(Heterogeneity: Not applicable)									
Test for overall effect: $Z = 1.08$	B(P = 0.28)	3)							
						0.01			(100

Favours Lower dose) (Favours Higher do

Data reported at 8 weeks.)

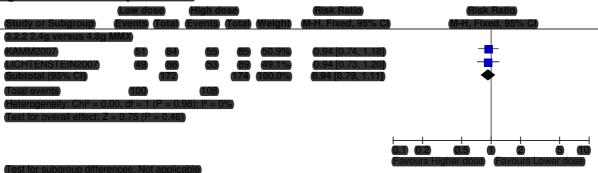


(1.1.7.2) (Mesalazine (MEZAVANT XL)

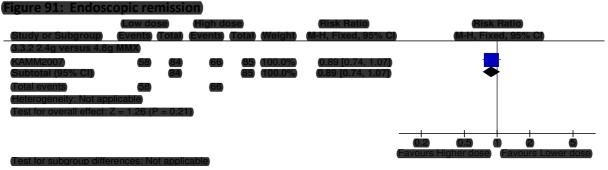


Data reported at 8 weeks.

Figure 90: Clinical improvement



Data reported at 8 weeks.



Data reported at 8 weeks.

Figure 92: Clinical and endoscopic remission

inguic sz. cillica					
	Low dose	High dose	Risk Ratio	Risk Ratio	
Study or Subgroup	Events (Total)	Events) (Total) (Weight	(M-H, Fixed, 95% Cl)	(M-H, Fixed, 95% CI)	
3.4.2 2.4g versus 4.8g	MMX				
KAMM2007	34 84	35 (85) (57.4%)	0.98 [0.68, 1.41]		
LICHTENSTEIN2007	30 88	26 89 42.6%	(1.17 [0.76, 1.80]		
Subtotal (95% CI)	172	(174) (100.0%	(1.06 [0.80, 1.40])	•	
(Total events)	64	61			
Heterogeneity: Chi ² = 0	.35, df = 1 (P = 0.5	$(55); ^2 = 0\%$			
(Test for overall effect: Z	2 = 0.42 (P = 0.68))				
			ŀ		10
				Favours Higher dose) (Favours Lower do	se
Toot for outparaup diffor	onege: Net englige	in lo			

(Test for subgroup differences: Not applicable)

Data reported at 8 weeks.)

Figure 93: Adverse events

(Figure 93: Advers	e events			
	Low dose	High dose	Risk Ratio	Risk Ratio
Study or Subgroup	Events (Total)	Events (Total) (Weight)	M-H, Fixed, 95% Cl	(M-H, Fixed, 95% CI)
3.5.1 1.2g versus 2.4g	MMX			
DHAENS2006	9 13	9 (14) (100.0%)	(1.08 [0.63, 1.83]	
Subtotal (95% CI)	(13)	(14) (100.0%)	(1.08 [0.63, 1.83])	
(Total events)	9	9		
(Heterogeneity: Not app				
(Test for overall effect: 2	Z = 0.27 (P = 0.79))			
(3.5.2 2.4g versus 4.8g	MMX)			
DHAENS2006	9 14	(10) (11) (22.9%)	0.71 [0.46, 1.09]	— — —
LICHTENSTEIN2007	44 88	38 89 77.1%	(1.17 [0.85, 1.61])	
Subtotal (95% CI)	102	(100) (100.0%)	(1.06 [0.81, 1.40]	\bullet
(Total events)	(53)	(48)		
Heterogeneity: Chi ² = 3	.78, df = 1 (P = 0.0	5); $I^2 = 74\%$		
Test for overall effect: Z	Z = 0.46 (P = 0.65))			
3.5.3 1.2g versus 4.8g	MMX			
DHAENS2006	9 13	(10) (11) (100.0%)	0.76 [0.51, 1.14]	
Subtotal (95% CI)	(13)	(11) (100.0%)	0.76 [0.51, 1.14]	
(Total events)	9	(10)		
(Heterogeneity: Not app				
(Test for overall effect: 2	Z = 1.31 (P = 0.19))			
				0.1 0.2 0.5 (1) (2) (5 (10)
			_	(Favours Lower dose) (Favours Higher dose)

Data reported at 8 weeks.

t for subaroup differen

= 1.95. df = 2 (P = 0.38). |² = 0°

Figure 94: Serious adverse events Study or Subgroup Events (rotal (vents) 6:00/0058 Eto Odds Ratio 0 0 Eto Odds Ratio 0 Eto Odds Ratio Eto Odds

Data reported at 8 weeks.

1.1.7.3 (Mesalazine (Asacol)

Figure 95: Clinical remission

	(Low dose)	High dose	(Risk Ratio)	Risk Ratio
Study or Subgroup			ht) (M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
4.2.1 1.6g versus 4.8				
(SCHROEDER1987) (Subtotal (95% CI))		9 <u>38</u> <u>100.0</u> 38 <u>100.0</u>		
(Total events)	1	9		
(Heterogeneity: Not ap				
Test for overall effect:	Z = 0.96 (P = 0.3)	34)		
4.2.2 2.4g versus 3.6g	g Asacol, 0≤2 we	eeks		
MIGLIOLI1990	3 24	7 (24) (100.0		
Subtotal (95% CI)	24	(24) (100.0	% (0.43 [0.13, 1.46])	
(Total events)	3			
(Heterogeneity: Not ap (Test for overall effect:		81		
	2 - 1.00 (1 - 0.1			
4.2.3 2.4g versus 3.6	g Asacol, >2 <u>≤</u> 4 v	weeks		
MIGLIOLI1990	9 24			
(Subtotal (95% CI))	24		% (0.82 [0.42, 1.61])	
(Total events) (Heterogeneity: Not ap	9 Dicable			
(Test for overall effect:		6)		
4.2.5 2.4g versus 3.6	g Asacol, >6 <mark>≤</mark> 8 v	veeks		_
(ITO2010A)	20 66			
(Subtotal (95% CI))			%) (0.67 [0.42, 1.05])	
(Total events) (Heterogeneity: Not ap	20 plicable	29		
(Test for overall effect:		18)		
(4.2.6 2.4g versus 4.8)				
(SANDBORN2009A) (Subtotal (95% CI))	65 <u>659</u> (359)	91) <u>365</u> (100.0 365 (100.0		
(Total events)	65	91		•
Heterogeneity: Not ap				
Test for overall effect:	Z = 2.22 (P = 0.0	(3)		
(A 0 7 0 Am vereine A 0				
(4.2.7 2.4g versus 4.8) (SANDBORN2009A)	<u>g Asacol, >456 v</u> (121) (347)		%) (0.81 [0.67, 0.98])	
(Subtotal (95% CI)	(121) (347)	(152) (353) (100.0 (353) (100.0		
(Total events)	(121)	(152)		-
Heterogeneity: Not ap	plicable			
Test for overall effect:	Z = 2.21 (P = 0.0	13)		
				<u>ian aiz ais a is a is a</u> i
Test for subaroup diffe	prences: Chi ² – 2	$19 df = 5 (P = 0.82) l^2$	- 0%	(Favours Higher dose) (Favours Lower dose)

(Test for subgroup differences: $Chi^2 = 2.19$, df = 5 (P = 0.82), $l^2 = 0$ %)

Figure 96: Clinical imp	provement			
	Low dose	(High dose)	Risk Ratio	(Risk Ratio)
Study or Subgroup		Events) (Total) (Weight)	(M-H, Fixed, 95% Cl)	(M-H, Fixed, 95% Cl)
4.3.1 1.6g versus 4.8g Asaco				
(SCHROEDER1987) (Subtotal (95% CI))			(0.37 [0.14, 0.99]) (0.37 [0.14, 0.99])	
(Total events)	3	28		
(Heterogeneity: Not applicable)	-	_		
Test for overall effect: $Z = 1.98$	(P = 0.05))			
(4.3.2 2.4g versus 3.6g Asaco	0<2 wooke			
(MIGLIOLI1990)	(11) (24)	(18) (24) (100.0%)	(0.61 [0.37, 1.00])	
Subtotal (95% CI)	24		0.61 [0.37, 1.00]	
Total events	11	18		
(Heterogeneity: Not applicable)				
(Test for overall effect: $Z = 1.96$	(P = 0.05)			
(4.3.3 2.4g versus 3.6g Asaco	l, >2 <u>≤</u> 4 weeks			
MIGLIOLI1990	14 24	(19) (24) (100.0%)	0.74 [0.50, 1.09]	
Subtotal (95% CI)	24	(24) (100.0%)	0.74 [0.50, 1.09]	
Total events	(14)	(19)		
(Heterogeneity: Not applicable) (Test for overall effect: Z = 1.51	(P = 0.12)			
(rest for overall effect. $Z = 1.51$	(r = 0.13)			
4.3.4 2.4g versus 3.6g Asaco	l, <6 <u>≤</u> 8 weeks			
(ITO2010A)	<u>30</u> <u>66</u>		0.71 [0.51, 0.98]	
Subtotal (95% CI)	66		(0.71 [0.51, 0.98])	-
(Total events) (Heterogeneity: Not applicable)	30	(41)		
(Test for overall effect: $Z = 2.09$	(P = 0.04)			
	(
(4.3.5 2.4g versus 4.8g Asaco	l, >2 <u>≤</u> 4 weeks)			_
(HANAUER2005 (moderate))	67 (130)		0.84 [0.68, 1.05]	
(HANAUER2007) (Subtotal (95% CI))	63 (150) (280)	(53) (137) (41.6%) (100.0%)	(1.09 [0.82, 1.44]) (0.94 [0.79, 1.12])	
(Total events)	(130)	(129)	0.04 [0.10, 1.12]	•
(Heterogeneity: $Chi^2 = 2.02$, df =				
Test for overall effect: Z = 0.66				
(4.3.6 2.4g versus 4.8g Asaco				
(HANAUER2005 (mild))	<u>1, >430 weeks</u> (21) (52)	(19) (58) (3.9%)	(1.23 [0.75, 2.02])	
(HANAUER2005 (moderate))	(77) (130)		$(0.83 \ [0.69, \ 0.99])$	
HANAUER2007	77 (150)		(0.92 [0.74, 1.14])	
SANDBORN2009A	251 383		0.93 [0.85, 1.03]	
(Subtotal (95% CI))	715	(707) (100.0%)	(0.92 [0.85, 1.00])	▼
(Total events) (Heterogeneity: Chi ² = 2.84, df =	(426)	(457)		
(Test for overall effect: $Z = 2.01$				
				(Favours Higher dose) (Favours Lower dose)
(Test for subgroup differences:	Chi² = 9.18, df =	= 5 (P = 0.10), P = 45.5%)		

Figure 97: Quality of life

or subaroup diffe

Low dose	High dose	Mean Difference	Mean Difference
Study or Subgroup (Mean) (SD) (Total) (M	ean) (SD) (Total) (Weight)	IV, Fixed, 95% CI	(IV, Fixed, 95% CI)
4.1.1 2.4g versus 4.8g Asacol			
(IRVINE2008 ASCEND) (37.3) (36.1) (154)	45.6 (33.62) (147) (44.5%	(-8.30 [-16.18, -0.42])	
(RVINE2008 ASCEND I) (38.9) (37.52) (195) (38.2 3.13 191 55.5%	(0.70 [-6.36, 7.76])	
Subtotal (95% CI)	(338) (100.0%)	(-3.31 [-8.56, 1.95])	•
Heterogeneity: Chi ² = 2.78, df = 1 (P = 0.10); l ² = 64%	6		
(Test for overall effect: $Z = 1.23$ (P = 0.22))			
		(50)	
		Favor	urs Higher dose) (Favours Lower dose)

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nces: Not applic

Data reported at baseline and 6 weeks.



Data reported at 6 weeks.

Figure 99: Clinical and endoscopic remission, random effects



Test for subgroup differences: Not applicable



Test for subgroup differences: $Chi^2 = 1.07$ df = 1 (P = 0.30) $l^2 = 6.59$

Figure 101: Clinical	and er	ndoscopio	: remi	ission,	2.4g versus 4.8	g Asacol, by ext	ent of disease
	Low dos	e (High	dose		Risk Ratio	Risk	Ratio
Study or Subgroup	Events (T	otal) (Events) (Total	Weight	M-H, Fixed, 95% Cl	M-H, Fix	ed, 95% Cl
4.9.2 All extents							
(HANAUER2005 (moderate))	23	(130) (25	(124	(41.1%)	0.88 [0.53, 1.46]		
HANAUER2007	30	(150) (35	136	58.9%	0.78 [0.51, 1.19]		+
Subtotal (95% CI)		280	260	100.0%)	0.82 [0.59, 1.14]		•
(Total events)	(53)	60)				
(Heterogeneity: Chi ² = 0.13, df =	1 (P = 0.7)	2); l ² = 0%)					
(Test for overall effect: Z = 1.20)	(P = 0.23)						
4.9.3 No proctitis							
SANDBORN2009A	_	383 (10	389	(100.0%)	(1.93 [0.91, 4.10])		
(Subtotal (95% CI))	(383	(389)	(100.0%)	(1.93 [0.91, 4.10]		
(Total events)	(19)	(10)				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.71	(P = 0.09))						
						0.1 0.2 0.5	
(Test for subgroup differences: (No.2 4 10	df 1 /D 0	0.4) 12	- 76 00/		Favours Higher dose	Favours Lower dose

Low dose (High dose) (Risk Ratio) (Risk Ratio) Study or Subgroup (Events) (Tota) (Veigh) (M-H, Fixed, 95% C) (M-H, Fixed, 95% C) (4.6.1 2.4g versus 3.6g Asacol) (TO2010A) 66 65 63 64 (00.0%) (1.02 [0.88, 1.19)
(4.6.1 2.4g versus 3.6g Asacol)
(Subtotal (95% Cl)) 66 64 (100.0% (1.02 [0.88, 1.19) +
(Total events) 66 63
(Heterogeneity: Not applicable)
(Test for overall effect: Z = 0.31 (P = 0.75))
(4.6.2 2.4g versus 4.8g Asaco)
(HANAUER2005 (moderate)) (49 (139 (57) (129 (31.5%) (0.80 [0.59, 1.07))
(HANAUER2007) 60 (154) (43 (147) (26:2%) (1.19 [0.88, 1.62)
SANDBORN2009A (79 683 60 689 (12.3%) (1.00 [0.76, 1.32)
(Subtotal (95% Cl)) 676 665 (100.0% (0.99 [0.83, 1.17) +
(Total events) (188) (185)
(Heterogeneity: Chi ² = 3.47, df = 2 (P = 0.18); l ² = 42%
(Test for overall effect: Z = 0.14 (P = 0.89))
(Favours Lower dose) (Favours Higher dose)

Test for subgroup differences: $Chi^2 = 0.10$, df = 1 (P = 0.75), $I^2 = 0\%$

Figure 103: Seri	ous adverse e	vents		
	Low dose	High dose	Risk Ratio	Risk Ratio
Study or Subgroup	Events (Total)	Events) (Total) (Weight)	(M-H, Fixed, 95% CI)	M-H, Fixed, 95% Cl
4.8.1 2.4g versus 3.6g Asa	acol			
ITO2010A	2 66	(2) (64) (100.0%)	(0.97 [0.14, 6.68])	
Subtotal (95% CI)	66	64 (100.0%)	0.97 [0.14, 6.68]	
(Total events)	2	2		
Heterogeneity: Not applicat	ble			
(Test for overall effect: $Z = 0$	1.03 (P = 0.98))			
4.8.2 2.4g versus 4.8g Asa	acol			
(HANAUER2005 (moderate)) 2 (139)	(1) (129) (17.2%)	(1.86 [0.17, 20.23])	
HANAUER2007	3 (154)	(1) (147) (17.0%)	2.86 [0.30, 27.22]	
SANDBORN2009A	6 383	(4) (389) (65.8%)	(1.52 [0.43, 5.36])	
Subtotal (95% CI)	676	(665) (100.0%)	(1.81 [0.67, 4.87])	
(Total events)	(1)	6		
(Heterogeneity: $Chi^2 = 0.23$,		= 0%)		
(Test for overall effect: Z = 1	.17 (P = 0.24))			
			F	
			(11 012 015 01 2 5 10 .
(Test for subgroup difference	as: Chi2 = 0.32 df =	1 (P = 0.57) 12 = 0%		Favours Lower dose (Favours Higher dose)
	55. Offic = 0.52, 01 =	1(1 - 0.57), 1 = 0.87		

1.1.7.4 (Mesalazine (Salofalk))

Figure 104:	Clinical re	emiss	ion					
	(Low do	se	(High do	ose		Risk Ratio	Risk	Ratio
Study or Subgrou	p Events	Total	Events	Total	Weight	(M-H, Fixed, 95% Cl	M-H, Fixe	ed, 95% Cl
5.1.1 1.5g versus	3.0g Salofalk)							
KRUIS2003	52	(103)	71	107	(100.0%)	0.76 [0.60, 0.96]	-	
Subtotal (95% CI)		103		107	100.0%	0.76 [0.60, 0.96]	•	
(Total events)	(52)		71					
Heterogeneity: Not	applicable							
(Test for overall effe	ect: Z = 2.29 (F	P = 0.02	2)					
5.1.2 3.0g versus	4.5g Salotalk							
(KRUIS2003)	71	(107)	(58)		(100.0%)	(1.21 [0.97, 1.51])		
Subtotal (95% CI)		(107)		(106)	100.0%)	(1.21 [0.97, 1.51])		
(Total events)	(71)		58					
(Heterogeneity: Not								
Test for overall effe	PCI: Z = 1.72 (F	y = 0.05	9])					
(5.1.3 1.5a versus	4 5a Salofalk							
(KRUIS2003)	<u>62</u>	(103)	(58)	(106)	(100.0%)	0.92 [0.71, 1.19]	-	-
Subtotal (95% CI)		103	00		(100.0%)	0.92 [0.71, 1.19]		
(Total events)	52		58				•	
Heterogeneity: Not								
Test for overall effe		o = 0.54						
							(0.1) (0.2) (0.5) (
		.:				70/	Favours Higher dose	(Favours Lower dose)

Test for subaroup differences: $Chi^2 = 8.23$, df = 2 (P = 0.02), $I^2 = 75.7\%$

Data reported at 8 weeks.

Figure 105:	clinical improve	ement		
	Low dose	High dose	Risk Ratio	Risk Ratio
Study or Subgroup	Events (Total)	Events (Total) (Weight)	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
5.2.1 1.5g versus 3.0)g Salofalk			
KRUIS2003	66 (103)	(80) (107) (100.0%)	0.86 [0.71, 1.03]	
Subtotal (95% CI)	103	(107) (100.0%)	0.86 [0.71, 1.03]	\bullet
Total events	66	80		
Heterogeneity: Not ap	oplicable			
(Test for overall effect)	: Z = 1.66 (P = 0.10)			
5.2.2 3.0g versus 4.5	og Salofalk			
KRUIS2003	80 107	70 (106) (100.0%)	(1.13 [0.95, 1.35]	
Subtotal (95% CI)	107	(106) (100.0%)	(1.13 [0.95, 1.35])	•
Total events	80	(70)		
Heterogeneity: Not ap	oplicable			
Test for overall effect:	: Z = 1.39 (P = 0.17)			
(5.2.3 1.5g versus 4.5	og Salotalk			
KRUIS2003	66 (103)	(70) (106) (100.0%)	0.97 [0.80, 1.18]	
Subtotal (95% CI)	(103)	(106) (100.0%)	0.97 [0.80, 1.18]	—
(Total events)	66	(70)		
Heterogeneity: Not ap	oplicable			
(Test for overall effect)	: Z = 0.30 (P = 0.77)			
				Favours Higher dose) (Favours Lower dose)
(Test for subgroup diff	erences: Chi ² = 4.70), df = 2 (P = 0.10), l ² = 5	7.4%	

Data reported at 8 weeks igure 106:) Adverse events S) ((108) (100.0%) (1.03 [0.83, 1.27] UIS2003) (102 8 10 % (108) (100.0 (108) (100.0 Ż Ó 0.5 0.2 5

a reported at 8 weeks.

L.1.7.5 Olsalazine

Figure 107: Clinical remission Low dose (High dose) Risk Ratio Study or Subgroup Events (Total (Events) (Total (Weight) (M-H, Fixed, 95% C) (7.1.2 2g versus 3g Olsalazine) (1) 92 (1) 91 (100.0%) 0.68 [0.33, 1.38] HANAUER1996 (1) 92 (1) 91 (100.0%) 0.68 [0.33, 1.38] Gubtotal (95% CI) (2) (1) (16) (16) (16) Heterogeneity: Not applicable (Fest for overall effect: Z = 1.06 (P = 0.29)) (P = 0.29) (P = 0.29)	(Risk Ratio (M-H, Fixed, 95% C)
(Test for subgroup differences: Not applicable) Data reported at 12 weeks.)	
Figure 108: (Clinical improvement) Low dose (High dose) Study or Subgroup (Events) (Total) (Veight) (M-H, Fixed, 95% C) (7.2.2 1.5g versus 3g Olsalazine)	(Risk Ratio) (M-H, Fixed, 95% Cl)
(MEYERS 1987) (4) (15) (14) (100.0%) (0.53 [0.20, 1.43]) Subtotal (95% Cl) (15) (14) (100.0%) (0.53 [0.20, 1.43]) (Total events) (4) (100.0%) (0.53 [0.20, 1.43]) (Heterogeneity: Not applicable) (7est for overall effect: Z = 1.25 (P = 0.21)) (15) (14) (100.0%) (15) (14)	
(Test for subgroup differences: Not applicable) Data reported at 3 weeks	0.01 0.1 0 (10 (10) Favours Higher dose (Favours Lower dose)
(Figure 109:) (Endoscopic remission) (Low dose) (High dose) (Risk Ratio) (Study or Subgroup) (Events) (Total) (Weight) (M-H, Fixed, 95% C	(Risk Ratio) (M-H, Fixed, 95% Cl)
(7.3.1 2g versus 3g Olsalazine) (HANAUER1996) 62 92 41 91 (100.0%) 0.77 [0.54, 1.11]) Subtotal (95% Cl) 92 91 (100.0%) 0.77 [0.54, 1.11]) (Total events) 62 41 (Heterogeneity: Not applicable) (Test for overall effect: Z = 1.41 (P = 0.16))	
(Test for subgroup differences: Not applicable) (Data reported at 12 weeks.)	O.1) O.2 O.5 (1) 2 (5) (10) (Favours Higher dose)

1.1.8 Interclass comparison

L.1.8.1) (Mesalazine comparison: Eudragit S 2.4g (400mg Asacol) versus Ethylcellulose (Pentasa) 2.25g

Figure 110:	Clinical re	missio	n						
	Eudragit S c	coated	Ethylcellulose	coated		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		(M-H, Fixed, 95%	
ITO2010A	(20)	66	(18)	63	(100.0%)	(1.06 [0.62, 1.81])			
(Total (95% CI))		66		63	(100.0%)	(1.06 [0.62, 1.81]		\bullet	
(Total events)	(20)		(18)						
Heterogeneity: Not ap	oplicable								
Test for overall effect	: Z = 0.22 (P = 0	.83))					avours Eth	ivicelulose) (Favou	rs Eudragit S

Data reported at 8 weeks.



Data reported at 8 weeks.)

Figure 112:	Adverse e	events)				
	Eudragit S o	coated	Ethylcellulose	e coated		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
ITO2010A	56	66	55	63	100.0%	0.97 [0.85, 1.12]	
(Total (95% CI))		66		63	(100.0%)	0.97 [0.85, 1.12]	•
(Total events)	(56)		(55)				
(Heterogeneity: Not a	oplicable						
Test for overall effect	: Z = 0.40 (P = 0).69))					(Favours Eudragit S) (Favours Ethylcelulose)

Data reported at 8 weeks.

Figure 113:	Serious a	dverse	events					
	Eudragit S c	oated	Ethylcellulose	coated		Risk Ratio	Risk	Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	(M-H, Fixed, 95% Cl	M-H, Fixe	d, 95% CI)
(ITO2010A)	2	66	3	63	(100.0%)	(<mark>0.64 [0.11, 3.68]</mark>)		
(Total (95% CI))		66		63	(100.0%)	0.64 [0.11, 3.68]		
(Total events)	2		3					
(Heterogeneity: Not a	oplicable							40 400
Test for overall effect	: Z = 0.50 (P = 0	.61)					(Favours Eudragit S)	Favours Ethylcelulose)

Data reported at 8 weeks.

1.1.8.2) (Mesalazine comparison: Eudragit L coated mesalazine (3g Salofalk) versus ethylcellulose coated (mesalazine (3g))

Figure 114:	Clinical re	emissio	n				
	Eudragit L o	coated	Ethylcellulose	coated		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
GIBSON2006	83	131	81	(127)	100.0%	0.99 [0.83, 1.19]	
(Total (95% CI))		131		127	(100.0%)	(0.99 [0.83, 1.19])	•
Total events	83		81				
(Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.07 (P = 0.07)).94))					Favours Ethylcellulose) (Favours Eudragit L)

Data reported at 8 weeks.



Data reported at 8 weeks.

Figure 116:	Endoscop	ic remi	ssion				
	Eudragit L o	coated	Ethylcellulose	coated		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
GIBSON2006	46	(109)	46	(106)	(100.0%)	(0.97 [0.71, 1.32])	
(Total (95% CI)		(109)		(106	(100.0%)	0.97 [0.71, 1.32]	•
(Total events)	46		46				
Heterogeneity: Not ap	oplicable						
(Test for overall effect	: Z = 0.18 (P = 0).86))					avours Ethylcellulose) (Favours Eudragit L)

Data reported at 8 weeks.

(Figure 117:) (Adverse events)

	Eudragit L	coated	Ethylcellulose	coated		Risk Ratio		Risk I	latio		
Study or Subgroup	Events	Total	Events	(Total) (We	ight	(M-H, Fixed, 95% CI)		M-H, Fixe	d, 95% CI)		
GIBSON2006	74	(131)	66	(127) (100	.0%)	(1.09 [0.87, 1.36])			-		
(Total (95% CI))		(131)		(127) (100).0%)	(1.09 [0.87, 1.36])			•		
(Total events)	(74)		66								
Heterogeneity: Not a	pplicable							05 1		-	- 10
(Test for overall effect	t: Z = 0.73 (P =	0.47))					(Favours E	Eudragit L	Favours E	thylcell	lulose

Data reported at 8 weeks.)

E	Carlin and a sure of a	
(Figure 118:	Serious adverse ev	ents)

	Eudragit L c	oated) (E	Ethylcellulose	coated	Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	(Total) (Weight	M-H, Fixed, 95% C)	M-H, Fixe	ed <u>, 95</u> % Cl)
GIBSON2006	4	(131)	2	(127) (100.0%	(1.94 [0.36, 10.40])				-
(Total (95% CI))		(131)		(127) (100.0%	(1.94 [0.36, 10.40])				-
Total events	4		2						
Heterogeneity: Not app	<i>.</i>					0.01	0.1		0 100
Test for overall effect:	Z = 0.77 <u>(</u> P = 0	.44))				(Favour	s Eudragit L	(Favours E	Ethylcellulose

Data reported at 8 weeks.)

_

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(Figure 119:	Hospitalis	ations				
	Eudragit L c	oated Et	hylcellulose	coated	Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	(Total) (Weight	(M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
GIBSON2006	4	131	2	(127) (100.0%	(1.94 [0.36, 10.40])	
(Total (95% CI))		(131)		(127) (100.0%	(1.94 [0.36, 10.40])	
Total events	4		2			
(Heterogeneity: Not a	pplicable					
(Test for overall effect	t: Z = 0.77 (P = 0	.44)				(Favours Eudragit L) (Favours Ethylcellulose)

Data reported at 8 weeks.)

1.1.8.3 (Mesalazine comparison: Eudragit S (Ipocol) versus Eudragit S (Asacol)

Figure 120:	Clinical remis	sion				
	(Thinner Eud-S (I	pocol) (I	hicker Eud -S (A	Asacol)	Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	(Total) (Weight)	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
FORBES2005	(12)	(46)	(12)	42 (100.0%)	0.91 [0.46, 1.81]	-
(Total (95% CI))		(46)		(42) (100.0%)	0.91 [0.46, 1.81]	•
Total events	(12)		(12)			
Heterogeneity: Not a	pplicable					
Test for overall effect	t: Z = 0.26 (P = 0.79))					Favours Thicken (Favours Thinner)

Data reported at 4 weeks.

Figure 121: A	dverse ever	nts				
	(Thinner Eud-S (I	pocol) (I	hicker Eud -S (A	Asacol	Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	(Total) (Weight)	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
(FORBES2005)	(34)	46	31	(42) (100.0%)	(1.00 [0.78, 1.28])	• • • • • • • • • • • • • • • • • • •
(Total (95% CI))		46		(42) (100.0%)	(1.00 [0.78, 1.28])	•
(Total events)	(34)		(31)			
Heterogeneity: Not appli	cable					
Test for overall effect: Z	= 0.01 (P = 0.99))					Favours Thinnen (Favours Thicken)

Data reported at 8 weeks.

Figure 122: Serious adverse events

	V								
	Thinner Eud-S	(Ipocol) (I	hicker Eud -S (A	Asacol)	Peto Odds Ratio		Peto Od	ds Ratio	
Study or Subgroup	Events	Total	Events	(Total) (Weight)	Peto, Fixed, 95% Cl		Peto, Fixe	ed, 95% Cl)
(FORBES2005)	0	46	8	(42) (100.0%)	(0.12 [0.01, 1.96])	•			
(Total (95% CI))		46		(42) (100.0%)	0.12 [0.01, 1.96]			_	
(Total events)	0		8						
(Heterogeneity: Not ap	· · · · · · · · · · · · · · · · · · ·								(100
(Test for overall effect:	Z = 1.49 (P = 0.14)					Favours	Thinner	(Favours 1	hicker

Data reported at 8 weeks.

 (Figure 123)
 (Colectomy)

 (Thinner Eud-S (Ipocol))
 (Thicker Eud -S (Asacol))
 (Peto Odds Ratio)
 (Peto Odds Ratio)

 Study or Subgroup)
 (Events)
 (Total)
 (Veight)
 (Peto, Fixed, 95% C)
 (Peto, Fixed, 95% C)

 (FORBES2005)
 0
 46
 (10
 42
 (100.0%)
 (0.12 [0.00, 6.23)

 (Total (95% Cl))
 (45
 (42
 (100.0%)
 (0.12 [0.00, 6.23)

 (Total events)
 0
 (1)
 (10)
 (10)
 (10)

 (Total events)
 0
 (1)
 (10)
 (10)
 (10)

 (Total events)
 0
 (1)
 (10)
 (10)
 (10)

 (Test for overall effect: Z = 1.05 (P = 0.30))
 Evenue: Thinkee
 Evenue: Thinkee

Data reported at 8 weeks.

(1.1.8.4) Mesalazine comparison: MEZAVANT XL versus Asacol

Figure 124:	linical remission	on			
	MMX	Asacol		Risk Ratio	Risk Ratio
Study or Subgroup	Events (Total	Events (Total	Weight	(M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
KAMM2007	35 84) (29) (86)	100.0%	(1.24 [0.84, 1.82]	
(Total (95% CI)	84	86	(100.0%)	(1.24 [0.84, 1.82]	
Total events	35	29			
(Heterogeneity: Not a	applicable				
Test for overall effect	et: Z = 1.06 (P = 0.2	29)			(Favours Asacol) (Favours MMX)

Data reported at 8 weeks.

Figure 125:	linical improver	nent			
	MMX	Asacol		Risk Ratio	Risk Ratio
Study or Subgroup	Events (Total)	Events (Total)	Weight	M-H, Fixed, 95% Cl	(M-H, Fixed, 95% Cl)
KAMM2007	51 84	48 86	(100.0%)	(1.09 [0.84, 1.40])	—
(Total (95% CI))	64	66	(100.0%)	(1.09 [0.84, 1.40]	•
Total events	51	48			
(Heterogeneity: Not a	upplicable)				
(Test for overall effec	t: Z = 0.65 (P = 0.52				(Favours Asacol) (Favours MMX)

Data reported at 8 weeks.

Figure 126: E	ndoscopic remi	ssion			
	(MMX)	Asacol		Risk Ratio	Risk Ratio
Study or Subgroup	Events (Total)	(Events) (Total)	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
KAMM2007	58 84	53 86	100.0%	(1.12 [0.90, 1.40])	
(Total (95% CI)	84	86	(100.0%)	(1.12 [0.90, 1.40]	•
(Total events)	58	53			
Heterogeneity: Not a					0.1 0.2 0.5 1 2 5 10
Test for overall effec	t: Z = 1.01 (P = 0.31				(Favours Asacol) (Favours MMX)

Data reported at 8 weeks.

Figure 127:	Clinical and o	endoscopic	remission		
	MMX	Asac	0	Risk Ratio	Risk Ratio
Study or Subgrou	ip) (Events) (T	otal (Events)	(Total) (Weight)	M-H, Fixed, 95% CI	(M-H, Fixed, 95% Cl)
KAMM2007	34	84 28	86 (100.0%)	(1.24 [0.83, 1.85])	
					•
(Total (95% CI))		84	86 (100.0%)	(1.24 [0.83, 1.85])	-
(Total events)	(34)	(28)			
Heterogeneity: Not					
(Test for overall effe	ect: Z = 1.07 (P =	= 0.29)			(Favours Asacol) (Favours MMX)

Data reported at 8 weeks.

Figure 128:	erious adverse	events			
	(MMX)	Asacol		Risk Ratio	Risk Ratio
Study or Subgroup) (Events) (Total)	Events (Total)	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
(KAMM2007)	1 84	2 86	(100.0%)	0.51 [0.05, 5.54]	
(Total (95% CI))	64	86	100.0%	(0.51 [0.05, 5.54])	
(Total events)		2			
Heterogeneity: Not a	applicable				
Test for overall effect	ot: Z = 0.55 (P = 0.5	8)			(Favours MMX Favours Asacol)

Data reported at 8 weeks.

1.1.8.5 Olsalazine versus sulphasalazine

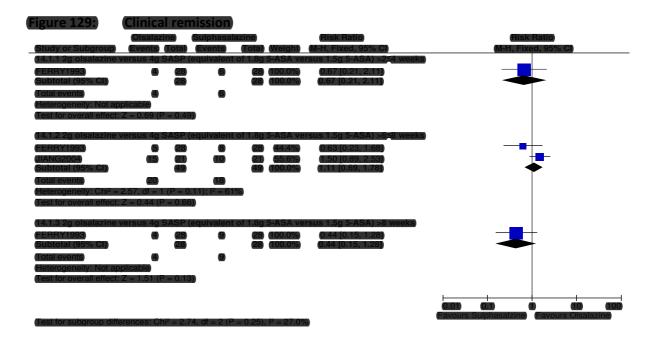
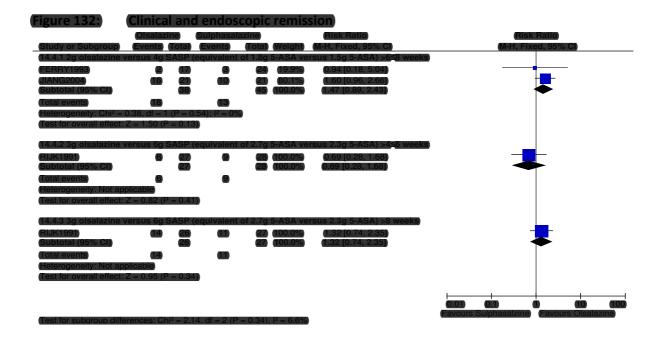


Figure 130: Clinical improvement

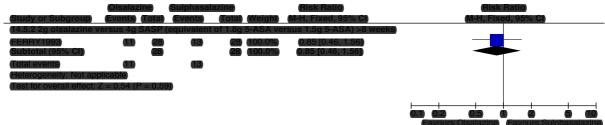
	(
	Olsalazi	ine) (Sulphasala	azine	Risk Ratio	BI	sk Ratio
Study or Subgroup	Events	Total	Events	(Total) (Weight)	M-H, Fixed, 95% Cl	M-H, F	ixed, 95% Cl
14.2.2 2g olsalazine	versus 4g S	SASP (e	quivalent	of 1.8g 5-ASA ve	ersus 1.5g 5-ASA) >6≤8 week	(5)	
(JIANG2004)	20	21	(15)	(21) (100.0%)	(1.33 [1.00, 1.78])		
Subtotal (95% CI)	—	21	_	21 100.0%	(1.33 [1.00, 1.78])		
(Total events)	20		(15)				
Heterogeneity: Not ap	plicable)		_				
(Test for overall effect:	Z = 1.97 (P	' = 0.05))				
						0.1 0.2 0.5	
						Favours Sulphasalazin	e) (Favours Olsalazine)

(lest for subgroup differences: Not applicable





gure 133: Adverse event



Test for subgroup differences: Not applicable

1.1.8.6 (Balsalazide versus mesalazine (all types))

Figure 134:	Clinical	remissi	on				
	Balsalaz	ide) (M	esalazin	10)		Risk Ratio	Risk Ratio
Study or Subgrou	p Events	(Total) (E	vents) (1	otal	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
(15.1.2 6.75g balsa	alazide (equiva	lent to 2.4	1g 5-AS/	A) ver	rsus 2.4g	mesalamine 052 weeks	
GREEN1998	62	50	21	(49)	(100.0%)	(1.49 [1.02, 2.19])	
Subtotal (95% Cl)		50		49	100.0%	(1.49 [1.02, 2.19])	◆
(Total events)	32		(21)				
(Heterogeneity: No							
Test for overall effe	ect: Z = 2.04 (P	= 0.04)					
(15.1.3 6.75g balsa	alazide (equiva	lent to 2.4	1g 5-AS/	A) ver	rsus 2.4g	mesalamine >2≤4 weeks)
GREEN1998	(35)	50	25	(49)	(100.0%)	(1.37 [0.99, 1.91])	
Subtotal (95% CI)) —	50	_	49	100.0%	(1.37 [0.99, 1.91])	▲
(Total events)	35		25				
Heterogeneity: No	t applicable)						
Test for overall effe	ect: Z = 1.88 (P	= 0.06)					
	alazide (equiva	lent to 2.4	1g 5-AS/	A) ver	rsus 2.4g	mesalamine >6 <u><</u> 8 weeks)
(GREEN1998)	(39)	(50)	22	(49)	(37.5%)	(1.74 [1.23, 2.45])	
(PRUITT2002)	68	(123)	38		62.5%	(1.05 [0.77, 1.45])	
(Subtotal (95% CI)	·	123	_	120	(100.0%)	(1.31 [1.04, 1.65])	
(Total events)			60				
Heterogeneity: Ch			$; I^2 = 77^2$	70)			
rest for overall en		-0.02					
(15.1.5 6.75g balsa	alazide (equiva	lent to 2.4	1g 5-AS/	A) ver	rsus 2.4g	mesalamine >8 weeks	_
GREEN1998	(44)	50	28	49	(100.0%)	(1.54 [1.18, 2.00])	
(Subtotal (95% CI)		50		49	(100.0%)	(1.54 [1.18, 2.00])	•
(Total events)	(44)		28				
Heterogeneity: No							
(Test for overall eff	ect: Z = 3.22 (P	= 0.001)					
Test for subaroup	differences Ch	i2 _ 0 03 <i>c</i>	\f_ 2 /Þ	_ 0.8'	2) 12 <u>0</u> 0/		(Favours Mesalazine) (Favours Balsalazide)

Figure 135:	linical impro	ovement		
	Balsalazide	Mesalazine	Risk Ratio	Risk Ratio
Study or Subgroup	Events (Total	(Events) (Total) (Weigh	nt) (M-H, Fixed, 95% Cl)	M-H, Fixed, 95% CI
15.2.1 6.75g balsalaz	ide (equivalent o	f 2.34g 5-ASA) versus 2	2.4g 5-ASA >6 <u>≤</u> 8 weeks	
LEVINE2002	22 34	(22) (38) (100.09	% (1.12 <u>[0.77, 1.61]</u>)	— <mark>—</mark> —
Subtotal (95% CI)	34	(38) (100.0)	% (1.12 [0.77, 1.61])	•
Total events	22	22		
(Heterogeneity: Not ap	olicable			
(Test for overall effect:	Z = 0.59 (P = 0.5			
				(Favours Mesalazine) (Favours Balsalazide)
(Teet for subaroup diffe	ronooc: Not annli	aabla		i avoaro moodiazido

Test for subgroup differences: Not applicable

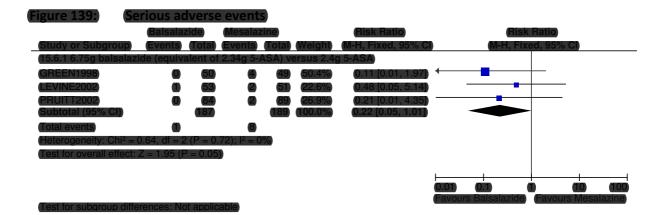


(Figure 137:) (Clinical and endoscopic remission at 8 weeks, random effects)

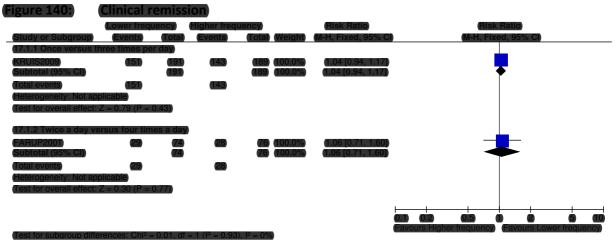
	Balsalaz	ide (Mesalaz	ine		(Risk Ratio)		Ris	c Ratio	
Study or Subgroup	Events	(Total) (E	Events	Total	Weight	M-H, Random, 95% C)	M-H, Ran	dom, 95% C	
(15.4.2 6.75g balsala	zide (equiva	lent of 2	.34g 5-A	ASA) ve	ersus 2.4	g 5-ASA >6 <u>≤</u> 8 weeks				
GREEN1998	(27)	(50)	(11)	49	(33.2%)	(2.41 [1.35, 4.30])				
LEVINE2002	8	35	7	36	20.7%	(1.18 [0.48, 2.90])			+	
PRUITT2002	39	84	36	89	46.0%	(1.15 [0.82, 1.61])		-		
Subtotal (95% CI)		169		174	(100.0%)	1.47 [0.88, 2.46]				
(Total events)	74		54							
Heterogeneity: Tau ²	= 0.12; Chi² =	⊧ 4.83, df	= 2 (P =	= 0.09);	$l^2 = 59\%$					
(Test for overall effect	:: Z = 1.49 <u>(</u> P	= 0.14)								
									<u>+ +</u>	
							(0.1) (0.2)	2 (0.5)	1 2	5 10
			_				(Favour	rs Mesalazine) (Favours B	alsalazide

Test for subgroup differences: Not applicable

Figure 138:	dverse events			
	Balsalazide	Mesalazine	Risk Ratio	Risk Ratio
Study or Subgroup	Events (Total)	(Events) (Total) (Weigh	t) (M-H, Fixed, 95% Cl)	M-H, Fixed, 95% CI
15.5.2 6.75g balsalaz	ide (equivalent of	2.34g 5-ASA) versus 2	.4g 5-ASA	
GREEN1998	24 50	35 49 30.29	(0.67 [0.48, 0.94])	
LEVINE2002	23 53	26 51 (22.6%	(0.85 [0.57, 1.28])	
PRUITT2002	45 84	57 89 47.2 %	0.84 [0.65, 1.08]	
Subtotal (95% CI)	187	(189) (100.0%	(0.79 [0.66, 0.95])	\bullet
(Total events)	92	(118)		
Heterogeneity: Chi ² =				
Test for overall effect:	Z = 2.54 (P = 0.01)			
			L	
(Test for subgroup diffe	erences: Not applic	able		avours Balsalazide Favours Mesalazine



1.1.9 (Oral aminosalicylates regimen comparison)



Data reported at 8 weeks.)

Figure 141: Clir	nical improv	ement						
Lo	w frequency (Hi	gh frequency		Risk Ratio		Risk Ratio		
Study or Subgroup Ev	rents) (Total) (E	vents (Total)	Weight (N	I-H, Fixed, 95% Cl)	M-H, Fixed, 9	5% CI	
(17.2.1 Twice a day versus	four times a day							
FARUP2001	58 74	58 (76)	100.0%)	(1.03 [0.86, 1.22])				
Subtotal (95% CI)	74	76	100.0%	(1.03 [0.86, 1.22])		•		
(Total events)	58	58						
Heterogeneity: Not applicab	ble							
(Test for overall effect: $Z = 0$.30 (P = 0.76))							
							1	
					0.1 0.2	0.5 1	0	5 10
					Favours Higher f	requency (Fav	ours Lower fre	quency
Test for subgroup difference	es: Not applicable)							

Data reported at 8 weeks.



Data reported at 8 weeks.)

 Figure 143:
 Adverse events

 Lower frequency
 (figher frequency)
 (fisk Ratio)

 Study or Subgroup
 (Events)
 (Tota)
 (Vents)
 (Tota)

 (17.4.1 Once versus three times per day)
 (KRUIS2009)
 65
 (191)
 61
 (189)
 (0.0.0%)
 0.89[0.66, 1.21)

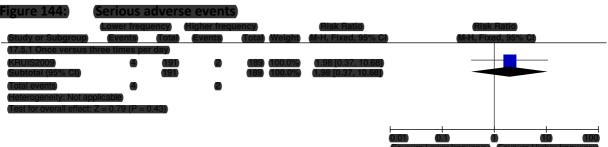
 (KRUIS2009)
 65
 (191)
 61
 (189)
 (0.0.0%)
 0.89[0.66, 1.21)

 (Total events)
 65
 61
 (Heterogeneity: Not applicable)
 (events)
 189
 (0.0.0%)
 0.89[0.66, 1.21)

 (Test for subgroup differences: Not applicable)
 (events)
 65
 10
 (events)
 61
 (events)

 (Test for subgroup differences: Not applicable)
 (events)
 63
 10
 (events)
 63
 10

 (Test for subgroup differences: Not applicable
 (events)
 (events)
 (events)
 (events)
 (events)
 (for subgroup)
 (for subgroup)



Test for subgroup differences: Not applicable

1.1.10 Oral aminosalicylates preparation comparison

1.1.10.1 Granules versus tablets (mesalazine)

Figure 145:	Clinical ren	nission			
	Granu	iles) (Tat	lets	Risk Ratio	Risk Ratio
Study or Subgro	up Events	(Total) (Even	s (Total) (Weig	ht M-H, Fixed, 95% C	(M-H, Fixed, 95% CI)
(18.1.1 >2≤4 weel	(S)				
MARAKHOUSKIZ	2005 (54)	(114) (4	8 (115) (100.0	(1.13 [0.85, 1.52]) -
Subtotal (95% C		(114)	(115) (100.0	(1.13 [0.85, 1.52]	\bullet
(Total events)	54	4	8		
Heterogeneity: No	ot applicable)	-			
(Test for overall ef	fect: Z = 0.86 (P	P = 0.39)			
(18.1.2 >6 <u>≤</u> 8 weel	(S				
FARUP2001	28	76 2	4) (77) (11.2	.%) (1.18 [0.76, 1.84])
MARAKHOUSKIZ	2005) (76)	(114) (7	8 (115) (36.3	(0.98 [0.82, 1.18]) 🕂
RAEDLER2004	(120)	(179) (11	2 (178) (52.5	(1.07 [0.91, 1.24]) – – – – – – – – – – – – – – – – – – –
Subtotal (95% C		369	(370) (100.0	1.05 [0.93, 1.18]	•
(Total events)	224	21	4		
Heterogeneity: Cl	ni² = 0.81, df = 2	! (P = 0.67); l ² =	= 0%)		
(Test for overall ef	fect: Z = 0.80 (P	r = 0.42)			
					(Favours Tablets) (Favours Granules)
(Test for subaroup	differences: Ch	i ² = 0.25. df =	1 (P = 0.62). I ² =	0%	

Figure 146: Clinical improvement, >6≤8 weeks

	Granules	Tablet	5	Risk Ratio	Risk Ratio
Study or Subgroup	Events (Total	Events	Total (Weight)	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
FARUP2001	58 76) 52	(77) (100.0%)	(1.13 [0.93, 1.38])	
(Total (95% CI))	76)	(77) (100.0%)	(1.13 [0.93, 1.38])	•
(Total events)	58	(52)			
(Heterogeneity: Not ap	olicable)				
Test for overall effect:	Z = 1.20 (P = 0.2	23)			(Favours Tablets) (Favours Granules)

Data reported at 8 weeks.)

Figure 147: End	oscopic remi	ssion, >6≤8 weeks		
	Granules	Tablets	Risk Ratio	Risk Ratio
Study or Subgroup	Events (Total)	(Events) (Total) (Weigh	t) (M-H, Fixed, 95% CI)	M-H, Fixed, 95% Cl
RAEDLER2004	67 (179)	(71) (178) (100.0%	0.94 [0.72, 1.22]	
(Total (95% CI))	(179)	(178) (100.0%	(0.94 [0.72, 1.22]	•
(Total events)	67	71		
Heterogeneity: Not app	licable			
Test for overall effect: 2	Z = 0.48 (P = 0.63			(Favours Tablets) (Favours Granules)

Data reported at 8 weeks.)

Figure 148: Clinical and endoscopic remission, >6≤8 weeks Risk Ratio Granules (Tablets) **Risk Ratio** Study or Subgroup ents (Total) (Events (Total) (Weight) RAEDLER2004) 61 (179)381 (59) (Total (95% CI)) .03 [0.77. 1.38] 100.0% otal events) 61 (59) progeneity: Not applicable (0.1)(10)(1 for overall effect: Z = 0.19 (P = 0.85))

Data reported at 8 weeks.

Figure 149: Adverse events, fixed effects

-	Granules	(Tablets)		Risk Ratio	Risk Ratio
Study or Subgroup	Events (Total	Events (Total)	Weight	M-H, Fixed, 95% Cl	(M-H, Fixed, 95% CI)
MARAKHOUSKI2005	36 (114	42 (118)	(49.0%)	0.89 [0.62, 1.28]	+
RAEDLER2004	(56) (181	43 (181)	(51.0%)	(1.30 [0.93, 1.83])	
Total (95% CI)	295	(299)	(100.0%)	(1.10 [0.86, 1.41])	•
(Total events)	92	85			
(Heterogeneity: Chi ² = 2.2	29, df = 1 (P = 0	.13); l² = 56%)			
Test for overall effect: Z	= 0.75 (P = 0.45				Favours Granules (Favours Tablets)

Figure 150: Adverse events, random effects

	Granules	Tablets	Risk Ratio	Risk Ratio
Study or Subgroup	(Events) (Total) (E	Events) (Total) (Weight)	M-H, Random, 95% Cl	M-H, Random, 95% Cl
MARAKHOUSKI2005	36 (114)	(42) (118) (48.6%)	(0.89 [0.62, 1.28])	-
RAEDLER2004	56 (181)	(43) (181) (51.4%)	(1.30 [0.93, 1.83])	—
(Total (95% Cl))	295	(299) (100.0%)	(1.08 [0.74, 1.57])	•
(Total events)	92	85		
Heterogeneity: Tau ² = 0.	04; Chi² = 2.29, df :	= 1 (P = 0.13); l² = 56%		
(Test for overall effect: Z	= 0.41 (P = 0.69))		(Fav	ours Granules) (Favours Tablets)

Figure 151: Serious adverse events

	Granules	(Tablets)		Risk Ratio	Risk Ratio
Study or Subgroup	Events (Tot	al) (Events) (Total)	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
MARAKHOUSKI2005	0 11	4 2 (118)	(29.1%)	0.21 [0.01, 4.26]	
(RAEDLER2004)	3 18	1 6 181	70.9%	0.50 [0.13, 1.97]	
(Total (95% CI))	29	5 299	100.0%	0.41 [0.12, 1.43]	
(Total events)	3	8			
Heterogeneity: Chi ² = 0.2	27, df = 1 (P =	0.60 ; $l^2 = 0\%$			
(Test for overall effect: Z	= 1.40 (P = 0.1	(6))			
					Favours Granules) (Favours Tablets)

Ulcerative colitis Appendix H: Forest plots and ROC curves

1.1.11 Oral corticosteroids

(1.1.11.1) Oral corticosteroids versus placebo

Figure 152: Clin	ical and endo	oscopic remission		
	Prednisone	Placebo	Risk Ratio	Risk Ratio
Study or Subgroup	Events (Total)	(Events) (Total) (Weigh	(M-H, Fixed, 95% Cl)	(M-H, Fixed, <mark>95% Cl</mark>)
LENNARDJONES1960	9 (19	(3) (18) (100.0%	(2.84 [0.91, 8.86])	
(Total (95% CI)	(19)	(18) (100.0%	a (2.84 [0.91, 8.86])	
(Total events)	9	3		
(Heterogeneity: Not applic	able		ł	
(Test for overall effect: Z =	1.80 (P = 0.07)			(Favours Placebo) (Favours Prednisone)

(1.1.11.2) Oral corticosteroids dose comparison

(1.1.11.3) (Prednisolone)

Figure 153:	linical impr	ovement	(0≤2 weeks)		
	Higher dose	Lower d	ose	Risk Ratio	Risk Ratio
Study or Subgroup	Events (Tot	tal Events	Total (Weight)	M-H, Fixed, 95% Cl	(M-H, Fixed, 95% Cl)
(3.1.1 40mg vs 20mg	prednisolone				
(BARON1962)	18 (20 9	20 (100.0%)	2.00 [1.21, 3.32]	
Subtotal (95% CI)	6	20)	20 (100.0%)	2.00 [1.21, 3.32]	
(Total events)	18	9			
(Heterogeneity: Not ap	plicable				
(Test for overall effect:	Z = 2.68 (P = 0.	.007))			
3.1.2 60mg vs 20mg j	prednisolone				
(BARON1962)		20 (9)	20 (100.0%)	2.00 [1.21, 3.32]	
(Subtotal (95% CI))		20)	(20) (100.0%)	(2.00 [1.21, 3.32])	
Total events	(18)	9			
Heterogeneity: Not ap					
(Test for overall effect:	$\angle = 2.68 (P = 0.)$.007))			
(3.1.3 60ma vs 40ma i	arednisolone				
			00 (100 00/)		
(BARON1962) (Subtotal (95% CI))		20) (<u>18)</u> 20)	(20) (100.0%) (20) (100.0%)	(1.00 [0.81, 1.23]) (1.00 [0.81, 1.23])	
(Total events)	48		20 100.070		Ť
(Heterogeneity: Not ap		10			
(Test for overall effect:		00)			
Tost of overall effect.	<u> </u>				

Figure 154:	Clinical and	d endoscop	oic remission	(0≤2 weeks)	
	Higher do	se (Lower d	dose	Risk Ratio	(Risk Ratio)
Study or Subgroup	Events	Total (Events)	(Total) (Weight)	M-H, Fixed, 95% Cl	(M-H, Fixed, 95% Cl)
3.2.1 40mg vs 20mg	prednisolon	e)			
BARON1962	10	20 4	20 (100.0%)	2.50 [0.94, 6.66]	
Subtotal (95% CI)		(20)	20 (100.0%)	2.50 [0.94, 6.66]	
Total events	10	4			
Heterogeneity: Not ap	plicable				
(Test for overall effect:	Z = 1.83 (P =	= 0.07))			
		_			
3.2.2 60mg vs 20mg	-				
BARON1962	(10)	20 4	20 (100.0%)	(2.50 [0.94, 6.66])	
Subtotal (95% CI)	_	20	(20) (100.0%)	2.50 [0.94, 6.66]	
(Total events)	(10	4			
(Heterogeneity: Not ap	-	0.07			
(Test for overall effect:	Z = 1.83 (P =	= 0.07))			
(3.2.3 60mg vs 40mg	prednisolon				
(BARON1962)	(10)	20 10	20 (100.0%)	(1.00 [0.54, 1.86])	
(Subtotal (95% CI))		20	20 (100.0%)	(1.00 [0.54, 1.86])	
(Total events)	10				Ť
Heterogeneity: Not an	plicable				
(Test for overall effect:	-	= 1.00))			
					(Favours Lower dose) (Favours Higher dose)

(Figure 155: Clinical and endoscopic remission at the end of treatment)

	Higher d	ose	Lower c	lose		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	(M-H, Fixed, 95% CI)
3.3.1 40mg vs 20mg	g prednisolo	ne					
BARON1962	13	20	6	(20)	(100.0%)	2.17 [1.03, 4.55]	
Subtotal (95% CI)		20		(20)	100.0%	(2.17 [1.03, 4.55])	
(Total events)	(13)		6				
Heterogeneity: Not a	pplicable						
(Test for overall effec	t: Z = 2.04 (P	= 0.04))				
		_					
3.3.2 60mg vs 20mg			_				
(BARON1962)	(13)	20	6	20	(100.0%)	(2.17 [1.03, 4.55])	
Subtotal (95% CI)		(20)	_	20	100.0%	2.17 [1.03, 4.55]	
(Total events)	(13)		6				
(Heterogeneity: Not a		0.04					
(Test for overall effec	t: Z = 2.04 (P	= 0.04))				
(3.3.3 60ma vs 40ma	nednisolo	ne					
(BARON1962)	(13)	(20)	13	20	(100.0%)	(1.00 [0.63, 1.58])	
Subtotal (95% CI)		20	10	20		(1.00 [0.63, 1.58])	
(Total events)	(13)		(13)				Ť
Heterogeneity: Not a			10				
Test for overall effec		= 1.00					
			,				
							0.1 0.2 0.5 1 2 5 10
							(Favours Lower dose) (Favours Higher dose)

Note: Data reported at 5 weeks for 20,40mg and 3 weeks for 60mg

Figure 156:	Hospitalis	ations				
	(Higher do	se) (Lower d	lose	Peto Odds Ratio	Peto Od	ds Ratio
Study or Subgrou	up Events	Total (Events)	(Total) (Weight)	Peto, Fixed, 95% Cl	Peto, Fix	ed, 95% Cl
(3.4.1 40mg vs 20)	mg prednisolon	8				
(BARON1962)	2	20 0	20 (100.0%)	(7.79 [0.47, 129.11])		
(Subtotal (95% CI)		20	(20) (100.0%)	7.79 [0.47, 129.11]		
(Total events)	2	0				
Heterogeneity: No						
Test for overall eff	ect: Z = 1.43 (P =	= 0.15))				
(3.4.2 60mg vs 20)	ma prodpisolon					
				7 20 [0 15 270 20]		
(BARON1962) (Subtotal (95% CI)	. •	20 0 20	(20) (<u>100.0%</u>) (20) (100.0%)	(7.39 [0.15, 372.38]) (7.39 [0.15, 372.38])		
(Total events)	· •					
(Heterogeneity: No	t annlicable)					
Test for overall eff		= 0.32))				
(3.4.3 60mg vs 40)	mg prednisolon	e				
(BARON1962)		20 2	(20) (100.0%)	(0.50 [0.05, 5.06])		
Subtotal (95% CI)		20	20 (100.0%)	0.50 [0.05, 5.06]		
(Total events)		2				
(Heterogeneity: No	t applicable)					
(Test for overall eff	ect: Z = 0.59 (P =	= 0.55))				
					L	
					0.01 0.1 (1 (10) (100)
					Favours Higher dose	Favours Lower dose

(Figure 157:) (A	dverse events			
	Higher dose	Lower dose	Risk Ratio	Risk Ratio
Study or Subgroup	Events (Total)	Events) (Total) (Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
3.7.1 40mg vs 20mg p	orednisolone			
BARON1962	4 20	(4) (20) (100.0%)		
Subtotal (95% CI)	20	(20) (100.0%	(1.00 [0.29, 3.45])	
Total events	4	4		
Heterogeneity: Not app				
(Test for overall effect: 2	Z = 0.00 (P = 1.00)			
(3.7.2 60mg vs 20mg p	vradnisolona			
(BARON1962)			(1.50 [0.50, 4.52])	
(Subtotal (95% CI)	6 20	(4) (20) (100.0% (20) (100.0%		
(Total events)		4		
Heterogeneity: Not app	licable			
(Test for overall effect: 2				
(3.7.3 60mg vs 40mg p	orednisolone			
BARON1962	6 20	4 (20) (100.0%	(1.50 [0.50, 4.52])	——————————————————————————————————————
Subtotal (95% CI)	20	(20) (100.0%	(1.50 [0.50, 4.52])	-
(Total events)	6	4		
Heterogeneity: Not app				
Test for overall effect: 2	Z = 0.72 (P = 0.47)			
			L	
			0.	a da
			Fa	avours Higher dose) (Favours Lower dose)

L.1.11.4 (Beclomethasone)

Figure 158:	Clinical imp	proveme	ent				
	Beclomethasone	e 10mg) (E	Beclomethasor	ne 5mg	Risk Ratio	Risk Ratio	
Study or Subgroup	Events	(Total)	Events	(Total) (Weigl	nt) (M-H, Fixed, 95% C	(M-H, Fixed, 95% CI)	
(RIZZELLO2001)	9	(19)	9	(19) (100.04	6 (1.00 [0.51, 1.95]	, <u> </u>	
(Total (95% CI))		19		(19) (100.0)	(1.00 [0.51, 1.95]		
Total events	9		9				
Heterogeneity: Not app	olicable						-
Test for overall effect:	Z = 0.00 (P = 1.00)					(Favours Higher dose) (Favours Lower do	bse

(Figure 159:) (Adverse events) Becomethasone 10ma (Becomethason

	Decionienasone	Tunig	Decioinethason	le onig		Felo Ouus hallo		Felo Ou	us natio		
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl		Peto, Fixe	ed, 95% CI)		
RIZZELLO2001	0	(19)	0	(19)	(100.0%)	(7.81 [0.47, 129.75])					
(Total (95% CI))		(19)		19	(100.0%)	(7.81 <u>[</u> 0.47, 129.75]					
Total events	2		0								
Heterogeneity: Not app	licable									(100	
Test for overall effect: 2	Z = 1.43 (P = 0.15))						Eavours Hi		Eavours Low	er dose	

(1.1.11.5) (Oral corticosteroids regimen comparison)

Figure 160:	Figure 160: Clinical remission (0≤2 weeks)												
	Prednisolone once	a day Pre	ednisolone fou	r times	Risk Ratio		Risk I	Ratio					
Study or Subgroup	Events	Total	Events	(Total) (Weight)	(M-H, Fixed, 95% CI)		M-H, Fixe	d, 95% Cl)					
POWELLTUCK1978	8	23	6	(22) (100.0%)	0.57 [0.16, 2.12]								
(Total (95% CI))		23		(22) (100.0%)	0.57 [0.16, 2.12]								
(Total events)	3		6				.						
(Heterogeneity: Not app	licable					0 1 0 2	05 4			40			
Test for overall effect: 2	Z = 0.83 (P = 0.40))				E	vours Four ti	mes a day	Favours On	ce a day				

Figure 161: Clinical improvement (0≤2 weeks)

	Prednisolone once	e a day) (P	rednisolone fo	ur times	Risk Ratio		Risk Rati	10	
Study or Subgroup	Events	Total	Events	(Total) (Weigh	t) (M-H, Fixed, 95% C		M-H, Fixed, 9	95% CI	
POWELLTUCK1978	14	23	12	(22) (100.0°	(1.12 [0.67, 1.85])			
(Total (95% CI))		23		(22) (100.04	a (1.12 [0.67, 1.85])		-	►	
(Total events)	14		(12)						
(Heterogeneity: Not app						01 02		2	6 10
(Test for overall effect: 2	Z = 0.43 (P = 0.67))					Favours Four ti	imes a day) (Fa	vours Once a	a day

Ulcerative colitis Appendix H: Forest plots and ROC curves

1.1.12 Oral corticosteroids route of administration comparison

1.1.12.1 Oral versus IM corticosteroids

Figure 162:	Clinical remis	sion				
	Oral corticoster	iods) (IM coi	ticosteriods		Risk Ratio	Risk Ratio
Study or Subgroup	Events	(Total) (Eve	nts (Tota	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% CI
(5.1.1 0 <u>≤</u> 2 weeks)						
(SOOD2002)	18	(19)	18 (21	(100.0%)	(1.11 [0.90, 1.36])	
Subtotal (95% CI)		(19)	21	(100.0%)	(1.11 [0.90, 1.36])	•
Total events	18		18			
Heterogeneity: Not a	pplicable					
(Test for overall effect	t: Z = 0.96 (P = 0.34))				
(5.1.2 6≤8 weeks)						
(SOOD2002)		19	18 (21	(100.0%)	(1.11 [0.90, 1.36])	
Subtotal (95% CI)		(19)	21	100.0%	(1.11 [0.90, 1.36])	
(Total events)	(18)		18			•
Heterogeneity: Not a						
(Test for overall effect	· · · · · · · · · · · · · · · · · · ·					
						Eavours IM (Eavours Oral)
						(Favours IM) (Favours Oral)

(Figure 163:) Adverse events

	Oral corticoste	riods	IM corticoste	eriods	Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	(Total) (Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
(SOOD2002)	0	(19	0	(21) (100.0%	(5.53 [0.71, 43.16])	
(Total (95% CI)		(19)		(21) (100.0%	5 .53 [0.71, 43.16]	
(Total events)	5					
(Heterogeneity: Not appl	icable					
(Test for overall effect: Z	= 1.63 (P = 0.10					(Eavours Oral) (Favours IM)

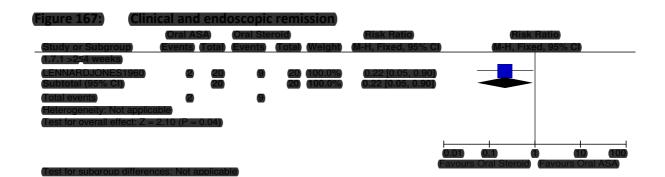
(1.1.13) (Oral aminosalicylates versus oral corticosteroids

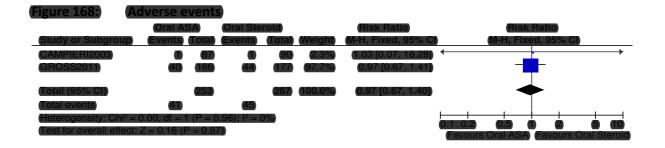
Figure 164: Clir	nical remissio	on		
	Oral ASA	Oral Steroid	Risk Ratio	Risk Ratio
Study or Subgroup	Events (Total)	Events (Total) (Weigh	(M-H, Fixed, 95% CI)	(M-H, Fixed, 95% Cl)
(1.1.1 >2 <u>≤</u> 4 weeks)				
CAMPIERI2003	50 80	(46) (73) (80.0%	(0.99 [0.78, 1.27]	
ROMANO2010	5 15	(12) (15) (20.0%)	0.42 [0.20, 0.89]	
Subtotal (95% CI)	95	88 (100.0%	0.88 [0.69, 1.11]	◆
Total events	55	58		
Heterogeneity: Chi ² = 4.	67, df = 1 (P = 0.4	03); l² = 79%)		
(Test for overall effect: Z	= 1.11 (P = 0.27)			
(1.1.2 >6 <mark>≤8 weeks</mark>)				
GROSS2011	91 (166)	(177) (100.0%)		
Subtotal (95% CI)	(166)	(177) (100.0%	(1.39 [1.10, 1.74])	\blacksquare
(Total events)	91	70		
(Heterogeneity: Not appli	cable			
(Test for overall effect: Z	= 2.80 (P = 0.00			
Toot for subgroup differe			(Fav	ours Oral Steroid) (Favours Oral ASA)

est for subgroup differences: Chi² = 7.56, df = 1 (P = 0.006), l² = 86.8%)

Figure 165: Cl	Figure 165: Clinical improvement												
	Oral ASA	Oral Steroid		Risk Ratio	Risk Ratio								
Study or Subgroup	Events (Tot	al (Events) (Tot	al) (Weight)	(M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl								
(1.3.1 >2 <u>≤</u> 4 weeks													
(CAMPIERI2003)	(59) (8	80 (57) (7	3 (100.0%)	(0.94 [0.79, 1.13])									
Subtotal (95% Cl)		0 7	3 100.0%	0.94 [0.79, 1.13]	\bullet								
(Total events)	59	57											
(Heterogeneity: Not ap	plicable)												
Test for overall effect:	Z = 0.63 (P = 0.00)	.53)											
(1.3.2 >6 <u>≤</u> 8 weeks)													
GROSS2011	(142) (16	6 (136) (17	7) (100.0%)	(1.11 [1.01, 1.23]									
Subtotal (95% CI)	(16	6 (17	7) (100.0%)	(1.11 [1.01, 1.23])	•								
(Total events)	(142)	(136)											
Heterogeneity: Not ap	plicable												
Test for overall effect:	Z = 2.06 (P = 0)	0.04]											
					Favours Oral Steroid) (Favours Oral ASA)								
Test for subaroup diffe	rences: Chi2 -	2.45 df = 1 (P = (<u>12) 2 - 50</u>	2%									

Figure 166:	ndoscopic	remission			
	Oral ASA	Oral Ste	roid	Risk Ratio	Risk Ratio
Study or Subgroup	Events (T	otal) (Events)	(Total) (Weight)	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
(1.5.1 >6 <mark>≤</mark> 8 weeks)					
GROSS2011	(105) (166 (88)	(177) (100.0%)	(1.27 [1.05, 1.54])	
Subtotal (95% CI)		166	(177) (100.0%)	(1.27 [1.05, 1.54])	◆
Total events	(105)	(88)			
Heterogeneity: Not ap	plicable				
(Test for overall effect:	Z = 2.51 (P =	= 0.01)			
d 5 0 - 0 weeks					
(1.5.2 >8 weeks)	-				
(ROMANO2010) (Subtotal (95% CI))	4		(<u>15)</u> (<u>100.0%</u>) (15) (<u>100.0%</u>)	0.36 [0.15, 0.89]	
	-	-	(15) (100.076)	0.36 <u>[0.15, 0.89]</u>)	
(Total events)	4	(11)			
(Heterogeneity: Not ap		0.02)			
(Test for overall effect:	Z = 2.22 (P =	= 0.03			
					0.1 0.2 0.5 1 2 5 10
(Test for subaroun diffe	prences Chi2	- 7 24 df - 1	$(P = 0.007)$ $l^2 = 8$	6.2%	Favours Oral Steroid) (Favours Oral ASA)







1.1.14 Oral aminosalicylates & oral steroids versus oral aminosalicylates & placebo

Figure 170: Clinical remission (>2≤4 weeks)

	Oral ASA & S	iteroid	Dral ASA & Pl	acebo	Risk Ratio		Risk Ratio			
Study or Subgroup	Events	Total	Events	(Total) (Weight	M-H, Fixed, 95% Cl)	M-H, Fixe	ed, 9 <mark>5%</mark> CI		
RIZZELLO2002	(34)	58	(21)	61 (100.0%	(1.70 [1.13, 2.56])					
(Total (95% CI)		58		61 (100.0%	(1.70 [1.13, 2.56])					
(Total events)	(34)		21							
Heterogeneity: Not app	olicable						-			
(Test for overall effect:	7 – 2 56 (P – 0)	(10				0.2	0.0		9	

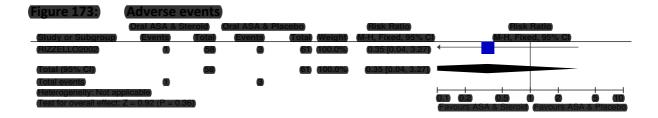
(Test for overall effect: Z = 2.56 (P = 0.01



Oral

0.0											
	Oral ASA & S	teroid	Dral ASA & Pl	lacebo		Risk Ratio		Ris	< Ratio)	
Study or Subgroup	Events	Total	Events	Total	Weight	(M-H, Fixed, 95% Cl)	M-H, Fix	ced, 95	% CI)	
RIZZELLO2002	44	58	31	61 (100.0%)	(1.49 [1.12, 1.99])				-	
(Total (95% CI))		58		61	100.0%	(1.49 [1.12, 1.99])				•	
Total events	(44)		31								
Heterogeneity: Not app	olicable										
(Test for overall effect: 2	Z = 2.74 (P = 0.0	006))					Eavor	U.S			





1.1.15 (Oral aminosalicylates versus topical aminosalicylates)

Figure 174:	Clinical re	emissi	on				
	Oral A	SA	Topical .	ASA	Risk Ratio	Risk	Ratio
Study or Subgrou	up (Events)	(Total)	Events	(Total) (Weigh	(M-H, Fixed, 95% C	M-H, Fixe	ed, 95% Cl
(1.1.1 0 <mark>≤2 weeks</mark>)							
GIONCHETTI1998 (Subtotal (95% Cl)		29 29	(18)	(29) (100.0% (29) (100.0%			
(Total events)	6		(18)				
Heterogeneity: No	t applicable)						
Test for overall eff	ect: Z = 2.81 (ł	P = 0.005	5)				
(1.1.2 >2 <u>≤</u> 4 weeks)					_	
GIONCHETTI1998	3 (12)	(29)	26	(29) (49.4%		, — — —	
PRANTERA2005	(23)	40	26	38 (50.6%			
(Subtotal (95% Cl)		69		67 (100.0%	0.65 [0.50, 0.86]	\bullet	
(Total events)	(35)		(52)				
Heterogeneity: Ch			- 11	77%			
(Test for overall eff	ect: Z = 3.07 (I	P = 0.002	2))				
(1.1.3 >6≤8 weeks							
(PRANTERA2005)	24		-	(38) (100.0%	(1.20 [0.80, 1.80])		
Subtotal (95% CI)		<u>40</u> 40	(19)	(38) (100.0%			
(Total events)	24		(19)				
Heterogeneity: No	_		15				
(Test for overall eff		- 0 38)					
Testion Overall en	ουι. <u>2</u> = 0.00 (ι	- 0.00					
						⊢ + − + −	
						0.1 0.2 0.5 (1 2 5 10
					(Favours Topical ASAs	Favours Oral ASAs

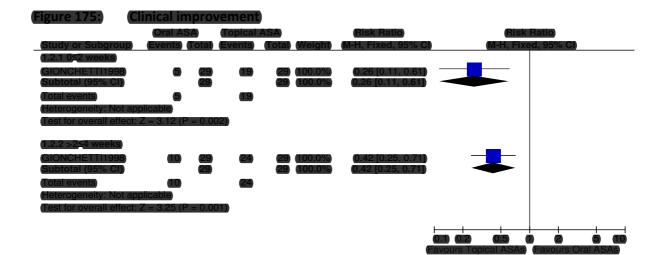


Figure 176:	Endosco	oic re	mission					
	Oral A	SA	Topical	ASA		Risk Ratio	Risk	Ratio
Study or Subgrou	p Events	(Total)	Events	(Total)	Weight	M-H, Fixed, 95% Cl	M-H, Fixe	ed, 95% Cl
(1.3.1 0 <u>≤</u> 2 weeks)								
GIONCHETTI1998) 4	(29)	(15)	(29)	(100.0%)	(0.27 [0.10, 0.71])		
Subtotal (95% CI))	29		29	100.0%	0.27 [0.10, 0.71]		
(Total events)	4		(15)					
Heterogeneity: Not	applicable							
(Test for overall effe	ect: Z = 2.66 (P = 0.00	08)					
(1.3.2 >2 <u>≤</u> 4 weeks)							_	
GIONCHETTI1998		(29)	21	(29)	(100.0%)	0.48 [0.27, 0.83]		
(Subtotal (95% CI))	29		(29)	(100.0%)	0.48 [0.27, 0.83]		
(Total events)	10		21					
(Heterogeneity: Not								
Test for overall effe	ect: Z = 2.65 (P = 0.00	08)					
(1.3.3 >6≤8 weeks)								
					(100.00/)			
(PRANTERA2005) (Subtotal (95% CI)	(18)	40 40	(14)	38	(100.0%)	(1.22 [0.71, 2.09]) (1.22 [0.71, 2.09])	-	
					100.070	1122 [017 1, 2105]		
(Total events) (Heterogeneity: Not	18) applicable		(14)					
Test for overall effe	· · · · · · · · · · · · · · · · · · ·	P = 0.4	71					
Hest for overall ene	501.2 = 0.73 (0.4						
							⊢ + − + − −	
						-	0.1 0.2 0.5	
							Favours Topical ASAs	Favours Oral ASAs

Figure 177: A	dverse eve	nts						
	Oral ASA	(Topical A	ASA		Risk Ratio	(Risk Ratio	
Study or Subgroup	(Events) (Tota	I (Events)	(Total) (W	eight)	M-H, Fixed, 95% Cl) <u>(M-H</u>	, Fixed, 95%	CI
GIONCHETTI1998	6 2	90	29	4.3%)	13.00 [0.77, 220.64])		_	
PRANTERA2005	6 4) (1)	39 9	95.7%	0.53 [0.22, 1.30]		┫┼	
(Total (95% Cl))	6		68 (10	0.0%	(1.07 [0.51, 2.23])		\bullet	
(Total events)	(12)	(11)						
(Heterogeneity: Chi ² = :	5.34, df = 1 (P =	: 0.02); l² = 8 ⁻	1%)					40 400
(Test for overall effect:	Z = 0.17 (P = 0)	86)				(Favours Oral A	SAs) (Favour	s Topical ASAs

1.1.16 Oral aminosalicylate versus oral & topical aminosalicylate

Figure 178:	Clinical rer	nission			
	Oral AS	A (Oral/ topic	al ASA	Risk Ratio	Risk Ratio
Study or Subgroup	b) (Events) (Total Events	(Total) (Weight)	M-H, Fixed, 95% Cl	(M-H, Fixed, 95% CI)
(3.1.1 >2 <u>≤</u> 4 weeks)					
MARTEAU2005	(16)	47 (25)	(57) (100.0%)	0.78 [0.47, 1.27]	
(Subtotal (95% CI)		47	(57) (100.0%)	0.78 [0.47, 1.27]	
(Total events)	(16)	(25)			
(Heterogeneity: Not					
(Test for overall effe	ct: $Z = 1.00$ (P	= 0.32)			
(3.1.2 >4≤6 weeks)					
(VECCHI2001)	55	67 55	63 (100.0%)	0.94 [0.81, 1.09]	—
(Subtotal (95% CI)	00	67 (55) (67)	63 (100.0%)	0.94 [0.81, 1.09]	•
(Total events)	55	55			•
Heterogeneity: Not					
Test for overall effe		= 0.41)			
<u></u>					
				Fav	(0.1 0.2) (0.5) (1) (2) (5) (10) ours Oral/ topical) (Favours Oral)
					ouro oran topical, il avouro oran



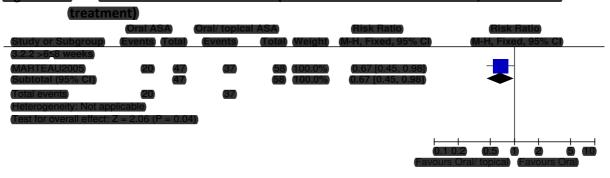
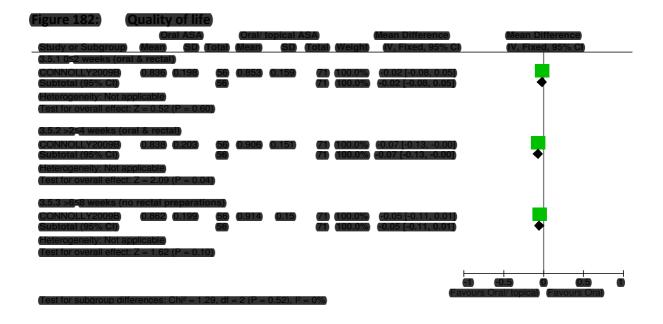


Figure 180: Clinical improvement

Oral ASA	Oral/ topical ASA	Risk Ratio	Risk Ratio
Study or Subgroup (Events) (Total	Events (Total) (Weight)	M-H, Fixed, 95% CI	(M-H, Fixed, 95% CI)
3.3.1 >2≤4 weeks			
MARTEAU2005 (29) (47	(51) (57) (100.0%)	(0.69 [0.54, 0.88])	
Subtotal (95% CI)	(57) (100.0%)	0.69 [0.54, 0.88]	\bullet
Total events (29)	61		
Heterogeneity: Not applicable			
(Test for overall effect: $Z = 3.01$ ($P = 0.0$	(03)		
3.3.2 >4 <u>≤</u> 6 weeks			
(VECCHI2001) (57) (67)	(57) (63) (100.0%)	0.94 [0.83, 1.07]	
Subtotal (95% CI)) (67)	63 (100.0%)	0.94 [0.83, 1.07]	•
(Total events) (57)	57		
Heterogeneity: Not applicable			
(Test for overall effect: $Z = 0.94$ ($P = 0.3$	(5))		
		Favour	s Oral/topical) (Favours Oral)

(Figure 181:) (Clinical improvement at 8 weeks (4 weeks combination treatment, 4 weeks oral)

treatmo	ent						
	Oral ASA	Oral/ topica	I ASA	Risk Ratio		Risk Ra	tio
Study or Subgroup	(Events) (Total	Events	(Total) (Wei	ght) (M-H, Fixed, 9	15% CI	M-H, Fixed,	95% CI
(3.4.2 >6≤8 weeks)							
MARTEAU2005	(32) (47	50	(58) (100.	0%) (0.79 [0.63,	0.99]		
Subtotal (95% CI)	47		(58) (100	0% 0.79 [0.63,	0.99]	\bullet	
(Total events)	32	50					
(Heterogeneity: Not app	licable						
Test for overall effect: 2	Z = 2.09 (P = 0.0)	04))					
					(Favours C	Dral/topical) (Fa	avours Oral)



(Figure 183:) (Endoscopic remission)

	Oral ASA	Oral/ topica	I ASA	Risk Ratio	Risk Ratio
Study or Subgroup	Events) (Tota	al Events	(Total) (Weight)	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
3.6.1 >4 <u>≤</u> 6 weeks					
VECCHI2001)	36 6	2 (41)	58 (100.0%)	0.82 [0.63, 1.07]	· · · · · · · · · · · · · · · · · · ·
Subtotal (95% CI)	6	2	58 (100.0%)	0.82 [0.63, 1.07]	➡
Total events	36	41			
Heterogeneity: Not app	olicable				
Test for overall effect:	Z = 1.43 (P = 0	.15)			
				0.	
				Favou	rs Oral/ topical) (Favours Oral)
(Test for subgroup diffe	rences: Not ap	plicable			

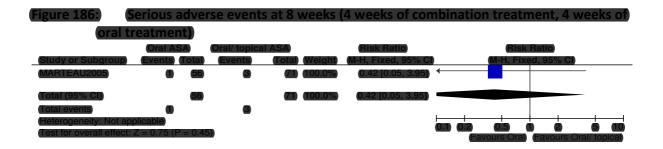
Figure 184:

Adverse events (6 weeks of combination treatment)

	Oral A	SA	Oral/ topica	al ASA	Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	(Total) (Weight)	M-H, Fixed, 95% Cl	l.	M-H, Fixe	ed, 95% CI	
VECCHI2001	5	67	4	63 (<u>100.0%</u>)	(1.18 [0.33, 4.18])				
(Total (95% CI))		67		63 (100.0%)	(1.18 [0.33, 4.18]				
(Total events)	5		4						
Heterogeneity: Not ap	olicable						05		
Test for overall effect:	Z = 0.25 (I	P = 0.80					Favours Oral	(Favours Oral/ topi	cal

(Figure 185: Adverse events at 8 weeks (4 weeks of combination treatment, 4 weeks of oral)

treatm	lent				
	Oral ASA	Oral/ topical	ASA	Risk Ratio	(Risk Ratio)
Study or Subgroup	Events (Total)	Events	(Total) (Weight)	(M-H, Fixed, 95% CI)	M-H, Fixed, 95% Cl
MARTEAU2005	28 56	24	(71) (100.0%)	(1.48 [0.97, 2.25]	
(Total (95% CI))	(56)		(71) (100.0%)	(1.48 [0.97, 2.25])	-
Total events	28	24			
(Heterogeneity: Not app	olicable				
(Test for overall effect:	Z = 1.84 (P = 0.0	7))			(Favours Oral) (Favours Oral/ topical)



Oral & topical aminosalicylate versus oral & topical aminosalicylate (different rectal) 1.1.17) (aminosalicylate doses)

Figure 187: Cole	ectomy at 12	weeks				
	Lower dose	Higher dose		Peto Odds Ratio	Peto Od	ds Ratio
Study or Subgroup	Events (Total	Events (Total)	Weight	Peto, Fixed, 95% Cl	Peto, Fix	ed, 95% CI
(4.4.1 1g versus 2g)						
(VANBODEGRAVEN1996)	0 9	() (1) (1)	100.0%)	(0.15 [0.00, 7.58])	←	
Subtotal (95% CI)	- 9	10	100.0%	0.15 [0.00, 7.58]		
(Total events)	0					
(Heterogeneity: Not applical	ole					
(Test for overall effect: $Z = 0$	0.95 (P = 0.34))					
(4.4.2 2g versus 4g)					. 💻	
VANBODEGRAVEN1996	1 10	2 (12)	100.0%	0.58 [0.05, 6.35]		
(Subtotal (95% Cl))	(10)	_	100.0%	0.58 [0.05, 6.35]		
(Total events)		2				
Heterogeneity: Not applical						
(Test for overall effect: Z = 0	0.44 (P = 0.66))					
4.4.3 1g versus 4d						
VANBODEGRAVEN1996			100.00/	0.16 [0.01. 2.80]	←	
(Subtotal (95% CI))	0 9		100.0%) 100.0%)	0.16 [0.01, 2.80]		
(Total events)		2				
Heterogeneity: Not applical	-	-				
(Test for overall effect: $Z = 1$						
					0.1 0.2 0.5 (
Test for subgroup difference	e^{1} Chi ² = 0.61 df	$-2(P-0.74)$ l^2-	0%		Favours Lower dose	Favours Higher dose

t for subaroup differences: Chi² = 0.61. df = 2 (P = 0.74). l² = 0%

Ulcerative colitis Appendix H: Forest plots and ROC curves

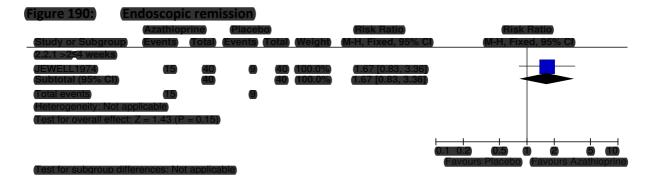
1.1.18 Immunomodulators

(1.1.18.1) (Methotrexate versus placebo)

(Figure 188: Clin	nical remi	ssion				
	Methotrex	cate	Placeb	0	Risk Ratio	(Risk Ratio)
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
1.2.1 >2<4 weeks						
OREN1996	2	30	3	37	0.82 [0.15, 4.61]	
(1.2.2 >6 <u>≤</u> 8 weeks)						
OREN1996	2	30	6	37	(0.41 [0.09, 1.89])	
1.2.3 >8 weeks						
OREN1996	6	(30)	8	(37)	0.93 [0.36, 2.37]	
						0.01 0.1 0 100
						(Favours Placebo) (Favours Methotrexate)

1.1.18.2 (Azathioprine versus placebo (in addition to corticosteroids)

Figure 189:	linical remis	ssion				
	Azathioprin	e Placebo		Risk Ratio	Risk	Ratio
Study or Subgroup	Events (To	otal) (Events) (Tota	al) (Weight)	M-H, Fixed, 95% Cl	M-H, Fixe	ed, 95% CI
2.1.1 >2 <u>≤</u> 4 weeks						
JEWELL1974	31	40 27 4	0 (100.0%)	(1.15 [0.87, 1.51])	-	-
Subtotal (95% CI)		40 4	0) (100.0%)	(1.15 [0.87, 1.51])	•	
(Total events)	31	27				
(Heterogeneity: Not ap	plicable					
Test for overall effect:	: Z = 0.99 (P = 0	.32)				
					01.02 05 0	
					(Favours Placebo)	(Favours Azathioprine)
Test for subgroup diffe	erences: Not ap	plicable				



L.1.18.3 (Tacrolimus versus placebo)

(Figure 191:) (Cli	nical rem	ission (0≤2	weeks)		
	Tacrolim	us Place	bo	Risk Ratio	Risk Ratio
Study or Subgroup	(Events)	Total Events	Total (Weight)	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
3.13.1 Low trough					
OGATA2006	2	(19) (1)	(17) (100.0%)	(1.79 [0.18, 18.02])	
Subtotal (95% CI)	-	19	(17) (100.0%)	(1.79 [0.18, 18.02]	
(Total events)	2				
(Heterogeneity: Not app	olicable	_			
(Test for overall effect:	Z = 0.49 (P =	= 0.62)			
(3.13.2 High trough)					
OGATA2006	4	20 1	(17) (67.7%)	(3.40 [0.42, 27.59])	
OGATA2012	3	32 0	(30) (32.3%)	6.58 [0.35, 122.21]	
Subtotal (95% CI)		52	47 (100.0%)	4.43 [0.81, 24.06]	
(Total events)	7				
(Heterogeneity: Chi ² = (0.13, df = 1 ($(P = 0.72); I^2 =$	0%)		
(Test for overall effect:)	Z = 1.72 (P :	= 0.09))			
					(a.c.) (a.c.) (b.c.) (b

Test for subgroup differences: $Chi^2 = 0.38$, df = 1 (P = 0.54), $I^2 = 0\%$



(Test for subgroup differences: $Chi^2 = 0.07$, df = 1 (P = 0.79), $l^2 = 0\%$

(Figure 193:) (En	doscopic	remission(0	l≤2 weeks		
	(Tacrolimu	is) (Placeb	0	Risk Ratio	Risk Ratio
Study or Subgroup	Events (T	otal (Events)	(Total) (Weight)	M-H, Fixed, 95% Cl	(M-H, Fixed, 95% Cl)
3.15.1 Low trough					
OGATA2006	8	18 2	(16) (100.0%)	(3.56 [0.88, 14.35])	
Subtotal (95% CI)		18	16 (100.0%)	3.56 [0.88, 14.35]	
(Total events)	8	2			
Heterogeneity: Not app	olicable				
(Test for overall effect:	Z = 1.78 (P =	0.07)			
3.15.2 High trough					
OGATA2006	(15)	19 2	(16) (34.5%)	(6.32 [1.69, 23.57])	
OGATA2012	(14)	32 4	30 65.5%	3.28 [1.22, 8.86]	
Subtotal (95% CI)		51	(46) (100.0%)	4.33 [1.97, 9.52]	
Total events	(29)	6			
(Heterogeneity: Chi ² = (, ,		1%		
(Test for overall effect:	Z = 3.64 (P =	0.0003)			
					0.01 0.1 0 100 100
				_	(Favours Placebo) (Favours Tacrolimus)

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Figure 195: Serious adverse events **Tacrolimus** Pla Peto O nts (Total) (Weight) Total (Ev 20 (100.0%) 20 (100.0%) 22 22 5 [0.13, 341.54] 0 liah trouah 20 (100. 10 (100. 21) 21) erall effec 1 (10)

(1.1.18.4) (Tacrolimus dose comparison)

(Figure 196: Clinical remission (0≤2 weeks)

	(Higher do:	se (Lower	dose		Risk Ratio	(Risk Ratio)
Study or Subgroup	Events (Total) (Events	(Total)	Weight	(M-H, Fixed, 95% Cl)	M-H, Fixed, 95% Cl
OGATA2006	4	20 2) (19)	(100.0%)	(1.90 [0.39, 9.20]	
(Total (95% CI)		20	(19)	100.0%	(1.90 [0.39, 9.20]	
(Total events)	4	2)			
Heterogeneity: Not app	olicable					
(Test for overall effect: 2	Z = 0.80 (P =	0.43)				(Favours Lower dose) (Favours Higher dose)





Figure 198:	ndoscopic re	emission (0≤2	: weeks		
	Higher dose	Lower dose		Risk Ratio	Risk Ratio
Study or Subgroup	Events (Tota	al) (Events) (Tota	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% CI
OGATA2006	(15) (1	9 8 (18	100.0%	(1.78 [1.01, 3.13])	
Total (95% CI)	1	9 (18	(100.0%)	(1.78 [1.01, 3.13])	
(Total events)	(15)	8			
Heterogeneity: Not ap	plicable				
(Test for overall effect:	Z = 1.99 (P = 0.0)	15)			(Favours Lower dose) (Favours Higher dose)
(Figure 199: S	erious adver	se events			
	Higher dose	Lower dose		Risk Ratio	Risk Ratio
Study or Subgroup	(Events) (Tota	al) (Events) (Total) (Weight)	(M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
OGATA2006	1 2	1 (1) (22	. (100.0%)	(1.05 [0.07, 15.69])	
	_				
Total (95% CI)	2	1 (22	(100.0%)	(1.05 [0.07, 15.69])	
(Total events)					
(Heterogeneity: Not ap					0.01 0.1 0 100
Test for overall effect:	Z = 0.03 (P = 0.9)				(Favours Higher dose) (Favours Lower dose)

1.2 Induction of remission for acute severe ulcerative colitis

1.2.1.1 IV ciclosporin (4mg/kg) and steroids versus placebo and steroids

Figure 200:	Colectomy (0≤2 w	eeks)						
	IV Ciclosporin & s	eroids	IV Placebo & st	eroids		Risk Ratio	Risl	k Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	CI M-H, Fix	ked, 95% Cl	
LICHTIGER1994	3	11	4	9	100.0%	0.61 [0.18, 2.06]			
Total (95% CI)		11		9	100.0%	0.61 [0.18, 2.06]			
Total events	3		4						
Heterogeneity: Not app	olicable						0.1 0.2 0.5		5 10
Test for overall effect: 2	Z = 0.79 (P = 0.43)						Ciclosporin & steroids	Placebo & ste	

Note: All patients received 100 mg of hydrocortisone IV every 8 hrs and hydrocortisone enemas nightly if the drug could be retained.

Figure 201: Clinical improvement (0≤2 weeks)

	IV Ciclosporin & steroids		IV Placebo & steroids		Risk Difference		Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
LICHTIGER1994	9	11	0	9	100.0%	0.82 [0.55, 1.08]	
Total (95% CI)		11		9	100.0%	0.82 [0.55, 1.08]	
Total events	9		0				
Heterogeneity: Not app Test for overall effect: 2		1)					-200 -100 0 100 200 Placebo & steroids Ciclosporin & steroids

1.2.1.2 IV ciclosporin (4mg/kg/day) versus IV steroids (40mg/day)

Figure 202:	Colectom	iy (0≤2	2 week	s)						
	IV Ciclos	porin	IV Stere	oids		Peto Odds Ratio	Peto Oc	Peto Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% C	I Peto, Fix	ed, 95% Cl		
DHAENS2001	2	14	0	15	100.0%	8.57 [0.51, 144.39]	I —			
Total (95% CI)		14		15	100.0%	8.57 [0.51, 144.39]	-			
Total events Heterogeneity: Not a Test for overall effec		= 0.14)	0				0.01 0.1 Favours IV Ciclosporin	1 10 Favours IV Ste	100 eroids	

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Figure 203: Clinical improvement (0≤2 weeks) – Day 7/8

	IV Ciclos	porin	IV Steroids			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
DHAENS2001	9	14	8	15	100.0%	1.21 [0.65, 2.23]	
Total (95% CI)		14		15	100.0%	1.21 [0.65, 2.23]	
Total events	9		8				
Heterogeneity: Not app	olicable						-+ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$
Test for overall effect:	Z = 0.60 (P	= 0.55)					Favours IV Steroids Favours IV Ciclosporin

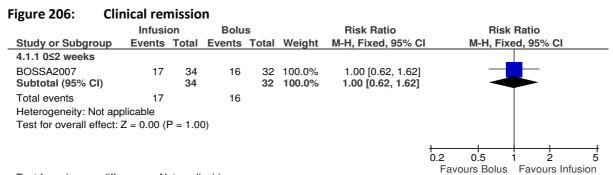
Ciclosporin dose comparison: 4 mg/kg versus 2 mg/kg 1.2.1.3

Figure 204:	Clinical in	Clinical improvement (0≤2 weeks)												
	4 mg IV Ciclos	sporin	2 mg IV Ciclo	osporin		Risk Ratio	Risk Ratio							
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI							
VAN2003	32	38	30	35	100.0%	0.98 [0.81, 1.19]								
Total (95% CI)		38		35	100.0%	0.98 [0.81, 1.19]								
Total events Heterogeneity: Not app Test for overall effect: 2		6)	30				0.5 0.7 1 1.5 2 Favours 2 mg Ciclosporin Favours 4 mg Ciclosporin							

1.2.1.4 Corticosteroid preparation comparison: IV (infusion) versus IV (bolus)

Figure 205: Colectomy Infusion Bolus **Risk Ratio Risk Ratio** Events Total Events Total Weight M-H, Fixed, 95% Cl M-H, Fixed, 95% CI Study or Subgroup 4.3.1 >2≤4 weeks BOSSA2007 0.94 [0.30, 2.95] 5 34 5 32 100.0% Subtotal (95% CI) 32 100.0% 34 0.94 [0.30, 2.95] Total events 5 5 Heterogeneity: Not applicable Test for overall effect: Z = 0.10 (P = 0.92) 0.01 100 0.1 10 1 Favours Infusion Favours Bolus

Test for subgroup differences: Not applicable



Test for subgroup differences: Not applicable

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Figure 207:	Adverse e	vents					
	Infus	ion	Bolu	s		Risk Ratio	Risk Ratio
Study or Subgro	up Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
BOSSA2007	13	34	15	32	100.0%	0.82 [0.46, 1.43]	
Total (95% CI)		34		32	100.0%	0.82 [0.46, 1.43]	
Total events	13		15				
Heterogeneity: No	ot applicable						+ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$
Test for overall ef	fect: Z = 0.71 (P = 0.4	8)				Favours Infusion Favours Bolus

1.3 Likelihood of surgery – Forest plots and Receiver Operator Characteristic (ROC) curves

1.3.1 Ho index

Figure 208: Ho Inde	x on	Da	у З					
Study	ΤР	FP	FN	ΤN	Sensitivity	Specificity	Sensitivity	Specificity
ACEITUNO2008 population 1	6	2	5	21	0.55 [0.23, 0.83]	0.91 [0.72, 0.99]	_	
ACEITUNO2008 population 2	5	5	4	24	0.56 [0.21, 0.86]	0.83 [0.64, 0.94]		
HO2004	51	27	9	80	0.85 [0.73, 0.93]	0.75 [0.65, 0.83]		

Source/Note: ACEITUNO2008 cut off ≥5 colectomy in first 3 months, HO2004 cut off≥4 colectomy during hospital admission

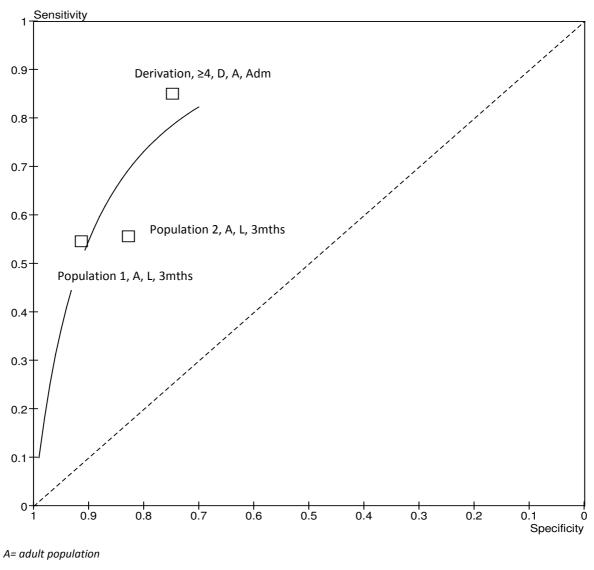


Figure 209: ROC curve - Ho index on Day 3

D= derivation study

L= low quality

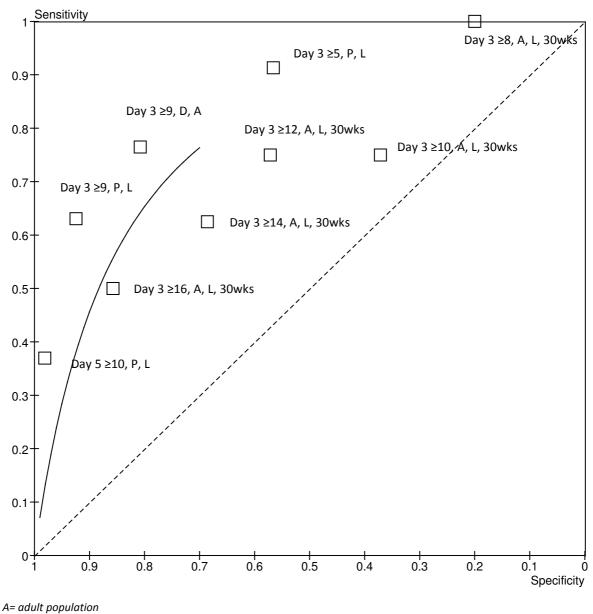
Adm = colectomy during hospital admission

3mths= colectomy within 3months of admission

1.3.2 **Lindgren Index**

Figure 210: Lindgren index (different time points and cut offs)

Study	ΤР	FP	FN	ΤN	Sensitivity	Specificity	Sensitivity	Specificity
BAUDET2010 Day 3 10+	6	22	2	13	0.75 [0.35, 0.97]	0.37 [0.21, 0.55]	_	
BAUDET2010 Day 3 12+	6	15	2	20	0.75 [0.35, 0.97]	0.57 [0.39, 0.74]		
BAUDET2010 Day 3 14+	5	11	3	24	0.63 [0.24, 0.91]	0.69 [0.51, 0.83]	_	
BAUDET2010 Day 3 16+	4	5	4	30	0.50 [0.16, 0.84]	0.86 [0.70, 0.95]		
BAUDET2010 Day 3 8+	8	28	0	7	1.00 [0.63, 1.00]	0.20 [0.08, 0.37]		
LINDGREN1998 Day 3 9+	13	5	4	21	0.76 [0.50, 0.93]	0.81 [0.61, 0.93]		
TURNER2008 Day 3 - 5+	42	23	4	30	0.91 [0.79, 0.98]	0.57 [0.42, 0.70]		
TURNER2008 Day 3 - 9+	29	4	17	49	0.63 [0.48, 0.77]	0.92 [0.82, 0.98]		
TURNER2008 Day 5 - 10+	17	1	29	52	0.37 [0.23, 0.52]	0.98 [0.90, 1.00]		
							0 0.2 0.4 0.6 0.8 1 0	0 0.2 0.4 0.6 0.8 1





D=derivation study, 30 days colectomy

30wks= 30wks colectomy

P= paediatric population, within admission colectomy

L= low quality

The \geq figures indicate the cut offs used.

Note: The adult population study were patients who were on infliximab

1.3.3 Seo Index

Figure 212: Seo index (different time points and cut offs)

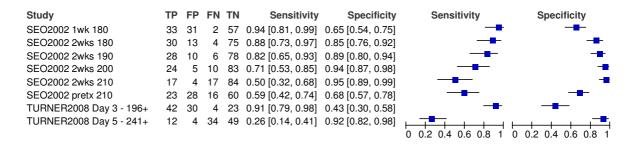
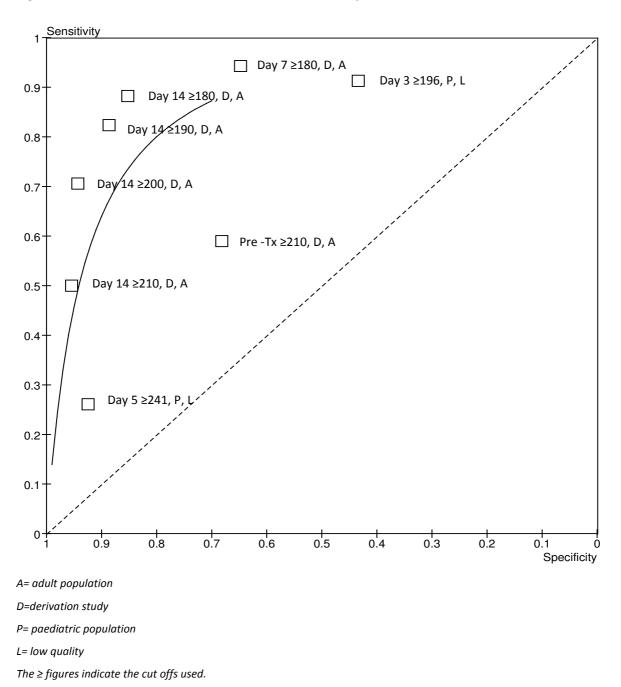


Figure 213: ROC curve for Seo Index (different time points and cut offs)

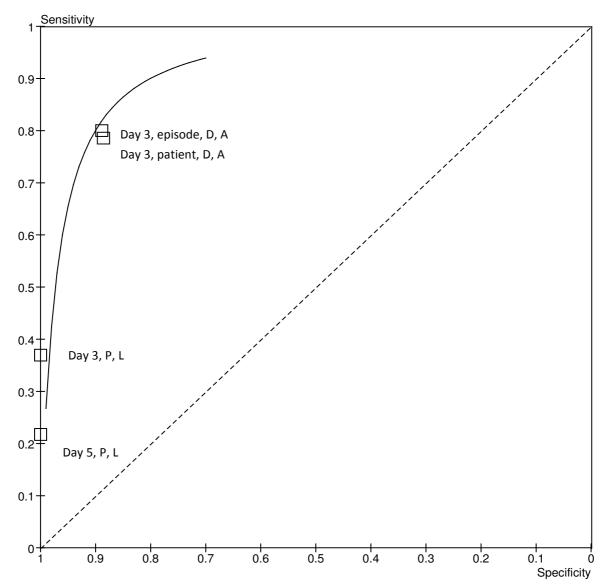


1.3.4 Travis Index

Figure 214: Travis index (different time	points)
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Study	ΤР	FP	FN	ΤN	Sensitivity	Specificity	Sensitivity	Specificity
TRAVIS1996 Day 3 episode	12	4	3	32	0.80 [0.52, 0.96]	0.89 [0.74, 0.97]		
TRAVIS1996 Day 3 patient	11	4	3	31	0.79 [0.49, 0.95]	0.89 [0.73, 0.97]		
TURNER2008 Day 3	17	0	29	53	0.37 [0.23, 0.52]	1.00 [0.93, 1.00]		-
TURNER2008 Day 5	10	0	36	53	0.22 [0.11, 0.36]	1.00 [0.93, 1.00]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1





Episode/ patient - denominator used for analysis

A= adult population

D=derivation study

P= paediatric population

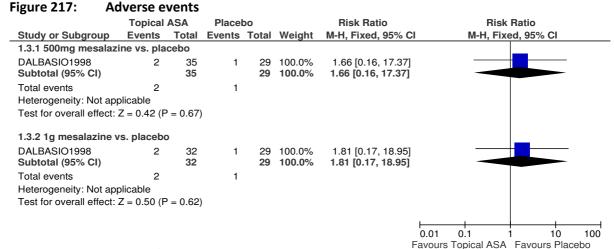
L=low quality

1.4 Maintenance of remission

1.4.1 Topical aminosalicylates

1.4.1.1 Topical aminosalicylates versus placebo (continuous)

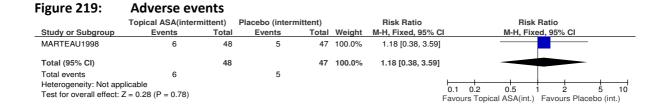
Figure 216:	Relap	ose (H	HR)						
	Topical	ASA	Placel	00				Hazard Ratio	Hazard Ratio
Study or Subgroup	Events	Total	Events	Total	O-E	Variance	Weight	Exp[(O-E) / V], Fixed, 95% C	Exp[(O-E) / V], Fixed, 95% Cl
1.1.1 500mg mesalazi	ine vs. pla	cebo							
DALBASIO1998 Subtotal (95% CI)	11	40 40	14	35 35	-3.8851	6.16	100.0% 1 00.0 %	0.53 [0.24, 1.17] 0.53 [0.24, 1.17]	
Total events	11		14						
Heterogeneity: Not app	olicable								
Test for overall effect:	Z = 1.57 (F	P = 0.12))						
1.1.2 800mg mesalazi	ine vs. pla	cebo							
DARIENZO1990 Subtotal (95% CI)	1	15 15	11	15 15	-3.1504	0.91667	100.0% 1 00.0%	0.03 [0.00, 0.25] 0.03 [0.00, 0.25]	
Total events	1		11						
Heterogeneity: Not app	olicable								
Test for overall effect:	Z = 3.29 (F	P = 0.00	1)						
1.1.3 1g mesalazine v	s. placebo	D							
DALBASIO1998 Subtotal (95% CI)	3	36 36	14	35 35	-4.2389	2.47059	100.0% 1 00.0 %	0.18 [0.05, 0.63] 0.18 [0.05, 0.63]	
Total events Heterogeneity: Not app	3 olicable		14						
Test for overall effect:	Z = 2.70 (F	P = 0.00	7)						
									0.01 0.1 1 10 100 Favours Topical ASA Favours Placebo
Test for subgroup diffe	rences: Ch	ni² = 7.24	4, df = 2 (P = 0.0	3), l ² = 72	.4%		·	



Test for subgroup differences: $Chi^2 = 0.00$, df = 1 (P = 0.96), $I^2 = 0\%$

1.4.1.2 Topical aminosalicylates versus placebo (intermittent)

Figure 218:	Relapse at	1 year	' (RR)					
	Topical ASA(interi	nittent)	Placebo (interi	nittent)		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% (CI M-H, Fixed, 95% CI	
MARTEAU1998	10	48	24	47	100.0%	0.41 [0.22, 0.76]	s] — <u> </u>	
Total (95% CI)		48		47	100.0%	0.41 [0.22, 0.76]		
Total events Heterogeneity: Not app Test for overall effect:			24				0.1 0.2 0.5 1 2 5 Favours Topical ASA(int.) Favours Placebo (int	10 t.)



1.4.1.3 Topical aminosalicylates dose comparison

Figure 220:	Relap	se (H	IR)								
	500mg mesalazin	e supp.	1g mesalazine	e supps.				Hazard Ratio	Hazard	Ratio	
Study or Subgroup	Events	Total	Events	Total	O-E	Variance	Weight	Exp[(O-E) / V], Fixed, 95%	CI Exp[(O-E) / V]	, Fixed, 95% Cl	
DALBASIO1998	11	40	3	36	3.26595205	2.35714	100.0%	4.00 [1.12, 14.33]]		
Total (95% CI)		40		36			100.0%	4.00 [1.12, 14.33]			
Total events Heterogeneity: Not app Test for overall effect: 2			3						0.01 0.1 1 Favours 500mg mesalazine	10 Favours 1g mesa	100 alazine
									. a. c. c. c. c. c. g modulatino	· _ · · · · · · · · · · · · · · · · · ·	

Figure 221: Adverse events

0	500mg mesalazin	e supp.	1g mesalazine	supps.		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	CI M-H, Fixed, 95% CI
DALBASIO1998	2	35	2	32	100.0%	0.91 [0.14, 6.12]	
Total (95% CI)		35		32	100.0%	0.91 [0.14, 6.12]	
Total events	2		2				
Heterogeneity: Not app Test for overall effect:							0.1 0.2 0.5 1 2 5 10 Favours 500mg mesalazine Favours 1g mesalazine

1.4.2 Topical corticosteroids

1.4.2.1 Topical corticosteroids versus placebo (intermittent)

Figure 222:	Relapse at 26 v	weeks					
	2mg budesonide e	enema	Placebo e	nema		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI
LINDGREN2002	16	39	19	37	100.0%	0.80 [0.49, 1.30]	
Total (95% CI)		39		37	100.0%	0.80 [0.49, 1.30]	-
Total events	16		19				
Heterogeneity: Not a	pplicable						1 + 1 + 1 + 1 + 1 + 1 + 1 + 1 + 1 + 1 +
Test for overall effect	:: Z = 0.90 (P = 0.37)						Favours Budesonide Favours Placebo

Note: 2mg Budesonide liquid enema twice a week versus placebo enema twice a week

Figure 223: Adverse events

0	2mg budesonide	enema	Placebo e	enema		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	CI M-H, Fixed, 95% CI
LINDGREN2002	28	39	24	37	100.0%	1.11 [0.81, 1.51]] -
Total (95% CI)		39		37	100.0%	1.11 [0.81, 1.51]	•
Total events	28		24				
Heterogeneity: Not app							0.1 0.2 0.5 1 2 5 10
Test for overall effect: 2	Z = 0.65 (P = 0.52)						Favours Budesonide Favours Placebo

1.4.3 Oral aminosalicylates

1.4.3.1 Oral aminosalicylates versus placebo

Figure 224:	Relapse (HR)	
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.84.6 ==									
	Oral A	SA	Placel	bo				Hazard Ratio	Hazard Ratio
Study or Subgroup	Events	Total	Events	Total	0-E	Variance	Weight	Exp[(O-E) / V], Fixed, 95% C	Exp[(O-E) / V], Fixed, 95% CI
ARDIZZONE1999C 12-24 mths	6	26	17	35	-5.7574	5.62483	10.6%	0.36 [0.16, 0.82]	
ARDIZZONE1999C 2 years +	5	28	6	23	-1.3866	2.72357	5.1%	0.60 [0.18, 1.97]	
HANAUER1996A 1.6g	18	58	33	63	-8.6777	11.6471	21.8%	0.47 [0.27, 0.84]	
MINER1995	35	103	56	99	-9.8949	21.5385	40.4%	0.63 [0.41, 0.96]	
WRIGHT1993	19	49	31	52	-7.75	11.78	22.1%	0.52 [0.29, 0.92]	
Total (95% CI)		264		272			100.0%	0.53 [0.41, 0.70]	•
Total events	83		143						
Heterogeneity: Chi ² = 1.70, df = 4	(P = 0.79)	; l ² = 0 ^c	%						
Test for overall effect: Z = 4.58 (P	< 0.00001)							0.01 0.1 1 10 1 Favours Oral ASA Favours Placeb

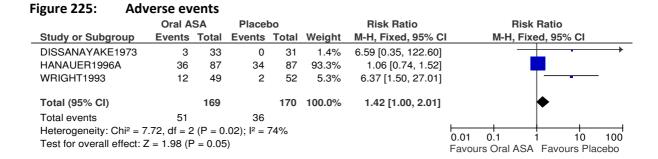


Figure 226: Serious adverse events

-	Oral A	SA	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% C	Peto, Fixed, 95% Cl
HANAUER1996A	1	87	1	87	100.0%	1.00 [0.06, 16.12]	
Total (95% CI)		87		87	100.0%	1.00 [0.06, 16.12]	
Total events	1		1				
Heterogeneity: Not app	olicable						
Test for overall effect:	Z = 0.00 (P = 1.0	0)				0.01 0.1 1 10 100 Favours Oral ASA Favours Placebo

Figure 227: Hospitalisations

	Oral A	SA	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
HAWKEY1997	6	99	1	111	100.0%	6.73 [0.82, 54.91]	
Total (95% CI)		99		111	100.0%	6.73 [0.82, 54.91]	
Total events	6		1				
Heterogeneity: Not app			-				0.01 0.1 1 10 100
Test for overall effect:	Z = 1.78 (I	= 0.03	8)				Favours Oral ASA Favours Placebo

1.4.4 Oral aminosalicylates dose comparison

1.4.4.1 Mesalazine (Asacol)

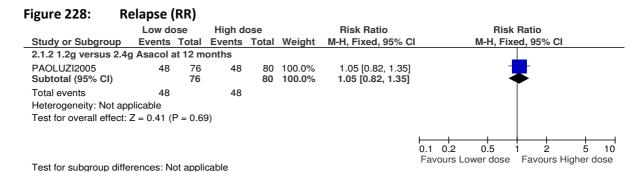


Figure 229: Relapse by frequency of relapses in the previous year (RR)

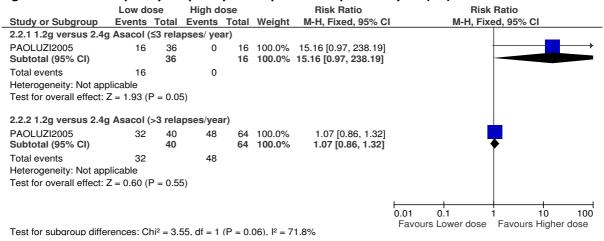


Figure 230: Adverse events

	Low do	ose	High d	ose		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
2.4.2 1.2g versus 2.4	g Asacol						
PAOLUZI2005 Subtotal (95% CI)	0	76 76	1	80 80	100.0% 1 00.0%	0.14 [0.00, 7.18] ← 0.14 [0.00, 7.18] ●	
Total events Heterogeneity: Not ap	0 plicable		1				
Test for overall effect:	Z = 0.97 (P = 0.3	3)				
						F	
						0.	.01 (0.1) 1 10 100

Favours Lower dose Favours Higher dose

1.4.4.2 Mesalazine (Salofalk)

Figure 231:	Relapse (RR)					
	Low do	se	High d	ose		Risk Ratio	Risk Ratio
Study or Subgrou	p Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
3.1.1 1.5g versus	3.0g Salofalk						
KRUIS2011 Subtotal (95% CI)	44	212 212	17	217 217	100.0% 1 00.0%	2.65 [1.56, 4.49] 2.65 [1.56, 4.49]	
Total events Heterogeneity: Not Test for overall effe		^D = 0.0	17 003)				
Test for subaroup (differences: No	ot appli	cable				0.1 0.2 0.5 1 2 5 10 Favours Lower dose Favours Higher dose

Test for subgroup differences: Not applicable

Figure 232: Adverse events

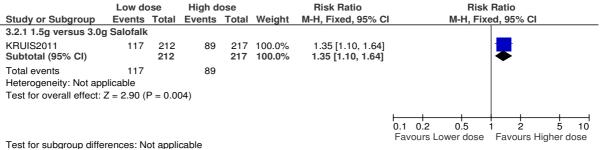


Figure 233: Serious adverse events

	Low do	ose	High d	ose		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
3.3.1 1.5g versus 3.0g	g Salofalk						
KRUIS2011	7	212	8	217	100.0%	0.90 [0.33, 2.43]	
Subtotal (95% CI)		212		217	100.0%	0.90 [0.33, 2.43]	
Total events	7		8				
Heterogeneity: Not app	olicable						
Test for overall effect:	Z = 0.22 (I	P = 0.8	3)				
							0.1 0.2 0.5 1 2 5 10
							Favours Lower dose Favours Higher dose

Test for subgroup differences: Not applicable

1.4.4.3 Olsalazine

Figure 234:	Relapse (RR)					
	Low do	se	High d	ose		Risk Ratio	Risk Ratio
Study or Subgrou	p Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
4.1.1 1.25g versus	2.0g olsalazi	ne (6 i	nonths)				
KRUIS1995 Subtotal (95% CI)	13	35 35	5	34 34	100.0% 1 00.0%	2.53 [1.01, 6.32] 2.53 [1.01, 6.32]	
Total events Heterogeneity: Not	13 applicable		5				
Test for overall effe	ect: Z = 1.98 (P	P = 0.05	5)				
4.1.3 1.0g versus	2.0g olsalazin	ie (12 i	months)				
TRAVIS1994 Subtotal (95% CI)	17	65 65	10	62 62	100.0% 1 00.0%	1.62 [0.81, 3.26] 1.62 [0.81, 3.26]	
Total events Heterogeneity: Not Test for overall effe		P = 0.18	10 3)				
Test for subgroup o	lifferences: Ch	ni² = 0.5	57, df = 1	(P = 0.	45), l² = 0'	%	0.1 0.2 0.5 1 2 5 10 Favours Lower dose Favours Higher dose

= 0.57, df = 1 (P = 0.45), l² st for subaroup differences: Chi² = 0%

Figure 235: Adverse events

0							
	Low do	ose	High d	ose		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% CI
4.9.4 1.25g versus 2.0)g olsalaz	ine (6	months)				
KRUIS1995	3	35	6	34	100.0%	0.49 [0.13, 1.79]	
Subtotal (95% CI)		35		34	100.0%	0.49 [0.13, 1.79]	
Total events	3		6				
Heterogeneity: Not app	olicable						
Test for overall effect:	Z = 1.09 (F	^D = 0.2	8)				
4.9.5 1.0g versus 2.0g	g olsalazir	ne (12 i	months)				
TRAVIS1994	26	65	34	62	100.0%	0.73 [0.50, 1.06]	
Subtotal (95% CI)		65		62	100.0%	0.73 [0.50, 1.06]	\bullet
Total events	26		34				
Heterogeneity: Not app	olicable						
Test for overall effect:	Z = 1.65 (F	^D = 0.1	0)				
	· ·						
							0.1 0.2 0.5 1 2 5 10
Test for subgroup diffe		-:2 0		(D 0	EC) 12 0	0/	Favours Lower dose Favours Higher dose

Test for subgroup differences: $Chi^2 = 0.35$, df = 1 (P = 0.56), $I^2 = 0\%$

1.4.4.4 Sulphasalazine

Figure 236: **Relapse (RR)** Low dose **Risk Ratio** High dose **Risk Ratio** Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% Cl M-H, Fixed, 95% Cl 5.1.3 2g versus 4g sulphasalazine 56 100.0% AZADKHAN1980 8 57 1.57 [0.55, 4.51] 5 Subtotal (95% CI) 57 56 100.0% 1.57 [0.55, 4.51] Total events 5 8 Heterogeneity: Not applicable Test for overall effect: Z = 0.84 (P = 0.40) 0.1 0.2 0.5 ż 5 10 1 Favours Lower dose Favours Higher dose

Test for subgroup differences: Not applicable

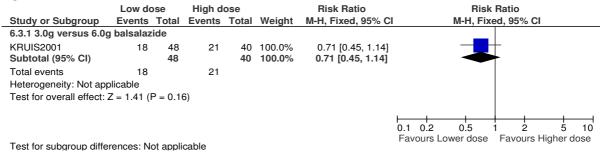
1.4.4.5 Balsalazide

Figure 237: Relapse (RR)

	Low do		High d			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
6.2.1 3g versus 6g ba	alsalazide	at 26 v	veeks				
KRUIS2001 Subtotal (95% CI)	13	48 48	3	40 40	100.0% 1 00.0%	3.61 [1.11, 11.79] 3.61 [1.11, 11.79]	
Total events Heterogeneity: Not ap	13 plicable		3				
Test for overall effect:	Z = 2.13 (I	P = 0.0	3)				
6.2.2 3g versus 6g ba	Isalazide	at 12 n	nonths				
GREEN1992 Subtotal (95% CI)	10	54 54	15	54 54	100.0% 1 00.0%	0.67 [0.33, 1.35] 0.67 [0.33, 1.35]	
Total events Heterogeneity: Not ap	10 plicable		15				
Test for overall effect:		P = 0.2	6)				
							Favours Lower dose Favours Higher dose

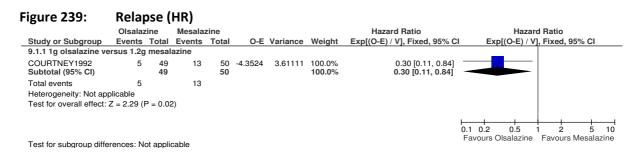
Test for subgroup differences: $Chi^2 = 5.78$, df = 1 (P = 0.02), l² = 82.7%

Figure 238: Adverse events



1.4.5 Interclass comparisons

1.4.5.1 Olsalazine versus mesalazine



1.4.5.2 Olsalazine versus sulphasalazine

Figure 240:	Rela	pse	(HR)							
	Olsalaz	ine	Sulphasa	Izine				Hazard Ratio	Hazaro	d Ratio
Study or Subgroup	Events	Total	Events	Total	O-E	Variance	Weight	Exp[(O-E) / V], Fixed, 95% C	I Exp[(O-E) / V]	, Fixed, 95% Cl
8.1.1 1g olsalazine ve	ersus 2g s	ulphas	alazine							
IRELAND1988	16	82	10	82	3.74239	6.15385	17.8%	1.84 [0.83, 4.05]	_	
NILSSON1995 Subtotal (95% CI)	59	161 243	55	161 243	6.99227	28.4649	82.2% 100.0%	1.28 [0.89, 1.85] 1.36 [0.98, 1.90]	-	•
Total events Heterogeneity: Chi ² = 0 Test for overall effect: 1	-	·		%						
Test for subgroup diffe	rences: No	ot appli	cable						0.1 0.2 0.5 Favours Olsalazine	1 2 5 10 Favours Sulphasalazine

Figure 241: Relapse (RR)

	Olsalazin	е	Sulphasa	azine		Risk Ratio	Risk Ratio
Study or Subgroup	Events T	otal	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
8.2.1 1g olsalazine ve	ersus 2g sul	phasa	alazine at	12 mont	hs		
KIILERICH1992	46	98	42	99	100.0%	1.11 [0.81, 1.51]	
Subtotal (95% CI)		98		99	100.0%	1.11 [0.81, 1.51]	•
Total events	46		42				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.64 (P =	= 0.52)				
8.2.2 1.25g olsalazine	e versus 2g	sulph	asalazine	at 6 moi	nths		
KRUIS1995	13	35	11	40	100.0%	1.35 [0.70, 2.62]	——————————————————————————————————————
Subtotal (95% CI)		35		40	100.0%	1.35 [0.70, 2.62]	
Total events	13		11				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.89 (P =	= 0.37)				
8.2.3 2g olsalazine ve	ersus 2g sul	phasa	alazine at	6 month	s		
KRUIS1995	5	34	11	40	100.0%	0.53 [0.21, 1.39]	
Subtotal (95% CI)		34		40	100.0%	0.53 [0.21, 1.39]	
Total events	5		11				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 1.29 (P =	= 0.20)				
8.2.4 2g olsalazine ve	ersus 4g sul	phasa	alazine at 4	48 week	s		
RIJK1992	6	23	7	23	100.0%	0.86 [0.34, 2.16]	
Subtotal (95% CI)		23		23	100.0%	0.86 [0.34, 2.16]	
Total events	6		7				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.33 (P =	= 0.74)				
							0.1 0.2 0.5 1 2 5 10
	_	_					Favours Olsalazine Favours Sulphasalazine
Test for subaroup diffe	erences: Chi ²	= 2.7	7. df = 3 (F	' = 0.43	$l^2 = 0\%$		

Test for subgroup differences: Chi^2 = 2.77, df = 3 (P = 0.43), I^2 = 0%

National Clinical Guideline Centre, 2013.

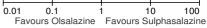
Figure 242:	Aaverse	even	ts				
	Olsala	zine	Sulphasal	azine		Risk Ratio	Risk Ratio
Study or Subgrou	p Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
8.4.1 1g olsalazine	e vs. 2g sulp	hasalaz	ine				
IRELAND1988	21	82	20	82	43.5%	1.05 [0.62, 1.78]	_
NILSSON1995	39	161	26	161	56.5%	1.50 [0.96, 2.34]	
Subtotal (95% CI)		243		243	100.0%	1.30 [0.93, 1.83]	
Total events	60		46				
Heterogeneity: Chi				0			
Test for overall effe	ect: $Z = 1.53$ (P = 0.13	5)				
8.4.2 1.25g olsalaz	zine vs. 2g si	ulphasa	lazine				
KRUIS1995	3	35	4		100.0%	0.86 [0.21, 3.57]	
Subtotal (95% CI)		35		40	100.0%	0.86 [0.21, 3.57]	
Total events	3		4				
Heterogeneity: Not							
Test for overall effe	ect: Z = 0.21 (P = 0.83	5)				
8.4.3 2g olsalazine	e vs. 2g sulp	hasalaz	ine				
KRUIS1995	6	34	4		100.0%	1.76 [0.54, 5.74]	
Subtotal (95% CI)		34		40	100.0%	1.76 [0.54, 5.74]	
Total events	6		4				
Heterogeneity: Not			.)				
Test for overall effe	C1.2 = 0.94 (P = 0.35))				
8.4.4 2g olsalazine	e vs. 4g sulp	hasalaz	ine				
RIJK1992	9	23	8		100.0%	1.13 [0.53, 2.40]	
Subtotal (95% CI)		23		23	100.0%	1.13 [0.53, 2.40]	
Total events	9		8				
Heterogeneity: Not							
Test for overall effe	ect: $Z = 0.30$ (P = 0.76)				
							0.1 0.2 0.5 1 2 5 10
Test for subaroup a	differences: C	hi² = 0.7	'1. df = 3 (P	= 0.87).	$l^2 = 0\%$		Favours Olsalazine Favours Sulphasalazine

Figure 242: Adverse events

Test for subgroup differences: $Chi^2 = 0.71$, df = 3 (P = 0.87), $I^2 = 0\%$

Figure 243: Serious adverse events

	Olsalaz	ine	Sulphasa	lazine		Peto Odds Ratio	Peto Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% CI	
3.5.2 1g olsalazine vs.	2g sulph	asalaz	ine					
NILSSON1995 Subtotal (95% CI)	1	161 161	0	161 161	100.0% 100.0%	7.39 [0.15, 372.38] 7.39 [0.15, 372.38]		
otal events	1		0					
Heterogeneity: Not app	licable							
est for overall effect: Z	Z = 1.00 (F	P = 0.32	2)					



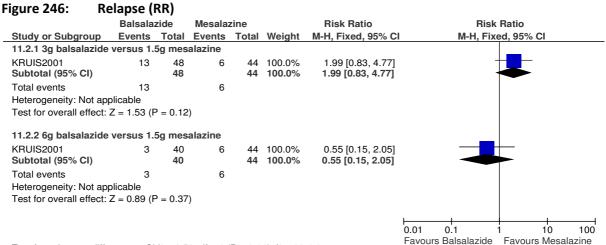
1.4.5.3 Mesalazine versus sulphasalazine

Figure 244:	Relapse	(RR)					
	Mesalaz	ine	Sulphasal	azine		Risk Ratio	Risk Ratio
Study or Subgrou	p Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
10.2.2 800mg-1.6g	mesalazine	versus	2-4g sulph	asalazir	пе		
RILEY1988A	18	48	17	44	100.0%	0.97 [0.58, 1.64]	
Subtotal (95% CI)		48		44	100.0%	0.97 [0.58, 1.64]	\rightarrow
Total events	18		17				
Heterogeneity: Not	applicable						
Test for overall effe	ct: Z = 0.11 (F	P = 0.9	1)				
							$0.1 \ 0.2 \ 0.5 \ 1 \ 2 \ 5 \ 10$
							Favours Mesalazine Favours Sulphasalazine
Test for subaroup d	lifferences: No	ot appli	cable				

1.4.5.4 Balsalazide versus mesalazine

Figure 245:	Relap	ose (HR)								
	Balsala	zide	Mesala	zine				Hazard Ratio	Hazard	Ratio	
Study or Subgroup	Events	Total	Events	Total	O-E	Variance	Weight	Exp[(O-E) / V], Fixed, 95% C	CI Exp[(O-E) / V]	, Fixed, 95% CI	
11.1.1 3g balsalazide	versus 1.	2g mes	alazine								
GREEN1998A Subtotal (95% CI)	13	49 49	16	46 46	-2.125	7.17241	100.0% 1 00.0 %	0.74 [0.36, 1.55] 0.74 [0.36, 1.55]		-	
Total events Heterogeneity: Not app Test for overall effect: 2		P = 0.43	16								
Test for subgroup diffe	rences: N	ot applic	able						0.1 0.2 0.5 1 Favours Balsalazide	25 Favours Mesala	10 zine

Test for subgroup differences: Not applic



Test for subgroup differences: $Chi^2 = 2.53$, df = 1 (P = 0.11), l² = 60.4%

Figure 247: **Adverse events**

	Balsala	zide	Mesala	zine		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
11.3.1 3.0g balsalazio	le vs. 1.2g	mesal	azine				
GREEN1998A Subtotal (95% CI)	30	49 49	30	46 46	100.0% 1 00.0%	0.94 [0.69, 1.28] 0.94 [0.69, 1.28]	
Total events	30		30				
Heterogeneity: Not app	olicable						
Test for overall effect:	Z = 0.40 (F	P = 0.69)				
11.3.2 3.0g balsalazio	le vs. 1.5g	mesal	azine				
KRUIS2001 Subtotal (95% CI)	18	48 48	20	44 44	100.0% 100.0%	0.82 [0.51, 1.34] 0.82 [0.51, 1.34]	
Total events	18		20				
Heterogeneity: Not app	olicable						
Test for overall effect:	Z = 0.77 (F	P = 0.44)				
11.3.3 6.0g balsalazio	le vs. 1.5g	mesal	azine				
KRUIS2001	21	40	20	44	100.0%	1.16 [0.75, 1.79]	
Subtotal (95% CI)		40		44	100.0%	1.16 [0.75, 1.79]	-
Total events	21		20				
Heterogeneity: Not app	olicable						
Test for overall effect:	Z = 0.65 (F	P = 0.52)				
							0.1 0.2 0.5 1 2 5 1
Test for subaroup diffe	roncos: Ch	$n^2 - 10$	7 df _ 2 /	D _ 0 5	Q) 12 _ 0%		Favours Balsalazide Favours Mesalazine

Test for subgroup differences: $Chi^2 = 1.07$, df = 2 (P = 0.58), $I^2 = 0\%$

Figure 248: Serious adverse events

	Balsala	zide	Mesalaz	zine		Risk Ratio	Risk Ratio					
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl					
11.4.2 3.0g balsalazide vs. 1.2g mesalazine												
GREEN1998A	2	49	3	46	100.0%	0.63 [0.11, 3.58]						
Subtotal (95% CI)		49		46	100.0%	0.63 [0.11, 3.58]						
Total events	2		3									
Heterogeneity: Not ap	plicable											
Test for overall effect:	Z = 0.53 (F	P = 0.60))									
							0.1 0.2 0.5 1 2 5 10					
							Favours Balsalazide Favours Mesalazine					

1.4.5.5 Mesalazine (Asacol) versus mesalazine (MEZAVANT XL)

Figure 249: Relapse (HR)

Asacol		MMX					Hazard Ratio	Hazard Ratio	
Study or Subgroup	Events	Total	Events	Total	0-E	Variance	Weight	Exp[(O-E) / V], Fixed, 95% Cl	Exp[(O-E) / V], Fixed, 95% CI
PRANTERA2009	50	167	39	156	3.30608	21.9101	100.0%	1.16 [0.77, 1.77]	
Total (95% CI)		167		156			100.0%	1.16 [0.77, 1.77]	-
Total events Heterogeneity: Not app Test for overall effect: 2		P = 0.48	39 3)						0.1 0.2 0.5 1 2 5 10 Favours Asacol Favours MMX

Figure 250: Adverse events

	Asaco	bl	MMX	C		Risk Ratio	Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl			
PRANTERA2009	99	169	92	162	100.0%	1.03 [0.86, 1.24]				
Total (95% CI)		169		162	100.0%	1.03 [0.86, 1.24]	•			
Total events	99		92							
Heterogeneity: Not app	olicable									
Test for overall effect:	Z = 0.33 (F	P = 0.74	4)				Favours Asacol Favours MMX			

Figure 251: Serious adverse events Asacol MMX **Risk Ratio Risk Ratio** Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% Cl M-H, Fixed, 95% Cl PRANTERA2009 5 169 6 162 100.0% 0.80 [0.25, 2.57] Total (95% CI) 169 162 100.0% 0.80 [0.25, 2.57] Total events 6 5 Heterogeneity: Not applicable 0.1 0.2 2 5 10 0.5 i Test for overall effect: Z = 0.38 (P = 0.71) Favours Asacol Favours MMX

1.4.5.6 Mesalazine (Asacol) versus mesalazine (Pentasa)

Figure 252:	Relaps	se (H	R)						
	Asacol P		Penta	Pentasa				Hazard Ratio	Hazard Ratio
Study or Subgroup	Events	Total	Events	Total	O-E	Variance	Weight	Exp[(O-E) / V], Fixed, 95% C	Exp[(O-E) / V], Fixed, 95% Cl
ITO2010B	13	65	13	64	-0.69	6.5	100.0%	0.90 [0.42, 1.94]	
Total (95% CI)		65		64			100.0%	0.90 [0.42, 1.94]	
Total events	13		13						
Heterogeneity: Not ap	plicable								1 + 1 + 1 + 1 + 1 + 1 + 1 + 1 + 1 + 1 +
Test for overall effect:	9)						Favours Asacol Favours Pentasa		

Figure 253: Adverse events

	Asac	ol	Penta	sa		Risk Ratio	Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-I	H, Fixe	d, 95%	CI	
ITO2010B	62	65	62	65	100.0%	1.00 [0.93, 1.08]					
Total (95% CI)		65		65	100.0%	1.00 [0.93, 1.08]			,		
Total events	62		62								
Heterogeneity: Not app Test for overall effect: 2		P = 1.00	0)				0.1 0.2 (Favours A	+).5 1 sacol	2 Favour	5 s Pen	10 tasa

Figure 254: Serious adverse events

-	Asaco	ol	Penta	sa		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
ITO2010B	2	65	1	65	100.0%	2.00 [0.19, 21.52]	
Total (95% CI)		65		65	100.0%	2.00 [0.19, 21.52]	
Total events	2		1				
Heterogeneity: Not app	olicable						0.01 0.1 1 10 100
Test for overall effect:	Z = 0.57 (F	D = 0.5	7)				0.01 0.1 1 10 100 Favours Asacol Favours Pentasa

1.4.6 Regimen comparison

1.4.6.1 Once a day versus more than once a day

Figure 255: Relapse (HR)

	0		•	· · ·						
		Once a	day	More than once	e a day				Hazard Ratio	Hazard Ratio
	Study or Subgroup	Events	Total	Events	Total	O-E	Variance	Weight	Exp[(O-E) / V], Fixed, 95% C	Exp[(O-E) / V], Fixed, 95% CI
	DIGNASS2009	40	146	62	157	-11.38	24.3137	34.6%	0.63 [0.42, 0.93]	
	HAWTHORNE2012	23	103	33	110	-4.6	13.55	19.3%	0.71 [0.42, 1.21]	
	SANDBORN2010	65	445	65	443	0.32	32.5	46.2%	1.01 [0.72, 1.42]	
	Total (95% CI)		694		710			100.0%	0.80 [0.63, 1.01]	•
	Total events	128		160						
	Heterogeneity: Chi ² = 3	.41, df = 2	2 (P = 0	.18); l² = 41%						0.1 0.2 0.5 1 2 5 10
	Test for overall effect: 2	3)								
Test for overall effect. $Z = 1.67$ (F = 0.00)										Favours Once a day Favours > Once a day

Figure 256: Relapse (RR)

•	•	• •							
	Once a	day	More than once	e a day		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	1	M-H, Fixed, 95% CI	
14.2.1 At 6 months									
KANE2003	1	12	1	10	100.0%	0.83 [0.06, 11.70]			-
Subtotal (95% CI)		12		10	100.0%	0.83 [0.06, 11.70]			
Total events	1		1						
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 0.14 (F	P = 0.89	9)						
14.2.2 At 1 year									
KAMM2008	19	171	14	191	27.7%	1.52 [0.78, 2.93]		+	
KANE2008	6	12	5	8	12.5%	0.80 [0.37, 1.74]			
KRUIS2011	44	212	29	218	59.8%	1.56 [1.02, 2.40]		- - -	
Subtotal (95% CI)		395		417	100.0%	1.45 [1.04, 2.03]		•	
Total events	69		48						
Heterogeneity: Chi ² =	2.37, df = 2	2 (P = 0	.31); l² = 16%						
Test for overall effect:	Z = 2.20 (F	P = 0.03	3)						
							++	+	

0.01 0.1 1 10 100 Favours Once a day Favours > Once a day

Test for subaroup differences: $Chi^2 = 0.17$, df = 1 (P = 0.68), $I^2 = 0\%$

Figure 257: Adverse events

-	Once a day		More than once a day			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
DIGNASS2009	75	175	68	187	21.9%	1.18 [0.91, 1.52]	+
HAWTHORNE2012	48	103	48	110	15.5%	1.07 [0.79, 1.44]	
KAMM2008	88	225	86	234	28.1%	1.06 [0.84, 1.34]	
KRUIS2011	117	212	105	218	34.5%	1.15 [0.95, 1.38]	+ - -
Total (95% CI)		715		749	100.0%	1.12 [1.00, 1.26]	•
Total events	328		307				
Heterogeneity: Chi ² = 0	0.50, df = 3	B(P = 0)	.92); l² = 0%				1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 -
Test for overall effect:	Z = 1.88 (F	P = 0.06		Favours Once a day Favours > Once a day			

Figure 258: Serious adverse events

	Once a day		More than once	ce a day More than once a day			Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% CI			
DIGNASS2009	6	175	4	187	13.1%	1.60 [0.46, 5.58]				
HAWTHORNE2012	7	103	2	110	6.5%	3.74 [0.79, 17.58]	+			
KAMM2008	9	225	9	234	29.9%	1.04 [0.42, 2.57]	_ + _			
KRUIS2011	7	212	6	218	20.0%	1.20 [0.41, 3.51]				
SANDBORN2010	18	512	9	511	30.5%	2.00 [0.91, 4.40]	+ - -			
Total (95% CI)		1227		1260	100.0%	1.61 [1.03, 2.53]	◆			
Total events	47		30							
Heterogeneity: Chi ² = 2.61, df = 4 (P = 0.63); l ² = 0%										
Test for overall effect:	Z = 2.08 (F	^D = 0.04	•)				0.01 0.1 1 10 100 Favours Once a day Favours > Once a day			

1.4.7 Regimen and dose comparison

1.4.7.1 Once a day, higher total dose versus twice a day, lower total dose

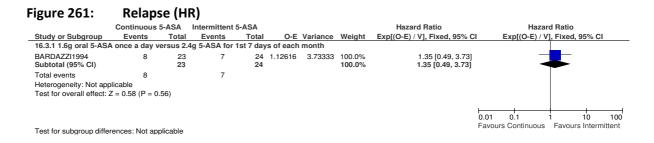
Figure 259:	Relaps	e (HF	र)						
	Higher dose, onc	e a day	Lower dose, twice	a day				Hazard Ratio	Hazard Ratio
Study or Subgroup	Events	Total	Events	Total	0-E	Variance	Weight	Exp[(O-E) / V], Fixed, 95% C	Exp[(O-E) / V], Fixed, 95% Cl
DHAENS2012	51	415	57	411	-3.14	26.92	100.0%	0.89 [0.61, 1.30]	
Total (95% CI)		415		411			100.0%	0.89 [0.61, 1.30]	
Total events Heterogeneity: Not app Test for overall effect: 2			57						0.1 0.2 0.5 1 2 5 10
Test for overall effect. 2	z = 0.01 (F = 0.55)								Favours Higher dose, o.d. Favours Lower dose, b.d.

Figure 260: Serious adverse events

	Higher dose, one	e a day	Lower dose, twi	e a day		Risk Ratio			F	Risk Rat	io		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C			М-Н,	Fixed, 9	95% CI		
DHAENS2012	6	415	3	411	100.0%	1.98 [0.50, 7.87]					_		
Total (95% CI)		415		411	100.0%	1.98 [0.50, 7.87]							-
Total events	6		3										
Heterogeneity: Not ap Test for overall effect:							0.1	0.2 urs Higher	0.5	1	2 vours Lov	5	10

1.4.8 Regimen comparison

1.4.8.1 Continuous versus intermittent oral aminosalicylates



1.4.9 Other combinations of oral and or topical aminosalicylates

1.4.9.1 Continuous oral aminosalicylates versus intermittent topical aminosalicylates

Figure 262:	Relap	se (HR)							
	Oral ASA	Topical ASA	A (Int.)				Hazard Ratio	Hazaro	I Ratio
Study or Subgroup	Events To	al Events	Total	0-E	Variance	Weight	Exp[(O-E) / V], Fixed, 95% C	I Exp[(O-E) / V]	, Fixed, 95% Cl
ANDREOLI1994	6	15 4	16	1.38881	2.4	39.9%	1.78 [0.50, 6.32]	_	
MANTZARIS1994	13	19 5	19	6.25296	3.61111	60.1%	5.65 [2.01, 15.85]		
Total (95% CI)	:	34	35			100.0%	3.57 [1.60, 7.93]		•
Total events	19	9							
Heterogeneity: Chi ² = ⁻	1.92, df = 1 (P	= 0.17); l ² = 48%	b					0.01 0.1 1	10 100
Test for overall effect:	Z = 3.12 (P =	0.002)							Favours Topical ASA(in

Figure 263: Adverse events

	Oral A	SA	Topical AS	A(int.)		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
DALBASIO1990	2	31	0	29	100.0%	7.16 [0.44, 117.45]	
Total (95% CI)		31		29	100.0%	7.16 [0.44, 117.45]	
Total events	2		0				
Heterogeneity: Not app Test for overall effect:		P = 0.1	7)				0.01 0.1 1 10 100 Favours Oral ASA Favours Topical ASA(in

Figure 264: Colectomy

	ral A ents		Topical AS	. ,		Peto Odds Ratio	Peto Odds Ratio
Ctudy or Cubaroup Ev	ents	Total					
Sludy of Subgroup EV		TOtal	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
MANTZARIS1994	1	19	0	19	100.0%	7.39 [0.15, 372.38]	
Total (95% CI)		19		19	100.0%	7.39 [0.15, 372.38]	
Total events	1		0				
Heterogeneity: Not applicat	ole						- - - - - - - - - -
Test for overall effect: Z = 1	.00 (l	P = 0.32	2)				Favours Oral ASA Favours Topical ASA(ir

1.4.9.2 Continuous oral aminosalicylates & intermittent topical aminosalicylates versus continuous oral aminosalicylates

Figure 265:	Relapse (HR)							
	Oral ASA +int Topic	al ASA	Oral A	SA				Hazard Ratio	Hazard Ratio
Study or Subgroup	Events	Total	Events	Total	0-E	Variance	Weight	Exp[(O-E) / V], Fixed, 95% Cl	Exp[(O-E) / V], Fixed, 95% Cl
DALBASIO1997	13	36	23	36	-6.7044	8.30556	83.3%	0.45 [0.23, 0.88]	
YOKOYAMA2007	2	11	10	13	-2.7679	1.66667	16.7%	0.19 [0.04, 0.87]	
Total (95% CI)		47		49			100.0%	0.39 [0.21, 0.72]	•
Total events	15		33						
Heterogeneity: Chi2 =	1.01, df = 1 (P = 0.31);	l ² = 1%						l l	0.01 0.1 1 10 100
Test for overall effect:	Z = 3.00 (P = 0.003)								urs Oral &Topical ASA Favours Oral ASA

1.4.10 Immunomodulators

1.4.10.1 Azathioprine versus placebo

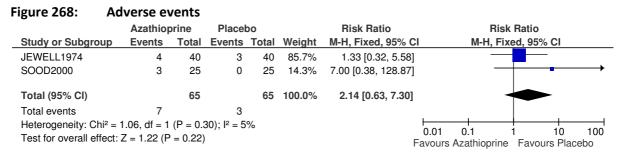
Figure 266:	Relap	se (H	IR)						
	Azathiop	orine	Placel	00				Hazard Ratio	Hazard Ratio
Study or Subgroup	Events	Total	Events	Total	O-E	Variance	Weight	Exp[(O-E) / V], Fixed, 95% C	I Exp[(O-E) / V], Fixed, 95% CI
1.1.1 Randomised wh	en in remi	ission							
HAWTHORNE1992 Subtotal (95% CI)	12	33 33	20	34 34	-5.65	7.5	72.4% 72.4%	0.47 [0.23, 0.96] 0.47 [0.23, 0.96]	
Total events Heterogeneity: Not app Test for overall effect: 2		= 0.04)	20						
1.1.2 Randomised wit	th active d	isease							
SOOD2002A Subtotal (95% CI)	4	17 17	10	18 18	-3.3129	2.85714	27.6% 27.6%	0.31 [0.10, 1.00] 0.31 [0.10, 1.00]	
Total events Heterogeneity: Not app Test for overall effect: 2		= 0.05)	10						
Total (95% CI)		50		52			100.0%	0.42 [0.23, 0.77]	-
Total events Heterogeneity: Chi ² = 0 Test for overall effect: 2 Test for subgroup diffe	Z = 2.79 (P	= 0.005	5)		6), l² = 0%	6		F	0.1 0.2 0.5 1 2 5 10 avours Azathioprine Favours Placebo

Note: HAWTHORNE1992- withdrawal study, some patients also took oral aminosalicylates, SOOD2002A- in addition to steroids and sulphasalazine in both arms.

Figure 267:	Relapse at	: 1 yea	ar (RR)				
	Azathiop	orine	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	b Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
1.2.2 Randomised	with active d	isease					
JEWELL1974	21	37	24	33	80.9%	0.78 [0.55, 1.11]	
SOOD2000 Subtotal (95% CI)	3	25 62	6	25 58	19.1% 100.0%	0.50 [0.14, 1.78] 0.73 [0.51, 1.04]	•
Total events Heterogeneity: Chi ²	24 = 0.49, df = 1	(P = 0.4	30 48); l² = 0	1%			
Test for overall effect	ct: Z = 1.76 (P	= 0.08)					
Test for subgroup d	ifferences: No	t applic:	able			F	0.1 0.2 0.5 1 2 5 10 avours Azathioprine Favours Placebo

Test for subgroup differences: Not applicable

Note: JEWELL1974- in addition to steroids in both arm, SOOD2000- in addition to steroids and sulphasalazine in both arms



Note: JEWELL1974- in addition to steroids in both arm, SOOD2000- in addition to steroids and sulphasalazine in both arms.

1.4.10.2 Azathioprine versus sulphasalazine

Figure 269:	Relapse	at 18	months	s (RR)					
	Azathio	orine	Sulphasa	lazine		Risk Ratio	Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fix	ed, 95% Cl	
SOOD2003	5	12	5	13	100.0%	1.08 [0.41, 2.83]			
Total (95% CI)		12		13	100.0%	1.08 [0.41, 2.83]			
Total events Heterogeneity: Not a Test for overall effec		P = 0.87)				0.1 0.2 0.5 Favours Azathioprine	1 2 Favours Sul	5 10 Iphasalazine

Note: Steroids were also taken in both arms

Figure 270: Adverse events

	Azathioprine Sulphasalazine					Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
SOOD2003	2	12	0	13	100.0%	8.79 [0.52, 149.55]	
Total (95% CI)		12		13	100.0%	8.79 [0.52, 149.55]	
Total events	2		0				
Heterogeneity: Not ap	plicable						- - - - - - - - - -
Test for overall effect:	Z = 1.50 (F	P = 0.13))				0.01 0.1 1 10 100 Favours Azathioprine Favours Sulphasalazine

Note: Steroids were also taken in both arms

1.4.10.3 Azathioprine versus azathioprine & olsalazine

Figure 271:	Relaps	e at (different time	point	s (RR)		
-	Azathio	orine	Azathioprine & Olsal	azine		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
3.1.1 1 year							
MANTZARIS2004	3	34	4	36	100.0%	0.79 [0.19, 3.29]	
Subtotal (95% CI)		34		36	100.0%	0.79 [0.19, 3.29]	
Total events	3		4				
Heterogeneity: Not ap	oplicable						
Test for overall effect:	: Z = 0.32 (F	9 = 0.75)	1				
3.1.2 2 years							
MANTZARIS2004	5	34	6	36	100.0%	0.88 [0.30, 2.63]	
Subtotal (95% CI)		34		36	100.0%	0.88 [0.30, 2.63]	
Total events	5		6				
Heterogeneity: Not ap	oplicable						
Test for overall effect:	Z = 0.22 (F	= 0.82))				
							Favours Azathioprine Favours AZA & Olsalazine
Test for subgroup diff	arancas Ch	i ² – 0 01	$1 df = 1 (P = 0.91) l^2 =$	0%			1 avours Azamophine T avours AZA & Olsalazine

Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.91), l² = 0%

Figure 272: Quality of life - IBDQ (better indicated by higher values)

	Azat	thiopri	ine	Azathioprin	Azathioprine & Olsalazine			Mean Difference		M	ean Differend	e	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl		IV	, Fixed, 95%	CI	
MANTZARIS2004	180	35.1	34	180	38	36	100.0%	0.00 [-17.13, 17.13]					
Total (95% CI)			34			36	100.0%	0.00 [-17.13, 17.13]			+		
Heterogeneity: Not ap Test for overall effect:		(P = 1	.00)					F	-100 avours /	- 50 AZA & Olsa	0 lazine Favou	50 Irs Azathiop	100 prine

Note: Steroid dependent ulcerative colitis. MIDs: +/- 3.965

Figure 273: Serious adverse events

	Azathio	orine	Azathioprine & Ols	alazine		Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI		
MANTZARIS2004	3	34	3	36	100.0%	1.06 [0.23, 4.89]			
Total (95% CI)		34		36	100.0%	1.06 [0.23, 4.89]			
Total events	3		3						
Heterogeneity: Not ap Test for overall effect:		9 = 0.94)	1				0.1 0.2 0.5 1 2 5 10 Favours Azathioprine Favours AZA & Olsalazine		

Note: Steroid dependent ulcerative colitis.

1.4.10.4 Methotrexate versus placebo

Figure 274: Relapse at 9 months (RR)

0	•		•				
	Methotrexate		Placebo		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
OREN1996	9	14	8	18	100.0%	1.45 [0.76, 2.76]	
Total (95% CI)		14		18	100.0%	1.45 [0.76, 2.76]	
Total events	9		8				
Heterogeneity: Not ap	plicable						1 + 1 + 1 + 1 + 1 + 1 + 1 + 1 + 1 + 1 +
Test for overall effect:	Z = 1.12 (P	= 0.26)					Favours Methotrexate Favours Placebo

Note: Some patients were also on mesalazine and/or steroids.

1.4.10.5 Methotrexate versus 5-aminosalicylic acid

Figure 275: Rela	apse at o	differ	ent tim	e poi	nts (RR)		
-	Methotre	xate	5-AS	Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
5.1.1 24 weeks							
MATEJIMENEZ2000 Subtotal (95% CI)	5	7 7	2	2 2	100.0% 1 00.0%	0.82 [0.41, 1.64] 0.82 [0.41, 1.64]	
Total events	5		2				
Heterogeneity: Not appli Test for overall effect: Z		= 0.58)					
5.1.2 56 weeks							
MATEJIMENEZ2000 Subtotal (95% CI)	6	7 7	2	2 2	100.0% 1 00.0%	0.97 [0.53, 1.79] 0.97 [0.53, 1.79]	
Total events Heterogeneity: Not appli Test for overall effect: Z		= 0.93)	2				
5.1.3 76 weeks							
MATEJIMENEZ2000 Subtotal (95% CI)	6	7 7	2		100.0% 1 00.0%	0.97 [0.53, 1.79] 0.97 [0.53, 1.79]	
Total events	6		2				
Heterogeneity: Not appli Test for overall effect: Z		= 0.93)					
).1 0.2 0.5 1 2 5 10
Test for subgroup differen				9 = 0.92	?), l ² = 0%	Fav	ours Methotrexate Favours 5-ASA

Note: In addition to steroids in both arms.

1.4.10.6 Mercaptopurine versus methotrexate

Figure 276: Relapse at different time points (RR)

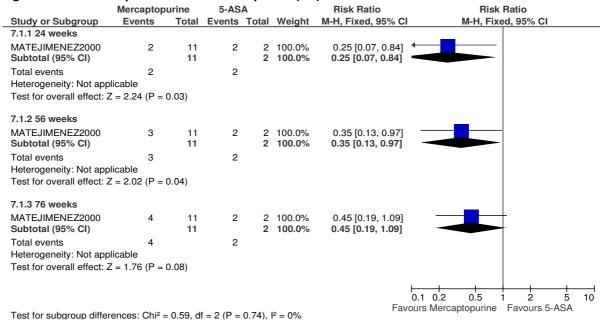
guic 270. IN	ciapse a	c unic	.i ciit tii	inc po	2000	, ing	
	Mercaptopurine		Methotrexate		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
6.1.1 24 weeks							
MATEJIMENEZ2000	2	11	5	7	100.0%	0.25 [0.07, 0.97]	←
Subtotal (95% CI)		11		7	100.0%	0.25 [0.07, 0.97]	
Total events	2		5				
Heterogeneity: Not appl	icable						
Test for overall effect: Z	= 2.00 (P =	0.05)					
6.1.2 56 weeks							
MATEJIMENEZ2000	3	11	6	7	100.0%	0.32 [0.12, 0.87]	
Subtotal (95% CI)		11		7	100.0%	0.32 [0.12, 0.87]	
Total events	3		6				
Heterogeneity: Not appl	icable						
Test for overall effect: Z	= 2.22 (P =	0.03)					
6.1.3 76 weeks							
MATEJIMENEZ2000	4	11	6	7	100.0%	0.42 [0.18, 0.98]	
Subtotal (95% CI)		11		7	100.0%	0.42 [0.18, 0.98]	
Total events	4		6				
Heterogeneity: Not appl	icable						
Test for overall effect: Z	= 2.00 (P =	0.04)					
	·	-					

0.1 0.2 0.5 1 2 5 10 Favours Mercaptopurine Favours Methotrexate

Test for subgroup differences: $Chi^2 = 0.45$, df = 2 (P = 0.80), $I^2 = 0\%$ Note: In addition to steroids in both arms.

1.4.10.7 Mercaptopurine versus 5-aminosalicylic acid

Figure 277: Relapse at different time points (RR)



Note: In addition to steroids in both arms.

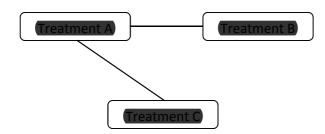
2.1

2 Appendix I: Induction NMA

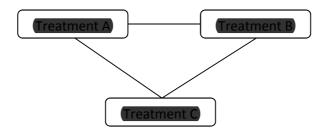
Please note that evidence on treatments for inducing remission in people with mild-to-moderate ulcerative colitis was reviewed in 2019. The updated evidence review and full current recommendations can be found on the NICE website.

The results of conventional meta-analyses of direct evidence alone (as presented in the GRADE) profiles in Chapter 5 and the Forest plots in Appendix H) does not help inform which intervention is) the most effective for the induction of remission of mild to moderate left-sided/extensive ulcerative colitis in adults. The challenge of interpretation has arisen for three reasons:

- (In isolation, each pair-wise comparison (for example; oral mesalazine versus oral balsalazide) does (not inform the choice among different oral, topical or combination treatments.)
- Direct evidence is not available for some pair-wise comparisons in randomised controlled trials (for example; oral mesalazine versus oral sulphasalazine). In the example below there are no trials looking at treatment B versus treatment C.



 There are frequently multiple overlapping comparisons known as "closed loops" in the NMA (where the estimates of an effect have been calculated either within the same trial or from) (multiple trials. Different trials may give slightly different point estimates)



To overcome these issues, a hierarchical Bayesian Network Meta-analysis (NMA) was performed. This type of analysis allows the synthesis of data from direct and indirect comparisons without) breaking randomisation and the ranking of different interventions. Two NMAs have been run, the first being the baseline scenario and the second which combined aminosalicylates together into low and high doses.

For the baseline NMA, in order of efficacy, the following networks have been reviewed?

- The proportion of people who are in clinical remission (author definition) at the end of the trial (<12 weeks)
- The proportion of people who have had clinical improvement (author definition) at the end of the (trial(≤12 weeks))
- (The proportion of people who have withdrawn from treatment due to adverse events(≤12 weeks)

For the combined NMA, the following networks have been reviewed:

- (The proportion of people who are in clinical remission (author definition) at the end of the trial ((<12 weeks))
- (The proportion of people who have withdrawn from treatment due to adverse events (≤ 12 weeks))

The analysis provided estimates of effect (with 95% credible intervals) for each intervention compared to one another. These estimates provide a useful clinical summary of the results and facilitate the formation of recommendations based on the best available evidence. Furthermore, these estimates will be used to parameterise treatment effectiveness in the de novo cost-effectiveness modelling.

Conventional fixed effects meta-analysis assumes that the relative effect of one treatment compared to another is the same across an entire set of trials. In a random effects model, it is assumed that the relative effects are different in each trial but that they are from a single common distribution and that this distribution is common across all sets of trials.

Network meta-analysis requires an additional assumption over conventional meta-analysis. The additional assumption is that intervention A has the same effect on people in trials of intervention A compared to intervention B as it does for people in trials of intervention A versus intervention C, and so on. Thus, in a random effects network meta-analysis, the assumption is that intervention A has the same effect distribution across trials of A versus B, A versus C and so on.

This specific method is usually referred to as mixed-treatment comparisons analysis but we will continue to use the term network meta-analysis to refer generically to this kind of analysis. We do so since the term "network" better describes the data structure, whereas "mixed treatments" could easily be misinterpreted as referring to combinations of treatments.

2.2 (Methods)

2.2.1) (Study selection and data collection)

To estimate the relative risks of different treatments used for the induction of remission, we performed an NMA that simultaneously used all the relevant RCT evidence from the clinical review. As with conventional meta-analyses, this type of analysis does not break the randomisation of the evidence, nor does it make any assumptions about adding the effects of different interventions. The effectiveness of a particular induction of remission strategy was derived only from randomised controlled trials that had that particular treatment in a trial arm.

From the outset, we sought to minimise any clinical or methodological heterogeneity by focusing the analysis on selected studies that matched the pre-defined NMA protocol. Doses of the drugs in the included RCTs were classed as low and high as indicated by the range of the doses in the British National Formulary (BNF).

Therefore, three networks of evidence were identified, defined by population and outcome measure.

For adults, young people and children with mild/moderate left sided/extensive ulcerative colitis:

- (Network 1: Proportion of people achieving clinical remission by the end of the trial (\leq 12 weeks)
- Network 2: Proportion of people achieving clinical improvement by the end of the trial(≤12) (weeks)

 Network 3: Proportion of people withdrawing from treatment due to adverse events by the end of the trial(<12 weeks)

To review the NMA protocol, see Appendix C.

2.2.2 Outcome measures

The NMA evidence reviews considered two clinical efficacy outcomes at up to 12 weeks of treatment identified from the clinical evidence review and considered by the GDG as the most important clinical outcomes. Withdrawals due to adverse events rather than drug related adverse events were chosen due to unclear reporting in the trials. Although this was not an outcome in the clinical review, it was chosen because it is thought to be the best approximate measure for this outcome.

2.2.3 Comparability of interventions

The interventions compared in the model were those found in the randomised controlled trials included in the clinical review presented in Chapter 5 of the full guideline and the Forest plots in Appendix H. If an intervention was evaluated in a study that met the inclusion criteria for the network (that is if it reported at least one of the outcomes of interest and matched the inclusion criteria for the network meta-analysis) then it was included in the network meta-analysis, otherwise it was excluded (see page 151, Excluded studies from the baseline NMA and page152, Additional excluded studies from the combined NMA).

The treatments included in each network for each NMA are shown in Table 1.

Table 1: (Induction of remission treatments included in the network meta-analyses of people) (with mild/moderate left sided/ extensive ulcerative colitis)

Baseline Network M	leta-Analysis	Combined Network Meta-Analysis			
(Network 1: Clinical) remission	(Network 2: Clinical) (improvement)	Network 3: Withdrawals due to adverse events	Network 1: Clinica) (remission)	Network 2: Withdrawals due to adverse events	
Placebo	Placebo	Placebo	Placebo	Placebo	
Low dose mesalazine	Low dose mesalazine	Low dose mesalazine	Low dose ASA	Low dose ASA	
High dose mesalazine	High dose mesalazine	High dose mesalazine	High dose ASA	High dose ASA	
High dose olsalazine	Low dose SASP	Low dose SASP	Oral prednisolone	Oral beclometasone	
Oral prednisolone	High dose olsalazine	High dose olsalazine	Oral) (beclometasone)	Mesalazine & beclometasone (oral)	
Balsalazide	Balsalazide	Balsalazide	Mesalazine & beclometasone (oral)	Oral and topical (mesalazine)	
Oral beclometasone	Oral) beclometasone	Oral) beclometasone	Oral and topical mesalazine		
Mesalazine &) beclometasone (oral)	Mesalazine & beclometasone (oral)	(Mesalazine & (beclometasone) (oral)			
Oral and topical (mesalazine)	Oral and topical mesalazine	Oral and topical mesalazine			
Low dose SASP					

National Clinical Guideline Centre, 2013.

2.2.4 (Statistical analysis)

A hierarchical Bayesian network meta-analysis (NMA) was performed using the software WinBUGS version 1.4. We adapted a three-arm random effects model template for the networks, from the University of Bristol website (https://www.bris.ac.uk/cobm/research/mpes/mtc.html). This model accounts for the correlation between study level effects induced by multi-arm trials.

In order to be included in the analysis, a fundamental requirement is that each treatment is connected directly or indirectly to every other intervention in the network. For each outcome a diagram of the evidence network was produced.

The model used was a random and fixed effects logistic regression model, with parameters estimated by Markov chain Monte Carlo simulation. Random effects models allow for the possibility that the true treatment effect may differ between trials. As it was a Bayesian analysis, for each parameter the evidence distribution is weighted by a distribution of prior beliefs. A non-informative prior distribution was used to maximise the weighting given to the data. These priors were normally distributed with a mean of 0 and standard deviation of 10,000. When a trial has reported zero event in a treatment arm (zero cell count), then a constant value of 1.0 has been added to both the number of events and the total number of people completed this trial in all of the arms in order to preserve the proportional efficacy of the intervention compared to the control treatment in that trial and to obtain non-infinite estimates of treatment effects and non-infinite variance. If there were no events in any of the arms, the study was excluded.

For the analyses, a series of 60,000 burn-in simulations were run to allow convergence and then a further 100,000 simulations were run to produce the outputs. Convergence was assessed by examining the history and kernel density plots.

We tested the goodness of fit of the model by calculating the residual deviance and deviance information criteria. If the residual deviance is close to the number of unconstrained data points (the number of trial arms in the analysis) then the model is explaining the data at a satisfactory level.

The results, in terms of relative risk, of pair-wise meta-analyses are presented alongside the NMA indirect evidence results. They only include studies meeting the inclusion criteria so may differ slightly from the clinical evidence review (Chapter 5 and the Forest plots in Appendix H) metaanalyses.

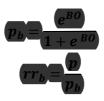
The aim of the NMA was to calculate treatment specific log odds ratios and relative risks for the response to be consistent with the comparative effectiveness results presented elsewhere in the clinical evidence review and for ease of interpretation. Let BO, θ , OR and p denote the baseline odds, treatment specific odds, treatment specific log odds ratio and absolute probability respectively. Then:



And:



Once the treatment specific probabilities for response are calculated, we divide them by the baseline probability (p_b) to get treatment specific relative risks (rr_b) :



National Clinical Guideline Centre, 2013.

This approach has the advantage that baseline and relative effects are both modelled on the same log odds scale, and also ensure that the uncertainty in the estimation of both baseline and relative effects is accounted for in the model.

Differences between treatments were considered significant at the 0.05 level if the 95% credible interval for the RR did not cross 1.

We also calculated the overall ranking of interventions according to their relative risk compared to control group and counting the proportion of simulations of the Markov chain in which each intervention had the highest relative risk.

A key assumption behind NMA is that the network is consistent. In other words, it is assumed that the direct and indirect treatment effect estimates do not disagree with one another. Discrepancies between direct and indirect estimates of effect may result from several possible causes. First, there is chance and if this is the case then the network meta-analysis results are likely to be more precise as they pool together more data than conventional meta-analysis estimates alone. Second, there could be differences between the trials included in terms of their clinical or methodological characteristics. Differences that could lead to inconsistency include:

- (Different populations (e.g. populations of mixed disease extent, age)
- Use of concomitant medications
- Different doses for drug treatments other than oral ASAs were the doses were not taken into account
- Different trial durations (longer trials are likely to have a higher proportion of patients achieving) (the outcome))
- Quality of the study (risk of bias)
- Different indexes and thresholds used to determine clinical remission and improvement

This heterogeneity is a problem for network meta-analysis but may be dealt with by subgroup) analysis or by carefully defining inclusion criteria. Inconsistency, caused by heterogeneity, was assessed subjectively by comparing the relative risk ratios from the direct evidence (from pair-wise meta-analysis) to the relative risk ratios from the combined direct and indirect evidence (from NMA). We assumed the evidence to be inconsistent where the relative risk ratio from the NMA did not fit within the confidence interval of the relative risk ratio from the direct comparison.

2.3 (Baseline NMA results)

A total of 28 studies met the inclusion criteria and were included in one or more of the three networks. Table 2 below gives a summary of the characteristics of included studies.



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Study	Comparators	Patient characteristics	(Disease extent)	Concurrent medication	(Outcomes reported)	Risk of bias Abbreviations: R- randomisation, AC- allocation Concealment, DB- double blind, DO- drop out rate
				azathioprine or similar drugs.		 (Limited) (information on) (DB)
GREEN1998 12 weeks trial	2.4g mesalazine (unspecified) 6.75g balsalazide	18-80 years Moderate or severe (but based on patients overall assessment not Truelove & Witts criteria)	 ≥12cm from anal margin. All patients have left sided, involvement of transverse colon or pancolitis. 	Topical steroid foam as relief) medication for use as required (Colifoam)) Previous use of mesalazine or balsalazide in the last year was: 10% and 4% respectively for both treatment groups.	 Clinical remission Withdrawals due to adverse events 	 Unclear R & AO DB no further (details) (High DO) (Risk of indirect) (population)
HANAUER1993 8 weeks trial	Placebo 1g mesalazine (Pentasa)- excluded 2g mesalazine (Pentasa) 4g mesalazine (Pentasa)	≥18 years Mild to moderate disease	All extents of disease. Unable to calculate % with left sided disease.	 (Not permitted to continue steroids,) (SASP, other mesalazine) (formulations [7 day washout],) (antispasmodics, antibiotics, NSAIDs) (and anti diarrhoeals (except) (Loperamide when absolutely) (necessary)) (90 day immunomodulator washout.) (Recent use of steroids for the) (placebo, 2g and 4g treatment) (groups was 28%, 21% and 29%) 	 Clinical remission Clinical (improvement) Withdrawals due (to adverse events) 	 Unclear R & AC DB no further (information) (High DO)
HANAUER1996 12 weeks trial	Placebo 2g olsalazine 3g olsalazine	Mild to moderate disease Abstract describes " no	Unknown – abstract.	respectively. For recent SASP use it was 42%, 41% and 40% respectively. No anti diarrhoeals allowed. No further information given.	 Clinical remission Withdrawals due to adverse events 	 Unclear R & AC (No baseline data) (as abstract)

(Study)	(Comparators)	Patient characteristics	(Disease extent)	Concurrent medication	Outcomes reported	(Risk of bias) (Abbreviations: R-) (randomisation, AC-) (allocation) (concealment, DB-) (double blind, DO-) (drop out rate)
	Both doses were combined as a (high dose)	(important differences) (in baseline) (demographics (age,) (gender and length of) (disease, duration of) (attack, endoscopy) (score and extent of) (disease, % newly) (diagnosed, stool/day) (and days with blood in) (stool.")				 High DO Extent unclear
HANAUER2005	2.4g mesalazine (Asacol) 4.8g mesalazine (Asacol) (Mild and moderate severity groups for both of the above)	18-75 years Moderate UC	34% left sided, 20.5% pancolitis.	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, sulphasalazine, 6-mercaptopurine, azathioprine, cyclosporine,	 Clinical (improvement) Withdrawals due (to adverse events) (moderate arms) (only) 	 Unclear R & AC DB no further (details)

(Study)	Comparators	Patient characteristics	(<u>Disease extent</u>)	Concurrent medication	Outcomes reported	Risk of bias Abbreviations: R- randomisation, AC- allocation concealment, DB- double blind, DO- drop out rate
(HANAUER2007)	2.4g mesalazine)	18-75 years	So% left sided or	metronidazole, antibiotics (other) (han topical). Prior treatment: 2.4g, 4.8g (Steroids (34%, 29%)) (Immunomodulators (2%, 4%)) (SASP (38%, 31%)) (Sulfa free 5-ASAs (41%, 41%) (Any oral ASA (60%, 57%)) (Topical therapy (36%, 37%)) Prohibited medication during the	• (Clinica)	Unclear R & AC
6 weeks trial	Asacol) 4.8g mesalazine Asacol)	Mild to moderate UC	(extensive disease)	(rial: Acetylsalicylic acid (other than a) (max. of 325mg for a cardio) (protective reason), NSAIDs, (mesalamine containing products, corticosteroids, immunomodulatory) agents, metronidazole antibiotics (other than topical) for >10days, topical therapies, anti diarrhoeal or (anti spasmodic medications, nicotine patches, products) (containing fish oils, investigational) (or marketed drug which could) (interfere with the drug evaluation.) Prior treatment: 2.4g, 4.8g	 (improvement) (Withdrawals due) (to adverse events) 	

(Study)	Comparators	Patient characteristics	(Disease extent)	Concurrent medication	Outcomes reported	(Risk of bias) (Abbreviations: R-) (randomisation, AC-) (allocation) (conceaiment, DB-) (double blind, DO-) (drop out rate)
				SASP (37%, 29%) Sulfa free 5-ASAs (40%, 48%) Topical therapy (44%, 41%)		
(HETZEL1986)	<u>Placebo</u> 2 <u>g olsalazine</u>	Mean age 45. No Inclusion criteria given or SD Mild to moderate	Left sided or proctitis. No % given.	Other therapy was ceased. Topical steroids or oral SASP but no other anti-diarrhoea medications were permitted up to 7 days prior to the start of the trial. Patients receiving oral steroids, azathioprine or other immunosuppressive, or antibiotics within 4 weeks of the trial were excluded.	 Clinical (mprovement) Withdrawals due to adverse events 	 Unclear R & AC (High DO) (No data on extent) (DB no further information given) (Unclear if validated clinica) measure
HIWATASHI201	2.25g mesalazine (Pentasa) versus 4g mesalazine (Pentasa)	15-64 years Severity: UCDAI score of 6-8 points moderately active UC	All extents apart from proctitis. Reports all patients to have left sided or enterocolitis	None described. A washout period was needed prior to the trial for many of the drugs used in ulcerative colitis.	 Clinical remission Clinical (improvement) Withdrawals due (to adverse events) 	 Unclear R & AC >10% difference (in missing data) (between) (treatment arms)
(TO2010A) 8 weeks trial	Placebo 2.25g mesalazine (Pentasa) 2.4g mesalazine (Asacol) 3.6g mesalazine (Asacol)	16-64 years Mild to moderate	All extents. Unable to calculate % with left sided disease.	Following participants were excluded: Mesalamine >2.25g/day or enemas, salazosulfapyridine >4.5g/day or suppositories, corticosteroids, cytapheresis within the last 14 days.	 Clinical remission Clinical (improvement) Withdrawals due (to adverse events) 	• (High DO)

Study	Comparators	Patient characteristics	Disease extent	Concurrent medication	Outcomes reported	(Risk of bias) (Abbreviations: R-) (randomisation, AC-) (allocation) (conceaiment, DB-) (double blind, DO-) (drop out rate)
	2.25g & 2.4g were combined as a low dose					
(JIANG2004) 8 weeks trial)	2g olsalazine 4g sulphasalazine	Mean age 32.6 years. No inclusion criteria were set for age. Severity- mild, moderate & severe (<10%)	Unclear	Eor 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.	 Clinical remission Clinical (improvement) 	 Unclear R & AO Unclear blinding Limited baseline (characteristic) Indirect (population)
KAMM2007 8 weeks trial	Placebo 2.4g mesalazine (Asacol) 2.4g mesalazine (MEZAVANT XL) Asacol & MEZAVANT XL Were combined as a low dose	≥18 years Mild to moderate UC 8 week trial	≥50% left sided (disease.)	No steroids within last 4 weeks, (immuosuppressants in previous 6) (weeks, antibiotics previous week), repeated treatment with NSAIDs (except for cardiac reasons). Could (have been on a stable <2g/day) (mesalamine in the 3-7 day) (screening, Prior treatment: Placebo, 2.4g) (Asacol, 2.4g MEZAVANT XL) (Steroids (1.2%, 2.4%, 2.3%) (Immunomodulators (0%, 0%, 1.2%)	 Clinical remission Clinical (improvement) Withdrawals due to adverse events 	 (High DO) (No further) (details on) (investigator) (blinding)
(LENNARDJONES) (1960) (3 weeks trial)	Placebo 40-60mg prednisolone then tapered after the 1 st week	Mean age 38 (SD12) and 41 (SD11) years for prednisolone and placebo groups respectively Little to no systemic	(Part or all of the (colon distal to the) (splenic flexure) ((no % give))	None stated.	 Clinical remission 	 Inadequate AC No blinding

Ulcerative colitis Appendix I: Induction NMA

(Study)	Comparators	Patient characteristics	Oisease extent	Concurrent medication	Outcomes reported	(Risk of bias) (Abbreviations: R-) (randomisation, AC-) (allocation) (concealment, DB-) (double blind, DO-) (drop out rate)
		upset and treated as an outpatient.				
EVINE2002 8 weeks trial	2.4g mesalazine (Asacol) 6.75g balsalazide	18-80 years Mild to moderate UC	 >60cm reported which was >50%. Can't determine % with left sided. 	Only inclusion/exclusion criteria information: no 5-ASA products in the last week, antibiotics in the last 2 weeks, immunosuppressive use in the last 3 months.	 Clinical (improvement) Withdrawals due (to adverse events) 	 Unclear R & AC DB no further information High DO Risk of indirect population
(LICHTENSTEIN2) (007) (8 weeks trial)	Placebo 2.4g mesalazine (MEZAVANT XL)	≥18 years Mild to moderate UC	► 50% left sided	Excluded if on maintenance (mesalamine >2.0g/day or within 2) (weeks of a dose reduction to ≤2g.) (Inadequate or failed response to (steroids or a mesalamine dose of >2g/day during relapse,) (immunosuppressant use within the (previous 6 weeks, systemic or) topical steroids within the previous (4 weeks, antibiotics in the last 7) (days, chronic NSAID use within 7) (days from baseline (apart from) (cardio-protection).) During the screening period (patients were allowed to continue) <2g/day mesalamine if they had (received this at screening. This was (stopped at baseline.)	 Clinical remission Clinical (improvement) Withdrawals due (to adverse events) 	 (High DO) (DB no further (information)
(MARTEAU2005/	(4g mesalazine)	>18 years	Extensive UC	Excluded if on oral maintenance	Clinical remission	Unclear R & AC

(Study)	Comparators	Patient characteristics	Disease extent	Concurrent medication	Outcomes reported	(Risk of bias) (Abbreviations: R-) (randomisation, AC-) (allocation) (concealment, DB-) (double blind, DO-) (drop out rate)
CONNOLLY2009 B 4 weeks trial data out of an 8 week trial (oral and topical combination (therapy was only used for 4 weeks, then oral (therapy alone was used for the (remaining 4 weeks)	(Pentasa) (4g mesalazine) (Pentasa) & 1g mesalazine (enema)	Mild to moderate UC		(treatment with a daily dose of >3g) (SASP, mesalazine, or 4-ASA within) (30 days, immunosuppressive agents) (in the last 90 days, chronic use of) (NSAIDs, corticosteroids within the) (last 7 days)	 (Clinica) (improvement) (Withdrawals due) (to adverse events) 	 >10% difference (in missing data) (between the (treatment arms) DB no further (information)
(MIGLIOLI1989) (4 week trial)	(Asacol) versus (Asacol) versus (Asacol) (Asacol)	18-65 years Severity: mild) Ulcerative colitis (clinical grading was done according to the) criteria modified from Truelove and Witts)	 20cm extent of disease No baseline characteristics so unable to determine percentages. 	Not described	 Clinical remission Clinical (improvement) 	 Unclear R & AC No baseline (characteristics) >10% missing) (data between (the treatment) (arms)
PRUITT2002 8 weeks trial	2.4g mesalazine (Asacol) 6.75g balsalazide	12-80 years Mild to moderate UC	<pre>≤40 and >40cm cut offs, so unable to determine ≥30cm. >40cm were 45.7% of the population</pre>	Medications not permitted during (the trial were:) Other 5-ASA products, 4-ASA (products) (steroids, NSAIDs, >1 dose/day of) (chronic low-dose aspirin,) (immunosuppressant's, antibiotics,)	 Clinical remission Withdrawals due (to adverse events) 	 Unclear R & AC Limited baseline (characteristic) Unclear DO DB, no further (information)

Study	Comparators	Patient characteristics	Disease extent	Concurrent medication	Outcomes reported	Risk of biasAbbreviations: R- randomisation, AC- allocationConcealment, DB- double blind, DO- drop out rategiven
				laxatives, anti-diarrhoeals, opiates, bile acid binders, topical rectal therapies.		given
(RIZZELLO2002) 4 week trial)	 3.2g mesalazine (Asacol) 3.2g mesalazine (Asacol) & 5mg (beclometasone) 	≥18 years Mild to moderately severe UC	All extensive or left sided	None allowed. Excluded if had steroid treatment in month prior to study, 5-ASA>3.2g/day or SASP >2g/day for 2 weeks prior to study	 Clinical remission Clinical (improvement) Withdrawals due) (to adverse events) 	 Difference in proportions missing between groups is >10%
(ROBINSON1988) (4 week trial)	Placebo Og olsalazine	Data taken from the Cochrane review. No patient Characteristics given in the abstract.	No extent data given in the abstract. Unclear.	No concurrent medications for UC were permitted.	 Clinical (improvement) Withdrawals due (to adverse events) 	 All methods Were unclear (R) AC, baseline characteristics) High DO Unclear scoring of outcomes
SANDBORN2009	2.4g mesalazine (Asacol) 4.8g mesalazine (Asacol)	18-75 years Moderate UC	► 50% left sided or extensive disease	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, investigational or marketed drug that might	 Clinical remission Clinical (improvement) Withdrawals due (to adverse events) 	None.

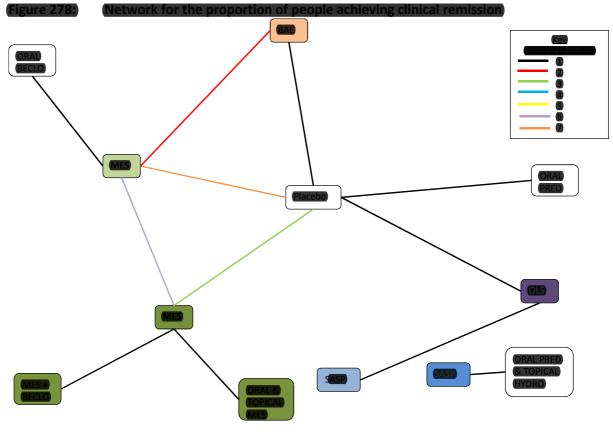
(Study)	(Comparators)	Patient characteristics	(Disease extent)	(Concurrent medication)	Outcomes reported	Risk of bias Abbreviations: R- randomisation, AC- allocation concealment, DB- double blind, DO- drop out rate
				interfere with the drug evaluation.		
SANDBORN2012 B 8 week trial	2.4g mesalazine (Asacol) versus placebo	Adults up to 75 years Severity: active mild to moderate ulcerative colitis for at least 6 months, UCDAI score of 4-10 points	Not proctitis. >50% left sided or extensive disease.	Not permitted. Other drugs used in ulcerative colitis were not allowed in the weeks prior to screening (different) lengths for different drugs).	 Clinical remission Clinical (improvement) Withdrawals due (to adverse events) 	 >10% difference (in missing data) (between the) (treatment arms)
(SCHERL2009) (8 week trial)	Placebo 6.6g balsalazide	≥ <u>18 years</u> Mild to moderate UC	≥20cm from the rectum. No % given	Not described. Excluded if taken ≥6.75g balsalazide or >2.4g mesalamine or equivalent in the 2 weeks prior to the trial, chronic immunosuppressive therapy or corticosteroids within 30 days of screening, topical ASAs for >2 consecutive days during screening.	 Clinical remission Clinical (improvement) (Withdrawals due) (to adverse events) 	 (High DO) (No baseline) (extent data)
SCHROEDER198	Placebo 1.6g mesalazine (Asacol) 4.8g mesalazine (Asacol)	Adults Mild to moderate UC	>50% left sided disease	No steroids or SASP within the last week or during the trial. Any other drugs for colitis were also prohibited in the trial.	 Clinical remission Clinical (improvement) (Withdrawals due) (to adverse events) 	 Unclear AC DB but no (further) (information) (High DO)
SELBY1985 2 week trial	Placebo 2g olsalazine	15-81 years Mild UC	All left sided disease	If on SASP this was stopped at entry (to the trial. Excluded patients on) (steroids or immunosuppressive) drugs) 65% of those in the olsalazine (groups took SASP prior to entry, and) 60% in the placebo group,	Clinical (improvement)	 Unclear R, AC & blinding

(Study)	Comparators	Patient characteristics	Oisease extent)	Concurrent medication	Outcomes reported	Risk of bias Abbreviations: R- randomisation, AC- allocation concealment, DB- double blind, DO- drop out rate
SNINSKY1991 6 week tria	Placebo 1.6g mesalazine (Asacol) 2.4g mesalazine (Asacol) Both doses were Combined as a low dose	18-75 years Mild to moderate UC Note: included patients if on SASP but still have active signs/symptoms.	All extents. Split by cm (<20, 20-40) and >40cm). As GDG definition left sided is greater than 30- 40 but less than 50cm, so could not separate out.	No use of steroids in the last month.) SASP and topical therapies discontinued 1 week prior to entry. Corticosteroids, aspirin, NSAIDs, metronidazole, 6-mercaptopurine, azathioprine, ciclosporin or other investigational drugs were not permitted.	 Clinical remission Clinical (improvement) Withdrawals due (to adverse events) 	 DB, no further (information) (given) Unclear DO

Ulcerative colitis Appendix I: Induction NMA

2.3.1 (Network 1: Clinical remission)

A total of 20 studies^{12,20,43,46,49,57,60,62,65,81,83,88,90,109,115,121-124,126} from the original evidence review met the inclusion criteria and reported clinical remission. One study¹³⁰ which met the inclusion criteria but did not connect into the network was also excluded. Figure 278 shows the network created by eligible comparisons for the NMA. The colour of the line connecting two treatments indicates the number of included studies that assessed that direct comparison. The studies from the original evidence review which have been excluded from the NMA are shown alongside their reason(s) for exclusion on page 151.



Note: Boxes are shaded from light and dark indicating low and high doses respectively.

(MES-mesalazine, BAL – balsalazide, SASP- sulphasalazine, OLS- olsalazine, PRED – prednisolone, BUDES- budesonide, (HYDRO- hydrocortisone. BECLO- beclometasone.)

The majority of the trials were double blind apart from one which was single blind¹² (and looked at oral beclometasone versus low dose mesalazine and one that was unblinded⁸¹ comparing) prednisolone to placebo. Eleven studies^{19,43,46,49,57,62,81,88,90,109,124} (had an unclear method of randomisation, allocation concealment or both. In nine studies^{46,49,60,62,81,90,109,123,126}, the percentage of patients with left sided or extensive disease was not able to be calculated either due to no baseline characteristic data being given, subgroups did not fit into the GDG definitions for extent of disease or an unknown/unclear inclusion criteria. When stated, the age for inclusion into the studies were mainly adults, ≥18 years, apart from three studies that included some young people with their inclusion criteria being 16-64years^{57,60} (and 12-80 years¹⁰⁹).

The trial data from the 20 studies included in the NMA for the proportion of people achieving clinical (remission are presented in Table 3.)

Table 3: Stu	dy data for the	network of the	proportion o	of people	e achie	eving cli	nical r	emissior	
				Compa 1	rator	Compa 2	rator	Compa	rator 3
			mparator	Event		Event		Event	
Study			8	No.		No.		No.	
CAMPIERI20	Mesalazine- Asacol (2.4g)	Beclometason e (5mg)	N/A	50	87	46	90	N/A	N/A
GREEN1998	Mesalazine (2.4g)	Balsalazide (6.75g)	N/A	28	49	44	50	N/A	N/A
HANAUER19 93	Placebo	(Mesalazine- Pentasa (2g)	Mesalazine - Pentasa (4g)	11	90	28	97	28	95
HANAUER19 96	Placebo	Olsalazine (2- 3g)	N/A	12	90	27	183	N/A	N/A
(TO2010A)	Placebo	(Mesalazine-) (Asacol (2.4g) (or Pentasa) (2.25g)	Mesalazine - Asacol (3.6g)	8	33	68	131	29	65
HIWATASHI2) 011	Mesalazine- Pentasa (2.25g)	(Mesalazine- Pentasa (4g)	N/A	9	63	13	60	N/A	N/A
JIANG2004	Olsalazine (2g)	Sulphasalazine (4g)	N/A	15	21	10	21	N/A	N/A
KAMM2007	Placebo	(Mesalazine-) (Asacol &) (MEZAVANT XL) (2.4g)	N/A	19	86	64	172	N/A	N/A
LENNARDJO NES1960	(<u>Placebo</u> (<u>(calcium</u>) (lactate)	(Prednisolone) (40-60mg first) (week, then (tapered)	N/A	8	18	9	19	N/A	N/A
LICHTENSTE N2007	Placebo	Mesalazine – MEZAVANT XL (2.4g)	N/A	16	85	33	88	N/A	N/A
MARTEAU20 057 CONNOLLY2 009B	(Mesalazine) ((4g)	(Mesalazine) ((4g) and) (topical) (mesalazine) ((1g) (Pentasa)	(NZA)	15	56	25	71	N/A	N/A
MIGLIOLI198	Mesalazine- Asacol (2.4g)	Mesalazine- Asacol (3.6g)	N/A	9	24	11	24	N/A	N/A
PRUITT2002	Mesalazine- Asacol (2.4g)	Balsalazide (6.75g)	N/A	38	89	38	84	N/A	N/A
RIZZELLO200	(Mesalazine – (Asacol (3.2g)	(Mesalazine-) (Asacol (3.2g) & beclometason (e (5mg)	N/A	21	61	34	58	N/A	N/A
SANDBORN2	Mesalazine - Asacol (2.4g)	Mesalazine- Asacol (4.8g)	N/A	121	383	152	389	N/A	N/A

				Comparator		Comparator 2		Comparator 3	
Study		Comparison		Event Noi		Event Noi		Event Nor	
SANDBORN2 012B	Placebo	Mesalazine- Asacol (2.4g)	N/A	20	121	31	124	N/A	N/A
SCHERL2009	Placebo	Balsalazide (6.6g)	N/A	19	83	64	166	N/A	N/A
SCHROEDER 1987	Placebo	Mesalazine- Asacol (1.6g)	Mesalazine - Asacol (4.8g)	2	38	1	1	9	38
SNINSKY199 1	Placebo	Mesalazine- Asacol (1.6g or) (2.4g)	N/A	2	52	12	106	N/A	

A fixed and random effects model was run to determine which model is preferred which is indicated by a lower deviance information criteria (DIC). An important difference is classed as a DIC difference of 2-5. The fixed effects model DIC value was 248.395 and the random effects model DIC was 249.424. Therefore the fixed effects model was used for this baseline analysis.

Table 4 summarizes the results of the conventional meta-analyses in terms of relative risk ratios (RRs) generated from studies directly comparing different interventions (head to head comparisons) which are presented in the white area, together with the results of the NMA in terms of RRs for every possible treatment comparison (grey area).

Out of the treatments that were compared in the NMA, the combination of oral mesalazine and beclometasone, oral and topical mesalazine, balsalazide, prednisolone, high dose mesalazine and low dose mesalazine were found to be significantly better than placebo (Table 4). In addition, all of these treatments were also found to be significantly better than low dose sulphasalazine. High dose mesalazine was significantly better than low dose mesalazine and high dose olsalazine. The combination of mesalazine and beclometasone was also significantly better at inducing clinical remission compared to high dose olsalazine, high and low dose mesalazine, balsalazide and oral beclometasone alone.

High dose olsalazine is indicated to have no clinical difference compared to placebo, and be statistically significant lower clinical remission compared to high dose mesalazine, balsalazide and the two combination treatments.

No inconsistency was found between the results of the direct and this network meta-analysis (the indirect (NMA) point median estimates were within the 95% confidence intervals of the known direct comparisons).

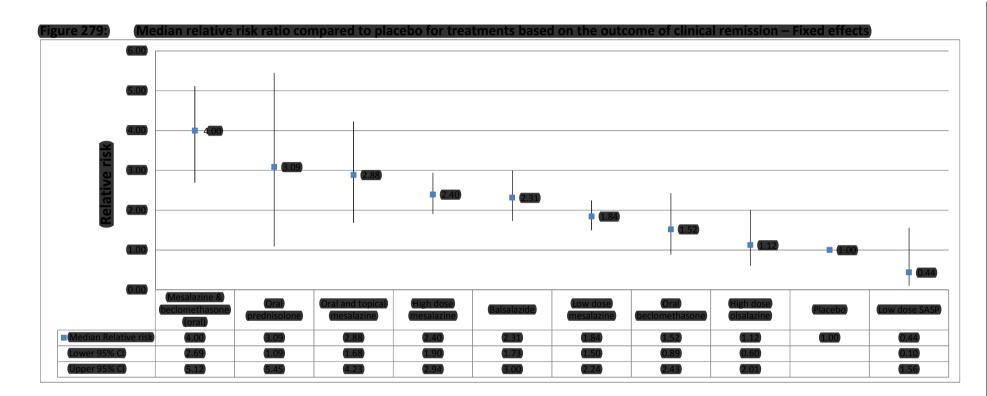
The residual deviance (44.14) closely matched the number of unconstrained data points (number of) (trial arms, n=41) indicating a goodness of fit for the model.

When the treatments were ranked in order of median relative risk (Figure 279) compared to placebo, the combination of oral mesalazine and beclometasone was the most highly ranked. It also had the highest probability of being the best treatment (67%).

However, due to the large overlapping confidence intervals of the different treatments, it is felt that there is insufficient evidence to be confident of one treatment's superiority compared to the

alternative treatment regimens for the induction of clinical remission in people with left sided or extensive ulcerative colitis compared to placebo.

Table 4: (Re	lative risk ratios	s (95% Cl) from o	conventional (w	/hite area) and r	network meta-a	inalyses (grey a	rea) for the pro	portion of peop	le in clinical
rer	mission at the e	nd of the trial –	1	T	1	1	1	1	1
Placebo	1.93	(3.21)	1.11	2.84	1.68				
	[1.51, 2.46]	(1.91, 5.39)	(0.59, 2.08)	(0.91, 8.86)	(1.09, 2.61)				
1.84	Low dose	1.27			1.27	0.89			
(1.50, 2.24)	mesalazine	((1.09, 1.48))			(1.02, 1.57)	(0.68, 1.17)			
2.40	1.30	(High dose)					(1.70)	1.23	
(1.90, 2.94)	(1.12, 1.50)	mesalazine					(1.13, 2.56)	(0.73, 2.07)	
1.12	0.61	0.47	High dose						0.67
(0.60, 2.01)	(0.32, 1.13)	(0.24, 0.87)	olsalazine						(0.39, 1.13)
3.09	1.67	1.29	2.70	Oral					
(1.09, 5.45)	(0.59, 3.09)	(0.45, 2.40)	(0.85, 6.56)	(prednisolone)					
2.31	1.26	0.97	2.06	0.75	Balsalazide				
(1.73, 3.00)	(0.95, 1.63)	(0.72, 1.29)	(1.08, 4.06)	(0.39, 2.17)					
1.52	0.83	0.64	1.36	0.50	0.66	Oral			
(0.89, 2.43)	(0.51, 1.26)	(0.38, 1.00)	(0.61, 2.94)	(0.22, 1.52)	(0.38, 1.09)	beclometaso ne			
4.00	2.16	1.66	3.52	1.28	1.72	2.60	Mesalazine &		
(2.69, 5.12)	(1.49, 2.86)	(1.17, 2.17)	(1.77, 6.98)	(0.64, 3.72)	(1.12, 2.48)	(1.49, 4.63)	beclometaso ne		
2.88	1.56	1.20	2.54	0.93	1.24	1.88	0.73	Oral & topical	
(1.68, 4.23)	(0.94, 2.29)	(0.74, 1.74)	(1.17, 5.39)	(0.42, 2.79)	(0.71, 1.96)	(0.98, 3.54)	(0.42, 1.19)	mesalazine	
0.44	0.24	0.18	0.39	0.15	0.19	0.29	0.11	0.15	Low dose
(0.10, 1.56)	(0.05, 0.86)	(0.04, 0.67)	(0.11, 1.19)	(0.03, 0.72)	(0.04, 0.70)	(0.06, 1.15)	(0.02, 0.42)	(0.03, 0.60)	SASP
Numbers in bold	denote statistically	significant results (S	95% CI do not inclu	de 1). All figures are	to 2 decimal places	s.			



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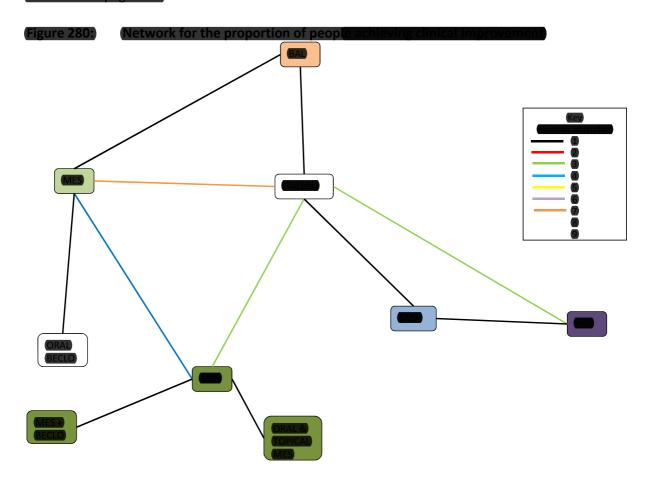
Ulcerative colitis Appendix I: Induction NMA

(Table 5:)	The probabilit	y of each treatment bein	g the best treatment	for achieving clinical
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remission	
	Probability of being the best treatment for achieving clinical
Treatment	remission – Fixed effects
Placebo	0%
Low dose mesalazine	0%
(High dose mesalazine)	0%
High dose olsalazine	0%
(Oral prednisolone)	26%
Balsalazide	0%
Oral beclometasone	0%
Mesalazine & beclometasone	67%
Oral & topical mesalazine	7%
Low dose sulphasalazine	0%

2.3.2 Network 2: Clinical improvement

A total of 23 studies^{12,20,30,40,51,52,50,57,60,62,63,82,83,80,9115,117,12120} from the original evidence review met the inclusion criteria and reported clinical improvement. Figure 280 shows the network created by eligible comparisons for the NMA. The colour of the line connecting two treatments indicates the number of included studies that assessed that direct comparison. The studies from the original evidence review which have been excluded from the NMA are shown alongside their reason(s) for exclusion on page 151.



Note: Boxes are shaded from light and dark indicating low and high doses respectively.

(MES-mesalazine, BAL – balsalazide, SASP- sulphasalazine, OLS- olsalazine, PRED – prednisolone, BUDES- budesonide,) (HYDRO- hydrocortisone, BECLO- beclometasone.)

(Most of the studies^{20,30,46,51,52,56,57,60,65,82,83,88,90,115,117,121-124,126}) were double blind, apart from two (studies^{62,125}) where the blinding was not clear and one study¹² (that was single blind.)

Twelve studies had an unclear method of randomisation and allocation

concealment^{46,51,52,56,57,62,82,90,117,125}, one study^{19,88,124} had unclear allocation concealment another study³⁰ unclear randomisation. In ten studies^{30,46,56,60,62,90,117,123,124,126}, the percentage of patients with left sided or extensive disease was not able to be calculated either due to no baseline characteristic data being given, subgroups did not fit into the GDG definitions for extent of disease or an unknown/ unclear inclusion criteria. When stated, all of the studies were an adult population apart from two studies^{57,60} (that also included some young people (16-64, 15-64 years).

The trial data from the 23 studies included in the NMA for the proportion of people achieving clinical improvement are presented in Table 6.

Table 6: S	tudy data for t	the network of	the proportion	on of pe	ople ach	nieving c	linical i	mprover	nent
				Compa	rator 1	Compa	rator 2	Compa	rator 3
Study				Event No.		Event No.		Event No.	
CAMPIERI2 003	Mesalazine- Asacol (2.4g)	Beclometaso ne (5mg)	N/A	59	87	57	90	N/A	N/A
DICK1964	Placebo	Sulphasalazi ne (4-6g)	N/A	9	23	14	21	N/A	N/A
HANAUER	Placebo	Mesalazine- Pentasa (2g)	Mesalazine- Pentasa (4g)	49	90	77	97	80	95
HANAUER 2005mild	Mesalazine- Asacol (2.4g)	Mesalazine- Asacol (4.8g)	N/A	21	52	19	58	N/A	N/A
HANAUER 2005mode rate	Mesalazine- Asacol (2.4g)	Mesalazine- Asacol (4.8g)	N/A	77	139	89	129	N/A	N/A
HANAUER	Mesalazine- Asacol (2.4g)	Mesalazine- Asacol (4.8g)	N/A	77	150	76	136	N/A	N/A
HETZEL198	Placebo	Olsalazine (2g)	N/A	2	15	6	15	N/A	N/A
HIWATASH	Mesalazine- Pentasa (2.25g)	Mesalazine- Pentasa (4g)	NZA	27	63	45	60	N/A	N/A
(ITO2010A)	Placebo	(Mesalazine- Asacol (2.4g) or Pentasa (2.25g)	Mesalazine- Asacol (3.6g)	9	33	61	131	41	65
JIANG2004	Olsalazine (2g)	Sulphasalazi) ne (4g)	N/A	20	21	15	21	N/A	N/A
(KAMM200) 7	Placebo	Mesalazine- Asacol & MEZAVANT XL (2.4g)	N/A	34	86	99	172	N/A	N/A

				Compa	rator 1	Compa	rator 2	Compa	rator 3
Study)				Event No:		Event No:	0	Event No:	
LEVINE200 2	Balsalazide (6.75g)	Mesalazine- Asacol (2.4g)	N/A	22	53	22	51	N/A	N/A
LICHTENST EIN2007	Placebo	Mesalazine MEZAVANT XL (2.4g)	N/A	22	85	49	83	N/A	N/A
MARTEAU 2005/ CONNOLLY 2009B	Mesalazine (4g)	Mesalazine (4g) and topical (mesalazine (1g) (Pentasa)	N/A	29	56	51)	71		N/A
MIGLIOLI1 989	Mesalazine – Asacol (2.4g)	Mesalazine — Asacol (3.6g)	N/A	1	24	18	24	N/A	N/A
ROBINSON 1988	Placebo	Olsalazine (3g)	N/A	16	48	25	50	N/A	N/A
RIZZELLO2	Mesalazine – Asacol (3.2g)	Mesalazine- Asacol (3.2g) & beclometaso ne (5mg)	N/A	31	61	44	53	N/A	N/A
SANDBOR N2009A	Mesalazine - Asacol (2.4g)	Mesalazine- Asacol (4.8g)	N/A	251	383	273	389	N/A	N/A
SANDBOR N2012B	Placebo	Mesalazine – Asacol (2.4g)	N/A	30	121	42	124	N/A	N/A
SCHERL200 9	Placebo	Balsalazide	N/A	83	83	92	166	N/A	N/A
SCHROEDE R1987	Placebo	Mesalazine- Asacol (1.6g)	Mesalazine- Asacol (4.8g)	7	33	8	1	28	68
SELBY1985	Placebo	Olsalazine (2g)	N/A	8	20	13	20	N/A	N/A
SNINSKY19 91	Placebo	Mesalazine- Asacol (1.6g) or 2.4g)	N/A	8	52	28	106	N/A	N/A

Table 7 summarises the results of the conventional meta-analyses in terms of relative risk ratios (RRs) generated from studies directly comparing different interventions (head to head comparisons) which are presented in the white area, together with the results of the NMA in terms of RRs for every possible treatment comparison (grey area).

A fixed and random effects model was run to determine which model is preferred which is indicated by lower deviance information criteria (DIC). An important difference is classed as a DIC difference of 2-5. The fixed effects model DIC value was 310.153 and the random effects model DIC was 306.416. Therefore the random effects model was used for this baseline analysis.

Out of the treatments that were compared in the NMA, all of the treatments apart from low dose sulphasalazine and oral beclometasone were significantly better than placebo for clinical improvement. The combination treatment of oral mesalazine and beclometasone was significantly better than all the other treatments that it was compared to for clinical improvement apart from the combination treatment of oral and topical mesalazine. Oral and topical mesalazine were significantly better than low dose mesalazine, low dose sulphasalazine, balsalazide and oral beclometasone. The higher dose of mesalazine was significantly better for clinical improvement than the lower dose.

No inconsistency was found between the results of the direct and this network meta-analysis (the) indirect (NMA) point median estimates were within the 95% confidence intervals of the known direct comparisons).

The residual deviance (51.86) closely matched the number of unconstrained data points (number of) (trial arms, n=49) indicating a goodness of fit for the model.

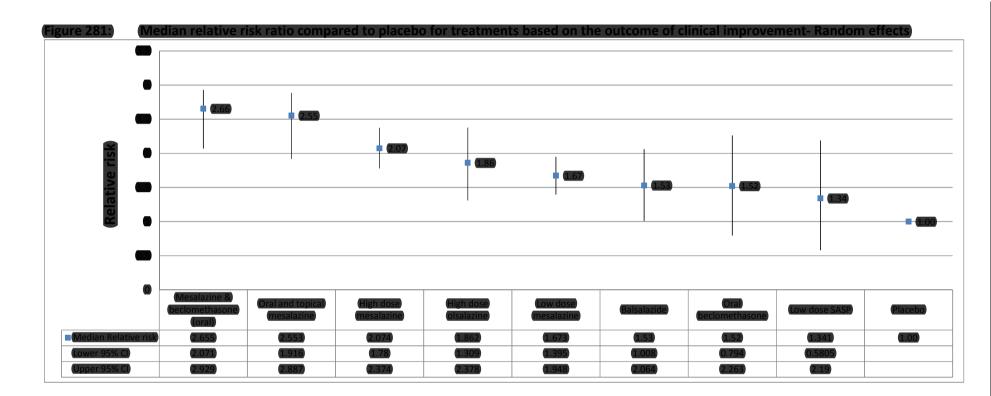
When the treatments were ranked in order of median relative risk (Table 8) compared to placebo, the combination of oral mesalazine and beclometasone had the highest ranking. It also had the highest probability of being the best treatment for clinical improvement (63%), followed second by the combination of an oral and topical mesalazine (36%). All the other treatments were ranked very low in achieving this outcome.

(Table 7:) (Rela	ative risk ratios (9	5% CI) from conve	entional (white ar	ea) and network	meta-analyses (g	rey area) for the	proportion of peo	ople with clinical
(imp	provement at the o	<u>end of the trial – r</u>	andom effects	T		1		T
Placebo	(1.54)	2.26	1.70	1.75	1.39			
	((1.34, 1.77))	((1.25, 4.07)	(0.94, 3.08)	((1.19, 2.57))	((1.03, 1.88))			
1.67	Low dose	1.20			0.96	0.93		
(1.40, 1.95)	mesalazine	(1.06, 1.36)			((0.61, 1.51))	((0.75, 1.16))		
2.07	1.24	High dose					(1.49 (1.12,	1.39
(1.78, 2.38)	((1.11, 1.43))	(mesalazine)					(1.99)	((1.04, 1.86))
1.34	0.80	0.65	Low dose SASP	1.33				
((0.58, 2.19))	(0.34, 1.35)	((0.28, 1.08))		((1.00, 1.78))				
1.86	1.11	0.90	1.39	High dose				
((1.31, 2.38))	(0.76, 1.51)	((0.62, 1.19)	((0.81, 3.13))	(olsalazine)				
1.53	0.91	0.74	1.14	0.82	Balsalazide			
(1.01, 2.06)	(0.61, 1.26)	((0.48, 1.01))	(0.60, 2.75)	((0.51, 1.30))				
1.52	0.91	0.73	1.13	0.82	0.99	Oral		
(0.79, 2.26)	(0.50, 1.33)	((0.39, 1.08))	(0.51, 2.86)	((0.41, 1.38))	(0.50, 1.74)	(beclometasone)		
2.66	1.57	1.27	1.95	1.41	1.71	1.72	Mesalazine &	
(2.07, 2.93)	((1.24, 1.90))	((1.01, 1.48))	(1.15, 4.54)	((1.01, 2.06)	((1.20, 2.63)	(1.11, 3.31)	(beclometasone)	1
2.55	1.51	1.22	1.88	1.36	1.65	1.66	0.96	Oral & topical
(1.92, 2.89)	(1.16, 1.85)	(0.94, 1.44)	(1.08, 4.41)	((0.94, 2.00)	(1.12, 2.55)	(1.06, 3.18)	(0.73, 1.24)	(mesalazine)
Numbers in bold d	enote statistically sign	nificant results (95% Cl	do not include 1). All	figures are to 2 decim	al places.			

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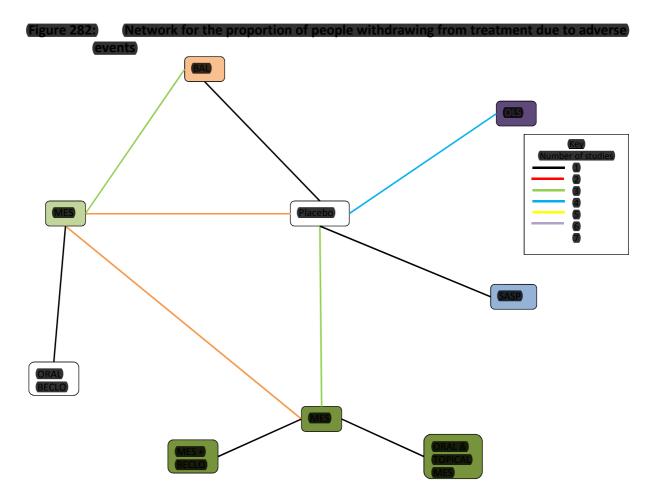


(Table 8:)	The probabilit	y of each treatment being	g the best treatment	for achieving clinical
I GIBIC OI		y of cuell dicuellicity being		Tor define this entited

improvement	
Treatment	Probability of being the best treatment for achieving clinical improvement – Random effects
Placebo	0%
Low dose mesalazine	0%
(High dose mesalazine)	0%
Low dose SASP	0%
(High dose olsalazine)	1%
Balsalazide	0%
Oral beclometasone	0%
(Mesalazine & beclometasone (oral))	63%
Oral and topical mesalazine	36%

2.3.3 (Network 3: Withdrawals due to adverse events

A total of 24 studies^{12,20,30,37,43,46,49,51,52,56,57,60,65,82,83,88,109,115,117,121-124,126} (from the original evidence) review met the inclusion criteria and reported withdrawals due to adverse events. Figure 282 shows the network created by eligible comparisons for the NMA. The colour of the line connecting two treatments indicates the number of included studies that assessed that direct comparison. The studies from the original evidence review which have been excluded from the NMA are shown alongside their reason(s) for exclusion on page 151.



Note: Boxes are shaded from light and dark indicating low and high doses respectively.

(MES-mesalazine, BAL – balsalazide, SASP- sulphasalazine, OLS- olsalazine, PRED – prednisolone, BUDES- budesonide,) (HYDRO- hydrocortisone, BECLO- beclometasone.)

The studies^{20,30,37,43,46,49,51,52,56,57,60,65,82,83,88,109,115,117,121-124,126} were all double blind apart from one study¹² that was single blind. Fourteen studies^{19,30,43,46,49,51,52,56,57,82,88,109,117,124} had an unclear method of randomisation, allocation concealment or both. In 11 studies^{30,37,43,46,49,56,60,109,117,123,126}, the percentage of patients with left sided or extensive disease was not able to be calculated either due to no baseline characteristic data being given, subgroups did not fit into the GDG definitions for extent of disease or an unknown/unclear inclusion criteria. Three studies^{57,60,109}, included young people in their inclusion criteria, 16-64 years, 12-80 and 15-64 years.

The trial data from the 24 studies included in the NMA for the proportion of people withdrawing due to adverse events are presented in Table 9.

(Table 9:) (S	tudy data for t	the network of	f the proportio	on of pe	ople wit	thdrawir:	ng due t	o adver:	se
events				Compa	rator 1	Compa	rator 2	Compa	rator 3
	arator	arator	arator						
Study				Event No.		Event No.		Event No.	
CAMPIERI2 003	Mesalazine- Asacol (2.4g)	Beclometaso ne (5mg)	N/A	0*	87*	1*	90*	N/A	N/A
DICK1964	Placebo	Sulphasalazi ne (4-6g)	N/A	0*	23*	1*	21*	N/A	N/A
FEURLE198	Placebo	Olsalazine (2g)	NZA	0*	53*	3*	52	N/A	N/A
GREEN199	Mesalazine (2.4g)	Balsalazide (6.75g)	N/A	1	49	1	50	N/A	N/A
HANAUER	Placebo	(Mesalazine- (Pentasa (2g))	Mesalazine- Pentasa (4g)	11	90	9	97	0	95
HANAUER	Placebo	Olsalazine (2-3g)	N/A	2	90	17	183	N/A	N/A
HANAUER 2005mode rate	Mesalazine- Asacol (2.4g)	Mesalazine- Asacol (4.8g)	N/A	4	139	4	129	N/A	N/A
HANAUER 2007	Mesalazine- Asacol (2.4g)	Mesalazine- Asacol (4.8g)	N/A	8	150	5	136	N/A	N/A
HETZEL198	Placebo	Olsalazine (2g)	N/A	0*	15*	2*	15*	N/A	N/A
HIWATASH 12011	Mesalazine – Pentasa (2.25g)	Mesalazine – Pentasa (4g)	N/A	2*	63	0*	60	N/A	N/A
(ITO2010A)	Placebo	Mesalazine- Asacol (2.4g) or Pentasa (2.25g)	Mesalazine- Asacol (3.6g)	0*	33*	5*	131*	2*	65*)
KAMM200	Placebo	Mesalazine-	N/A	2	86	2	172	N/A	N/A

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				Compa	rator 1	Compa	rator 2	Compar	rator 3
Study	Omparato		Comparator	Event Nor		Event No:		Event No:	•
		(XL (2.4g)							
LEVINE200	Balsalazide (6.75g)	Mesalazine- Asacol (2.4g)	N/A	1	53	5	51	N/A	N/A
LICHTENST EIN2007	Placebo	Mesalazine- MEZAVANT XL (2.4g)	N/A	11	85	6	88	N/A	N/A
MARTEAU 2005/ CONNOLLY 2009B	(4g)	Mesalazine ((4g) and (topical) (mesalazine (1g) (Pentasa)	N/A)	6	56	•	71	N/A	N/A
PRUITT200	Mesalazine- Asacol (2.4g)	Balsalazide (6.75g)	N/A	6	89	3	84	N/A	N/A
RIZZELLO2	Mesalazine – Asacol (3.2g)	Mesalazine- Asacol (3.2g) & beclometaso ne (5mg)	N/A		61		58	N/A	N/A
ROBINSON 1988	Placebo	Olsalazine (3g)	N/A	0	48	3	50	N/A	N/A
SANDBOR N2009A	Mesalazine - Asacol (2.4g)	Mesalazine- Asacol (4.8g)	N/A	15	383	15	389	N/A	N/A
SANDBOR N2012B	Placebo	Mesalazine- Asacol (3.6g)	N/A	10	121	7	124	N/A	N/A
SCHERL200	Placebo	Balsalazide (6.6g)	N/A	10	83	15	166	N/A	N/A
SCHROEDE R1987	Placebo	Mesalazine- Asacol (1.6g)	Mesalazine- Asacol (4.8g)	2	38	1	11	1	38
(SNINSKY19) 91	Placebo	Mesalazine- Asacol (1.6g or 2.4g)	N/A	0*	52*	2*	106*	N/A	N/A

(a)~* due to one arm having zero events, one was added to all the numerators and denominators in the analysis

Table 10 summaries the results of the conventional meta-analyses in terms of relative risk ratios (RRs) generated from studies directly comparing different interventions (head to head comparisons) which are presented in the white area, together with the results of the NMA in terms of RRs for every possible treatment comparison (grey area).

A fixed and random effects model was run to determine which model is preferred which is indicated by lower deviance information criteria (DIC). An important difference is classed as a DIC difference of 2-5. The fixed effects model DIC value was 217.852 and the random effects model DIC was 220.147. Therefore the fixed effects model was used for this baseline analysis.

Out of the treatments that were compared in the NMA, the only treatment to demonstrate a significant difference in withdrawals due to adverse event compared to placebo is high dose

olsalazine. There is also a significantly higher withdrawals with high dose olsalazine compared to low, dose mesalazine, high dose mesalazine, balsalazide and both combination treatments (mesalazine) and beclometasone, oral and topical mesalazine).

No inconsistency was found between the results of the direct and this network meta-analysis (the indirect (NMA) point median estimates were within the 95% confidence intervals of the known direct comparisons).

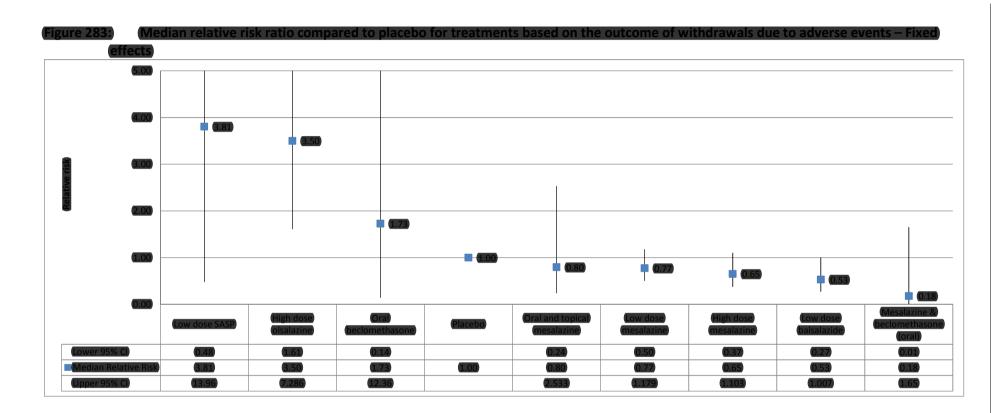
The residual deviance (39.48) was close to the number of unconstrained data points (number of trial) (arms, n=45) indicating a goodness of fit for the model.

The probability of the treatment being the best (fewer withdrawals due to adverse events) was highest in oral mesalazine and beclometasone (75%) and balsalazide (12%).

Table 10: (Rel	lative risk ratios (9	5% CI) from conv	entional (white ar	ea) and network	meta-analyses (g	grey area) for the	proportion of pe	ople who
wit	thdrew due to adv	erse events at the	end of the trial –	Fixed effect	-	-	-	
Placebo	0.71	0.67	3.27	3.72	0.75			
	(0.44, 1.13)	((0.31, 1.46))	(0.37, 29.18)	[1.43, 9.67]	(0.35, 1.60)			
0.77	Low dose	0.84			0.42	1.93		
(0.50, 1.18)	mesalazine	(0.55, 1.28)			(0.15, 1.18)	(0.18, 20.95)		
0.65	0.84	High dose					0.35	1.18
(0.37, 1.10)	(0.55, 1.27)	mesalazine					(0.04, 3.27)	(0.45, 3.13)
3.81	4.92	5.84	Low dose SASP					
(0.48, 13.96)	(0.59, 19.91)	(0.69, 25.03)		_	_			
3.50	4.52	5.38	0.92	High dose				
(1.61, 7.29)	(1.87, 10.61)	(2.09, 13.48)	(0.19, 8.29)	olsalazine				
0.53	0.68	0.81	0.14	0.15	Balsalazide			
(0.27, 1.01)	(0.35, 1.33)	(0.38, 1.76)	(0.03, 1.21)	(0.06, 0.41)				
1.73	2.22	2.65	0.48	0.50	3.26	(Oral)		
(0.14, 12.36)	(0.19, 15.86)	(0.22, 19.72)	(0.03, 8.44)	(0.04, 4.12)	(0.25, 25.84)	(beclometasone)		
0.18	0.23	0.27	0.05	0.05	0.33	0.10	Mesalazine &	
(0.01, 1.65)	(0.01, 2.09)	((0.01, 2.39)	((0.00, 1.02))	(0.00, 0.55)	((0.01, 3.40)	((0.00, 2.85))	(beclometasone)	
0.80	1.03	1.22	0.21	0.23	1.50	0.46	4.58	Oral & topical
(0.24, 2.53)	(0.32, 3.17)	(0.42, 3.51)	(0.03, 2.27)	(0.05, 0.92)	(0.40, 5.49)	(0.05, 6.88)	(0.39, 155.30)	mesalazine
Numbers in bold a	denote statistically sigr	nificant results (95% Ci	do not include 1). All	figures are to 2 decir	nal places.)			

NOTE: If no events occurred in one treatment arm, one was added to the numerator and denominator of all arms. Th

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(Table 11:) (The probability of each treatment b	leing the best treatment for withdrawais due to
adverse events	
	Probability of being the best treatment for having
	the fewest withdrawals due to adverse events –
Treatment	(Fixed effects)
Placebo	0%
Low dose mesalazine	0%
High dose mesalazine	2%
Low dose SASP	1%
High dose olsalazine	0%
Balsalazide	12%
Oral beclometasone	6%
Mesalazine & beclometasone (oral)	75%
Oral and topical mesalazine	5%

2.3.4 (Sensitivity analysis – Time points)

A sensitivity analysis was carried out to look at the different time points at which the data from the trial was reported. Time until remission or clinical improvement was considered an important) element in the induction of remission. Due to a lack of published hazard ratio data in the clinical review, the trial data was presented in relative risk ratios at the following time points;

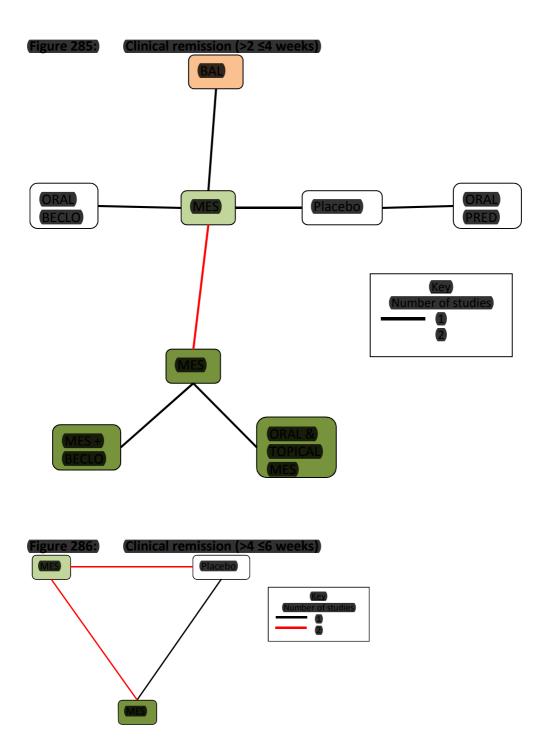
- 0≤2 weeks
- >2 ≤4 weeks
- >4 ≤6 weeks
- <>6 ≤8 weeks
- Sweeks

In the baseline networks, the end of trial data was used. However, the GDG felt that it was important to determine whether the event rates differed at the four time intervals for the included treatments, and whether the ranking of their effectiveness changed. A sensitivity analysis was to be carried out looking at the networks for clinical remission and clinical improvement at the different time points. Some studies reported data at more than one time point within the trial. In this scenario there is no risk of double counting the data as they will be in different networks. This data has therefore been included.

The following figures illustrate the direct comparisons that were available for each time point and outcome:)

(Figure 284:) (Clinical remission (0≤2 weeks))







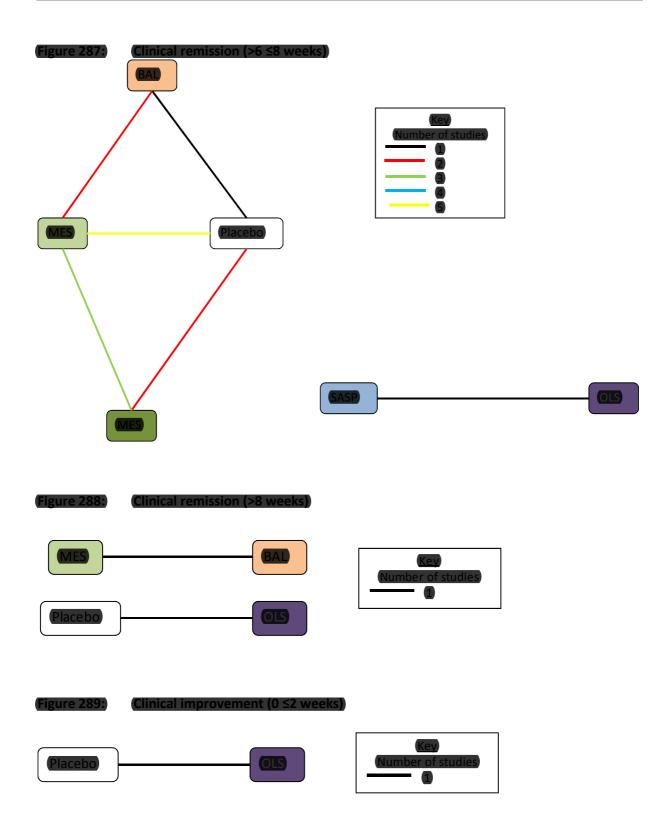
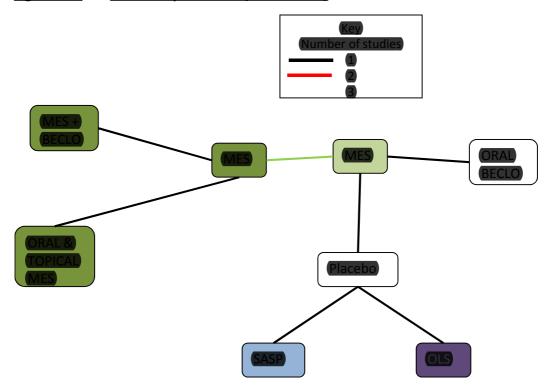
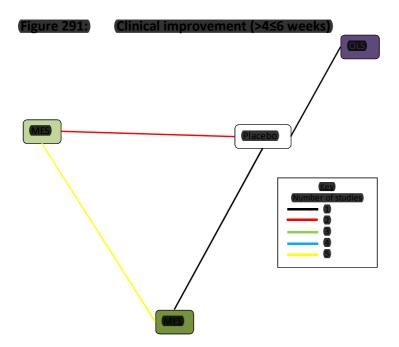
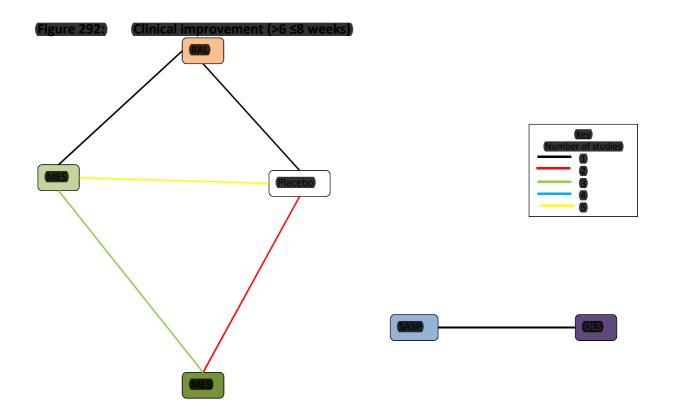


Figure 290: Clinical improvement (>2 ≤4 weeks)







2.3.5 (Clinical remission)

There were three networks which did not have a closed loop so therefore the NMA could not be internally validated, and was not carried out ($0 \le 2$, $>2 \le 4$ weeks, >8 weeks). The network for clinical) remission at >4weeks ≤ 6 weeks would not provide very useful results as there were only two treatments (high and low dose mesalazine) that are connected together with a placebo group. The >6 weeks ≤ 8 weeks subgroup, would provide results on low, high dose mesalazine, balsalazide and placebo. The NMA was not run comparing the two subgroups (>4 ≤ 6 weeks, >6 weeks ≤ 8 weeks) because it would have only produced results comparing high and low dose mesalazine (balsalazide was only included for one time point) and placebo.

2.3.6 (Clinical improvement)

Similarly to the clinical remission networks, there were two networks which did not contain a closed loop $(0 \le 2 \text{ weeks.} \ge 2 \le 4 \text{ weeks})$ and there was no data available at > 8 weeks.

The other two time points had a closed loop but only had 4 treatments to compare (>4≤6 weeks and) >6 ≤8 weeks respectively), only three of which could be compared across networks, low dose mesalazine, high dose mesalazine and placebo. The results of these would not be sufficient to impact the base case ranking of the NMA, so therefore the NMA scenario was not run.

2.4 Combined NMA results

A combined NMA was run following the results of the baseline analysis to look at the relationship between low and high dose aminosalicylates, beclometasone dipropionate and the combination treatments, oral mesalazine and oral beclometasone dipropionate, oral mesalazine and topical mesalazine. The analysis informed the inputs into the original health economic model. From the baseline NMA results, high dose olsalazine was seen as an outlier. It was shown to have no statistically significant difference in clinical remission rates compared to placebo and low dose aminosalicylates (mesalazine and sulphasalazine) and had lower clinical remission rates compared to high dose alternative treatment options. It also had a statistically significant higher withdrawals due to adverse events rate compared to many of the other comparators. It was on this basis, that it was decided to be excluded from the combined NMA and health economic model.

The outcomes used in the health economic model consist of clinical remission and withdrawals due to adverse events, so for the combined NMA, clinical improvement was not analysed.

2.4.1 (Network 1: Clinical remission)

17 studies from the baseline NMA were included in the clinical remission combined network, with one study⁵² (being excluded due to one of its two comparators being high dose olsalazine.)

For the analyses, a series of 60,000 burn-in simulations were run to allow convergence and then a further 100,000 simulations were run to produce the outputs. Convergence was assessed by examining the history and kernel density plots. A fixed effects model was run as per the baseline NMA.

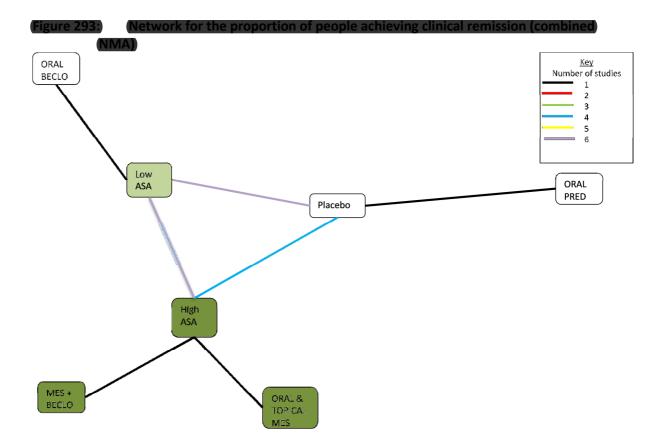


Table 12 summaries the results of the conventional meta-analyses in terms of relative risk ratios (RRs) generated from studies directly comparing different interventions (head to head comparisons)) which are presented in the white area, together with the results of the NMA in terms of RRs for every possible treatment comparison (grey area).

Out of the treatments that were compared in the NMA, all of the treatments apart from oral beclometasone dipropionate had a significant difference in the proportion of people in clinical remission compared to placebo. The combination treatment of oral mesalazine and beclometasone.

dipropionate was significantly better than low dose ASA, high dose ASA and oral beclometasone dipropionate alone. High dose oral ASA was significantly better than low dose oral ASA.

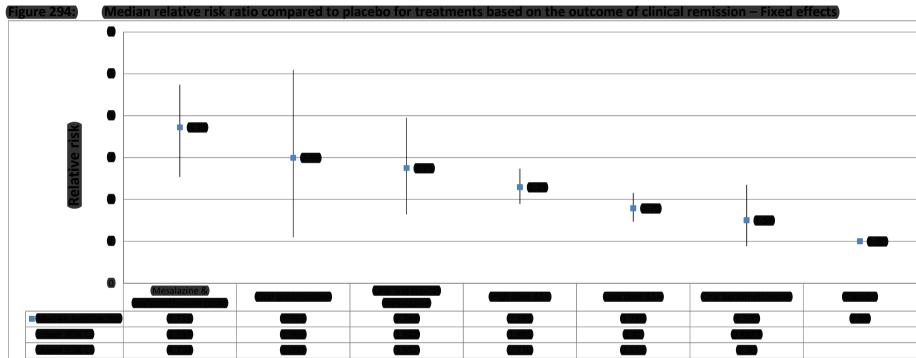
No inconsistency was found between the results of the direct and this network meta-analysis (the indirect (NMA) point median estimates were within the 95% confidence intervals of the known direct comparisons).

The residual deviance (40.25) was close to the number of unconstrained data points (number of trial) (arms, n=37) indicating a goodness of fit for the model.)

The probability of the treatment being the best (higher proportion of people in clinical remission) was highest in oral mesalazine and beclometasone (64%).

Table 14 shows the log odds ratios which are the inputs used for the health economic model.

(Table 12:) (Relative ris	sk ratios (95% CI) from	conventional (white	area) and network me	eta-analyses (grey area	a) for the proportion o	f people in clinical
	at the end of the trial					
Placebo	1.93	2.30	2.84			
	(1.51, 2.46)	(1.65, 3.22)	(0.91, 8.86)			
1.79	Low dose ASA	(1.27)		0.89		
(1.47, 2.16)		(1.12, 1.44)		(0.68, 1.17)		
2.29	1.28	High dose ASA			1.70	1.23
(1.89, 2.74)	(1.12, 1.46)				(1.13, 2.56)	(0.73, 2.07)
2.99	1.67	1.30	Oral prednisolone			
(1.10, 5.10)	(0.61, 2.97)	(0.47, 2.31)				
1.50	0.84	0.66	0.51	Oral beclometasone		
(0.88, 2.35)	(0.52, 1.27)	(0.40, 1.01)	(0.23, 1.50)			
3.72	2.07	1.61	1.24	2.45	Mesalazine &	
(2.54, 4.74)	(1.44, 2.72)	(1.14, 2.09)	(0.64, 3.48)	(1.43, 4.33)	beclometasone	
2.75	1.53	1.20	0.92	1.82	0.74	Oral & topical
(1.64, 3.95)	(0.94, 2.22)	(0.74, 1.70)	(0.43, 2.65)	(0.96, 3.39)	(0.43, 1.21)	mesalazine





(Table 13:) (The probability of each treatment being the best treatment for achieving clinical
--

remission	
	Probability of being the best treatment for
Treatment	achieving clinical remission – Fixed effects
Placebo	0%
Low dose ASA	0%
(High dose ASA)	0%
Oral prednisolone	28%
Oral beclometasone	0%
Mesalazine & beclometasone (oral)	64%
Oral and topical mesalazine	7%

Table 14:) The log odds ratio compared to placebo for achieving clinical remission

Treatment	Mean	SD	2.5% CI	Median	97.5% CI
Low dose ASA	0.75	0.14	0.48	0.75	1.03
High dose ASA	1.13	0.15	0.83	1.13	1.44
Oral prednisolone	1.64	0.83	0.11	1.61	3.36
Oral beclometasone	0.51	0.34	-0.15	0.51	1.17
Mesalazine &	2.11	0.42	1.30	2.10	2.95
beclometasone (oral)					
Oral and topical mesalazine	1.45	0.42	0.63	1.44	2.27

2.4.2 Network 2: Withdrawals due to adverse events

19 studies from the baseline NMA were included in the withdrawals due to adverse events combined network, with four studies^{37,49,56,117} being excluded due to one of its two comparators being high dose olsalazine.

For the analyses, a series of 60,000 burn-in simulations were run to allow convergence and then a further 100,000 simulations were run to produce the outputs. Convergence was assessed by examining the history and kernel density plots. A fixed effects model was run as per the baseline NMA.

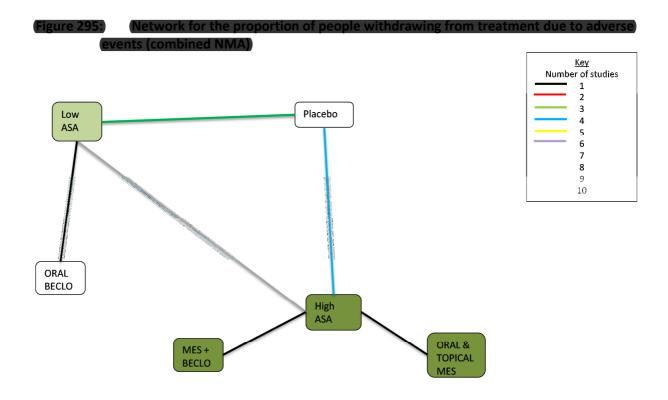


Table 15 summaries the results of the conventional meta-analyses in terms of relative risk ratios (RRs) generated from studies directly comparing different interventions (head to head comparisons) (which are presented in the white area, together with the results of the NMA in terms of RRs for every, possible treatment comparison (grey area).

Out of the treatments that were compared in the NMA, only high dose oral ASA had a statistically significant difference, which was demonstrated to have a lower withdrawals due to adverse events compared to placebo.

No inconsistency was found between the results of the direct and this network meta-analysis (the indirect (NMA) point median estimates were within the 95% confidence intervals of the known direct comparisons).

The residual deviance (34.3) was close to the number of unconstrained data points (number of trial) arms, n=41) indicating a reasonable goodness of fit for the model.)

The probability of the treatment being the best (lower proportion of people withdrawing due to adverse events) was highest in oral mesalazine and beclometasone (80%).

Table 18 shows the log odds ratios which are the inputs used for the health economic model.

(Table 15:) (Relative risk ratios (95% CI) from conventional (white area) and network meta-analyses (grey area) for the proportion of people who							
withdrew due	withdrew due to adverse events at the end of the trial – Fixed effects)						
Placebo	0.77	0.71					
	(0.49, 1.21)	(0.41, 1.22)					
0.53	Low dose ASA	0.75	1.93				
(0.80, 1.94)		(0.51, 1.11)	(0.18, 20.95)				
0.63	0.78	High dose ASA		0.35	1.18		
(0.40, 0.98)	(0.54, 1.13)			(0.04, 3.27)	(0.45, 3.13)		
1.78	2.21	2.83	Oral beclometasone				
(0.15, 10.68)	(0.20, 13.32)	(0.24, 17.38)					
0.17	0.21	0.27	0.09	Mesalazine &			
(0.01, 1.56)	(0.01, 1.90)	(0.01, 2.38)	(0.00, 2.58)	beclometasone			
0.76	0.95	1.22	0.43	4.53	Oral & topical		
(0.24, 2.34)	(0.31, 2.86)	(0.42, 3.46)	(0.05, 6.26)	(0.40, 152.60)	mesalazine		
Numbers in bold denote statistically significant results (95% Cl do not include 1). All figures are to 2 decimal places.							

Table 16: (Relative risk ratios (95% CI) from conventional (white area) and network meta-analyses (grey area) for the proportion of people who							
	withdrew due to adverse events at the end of the trial – Fixed effects						
Placebo	0.77	0.71					
	(0.49, 1.21)	(0.41, 1.22)					
0.53	Low dose ASA	0.75	1.93				
(0.80, 1.94)		(0.51, 1.11)	(0.18, 20.95)				
0.63	0.78	High dose ASA		0.35	1.18		
(0.40, 0.98)	(0.54, 1.13)			(0.04, 3.27)	(0.45, 3.13)		
1.78	2.21	2.83	Oral beclometasone				
(0.15, 10.68)	(0.20, 13.32)	(0.24, 17.38)					
0.17	0.21	0.27	0.09	Mesalazine &			
(0.01, 1.56)	(0.01, 1.90)	(0.01, 2.38)	(0.00, 2.58)	beclometasone			
0.76	0.95	1.22	0.43	4.53	Oral & topical		
(0.24, 2.34)	(0.31, 2.86)	(0.42, 3.46)	(0.05, 6.26)	(0.40, 152.60)	mesalazine		
Numbers in bold denote statistically significant results (95% CI do not include 1). All figures are to 2 decimal places.							
(NOTE: If no events occurred in one treatment arm, one was added to the numerator and denominator of all arms. This was also done for the direct comparisons, to ensure consistency.)							

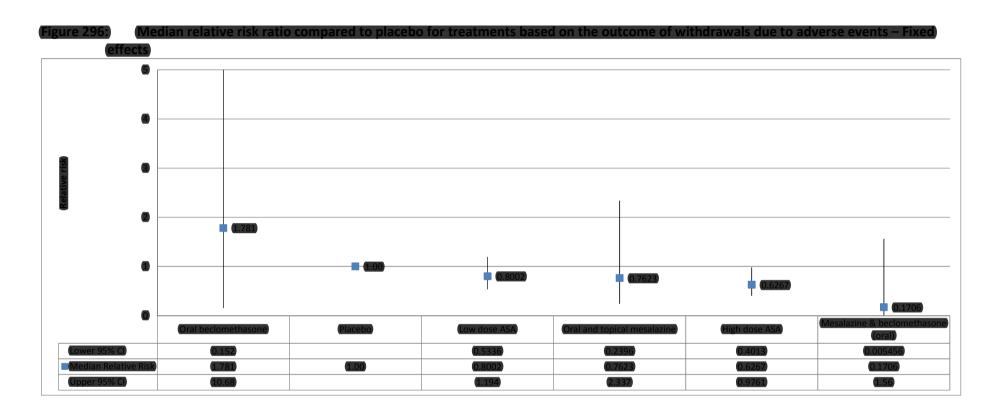


Table 17: Probability of being the best treatment for having the fewest withdrawals due to

auverse events – Fixed effects					
	Probability of being the best treatment for				
Treatment	withdrawals due to adverse events – Fixed effects				
Placebo	0%				
Low dose ASA	1%				
High dose ASA	6%				
Oral beclometasone	6%				
Mesalazine & beclometasone (oral)	80%				
Oral and topical mesalazine	7%				

Table 18: (The log odds ratio compared to placebo for having the fewest withdrawals due to

adverse events					
Treatment	Mean	SD	2.5% CI	Median	97.5% CI
Low dose ASA	-0.24	0.22	-0.67	-0.24	0.19
High dose ASA	-0.50	0.24	-0.96	-0.50	-0.03
Oral beclometasone	0.77	1.54	-1.96	0.65	4.20
Mesalazine &	-1.98	1.46	-5.29	-1.84	0.49
(beclometasone (oral)					
Oral and topical mesalazine)	-0.28	0.63	-1.49	-0.29	0.97

2.5 Discussion

Based on the results of conventional meta-analyses of direct evidence, as has been previously presented in Chapter 5 and the Forest plots in Appendix H deciding upon the most effective intervention for the induction of remission of people with mild to moderate left sided or extensive ulcerative colitis is difficult. In order to overcome the difficulty of interpreting the conclusions from these numerous separate comparisons, NMA of the direct evidence were performed by preserving the trial randomization and minimizing bias.

Our analyses on people with left sided or extensive ulcerative colitis were based on a total of 28 studies of 10 different interventions (7 mono-therapies, 2 combination therapies). The studies formed a network for each outcome.

The findings from the NMA will be used to facilitate the GDG in decision making when developing, recommendation for the induction of remission of people with left sided or extensive ulcerative colitis and as a base for the cost-effectiveness analysis.

Baseline NMA

In the first network of achieving clinical remission (author defined) by the end of the trial (≤12) weeks), the combination treatments (oral mesalazine & beclometasone, oral & topical mesalazine), balsalazide, prednisolone, high dose mesalazine and low dose mesalazine were significantly more) effective than placebo. All of these treatments were also significantly better than low dose sulphasalazine. The combination treatment of mesalazine and beclometasone was significantly better than six other treatments and was found to have the highest probability of being the best treatment. The ranking of these treatments for median relative risks need to be interpreted with caution due to the large confidence intervals of the treatments effects and because they all overlap each other.

In the second network of achieving clinical improvement (author defined) by the end of the trial (<12) weeks), the combination of mesalazine and beclometasone, oral and topical mesalazine, high dose mesalazine, high dose olsalazine, balsalazide and low dose mesalazine were significantly more effective than placebo. The combination treatment oral mesalazine and beclometasone was significantly better than all of the other treatments analysed apart from the other combination treatment (oral and topical mesalazine). Both the combination treatments were the most highly ranked with the greatest probability of being the most effective treatment.

In the third network of withdrawals due to adverse events by the end of the trial (<12weeks), high dose olsalazine had a significantly higher event rate compared to the majority of other treatment) options compared. Mesalazine and beclometasone combination treatment had the highest probability of the lowest withdrawals due to adverse events followed by balsalazide.

Combined NMA

Network 1 of the combined NMA also demonstrated the mesalazine and beclometasone dipropionate treatment combination to have a significantly higher proportion of people in clinical remission compared to low dose ASA, high dose ASA and oral beclometasone dipropionate alone. Again, it came out as having the highest probability of being the most effective treatment.

Network 2 of the combined NMA did not show any significant differences for withdrawals due to adverse events apart from high dose mesalazine which was lower than placebo. Similar to Network 1, the combination treatment of mesalazine and beclometasone dipropionate had the highest probability of being the best treatment, this time with the lowest withdrawals due to adverse events.

All of the networks seem to fit very well, as demonstrated by residual deviance and no inconsistencies in the networks found.

There was a lack of evidence for the 7 mono-therapies and 2 combination therapies included in the baseline NMA, for both the clinical remission and improvement outcomes at the different time points. The results would have been very limited (to two treatments), had to be taken in isolation and would not have had a meaningful result.

In summary, our NMA analysis on left sided or extensive ulcerative colitis networks focussed on three of the important clinical outcomes for assessing efficacy of medical treatments by 12 weeks.

Our NMA results should be considered within its following limitations:

- (Firstly, the number of studies included for some comparisons, for example evaluating oral) (prednisolone there was only one trial which was relatively small and unblinded. That was the (reason for observing the very wide confidence intervals in the relative risks for this drug)
- (The sample size of the studies comparing sulphasalazine were quite small (15-23 per arm), in (addition to the limited number of studies assessing sulphasalazine (two studies))
- Many of the comparisons are based on single studies. The combination treatments which are (favourably ranked are both based on single studies)
- Due to the lack of published studies meeting our inclusion criteria, many treatments that could be used in the treatment of left sided or extensive colitis do not appear in our networks so it is unclear where those treatments would lie in the ranking of effectiveness for example, oral prednisolone for clinical improvement and withdrawals due to adverse events
- The studies varied in trial duration from 2-12 weeks which may have had an impact on the effectiveness of different treatments (less effective in shorter trials, more effective if a longer) (trial). We were unable to do a meaningful sensitivity analysis on this due to the lack of trial) comparison data)
- Many of the studies did not give a breakdown of the extent of the disease and are at risk of being an indirect population

- The studies used different indexes to assess clinical remission and improvement
- As with all meta-analyses, the studies available for analysis could be influenced by publication (bias; however, no standardized methods have been fully developed to assess this type of bias in) (an NMA)

It should be noted that this analysis did not take into account if the patients were on maintenance treatment when they had a relapse of ulcerative colitis. In the majority of studies where patients remained on maintenance treatment at a stable dose throughout the duration of the trial was not thought to have a significant impact on the results.

2.6 Conclusion

This analysis allowed us to combine the findings from many different comparisons presented in the clinical reviews for the induction of remission of adults with mild to moderate left sided/ extensive ulcerative colitis even when direct comparative data was lacking.

Combination treatment, oral mesalazine and beclometasone came out as having the highest clinical remission and clinical improvement median relative risk ratios compared to placebo, and had the highest probability of being the most effective treatment with the fewest withdrawals due to adverse events. In the baseline NMA high dose olsalazine compared to the majority of treatments had significantly higher withdrawals due to adverse events.

2.7 Appendices

2.7.1 (Excluded studies from the baseline NMA)

	e review which were excluded from the baseline
NMA	
Study	Reason for exclusion
ANDUS2010 ²	Proctitis population
(ARDIZZONE1999 ³)	Preparation comparison
BARMEIR2003	Proctitis and proctosigmoiditis population
BARON1962	Prednisolone dosing only
BIANCONE2007 ⁸	(Preparation comparison)
(BINDER1987/ANON1987 ⁹	Proctitis and proctosigmoiditis population
CAMPIERI1988 ¹³	Preparation comparison
CAMPIERI1990 ¹³	Proctosigmoiditis population
CAMPIERI1990A ^{TS}	Proctitis and proctosigmoiditis population
CAMPIERI1991	<50% left sided/ extensive disease
CAMPIERI1991A ¹⁷	Unclear type of 5-ASA
CAMPIERI1993 ^{TB}	Mixed severity and dose comparison
CORTOT200823	Preparation comparison
DANIELSSON198727	Does not report any of the three outcomes
DHAENS200629	MEZAVANT XL dose comparison
(FARUP1995 ³⁴⁾	Proctitis and proctosigmoiditis population
(FARUP2001)	Regimen comparison
(FERRY1993 ³⁶	(Paediatric population)
FORBES2005 ^{3B}	Mesalazine comparison

Study	Reason for exclusion
(GIBSON2006 ³⁹	(Mesalazine comparison)
GIONCHETTI199840	Proctitis population
GROSS200644	Proctitis and proctosigmoiditis population
GROSS201143	<50% left sided/ extensive disease
(HANAUER1998 ⁴⁸⁾	Proctitis and proctosigmoiditis population
HANAUER1998A	Topical preparation comparison
(HARTMAN2010 ⁵³⁾	<50% left sided/extensive disease. Note author defines left sided as >60cm.
JEWELL1974 ⁶¹	Immunomodulators are not included in the NMA
KOLKMAN2004	Regimen comparison
KRUIS2003	Dose was below low BNF dose, other doses were (both high (so no comparator arm))
(KRUIS2009 ⁷³⁾	Regimen comparison
LAMET2005 ⁷² & 2011 ⁷⁹	(Regimen comparison)
LAURITSEN198678	Proctitis and proctosigmoiditis population
LEE1996	<50% left sided/ extensive disease
LEMANN1995	Topical preparation comparison
LINDGREN2002	Dose comparison only
LOFTBERG1994	Topical preparation comparison
MARAKHOUSKI2005	Regimen comparison
(MEYERS1987 ⁸⁹	<50% left sided/ extensive disease
OGATA200699	(Immunomodulators are not included in the NMA)
OREN1996	(Immunomodulators are not included in the NMA)
POKROTNIEKS2000	<50% left sided/ extensive disease
(PORRO1994 ¹⁰³	<50% left sided/ extensive disease
POWELLTUCK1978	Regimen comparison
(PRANTERA2005 ¹⁰⁷	(MEZAVANT XL comparison)
RAEDLER2004	Regimen comparison
RIJK1991	Does not report any of the three outcomes
RIZZELLO2001	(Beclometasone dosing only)
ROMANO2010 ¹¹⁸	Paediatric population
SOOD2002 ¹²²	Preparation comparison
TARPILA1994	(Proctitis population)
VANBODEGRAVEN1996	Does not report any of the three outcomes
VECCHI2001 ¹³²	<50% left sided/extensive disease
WILLIAMS1987 ¹³³	(Proctitis population)
(WILLOUGHBY1986 ¹³²⁾	Topical preparation comparison
ZINBERG1990 ¹³⁹	<50% left sided/extensive disease

2.7.2 (Additional excluded studies from the combined NMA)

Table 20:	Studies from the direct combined NMA	clinical evidence	review which w	vere excluded	from the
Study			Reason for exclus	sion	

Study	Reason for exclusion
EEURLE1989 ³⁷⁾	High dose olsalazine treatment arm
HANAUER1996 ⁴⁹	High dose olsalazine treatment arm
HETZEL1986 ⁵⁹	High dose olsalazine treatment arm
(IANG2004 ⁶²	High dose olsalazine treatment arm
ROBINSON1988	High dose olsalazine treatment arm

(2.7.3) (WinBUGs codes)

2.7.3.1 (Random effects model)

(model{

for (i in 1:NS)

Ð

Events[i] <- r[i,1]*equals(t[i,1],1)</pre>

Numpatients[i] <- n[i,1]*equals(t[i,1],1)

 $\left\{ \right\}$

totEvents<-sum(Events[])

totNumpatients<-sum(Numpatients[])

BR<- totEvents/totNumpatients

for(i in 1:NS){

w[i,1] < -0

delta [i,t[i,1]] < -0

[mu[i] ~ dnorm(0,.0001)

for (k in 1:na[i]) {

r[i,k] ~ dbin(p[i,t[i,k]],n[i,k]))

logit(p[i,t[i,k]])<-mu[i] + delta[i,t[i,k]])

(rhat[i,k] <- p[i,t[i,k]] * n[i,k])</pre>

(dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k])) + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k]))))

{

sdev[i]<- sum(dev[i,1:na[i]])

for (k in 2:na[i]) {

delta[i,t[i,k]] ~ dnorm(md[i,t[i,k]],taud[i,t[i,k]])

md[i,t[i,k]] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]

taud [i,t[i,k]] < -tau * 2 * (k - 1) / k

w[i,k] <- (delta[i,t[i,k]] - d[t[i,k]] + d[t[i,1]])

sw[i,k] <-sum(w[i,1:k-1])/(k-1) }

d [1] <- 0

for (k in 2:NT){d[k] ~ dnorm(0,.0001) }

sd~dunif(0,2)

tau<-1/pow(sd,2)

(rr [1] < -1)

for (k in 2:NT) {logit(v[k])<-logit(BR)+d[k])

rr[k] < -v[k]/BR

T[k] < -v[k]/BR

sumdev <- sum(sdev[])</pre>

for (k in 1:NT) {

(rk[k]<-NT+1-rank(rr[],k))</pre>

best[k]<-equals(NT+1-rank(rr[],k),1)}

for (c in 1:(NT-1))

{ for (k in (c+1):NT)

{ lor[c,k] <- d[k] - d[c]

log(or[c,k]) <- lor[c,k]</pre>

Irr[c,k] <- log(rr[k]) - log(rr[c])</pre>

(log(rrisk[c,k]) <- lrr[c,k] } }</pre>

(2.7.3.2) (Fixed effects model)

(model{

for (i in 1:NS)

ł

Events[i] <- r[i,1]*equals(t[i,1],1)

Numpatients[i] <- n[i,1]*equals(t[i,1],1)

6

totEvents<-sum(Events[])

totNumpatients<-sum(Numpatients[])

BR<- totEvents/totNumpatients)

for(i in 1:NS){

#w[i,1] < -0

#delta [i,t[i,1]] < -0

(mu[i] ~ dnorm(0,.0001))

for (k in 1:na[i]) {

r[i,k] ~ dbin(p[i,t[i,k]],n[i,k])

logit(p[i,t[i,k]])<-mu[i] + d[t[i,k]] - d[t[i,1]])

rhat[i,k] <- p[i,t[i,k]] * n[i,k]

(dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k])) + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))

sdev[i]<- sum(dev[i,1:na[i]])</pre>

#for (k in 2:na[i]) {

#delta[i,t[i,k]] ~ dnorm(md[i,t[i,k]],taud[i,t[i,k]])

#md[i,t[i,k]] <- d[t[i,k]] - d[t[i,1]] + sw[i,k])

#taud [i,t[i,k]] < -tau * 2 * (k - 1) / k

#w[i,k] <- (delta[i,t[i,k]] - d[t[i,k]] + d[t[i,1]])

#sw[i,k] <-sum(w[i,1:k-1])/(k-1) }

d [1] <- 0

for (k in 2:NT){d[k] ~ dnorm(0,.0001) }

#sd~dunif(0,2)

#tau<-1/pow(sd,2)</pre>

(rr [1] < -1

for (k in 2:NT) {logit(v[k])<-logit(BR)+d[k])

rr[k] < -v[k]/BR

T[k] < -v[k]/BR

sumdev <- sum(sdev[])</pre>

for (k in 1:NT) {

rk[k]<-NT+1-rank(rr[],k)

best[k]<-equals(NT+1-rank(rr[],k),1)}

for (c in 1:(NT-1))

{ for (k in (c+1):NT)

{ lor[c,k] <- d[k] - d[c]

log(or[c,k]) <- lor[c,k]</pre>

(Irr[c,k] <- log(rr[k]) - log(rr[c]))</pre>

log(rrisk[c,k]) <- lrr[c,k] } }</pre>

- (2.7.4) (Treatment codes)
- (2.7.4.1) (Baseline NMA)
- 2.7.4.1.1 (Clinical remission)
 - 1. Placebo
 - 2. Low dose mesalazine
 - 3. High dose mesalazine
 - 4. High dose olsalazine
 - **(5.) O**ral prednisolone
 - 6. Balsalazide
 - 7. Oral beclometasone
 - 8. Mesalazine & beclometasone (oral)
 - 9. Oral and topical mesalazine
 - 10. Low dose SASP

2.7.4.1.2 (Clinical improvement)

- 1. Placebo
- 2. Low dose mesalazine
- 3. (High dose mesalazine)
- 4. Low dose SASP
- 5. High dose olsalazine
- 6. Balsalazide
- 7. Oral beclometasone
- 8. Mesalazine & beclometasone (oral)
- 9. Oral and topical mesalazine
- **(2.7.4.1.3)** (Withdrawals due to adverse events)
 - Placebo
 Low dose mesalazine
 (High dose mesalazine)

	4.	Low dose SASP			
	5.	High dose olsalazine			
	6.	Balsalazide			
	7.	Oral beclometasone			
	8.	Mesalazine & beclometasone (oral)			
	9.	Oral and topical mesalazine			
2.7.4.2	Combi	ined NMA			
2.7.4.2.1	Clinica	d remission			
	1.	Placebo			
	2.	Low dose ASA			
	3.	High dose ASA			
	4.	Oral prednisolone			
	5.	Oral beclometasone			
	6.	Mesalazine & beclometasone (oral)			
	7.	Oral and topical mesalazine			
2.7.4.2.2	Withd	rawals due to adverse events			
	1.	Placebo			
	2.	Low dose ASA			
	3.	High dose ASA			
	4.	Oral beclometasone			
	5.	Mesalazine & beclometasone (oral)			
	6.	Oral and topical mesalazine			
2.7.4.3	WinBl	JGS data code for the baseline NMA			
2.7.4.3.1	Netwo	ork 1 Clinical remission – fixed effect s			
	list()				
	d=c(N/	٩,0,0,0,0,0,0,0,0,0,0,0,0,0,),			
	mu=c(-2,-3,0,1,0,0,-1,-1,1,-1,3,1,2,2,-3,1,3,-2,-3),			
	list(NS	=19,NT=10)			
	r[,1] n	[,1] r[,2] n[,2] r[,3] n[,3] r[,4] n[,4] r[,5] n[,5] t[,1] t[,2] t[,3])	t[,4]	t[,5]	[]
	2 52 1	2 106 NA 1 NA 1 NA 1 1 2 NA NA NA 2			
	19 86	64 172 NA 1 NA 1 NA 1 1 2 NA NA NA 2			

16 85 33 88 NA 1 NA 1 NA 1 1 2 NA NA NA 2

20 121 31 124 NA 1 NA 1 NA 1 1 2 NA NA NA 2

3 33 38 131 29 65 NA 1 NA 1 1 2 3 NA NA 3

11 90 28 97 28 95 NA 1 NA 1 1 2 3 NA NA 3

2 38 1 11 9 38 NA 1 NA 1 1 2 3 NA NA 3

12 90 27 183 NA 1 NA 1 NA 1 1 4 NA NA NA 2

3 18 9 19 NA 1 NA 1 NA 1 1 5 NA NA NA 2

19 83 64 166 NA 1 NA 1 NA 1 1 6 NA NA NA 2

121 383 152 389 NA 1 NA 1 NA 1 2 3 NA NA NA 2

9 63 13 60 NA 1 NA 1 NA 1 2 3 NA NA NA 2

9 24 11 24 NA 1 NA 1 NA 1 2 3 NA NA NA 2

28 49 44 50 NA 1 NA 1 NA 1 2 6 NA NA NA 2

38 89 38 84 NA 1 NA 1 NA 1 2 6 NA NA NA 2

50 87 46 90 NA 1 NA 1 NA 1 2 7 NA NA NA 2

21 61 34 58 NA 1 NA 1 NA 1 3 8 NA NA NA 2

16 56 25 71 NA 1 NA 1 NA 1 3 9 NA NA NA 2

15 21 10 21 NA 1 NA 1 NA 1 4 10 NA NA NA 2

(END)

2.7.4.4) (Network 2 Clinical improvement – random effects)

list(

d=c(NA,0,0,0,0,0,0,0,0),

sd=.2,

mu=c(1,-1,-1,-2,0,2,-3,2,2,1,2,-1,2,-2,0,-1,0,0,-3,-3,3,-1,-3),delta = structure(.Data = c(NA,-

3,NA,NA,NA,NA,NA,NA,NA,NA,O,NA,NA,NA,NA,NA,NA,NA,NA,-

),.Dim=c(23,9))))

(list(NS=23,NT=9)

2.7.4.5

2 86 2 172 NA 1 NA 1 NA 1 1 2 NA NA NA 2
1 53 3 107 NA 1 NA 1 NA 1 1 2 NA NA NA 2
11 85 5 88 NA 1 NA 1 NA 1 1 2 NA NA NA 2
10 121 7 124 NA 1 NA 1 NA 1 1 2 NA NA NA 2
11 90 9 97 7 95 NA 1 NA 1 1 2 3 NA NA 3
1 34 6 132 3 66 NA 1 NA 1 1 2 3 NA NA 3
2 38 1 11 1 38 NA 1 NA 1 1 2 3 NA NA 3
1 24 3 22 NA 1 NA 1 NA 1 1 4 NA NA NA 2
1 54 4 53 NA 1 NA 1 NA 1 1 5 NA NA NA 2
1 16 3 16 NA 1 NA 1 NA 1 1 5 NA NA NA 2
1 48 3 50 NA 1 NA 1 NA 1 1 5 NA NA NA 2
2 90 17 183 NA 1 NA 1 NA 1 1 5 NA NA NA 2
10 83 15 166 NA 1 NA 1 NA 1 1 6 NA NA NA 2
4 139 4 129 NA 1 NA 1 NA 1 2 3 NA NA NA 2
8 150 5 136 NA 1 NA 1 NA 1 2 3 NA NA NA 2
(15 383 15 389 NA 1 NA 1 NA 1 2 3 NA NA NA 2
3 64 1 61 NA 1 NA 1 2 3 NA NA NA 2
1 49 1 50 NA 1 NA 1 NA 1 2 6 NA NA NA 2
6 89 3 84 NA 1 NA 1 NA 1 2 6 NA NA NA 2
5 51 1 53 NA 1 NA 1 NA 1 2 6 NA NA NA 2
1 88 2 91 NA 1 NA 1 NA 1 2 7 NA NA NA 2
3 61 1 58 NA 1 NA 1 NA 1 3 8 NA NA NA 2
6 56 9 71 NA 1 NA 1 NA 1 3 9 NA NA NA 2
END
WinBUGS data code for the combined NMA
Network 1 Clinical remission – fixed effects
list()
d=c(NA,0,0,0,0,0,0),
mu=c(-3,-1,2,3,3,0,-3,-3,-3,-1,0,0,-2,-2,-3,0,-1),
list(NS=17,NT=7)
r[,1] n[,1] r[,2] n[,2] r[,3] n[,3] r[,4] n[,4] r[,5] n[,5] t[,1] t[,2] t[,3] t[,4] t[,5] na[]

National Clinical Guideline Centre, 2013.

2.7.4.6

2.7.4.6.1

2 51 12 103 NA 1 NA 1 NA 1 1 2 NA NA NA 2

19 84 64 170 NA 1 NA 1 NA 1 1 2 NA NA NA 2

16 74 33 83 NA 1 NA 1 NA 1 1 2 NA NA NA 2

20 121 31 124 NA 1 NA 1 NA 1 1 2 NA NA NA 2

3 32 38 125 29 62 NA 1 NA 1 1 2 3 NA NA 3

11 79 28 88 28 88 NA 1 NA 1 1 2 3 NA NA 3

2 36 1 10 9 37 NA 1 NA 1 1 2 3 NA NA 3

19 73 64 151 NA 1 NA 1 NA 1 1 3 NA NA NA 2

3 18 9 19 NA 1 NA 1 NA 1 1 4 NA NA NA 2

121 368 152 374 NA 1 NA 1 NA 1 2 3 NA NA NA 2

28 48 44 49 NA 1 NA 1 NA 1 2 3 NA NA NA 2

38 83 38 81 NA 1 NA 1 NA 1 2 3 NA NA NA 2

9 63 13 60 NA 1 NA 1 NA 1 2 3 NA NA NA 2

9 24 11 24 NA 1 NA 1 NA 1 2 3 NA NA NA 2

50 86 46 88 NA 1 NA 1 NA 1 2 5 NA NA NA 2

21 58 34 57 NA 1 NA 1 NA 1 3 6 NA NA NA 2

16 56 25 71 NA 1 NA 1 NA 1 3 7 NA NA NA 2

END

2.7.4.7 (Network 2 Withdrawals due to adverse events – fixed effects)

list(

d=c(NA,0,0,0,0,0),

mu=c(3,-3,1,1,1,2,1,0,-3,0,2,1,0,2,2,-3,2,0,0),

list(NS=19,NT=6)

(r[,1] n[,1] r[,2] n[,2] r[,3] n[,3] r[,4] n[,4] r[,5] n[,5] t[,1] t[,2] t[,3] (t[,4) (t[,5) (na[]

2 86 2 172 NA 1 NA 1 NA 1 1 2 NA NA NA 2

1 53 3 107 NA 1 NA 1 NA 1 1 2 NA NA NA 2

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1 24 3 22 NA 1 NA 1 NA 1 1 2 NA NA NA 2

10 121 7 124 NA 1 NA 1 NA 1 1 2 NA NA NA 2

11 90 9 97 7 95 NA 1 NA 1 1 2 3 NA NA 3

1 34 6 132 3 66 NA 1 NA 1 1 2 3 NA NA 3

2 38 1 11 1 38 NA 1 NA 1 1 2 3 NA NA 3

10 83 15 166 NA 1 NA 1 NA 1 1 3 NA NA NA 2

4 139 4 129 NA 1 NA 1 NA 1 2 3 NA NA NA 2

8 150 5 136 NA 1 NA 1 NA 1 2 3 NA NA NA 2

15 383 15 389 NA 1 NA 1 NA 1 **2** 3 NA NA NA **2**

1 49 1 50 NA 1 NA 1 NA 1 2 3 NA NA NA 2

6 89 3 84 NA 1 NA 1 NA 1 2 3 NA NA NA 2

5 51 1 53 NA 1 NA 1 NA 1 2 3 NA NA NA 2

3 64 1 61 NA 1 NA 1 NA 1 2 3 NA NA NA 2

1 88 2 91 NA 1 NA 1 NA 1 2 4 NA NA NA 2

3 61 1 58 NA 1 NA 1 NA 1 3 5 NA NA NA 2

6 56 9 71 NA 1 NA 1 NA 1 3 6 NA NA NA 2

(END)

Note: r[], number of events by trial arm; n[], total number of participants by trial arm; t[], treatment code; na[], number of trial arms

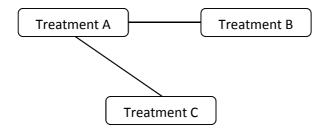
3 Appendix J: Maintenance NMA

Network meta-analysis of medical treatments for the maintenance of remission in people with left sided or extensive ulcerative colitis

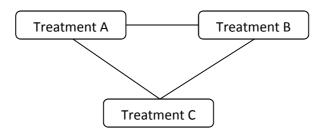
3.1 Introduction

The results of conventional meta-analyses of direct evidence alone (as presented in the GRADE profiles in Chapter 7 and the Forest plots in Appendix H) does not help inform which intervention is the most effective for the maintenance of remission in people with left-sided or extensive ulcerative colitis. The challenge of interpretation has arisen for three reasons:

- In isolation, each pair-wise comparison (for example; oral mesalazine versus oral balsalazide) does not inform the choice among treatments.
- Direct evidence is not available for some pair-wise comparisons in randomised controlled trials (for example; oral balsalazide versus oral sulphasalazine). In the example below there are no trials looking at treatment B versus treatment C.



• There are frequently multiple overlapping comparisons known as "closed loops" in the NMA where the estimates of an effect have been calculated either within the same trial or from multiple trials. Different trials may give slightly different point estimates



To overcome these issues, a hierarchical Bayesian Network Meta-analysis (NMA) was performed. This type of analysis allows the synthesis of data from direct and indirect comparisons without breaking randomisation and the ranking of different interventions. In this case, in order of efficacy, the following networks have been reviewed:

- Rate of relapse (author definition) by the end of the trial (minimum 6 months)
- Proportion of people withdrawing from treatment by the end of the trial (minimum 6 months)

The analysis provided estimates of effect (with 95% credible intervals) for each intervention compared to one another. These estimates provide a useful clinical summary of the results and facilitate the formation of recommendations based on the best available evidence. Two NMAs run, the first being the baseline scenario and the second which combined aminosalicylates into low and high doses.

For the baseline NMA, in order of efficacy, the following networks have been reviewed:

- Rate of relapse (author definition) by the end of the trial (minimum 6 months)
- Proportion of people withdrawing from treatment by the end of the trial (minimum 6 months)

For the combined NMA, the following networks have been reviewed:

- Rate of relapse (author definition) by the end of the trial (minimum 6 months)
- Proportion of people withdrawing from treatment by the end of the trial (minimum 6 months)

The analysis provided estimates of effect (with 95% credible intervals) for each intervention compared to one another. These estimates provide a useful clinical summary of the results and facilitate the formation of recommendations based on the best available evidence. Furthermore, these estimates will be used to parameterise treatment effectiveness in the de novo cost-effectiveness modelling.

Conventional fixed effects meta-analysis assumes that the relative effect of one treatment compared to another is the same across an entire set of trials. In a random effects model, it is assumed that the relative effects are different in each trial but that they are from a single common distribution and that this distribution is common across all sets of trials.

Network meta-analysis requires an additional assumption over conventional meta-analysis. The additional assumption is that intervention A has the same effect on people in trials of intervention A compared to intervention B as it does for people in trials of intervention A versus intervention C, and so on. Thus, in a random effects network meta-analysis, the assumption is that intervention A has the same effect distribution across trials of A versus B, A versus C and so on.

This specific method is usually referred to as mixed-treatment comparisons analysis but we will continue to use the term network meta-analysis to refer generically to this kind of analysis. We do so since the term "network" better describes the data structure, whereas "mixed treatments" could easily be misinterpreted as referring to combinations of treatments.

3.2 Methods

3.2.1 Study selection and data collection

To estimate treatment effects of the different drugs used for the maintenance of remission, we performed an NMA that simultaneously used all the relevant RCT evidence from the clinical review. As with conventional meta-analyses, this type of analysis does not break the randomisation of the evidence, nor does it make any assumptions about adding the effects of different interventions. The effectiveness of a particular maintenance of remission strategy was derived only from randomised controlled trials that had that particular treatment in a trial arm.

From the outset, we sought to minimise any clinical or methodological heterogeneity by focusing the analysis on selected studies that matched the pre-defined NMA protocol. Doses of the drugs in the included RCTs were classed as low and high as defined by the GDG.

Therefore, two networks of evidence were identified, defined by population and outcome measure.

For adults, young people and children with in remission who had previously had a mild to moderate flare of left sided or extensive ulcerative colitis:

• Network 1: Rate of relapse (author definition) by the end of the trial (minimum 6 months)

• Network 2: Proportion of people withdrawing from treatment by the end of the trial (minimum 6 months)

To review the NMA protocol, see Appendix C.

3.2.2 Outcome measures

The NMA evidence reviews considered one clinical efficacy outcome - the rate of relapses. This was one of the clinical efficacy outcomes identified from the clinical evidence review and considered by the GDG as the most important clinical outcome. The second outcome was any form of withdrawals from treatment. This was used rather than withdrawals due to treatment specific adverse events due to unclear reporting in the trials.

3.2.3 Comparability of interventions

The interventions compared in the model were those found in the randomised controlled trials included in the clinical review already presented in Chapter 7 of the full guideline and the Forest plots in Appendix H of the full guideline. If an intervention was evaluated in a study that met the inclusion criteria for the network (that is if it reported at least one of the outcomes of interest and matched the inclusion criteria for the network meta-analysis) then it was included in the network meta-analysis, otherwise it was excluded (see page 187 for excluded studies from the baseline NMA and combined NMA).

The treatments included in each network for each NMA are shown in Table 21.

Table 21: Maintenance of remission treatments included in the network meta-analyses of people in remission with ulcerative colitis

Baseline Network Meta-Analysis		Combined Network Meta-Analysis		
Network 1: Relapse Network 2: Withdrawals		Network 1: Relapse	Network 2: Withdrawals	
Placebo	Placebo	Placebo	Placebo	
High dose Pentasa	High dose Pentasa	Low dose ASA	Low dose ASA	
Low dose Asacol	Low dose Asacol	High dose ASA	High dose ASA	
High dose Asacol	High dose Asacol			
Low dose Olsalazine	Low dose Olsalazine			
High dose Olsalazine	High dose Olsalazine			
Low dose SASP	Low dose SASP			
High dose SASP	High dose SASP			
Low dose Salofalk	Low dose Salofalk			
High dose Salofalk	High dose Salofalk			
Low dose Balsalazide Low dose Balsalazide				
High dose Balsalazide	High dose Balsalazide			

3.2.4 Statistical analysis

In order to be included in the analysis, a fundamental requirement is that each treatment is connected directly or indirectly to every other intervention in the network. For each outcome a diagram of the evidence network was produced (see Figure 278 and Figure 299).

Network 1: Relapse

Some trials eligible for inclusion in the NMA reported relapses in terms of hazard ratio. The remainder of the trials reported cumulative count statistics; that is the number of people who had a relapse at a specific time point. In order to combine data from all the studies, a multi-statistic evidence synthesis using WinBUGS version 1.4 software was conducted according to methodology

described by Woods 2010¹³⁵. This allowed hazard ratio statistics and cumulative count statistics to be combined within a single network meta-analysis on the log hazard scale. The count statistics used are presented in Table 3. The relapse data was made conditional on not having withdrawn from treatment. In order to do this, for studies that reported count statistics, the number of people who withdrew from the study was excluded from the number of people who completed the study. The proportion of people who relapsed was then based on the number of people left in the study.

The hazard ratio statistics are presented in Table 24, along with the derived estimates of the mean log hazard ratio and its standard error. These were calculated using the formulae below:

$$\overline{In(HR)} = \frac{In(HRuci) + In(HRlci)}{2}$$

$$se = \frac{In(HRuci) - In(HRlci)}{2 \times 1.96}$$

A random effects analysis of the network was conducted. Random effects models allow for the possibility that the true treatment effect may differ between trials. As it was a Bayesian analysis, for each parameter the evidence distribution is weighted by a distribution of prior beliefs. A non-informative prior distribution was used to maximise the weighting given to the data. These priors were normally distributed with a mean of 0 and standard deviation of 10,000.

For the analyses, a series of 10,000 burn-in simulations were run to allow convergence and then a further 60,000 simulations were run to produce the outputs. Convergence was assessed by examining the history and kernel density plots.

The output from the NMA was treatment-specific log hazards. The overall ranking of treatments compared to placebo was calculated. In addition, the proportion of simulations of the Markov chain in which each intervention had the lowest log hazard was recorded.

Network two: Withdrawals

A hierarchical Bayesian network meta-analysis was performed using WinBUGS version 1.4 software. A three-arm random effects logistic regression model template, obtained from the University of Bristol website (https://www.bris.ac.uk/cobm/research/mpes/mtc.html) was adapted. This model accounts for the correlation between study level effects induced by multi-arm trials. The parameters were estimated by Markov chain Monte Carlo simulation. Random effects models allow for the possibility that the true treatment effect may differ between trials. As it was a Bayesian analysis, for each parameter the evidence distribution is weighted by a distribution of prior beliefs. A noninformative prior distribution was used to maximise the weighting given to the data. These priors were normally distributed with a mean of 0 and standard deviation of 10,000. Any study that reported no events in any of the arms was excluded.

For the analyses, a series of 10,000 burn-in simulations were run to allow convergence and then a further 60,000 simulations were run to produce the outputs. Convergence was assessed by examining the history and kernel density plots.

The aim of the NMA was to calculate treatment specific log odds ratios and relative risks for the response to be consistent with the comparative effectiveness results presented elsewhere in the clinical evidence review and for ease of interpretation. Let BO, $\tilde{\theta}$, \widetilde{OR} and p denote the baseline odds, treatment specific odds, treatment specific log odds ratio and absolute probability respectively. Then:

$$\widetilde{\theta} = Ln(\widetilde{OR}) + Ln(BO)$$

And:

$$p = rac{e^{\widetilde{ heta}}}{1+e^{\widetilde{ heta}}}$$

Once the treatment specific probabilities for response are calculated, we divide them by the baseline probability (p_b) to get treatment specific relative risks (rr_b) :

$$p_b = \frac{e^{BO}}{1 + e^{BO}}$$
$$rr_b = \frac{p}{p_b}$$

This approach has the advantage that baseline and relative effects are both modelled on the same log odds scale, and also ensure that the uncertainty in the estimation of both baseline and relative effects is accounted for in the model.

Differences between treatments were considered significant at the 0.05 level if the 95% credible interval for the RR did not cross 1.

We also calculated the overall ranking of interventions according to their relative risk compared to control group and counting the proportion of simulations of the Markov chain in which each intervention had the highest relative risk.

Tests for inconsistency

A key assumption behind NMA is that the network is consistent. In other words, it is assumed that the direct and indirect treatment effect estimates do not disagree with one another. Discrepancies between direct and indirect estimates of effect may result from several possible causes. First, there is chance and if this is the case then the network meta-analysis results are likely to be more precise as they pool together more data than conventional meta-analysis estimates alone. Second, there could be differences between the trials included in terms of their clinical or methodological characteristics. Differences that could lead to inconsistency include:

- Different populations (e.g. populations of mixed disease extent, age)
- Use of concomitant medications
- Different doses for drug treatments other than oral ASAs were the doses were not taken into account
- Different trial durations (longer trials are likely to have a higher proportion of patients achieving the outcome)
- Quality of the study (risk of bias)
- Different indexes and thresholds used to determine clinical remission and improvement

This heterogeneity is a problem for network meta-analysis but may be dealt with by subgroup analysis or by carefully defining inclusion criteria. Inconsistency, caused by heterogeneity, was assessed subjectively by comparing the hazard ratios from the direct evidence (from pair-wise meta-analysis) to the hazard ratios from the combined direct and indirect evidence (from NMA). We assumed the evidence to be inconsistent where the hazard ratio from the NMA did not fit within the confidence interval of the hazard ratio from the direct comparison.

3.3 Baseline NMA results

A total of 18 studies met the inclusion criteria and were included in either or both of the networks. Table 22 below gives a summary of the characteristics of included studies.

Study	Comparators	Patient characteristics	Disease extent	Previous medication	Outcomes reported	Risk of bias
MINER1995 48 week trial	4g mesalazine (Pentasa) versus placebo	18 years or older Previously diagnosed ulcerative colitis in remission (sigmoidoscopic index of <5, mean of <5 stools/day, absence of rectal bleeding)	Pan colitis or left sided colitis.	Prior use of various medications, oral steroid, rectal therapy and sulphasalazine. Immunosuppressants and oral/rectal steroids required a 90 and 60 day wash out respectively, prior to baseline	Relapse Withdrawals	Unclear method of randomisation and allocation concealment Double blind but no further information was given >10% difference in missing data between the treatment arms
HANAUER1996A 6 month trial	1.6g mesalazine (Asacol) versus placebo The 0.8g mesalazine arm has not been included as it is below the recommended dosing regimen.	18-75 years 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	All extents of disease. >50% left sided or extensive in the two treatment groups.	Previously treated with 2-4g sulphasalazine per day or 0.8- 1.6g of any oral mesalazine per day. Dose had to be kept constant for at least 1 month before study entry.	Relapse	Unclear allocation concealment Unclear who dropped out from which treatment group Double blind but no further information was given
WRIGHT1993 12 month trial	2g olsalazine versus placebo	18-75 years Inactive UC diagnosed by Truelove & Witts criteria	No restrictions described. Unable to calculate % with left sided/ extensive colitis.	Unknown. Therapy of last attack was described (oral and/or rectal corticosteroids).	Relapse Withdrawals	Unclear method of randomisation and allocation concealment Double blind but no further information was given

Study	Comparators	Patient characteristics	Disease extent	Previous medication	Outcomes reported	Risk of bias
ARDIZZONE1999c 12 month trial	1.2g mesalazine (Asacol) versus placebo	18-75 years Confirmed diagnosis of intermittent chronic ulcerative colitis in stable remission for at least 1 month	All extents of disease. >50% left sided or extensive colitis in the two treatment groups.	2g/ day of sulphasalazine or 0.8-1.5g mesalazine/ day	Relapse Withdrawals	Unclear method of randomisation and allocation concealment Double blind but no further information was given
COURTNEY1992 12 month trial	1g olsalazine versus 1.5g mesalazine (Asacol)	16-75 years UC in remission	All extents >50% left sided or extensive colitis	Unknown.	Relapse Withdrawals	Single blind
GREEN1998A 12 month trial	3g balsalazide versus 1.2g mesalazine (Asacol)	18-80 years UC symptoms requiring treatment with maintenance therapy. Remission declared up to a maximum of 1 year before entry to the study	Not described.	Some patients had previous use of balsalazide or mesalazine in the last year.	Relapse Withdrawals	Unclear method of randomisation and allocation concealment no extent data given at baseline High dropout rate (but <10% difference between treatment arms)
IRELAND1988 6 month trial	1g olsalazine versus 2g sulphasalazine	17-75 years UC in remission, no relapse for 6 months	All extents >50% left sided or extensive colitis	Majority of the patients were on sulphasalazine prior to the trial	Relapse Withdrawals	Unclear method of randomisation and allocation concealment Stated to be double blind but no further information was given

Ulcerative colitis Appendix J: Maintenance NMA

Study	Comparators	Patient characteristics	Disease extent	Previous medication	Outcomes reported	Risk of bias
NILSSON1995 6 month trial	1g olsalazine versus 2g sulphasalazine	Age inclusion not described. Remission for the last 2 months, with at least 2 episode of active colitis during the last 5 years	All extents. >50% left sided or extensive colitis	Sulphasalazine tolerant population.	Relapse Withdrawals	Unclear method of randomisation and allocation concealment Stated to be double blind but no further information was given
DISSANAYAKE1973 6 month trial	2g sulphasalazine versus placebo	Age inclusion not described. Prolonged remission while on sulphasalazine maintenance therapy.	Not described.	Sulphasalazine 0.5g, 4 times a day.	Relapse There were no withdrawals	Unclear method of randomisation No baseline characteristics data given
SANDBERGGERTZE N1986 6 month trial	1g olsalazine versus placebo	No age limits Patients who after 6 months of medication with olsalazine were in remission and off steroids. If patients were not in remission at the start of the trial they were re- evaluated at 2 months and if in remission, they were then entered into the trial.	No extent limit. Unclear what percentage was left sided/extensive (note: subgroup data on extensive disease has been used in the analysis).	Patients were unable to tolerate sulphasalazine. They had all previously been on olsalazine.	Relapse There were no withdrawals	Unclear method of randomisation and allocation concealment Double blind but no further information was given Very limited baseline characteristics
PAOLUZI2005 12 month trial	1.2g mesalazine (Asacol) versus 2.4g mesalazine (Asacol)	>18 years Recent disease relapse (within the last 3 months) prior to the study who have been appropriately treated until remission had been achieved.	>20cm from the anus. >50% left sided or extensive colitis.	Previous activity was mild to moderate disease and the treatment consisted of oral and topical mesalazine.	Relapse Withdrawals	Unclear method of randomisation and allocation concealment Single blind, open label

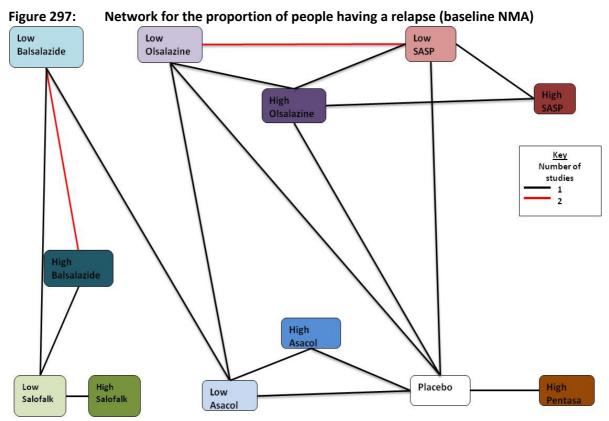
Study	Comparators	Patient characteristics	Disease extent	Previous medication	Outcomes reported	Risk of bias
TRAVIS1994 12 month trial	1g olsalazine versus 2g olsalazine	Age inclusion not described. Remission for 3 months or more	No restriction described. >50% left sided or extensive colitis.	Unknown.	Relapse	Unclear method of randomisation and allocation concealment Unclear blinding Unclear dropout rate Unclear outcome assessment
KRUIS1995 6 month trial	1.25g olsalazine versus 2g olsalazine versus 2g sulphasalazine	15-77 years Remission for less than 12 months	All extents Two treatment groups have 50% left sided or extensive colitis.	Unknown.	Relapse Withdrawals are not reported by subgroup, only overall	Unclear allocation concealment States to be double blind, there was no information given on physician blinding >10% difference in missing data between some of the treatment arms
RIJK1992 48 week trial	2g olsalazine versus 4g sulphasalazine	16-78 years Remission for not longer than 2 years. Active UC in the past.	Unclear the % of left sided and extensive colitis	Unknown.	Relapse Withdrawals	Unclear method randomisation and allocation concealment Limited baseline characteristics >10% difference in missing data between the treatment arms Double blind but

Study	Comparators	Patient characteristics	Disease extent	Previous medication	Outcomes reported	Risk of bias
						no further information was given
AZADKHAN1980 6 month trial	2g sulphasalazine versus 4g sulphasalazine	Age inclusion not described. Just states ulcerative colitis needs to be in remission as the inclusion criteria.	No restriction described. Unknown extent.	163/170 patients were on 2g sulphasalazine prior to the trial.	Relapse No withdrawals	Unclear method of randomisation and allocation concealment Unclear blinding Very limited baseline characteristics
GREEN1992 12 month trial	3g balsalazide versus 6g balsalazide	19-78 years Clinical and sigmoidoscopic remission	 ≥15cm at some point in their illness. >50% left sided or extensive colitis. 	All were maintained on a 5-ASA preparation alone prior to the trial.	Relapse Withdrawals	Unclear method of randomisation and allocation concealment Double blind but no further information was given
KRUIS2001 26 week trial	3g balsalazide versus 6g balsalazide versus 1.5g mesalazine (Salofalk)	18-70 years Clinical and endoscopic remission with a history of at least 2 previous attacks	UC involving at least the rectum and sigmoid colon >50% left sided or extensive colitis	Around 50% had used 5-ASA prior to the trial.	Relapse Withdrawals	Unclear method of randomisation and allocation concealment Double blind but no further information was given >10% difference in missing data between two treatment arms
KRUIS2011	1.5g mesalazine	18-75 years	Mucosal	Unclear what previous	Relapse	

Study	Comparators	Patient characteristics	Disease extent	Previous medication	Outcomes reported	Risk of bias
12 month trial	(Salofalk) versus 3.0g mesalazine (Salofalk)	Last active episode had ended within the 3 months prior to study entry	inflammation extending at least 15cm. No further details are	treatment was. Information only given for treatment of last acute episode.	Withdrawals	
			given.			

3.3.1 Network 1: Relapse

A total of 18 studies^{4,22,32,41,42,47,58,72,73,75,91,98,101,113,119,129,136} from the original evidence review met the inclusion criteria and reported relapse as an outcome. Figure 278 shows the network created by eligible comparisons for the NMA. The colour of the line connecting two treatments indicates the number of included studies that assessed that direct comparison. The studies from the original evidence review which have been excluded from the NMA are shown alongside their reason (s) for exclusion on page 187.



Note: Boxes are shaded from light and dark indicating low and high doses respectively.

There were 11 double blind trials, two single blind and five with unclear blinding. 17 trials had an unclear method of randomisation, allocation concealment or both. In seven studies, the percentage of patients with left sided or extensive disease was not able to be calculated either due to no baseline characteristic data being given, subgroups did not fit into the GDG definitions for extent of disease or an unknown/unclear inclusion criteria. There were nine studies that included adults ≥18 years, five studies that included some young people with their inclusion criteria being 16-78 years and 15-77 years, 17-75 years, 16-75 years and five studies did not describe the age inclusion criteria.

The data from the 18 studies included in the NMA are presented below. Table 3 lists studies that provided relapse data in the form of count statistics. Table 24 lists studies that provided relapse data in form of hazard ratios.

				Compa 1	rator	Compa 2	rator	Compar	rator 3
Study	Comparator 1	Comparator 2	Comparator 3	Event No.	N	Event No.	N	Event No.	N
Dissanayake 1973	Placebo	SASP (2g)	NA	17	31	4	33	NA	NA
Sandberg-Gertzen 1986	Placebo	Olsalazine (1g)	NA	22	49	12	52	NA	NA
Paolezi 2005	Asacol (1.2g)	Asacol (2.4g)	NA	48	68	48	72	NA	NA
Travis 1994	Olsalazine (2g)	Olsalazine (1g)	NA	10	62	17	65	NA	NA
Kruis 1995	Olsalazine (2g)	SASP (2g)	NA	5	29	11	36	NA	NA
Rijk 1982	Olsalazine (2g)	SASP (4g)	NA	6	15	7	19	NA	NA
Azadkhan 1980	SASP (2g)	SASP (4g)	NA	8	57	5	56	NA	NA
Green 1992	Balsalazide (3g)	Balsalazide (6g)	NA	10	44	15	47	NA	NA
Kruis 2001	Balsalazide (3g)	Balsalazide (6g)	Salofalk (1.5g)	13	27	3	34	6	29
Kruis 2011	Salofalk (1.5g)	Salofalk (3g)	NA	44	195	17	193	NA	NA

Table 23: Relapse data: studies reporting count statistics

Table 24: Relapse data: studies reporting hazard ratio

Study	Treatment	Base	HR	HR (LCI)	HR (UCI)	LN(HR)	se (LN(HR))
Miner 1995	Pentasa (4g)	Placebo	0.63	0.41	0.96	-0.46	0.22
Hanauer 1996A	Asacol (1.6g)	Placebo	0.47	0.27	0.84	-0.76	0.29
Wright 1993	Olsalazine (2g)	Placebo	0.52	0.29	0.92	-0.65	0.29
Adrizzone 1999c	Asacol (1.2g)	Placebo	0.60	0.18	1.97	-0.51	0.61
	Olsalazine	Asacol					
Courtney 1992	(1g) Balsalazide	(1.2g) Asacol	0.30	0.11	0.84	-1.20	0.52
Green 1998A	(3g) Olsalazine	(1.2g)	0.74	0.36	1.55	-0.30	0.37
Ireland 1988	(1g)	SASP (2g)	1.84	0.83	4.05	0.61	0.40

Study	Treatment	Base	HR	HR (LCI)	HR (UCI)	LN(HR)	se (LN(HR))
Nilsson 1995	Olsalazine (1g)	SASP (2g)	1.28	0.89	1.85	0.25	0.19

Table 25 summaries the results of the conventional meta-analyses and the NMA in terms of hazard ratios (HRs). The white area contains data generated from studies directly comparing different interventions (head to head comparisons) while the results of the NMA are presented in the grey area.

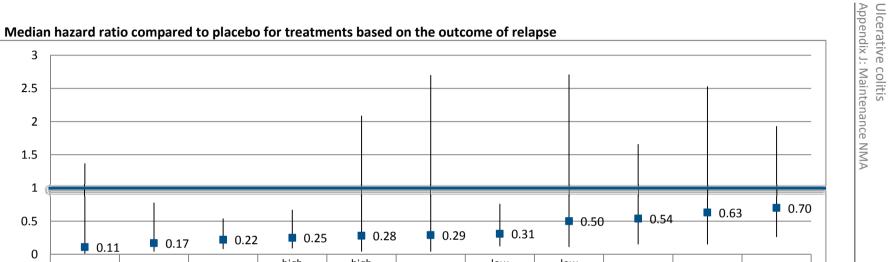
Out of the treatments that were compared in the NMA, low and high doses of olsalazine and low and high doses of sulfasalazine were found to be significantly better than placebo (Table 25).

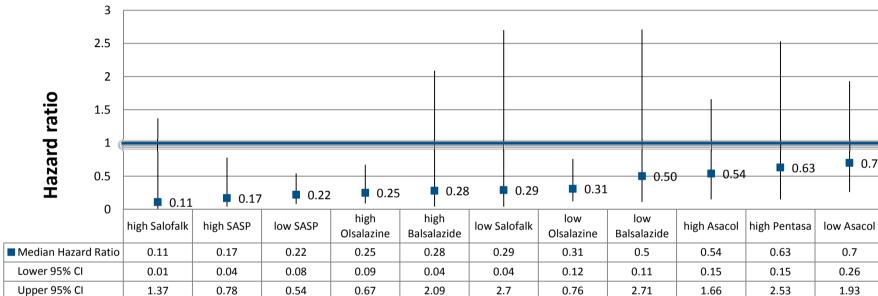
No inconsistency was found between the results of the direct and this network meta-analysis (the indirect (NMA) point median estimates were within the 95% confidence intervals of the known direct comparisons).

The median hazard ratio of all treatments compared to placebo is shown in Figure 298. Again it shows that low and high doses of olsalazine and low and high doses of sulfasalazine are significantly better than placebo. However, due to the overlapping confidence intervals of the different treatments, it is felt that there is insufficient evidence to be confident of one treatment's superiority compared to the alternative treatment for the maintenance of remission compared to placebo.

	0.63	0.47	0.41	0.60							
Placebo	(0.41,0.96)	(0.27,0.84)	(0.23,0.73)	(0.18,1.97)							
0.63	high										
(0.15,2.53)	Pentasa										
0.54	0.88										
(0.15,1.66)	(0.15,5.5)	high Asacol									
0.25		0.46	high								
	0.4 (0.07,2)		Olsalazine								
0.70	1.08	1.24	2.71				0.74				
(0.26,1.93)	(0.18,6.69)	(0.34,3.81)	(0.81,12.11)	low Asacol		0.30 (0.11,0.84)	(0.36,1.55)				
0.22	0.35	0.4	0.88	0.33							
(0.08,0.54)		(0.08,1.67)	(0.33,2.71)	(0.08,1.14)	low SASP	1.36 (0.98,1.90)					
0.31	0.5	0.57	1.25	0.46	1.43						
(0.12,0.76)		(0.13,2.13)	(0.5,3.74)	(0.14,1.39)	(0.62,3.4)	low Olsalazine					
0.5	0.79	0.92	2.00	0.74	2.32	1 (2 (2 2 4 2 0 2)	low				
(0.11,2.71)	(0.06,9.31)	(0.1,5.93)	(0.26,20.32)	(0.15,3.39)	(0.27,20.73)	1.62 (0.2,13.08)	Balsalazide				
0.17	0.28	0.31	0.69	0.25	0.79		0.35				
(0.04,0.78)	(0.04,1.89)	(0.05,1.77)	(0.2,2.7)	(0.05,1.29)	(0.21,2.93)	0.56 (0.13,2.24)	(0.03,3.78)	high SASP			
0.29	0.45	0.52	1.14	0.42	1.30		0.57	1.65	low		
(0.04,2.7)	(0.02,7.61)	(0.03,5.72)	(0.08,18.37)	(0.04,3.76)	(0.09,17.95)	0.92 (0.07,11.19)	(0.11,2.48)	(0.1,33.26)	Salofalk		
0.11	0.16	0.18	0.4	0.15	0.46		0.2	0.58	0.35		
(0.01,1.37)	(0.01,3.7)	(0.01,2.86)	(0.02,8.54)	(0.01,1.8)	(0.02,8.39)	0.32 (0.02,5.79)	(0.03,1.45)	(0.02,13.96)	(0.08,1.31)	high Salofalk	
0.28	0.45	0.53	1.15	0.42	1.33		0.57	1.67	1.02	2.92	high
(0.04,2.09)	(0.03,6.26)	(0.04,4.13)	(0.1,13.63)	(0.05,2.57)	(0.1,13.14)	0.93 (0.08,8.82)	(0.17,1.59)	(0.11,23.74)	(0.19,4.76)	(0.35,24.65)	Balsalazi

Numbers in bold denote statistically significant results (95% CI do not include 1). All figures are to 2 decimal places. Numbers in red are relative risks obtained based on direct evidence.





2.09

0.76

2.71

1.66

2.53

1.93

Bold horizontal line denotes the line of no effect.

Figure 298:

3.3.2 Network 2: Withdrawals

A total of 13 studies from the original evidence review met the inclusion criteria and reported withdrawals. Figure 299 shows the network created by eligible comparisons for the NMA. The colour of the line connecting two treatments indicates the number of included studies that assessed that direct comparison. The studies from the original evidence review which have been excluded from the NMA are shown on page 187 alongside their reason(s) for exclusion.

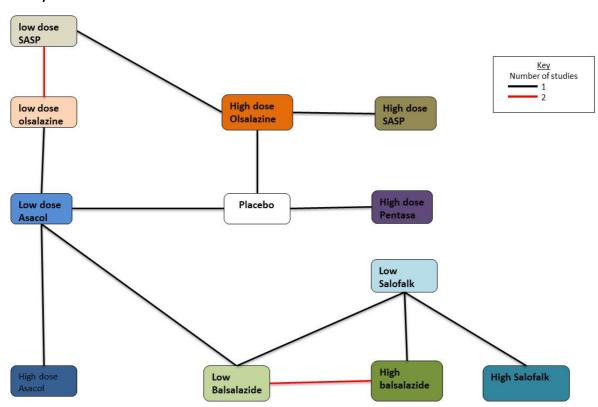


Figure 299: Network for the proportion of people withdrawing from treatment (baseline NMA)

Note: Boxes are shaded from light and dark indicating low and high doses respectively.

There were nine double blind studies, two single blind studies and two with unclear blinding. 11 studies had an unclear method of randomisation, allocation concealment or both. In four studies, the percentage of patients with left sided or extensive disease was not able to be calculated either due to no baseline characteristic data being given, subgroups did not fit into the GDG definitions for extent of disease or an unknown/unclear inclusion criteria. Three studies included young people in their inclusion criteria, 16-78 years, 15-77 years and 17-75 years.

The trial data from the 13 studies included in the NMA for the proportion of people withdrawing from treatment are presented in Table 9.

	_		~	Compa	rator 1	Compa	rator 2	Compa	rator 3
Study	Comparator 1	Comparator 2	Comparator 3	Event No.	N	Event No.	N	Event No.	N
Miner 1995	Placebo	Pentasa (4g)	NA	41	102	20	103	NA	NA
Adrizzone 1999c	Placebo	Asacol (1.2g)	NA	7	58	11	54	NA	NA
Wright 1993	Placebo	Olsalazine (2g)	NA	5	52	12	49	NA	NA
Courtney 1992	Asacol (1.2g)	Olsalazine (1g)	NA	10	50	8	49	NA	NA
Paolezi 2005	Asacol (1.2g)	Asacol (2.4g)	NA	8	76	8	80	NA	NA
Green 1998A	Asacol (1.2g)	Balsalazide (3g)	NA	9	50	13	49	NA	NA
Rijk 1982	Olsalazine (2g)	SASP (4g)	NA	8	23	4	23	NA	NA
Ireland 1988	Olsalazine (1g)	SASP (2g)	NA	19	82	11	82	NA	NA
Nilsson 1995	Olsalazine (1g)	SASP (2g)	NA	14	161	17	161	NA	NA
Green 1992	Balsalazide (3g)	Balsalazide (6g)	NA	10	54	7	54	NA	NA
Kruis 2001	Balsalazide (3g)	Balsalazide (6g)	Salofalk (1.5g)	21	48	6	40	15	44
Kruis 2011	Salofalk (1.5g)	Salofalk (3g)	NA	17	212	24	217	NA	NA
Kruis 1995	Olsalazine (2g)	SASP (2g)	NA	5	34	4	40	NA	NA

Table 26: Study data for the network of the proportion of people withdrawing from treatment

Table 27 summaries the results of the conventional meta-analyses in terms of relative risk ratios (RRs) generated from studies directly comparing different interventions (head to head comparisons) which are presented in the white area, together with the results of the NMA in terms of RRs for every possible treatment comparison (grey area).

None of the treatments compared in the NMA demonstrated a significant difference in withdrawals compared to placebo.

No inconsistency was found between the results of the direct and this network meta-analysis. No inconsistency was found between the results of the direct and this network meta-analysis (the indirect (NMA) point median estimates were within the 95% confidence intervals of the known direct comparisons). The median hazard ratio of all treatments compared to placebo is shown in Figure 300. It shows the overlapping confidence intervals of the different treatments.

Placebo	0.48 [0.31, 0.76]		3.50 [0.95,12.90]		1.69 [0.71, 4.04]						
0.56 (0.06, 1.93)	High Pentasa										
1.54 (0.26,3.02)	6.4 (0.35,28.53)	Low Asacol		0.82 [0.35, 1.89]	0.95 [0.38, 2.40]	1.47 [0.69, 3.13]					
2.63 (0.78,3.38)	10.79 (0.98,46.1)	2.83 (0.47,10.3)	High Olsalazine					0.50 [0.17, 1.43]			
1.4 (0.08,3.2)	5.85 (0.14,27.18)	0.96 (0.14,2.42)	0.68 (0.04,2.1)	Low Olsalazine			0.85 [0.53, 1.36]				
1.51 (0.1,3.23)	6.32 (0.16,29.08)	1.05 (0.17,2.61)	0.74 (0.04,2.25)	2.26 (0.15,9.09)	High Asacol						
1.87 (0.18,3.29)	7.68 (0.29,33.87)	1.37 (0.3,3.31)	0.9 (0.08,2.65)	3 (0.27,12.09)	2.59 (0.25,10.08)	Low balsalazide			0.47 [0.26 <i>,</i> 0.84]	0.78 [0.46,1.3]	
1.29 (0.05,3.22)	5.45 (0.08,26.21)	0.89 (0.07,2.52)	0.63 (0.02,2.01)	0.96 (0.25,2.09)	1.86 (0.07,6.5)	1.07 (0.05,3.71)	Low SASP				
2.07 (0.15,3.37)	8.54 (0.24,38.09)	2.24 (0.1,8.52)	0.77 (0.11,1.3)	8.44 (0.11,24.79)	5.61 (0.1,20.82)	3.51 (0.08,11.08)	20.32 (0.12,42.71)	High SASP			
1.27 (0.05,3.21)	5.49 (0.09,26.1)	0.89 (0.08,2.52)	0.62 (0.02,2.03)	1.96 (0.07,8.09)	1.73 (0.07,6.66)	0.65 (0.14,1.24)	3.8 (0.08,14.48)	2.3 (0.03,9.19)	High balsalazide	2.27 [0.98,5.2]	
1.74 (0.09,3.33)	7.26 (0.15,32.51)	1.31 (0.13,3.71)	0.83 (0.04,2.55)	2.96 (0.13,12.12)	2.79 (0.12,10.06)	1.00 (0.21,2.29)	5.77 (0.14,21.72)	3.08 (0.05,12.46)	2.05 (0.45,7.01)	Low Salofalk	1.38 [0.76, 2.49]
1.94 (0.07,3.38)	7.98 (0.13,35.82)	1.54 (0.1,4.61)	0.94 (0.03,2.78)	3.66 (0.1,14.62)	3.34 (0.09,12.31)	1.25 (0.13,3.45)	7.3 (0.11,25.77)	3.41 (0.04,13.2)	2.88 (0.28,11.01)	1.32	High Salofalk

Numbers in bold denote statistically significant results (95% CI do not include 1). All figures are to 2 decimal places.

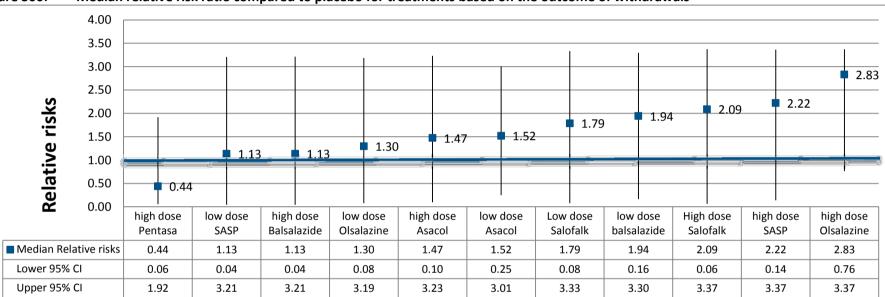


Figure 300: Median relative risk ratio compared to placebo for treatments based on the outcome of withdrawals

Bold horizontal line denotes the line of no effect

3.4 Combined NMA results

The GDG reviewed the results of the baseline NMA and considered that there were no clinically significant differences between the low dose oral ASAs. This was the same for the high dose oral ASAs. A dose effect was not observed between lower and higher doses of ASAs but in the clinical review a dose relationship was suggested. It was thought that the same groupings should be used as in the induction NMAs because the event rates are so small and there is large uncertainty so grouping them in low and high doses may strengthen the power to demonstrate an effect.

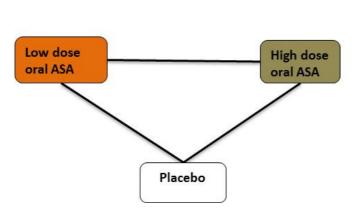
Based on this, a second NMA (combined NMA) was conducted to inform the health economic model. This combined all low dose ASAs into one treatment group, and all high dose ASAs into another treatment group. The two networks for the combined NMA are described below.

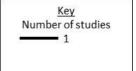
Network 1: Relapses

Five studies^{22,42,58,98,113} which were included in the baseline analysis were excluded as they compared the same dose ranges of ASAs for example, a low dose versus a low dose or a high dose versus a high dose. The methodology described in section 3.2.4 was used. The network is shown in Figure 301.

For the analyses, a series of 60,000 burn-in simulations were run to allow convergence and then a further 100,000 simulations were run to produce the outputs. Convergence was assessed by examining the history and kernel density plots.

Figure 301: Network for the proportion of people having a relapse (combined NMA)





The results are presented in Table 28 and Table 29 along with the results of the individual treatments.

Table 28: Hazard ratio of low dose oral ASA versus placebo

Drug	Hazard ratio from Baseline NMA (95% Cl)	Hazard ratio from combined NMA (95% CI)
Low dose Salofalk	0.29 (0.04, 2.7)	0.49 (0.24, 0.93)
Low dose Asacol	0.70 (0.26, 1.93	
Low dose SASP	0.22 (0.08, 0.54)	
Low dose Olsalazine	0.31 (0.12, 0.76)	
Low dose Balsalazide	0.50 (0.11, 2.71)	

Drug	Hazard ratio from Baseline NMA (95% Cl)	Hazard ratio from combined NMA (95% CI)
High dose Salofalk	0.11(0.01, 1.37)	0.36 (0.18, 0.67)
High dose Asacol	0.54(0.15, 1.66)	
High dose SASP	0.17(0.04, 0.78)	
High dose Olsalazine	0.25(0.09, 0.67)	
High dose Balsalazide	0.28(0.04, 2.09)	

Table 29: Hazard ratio of high dose oral ASA versus placebo

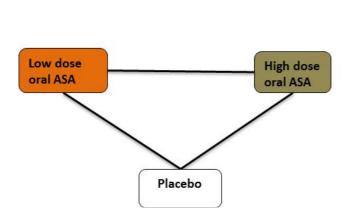
Network 2: Withdrawals

Five studies^{22,42,58,98,113} which were included in the baseline analysis NMA were excluded as they compared the same dose ranges of ASAs for example, a low dose versus a low dose or a high dose versus a high dose. The methodology described in section 3.2.4 was used. The network is shown in Figure 302.

For the analyses, a series of 60,000 burn-in simulations were run to allow convergence and then a further 100,000 simulations were run to produce the outputs. Convergence was assessed by examining the history and kernel density plots.

The output from the NMA was odds ratios to aid calculations in the maintenance of remission health economic model. The results are shown in Table 30 and Table 31 along with the results of the individual treatments.

Figure 302: Network for the proportion of people withdrawing from treatment (combined NMA)



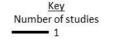


Table 30: odds ratio of low dose oral ASA versus placebo

Drug	Odds ratio from Baseline NMA (95% Cl)	Odds ratio from combined NMA (95% Cl)
Low dose Salofalk	1.79 (0.08, 3.33)	1.71(0.34,11.4)
Low dose Asacol	1.52 (0.25, 3.01)	
Low dose SASP	1.13 (0.04, 3.21)	
Low dose Olsalazine	1.30 (0.08, 3.19)	
Low dose Balsalazide	1.94 (0.16, 3.30)	

Table 31: odds ratio of high dose oral ASA versus placebo

	Odds ratio from Baseline NMA	Odds ratio from combined NMA
Drug	(95% CI)	(95% CI)
High dose Salofalk	2.09 (0.06, 3.37)	1.18(0.27,7.08)
High dose Asacol	1.47 (0.10, 3.23)	
High dose SASP	2.22 (0.14, 3.37)	

Drug	Odds ratio from Baseline NMA (95% Cl)	Odds ratio from combined NMA (95% CI)
High dose Olsalazine	2.83 (0.76, 3.37)	
High dose Balsalazide	1.13 (0.04, 3.21)	

3.5 Discussion

Based on the results of conventional meta-analyses of direct evidence, as has been previously presented in Chapter 7 and Appendix H, deciding upon the most effective intervention for the maintenance of remission of people with mild to moderate left sided or extensive ulcerative colitis is difficult. In order to overcome the difficulty of interpreting the conclusions from these numerous separate comparisons, NMA of the direct evidence were performed by preserving the trial randomization and minimizing bias.

Our analysis was based on a total of 18 studies of 12 different interventions. The studies formed a network for each outcome.

The findings from the NMA will be used to facilitate the GDG in decision making when developing recommendations for the maintenance of remission in people with left sided or extensive ulcerative colitis and as a base for the cost-effectiveness analysis.

Baseline NMA

In the first network of rate of relapse, low and high doses of Olsalazine and low and high doses of Sulfasalazine were significantly more effective than placebo. However, the ranking of these treatments for median relative risks need to be interpreted with caution due to the overlapping of their confidence intervals of the treatments.

In the second network of withdrawals, none of the treatments were significant compared to either placebo or each other.

Combined NMA

In the first network, high dose ASA was more effective than either low dose ASA or placebo. In the second network, there was a higher probability of withdrawing from low dose ASA than from high dose ASA.

In summary, the NMA analysis focused on two of the important clinical outcomes for assessing efficacy of medical treatments in maintaining remission. The results should be interpreted with caution due to several limitations of the analysis as described below.

Limitations:

- Almost all comparisons were based on single studies.
- A few of the comparisons were small studies (large confidence intervals).
- Poor quality studies.
- The use of SASP tolerant populations in trials could favour the efficacy of SASP compared to other ASAs.
- Varying times in remission prior to enrolling in trial could bias the results.
- Many of the studies did not give a breakdown of the extent of the disease and are at risk of being an indirect population.
- Use of different indexes for remission.
- The definition of low and high doses may influence the efficacy of treatments depending on what group they fall into.

• As with all meta-analyses, the studies available for analysis could be influenced by publication bias; however, no standardized methods have been fully developed to assess this type of bias in an NMA.

3.6 Conclusion

This analysis allowed us to combine the findings from many different comparisons presented in the clinical reviews for the maintenance of remission of adults with mild to moderate left sided/ extensive ulcerative colitis even when direct comparative data was lacking.

Low and high doses Olsalazine and low and high doses of Sulphasalazine were significantly better than placebo in maintaining remission. The superiority of one drug over another drug could be determined, however, high doses of oral ASA were better than low doses of oral ASA. In terms of withdrawals, the superiority of one drug over another drug could be determined.

3.7 Appendices

3.7.1 Excluded studies

3.7.1.1 Baseline NMA

Table 32: Studies from the direct clinical evidence review which were excluded from the NMA

Study	Reason for exclusion
BARDAZZI1994 ⁶	Regimen comparison
DALBASIO1997 ²⁴	Rectal preparations are excluded
DHAENS2012 ²⁶	Dose and regimen comparison
DIGNASS2009 ³¹	Mesalazine comparison
HAWKEY1997 ⁵⁴	No outcomes
ITO2010B ⁵⁹	Regimen comparison
KAMM2008 ⁶⁴	MEZAVANT XL 4.8g is excluded
KANE2003 ⁶⁷	Regimen comparison
KANE2008 ⁶⁶	Dose and regimen comparison
KILLERICH1992 ⁶⁸	<50% left sided or extensive disease
MISIEWICZ1965 ⁹²	One treatment arm <50% left sided or extensive disease
PRANTERA2009 ¹⁰⁶	Mesalazine comparison
RIIS1973 ¹¹¹	Mixed sulphasalazine dose (2-6 tablets). Unclear dosing and can't separate out.
RILEY1988A ¹¹⁴	<50% left sided or extensive disease
SANDBORN2010 ¹²⁰	Dose and regimen comparison
YOKOYAMA2007 ¹³⁸	Rectal preparations are excluded

3.7.1.2 Combined NMA

Study	Reason for exclusion
COURTNEY1992 ²²	Low dose versus low dose aminosalicylate
GREEN1998A ⁴²	Low dose versus low dose aminosalicylate
IRELAND1988 ⁵⁸	Low dose versus low dose aminosalicylate

Study	Reason for exclusion
NILSSON1995 ⁹⁸	Low dose versus low dose aminosalicylate
RIJK1992 ¹¹³	High dose versus high dose aminosalicylate

3.7.2 WinBUGs codes

3.7.2.1 Relapse: random effects model

```
model{
#Define Prior Distributions
#on random tx effect variance
sd~dunif(0,5)
reTau < - 2/pow(sd,2)
#On tx effect mean
beta[1] < -0
for (tt in 2:nTx){
beta[tt]~dnorm(0,1.0E-6)
}
#On individual study baseline effect
for(ss in 1:nStudies){
alpha[ss] ~ dnorm(0,1.0E-6)
}
#Define random effect
for (ss in 1:nStudies){
for(tt in 1:nTx){
re[ss,tt]~dnorm(0,reTau)
}
}
#Fit data
#For hazard ratio reporting studies
for(ii in 1:LnObs ){
Lmu[ii] < - alpha[Lstudy[ii]]*multi[ii] + re[Lstudy
[ii],Ltx[ii]] -
re[Lstudy[ii],Lbase[ii]] + beta[Ltx[ii]] - beta
[Lbase[ii]]
Lprec[ii] < - 1/pow(Lse[ii],2)</pre>
Lmean[ii] ~ dnorm(Lmu[ii],Lprec[ii])
}
#For binary data reporting studies
for(ss in 1:BnObs){
logCumHaz[ss] < - alpha[Bstudy[ss]] + re[Bstudy
[ss],Btx[ss]] -
re[Bstudy[ss],Bbase[ss]] + beta[Btx[ss]] - beta
[Bbase[ss]]
cumFail[ss] < - 1-exp(-1*exp(logCumHaz[ss]))
Br[ss] ~ dbin(cumFail[ss], Bn[ss])
}
# Calculate HRs
for (hh in 2:nTx) {
hr[hh] < -exp(beta[hh])
}
# Ranking plot
for (II in 1:nTx) {
for (mm in 1:nTx) {
rk[ll,mm] < - equals(ranked(beta[],mm),beta[ll])
}
```

} }

(NA,0.5,0.5,0.5),sd = 1)

3.7.2.2 Withdrawals: random effects model

```
model{
```

for (i in 1:NS)

```
{
```

Events[i] <- r[i,1]*equals(t[i,1],1)</pre>

```
Numpatients[i] <- n[i,1]*equals(t[i,1],1)</pre>
```

```
}
```

totEvents<-sum(Events[])

totNumpatients<-sum(Numpatients[])

BR<- totEvents/totNumpatients

```
for(i in 1:NS){
```

```
w[i,1] < -0
```

```
delta [i,t[i,1]] < -0
```

```
mu[i] ~ dnorm(0,.0001)
```

```
for (k in 1:na[i]) {
```

```
r[i,k] ~ dbin(p[i,t[i,k]],n[i,k])
```

```
logit(p[i,t[i,k]])<-mu[i] + delta[i,t[i,k]]</pre>
```

rhat[i,k] <- p[i,t[i,k]] * n[i,k]

```
dev[i,k] <-2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k])) + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
```

}

```
sdev[i]<- sum(dev[i,1:na[i]])</pre>
```

for (k in 2:na[i]) {

delta[i,t[i,k]] ~ dnorm(md[i,t[i,k]],taud[i,t[i,k]])

```
md[i,t[i,k]] <- d[t[i,k]] - d[t[i,1]] + sw[i,k]
```

```
taud [i,t[i,k]] < -tau * 2 * (k - 1) / k
```

```
w[i,k] <- (delta[i,t[i,k]] - d[t[i,k]] + d[t[i,1]])
sw[i,k] <-sum(w[i,1:k-1])/(k-1) }
}
d [1] <- 0
for (k in 2:NT){d[k] ~ dnorm(0,.0001) }
sd~dunif(0,2)
tau<-1/pow(sd,2)
rr [1] < -1
for (k in 2:NT) {logit(v[k])<-logit(BR)+d[k]</pre>
rr[k]<-v[k]/BR
T[k] < -v[k]/BR
sumdev <- sum(sdev[])</pre>
for (k in 1:NT) {
rk[k]<-NT+1-rank(rr[],k)</pre>
best[k]<-equals(NT+1-rank(rr[],k),1)}</pre>
for (c in 1:(NT-1))
{ for (k in (c+1):NT)
{ lor[c,k] <- d[k] - d[c]
log(or[c,k]) <- lor[c,k]
lrr[c,k] <- log(rr[k]) - log(rr[c])
log(rrisk[c,k]) <- lrr[c,k] \} \}
```

3.7.3 Treatment codes

3.7.3.1 Baseline NMA: Relapse

- 1. Placebo
- 2. High Pentasa
- 3. high Asacol
- 4. high Olsalazine
- 5. Low Asacol
- 6. Low SASP
- 7. Low Olsalazine
- 8. Low Balsalazide
- 9. High SASP
- 10.Low Salofalk
- 11. High Salofalk

12. High Balsalazide

3.7.3.2 Baseline NMA: Withdrawals

- 1. Placebo
- 2. High Pentasa
- 3. high Asacol
- 4. high Olsalazine
- 5. Low Olsalazine
- 6. High Asacol
- 7. Low Balsalazide
- 8. Low SASP
- 9. High SASP
- 10. High Balsalazide
- 11.Low Salofalk
- 12. High Salofalk

3.7.3.3 Combined NMA: Relapse

- 13.Placebo
- 14. High dose ASA
- 15.Low dose ASA

3.7.3.4 Combined NMA: Withdrawals

16.Placebo17.Low dose ASA18.High dose ASA

3.7.4 Forest plots

3.7.4.1 Oral Aminosalicylates versus placebo

Figure 303: F	Relapse (H	HR)							
	Oral A	SA	Place	bo				Hazard Ratio	Hazard Ratio
Study or Subgroup	Events	Total	Events	Total	0-E	Variance	Weight	Exp[(O-E) / V], Fixed, 95% C	CI Exp[(O-E) / V], Fixed, 95% CI
1.1.1 High Pentasa									
MINER 1995 Subtotal (95% CI)	35	103 103	56	99 99	-9.8949	21.5385	42.6% 42.6%	0.63 [0.41, 0.96] 0.63 [0.41, 0.96]	●
Total events	35		56						
Heterogeneity: Not applicat Test for overall effect: Z = 2									
1.1.2 Low Asacol									
ARDIZZONE1999C 12-24 I	mths 6	26	17	35	-5.7574	5.62483	11.1%	0.36 [0.16, 0.82]	
HANAUER1996A 1.6g Subtotal (95% CI)	18	58 84	33	63 98	-8.6777	11.6471	23.0% 34.1%	0.47 [0.27, 0.84] 0.43 [0.27, 0.69]	•
Total events Heterogeneity: $Chi^2 = 0.29$, Test for overall effect: Z = 3); I ² = 0 ⁴	50 %						
1.1.3 High olsalazine									
WRIGHT1993 Subtotal (95% CI)	19	49 49	31	52 52	-7.75	11.78	23.3% 23.3%	0.52 [0.29, 0.92] 0.52 [0.29, 0.92]	•
Total events Heterogeneity: Not applicat Test for overall effect: Z = 2			31						
Total (95% CI)		236		249			100.0%	0.53 [0.40, 0.70]	•
Total events Heterogeneity: Chi ² = 1.66, Test for overall effect: Z = 4 Test for subgroup difference	.51 (P < 0.0000	1)		l² = 0%	5				0.01 0.1 1 10 100 Favours Oral ASA Favours Placebo
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Figure 304: Relapse (RR)

	Oral A	SA	Place	oo		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl	
1.3.1 Low olsalazine								
SANDBERGGERTZEN1986 Subtotal (95% CI)	12	52 52	22	49 49	56.4% 56.4%	0.51 [0.29, 0.92] 0.51 [0.29, 0.92]	→	
Total events	12		22					
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.23	(P = 0.03)						
1.3.2 Low sulphasalazine								
DISSANAYAKE1973 Subtotal (95% CI)	4	33 33	17	31 31	43.6% 43.6%	0.22 [0.08, 0.58] 0.22 [0.08, 0.58]	•	
Total events Heterogeneity: Not applicable	4		17					
Test for overall effect: $Z = 3.04$	(P = 0.00	2)						
Total (95% CI)		85		80	100.0%	0.39 [0.23, 0.64]	•	
Total events	16		39					
Heterogeneity: Chi2 = 2.18, df =	= 1 (P = 0.	.14); l² =	= 54%				0.01 0.1 1 10	10
Test for overall effect: Z = 3.75	(P = 0.00)	02)					Favours Oral ASA Favours Plac	10 200
Test for subgroup differences:	Chi² = 2.1	2, df = 1	1 (P = 0.1	5), l² =	52.9%			
uraa, dagart Course tout	h							

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Figure 305: Withdrawals

	Oral A	-	Placel			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
.2.1 High Pentasa							
/INER1995	20	103	41	102	78.0%	0.48 [0.31, 0.76]	
Subtotal (95% CI)		103		102	78.0%	0.48 [0.31, 0.76]	•
otal events	20		41				
leterogeneity: Not applicable							
Test for overall effect: Z = 3.11 (P	= 0.002)						
.2.2 Low Asacol							
RDIZZONE1999C 12-24 mths	11	54	7	58	12.8%	1.69 [0.71, 4.04]	
Subtotal (95% CI)		54		58	12.8%	1.69 [0.71, 4.04]	
otal events	11		7				
leterogeneity: Not applicable							
est for overall effect: Z = 1.18 (P	= 0.24)						
.2.3 High olsalazine							
VRIGHT1993	12	49	5	52	9.2%	2.55 [0.97, 6.70]	
Subtotal (95% CI)		49		52	9.2%	2.55 [0.97, 6.70]	◆
otal events	12		5				
leterogeneity: Not applicable							
Test for overall effect: Z = 1.89 (P	= 0.06)						
Total (95% CI)		206		212	100.0%	0.83 [0.58, 1.18]	•
otal events	43		53				
leterogeneity: Chi ² = 13.03, df = 2	2 (P = 0.00	01); l ² =	85%				
est for overall effect: Z = 1.06 (P	= 0.29)						0.01 0.1 1 10 1 Favours Oral ASA Favours Placeb
est for subgroup differences. Chi	² = 12.94,	df = 2 (P = 0.002	2), l ² = 8	84.5%		I avours Oral ASA I avours Flaced
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3.7.4.2 Asacol dose comparison

Figure 306: Relapse (RR) – low versus high dose

				-				
	Lower dose of mesalaz	zine	Higher dose of mesalazine	Э		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events To	tal	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl	
2.1.2 1.2 versus 2.4g at	12 months							
PAOLUZI2005 Subtotal (95% CI)	48	68 68			100.0% 100.0%	1.06 [0.85, 1.32] 1.06 [0.85, 1.32]		
Total events	48		48					
Heterogeneity: Not appli	cable							
Test for overall effect: Z	= 0.50 (P = 0.62)							
							0.1 0.2 0.5 1 2 Favours Lower dose Favours High	5 10
Test for subaroup differe	ences: Not applicable							101 0030
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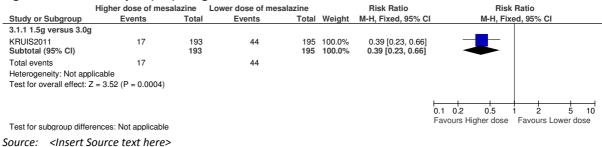
Figure 307: Withdrawals

0		-							
	Higher dose of me	salazine	Lower dose of mes	salazine		Risk Ratio	Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fix	ed, 95% Cl	
PAOLUZI2005	8	80	8	76	100.0%	0.95 [0.38, 2.40]	-		
Total (95% CI)		80		76	100.0%	0.95 [0.38, 2.40]			
Total events	8		8						
Heterogeneity: Not app	olicable								100
Test for overall effect: 2	Z = 0.11 (P = 0.91)						0.01 0.1 Favours Lower dose	1 10 Favours Higher	

Source: <Insert Source text here>

3.7.4.3 Salofalk dose comparison

Figure 308: Relapse (HR) - high versus low dose



3.7.4.4 **Olsalazine dose comparison**

Figure 309: Relapse (RR) - low versus high dose Lower dose Higher dose **Risk Ratio Risk Ratio** Events Total Events Total Weight Study or Subgroup M-H, Fixed, 95% Cl M-H, Fixed, 95% Cl 4.1.3 1.0g versus 2.0g (12 months) TRAVIS1994 10 62 100.0% 1.62 [0.81, 3.26] 17 65 Subtotal (95% CI) 65 62 100.0% 1.62 [0.81, 3.26] Total events 17 10 Heterogeneity: Not applicable Test for overall effect: Z = 1.35 (P = 0.18) 0.1 0.2 0.5 ż 5 10 1 Favours Lower dose Favours Higher dose Test for subgroup differences: Not applicable

Source: <Insert Source text here>

3.7.4.5 Sulphasalazine dose comparison

Relapse (RR) – high versus low dose Figure 310:

Higher d Events	lose Total	Lower d Events		Weight	Risk Ratio	Risk Ratio
	Total	Events	Total	Weight	MILL Fixed OFM O	
-					M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
-						
5	56 56	8	57 57	100.0% 1 00.0%	0.64 [0.22, 1.83] 0.64 [0.22, 1.83]	
5 licable		8				
L = 0.84 (P	9 = 0.40)				
oncos: No	t applie	abla				0.1 0.2 0.5 1 2 5 10 Favours Higher dose Favours Lower dose
	5 cable = 0.84 (P	5 5 cable = 0.84 (P = 0.40	56 58	56 57 5 8 cable = 0.84 (P = 0.40)	56 57 100.0% 5 8 cable = 0.84 (P = 0.40)	56 57 100.0% 0.64 [0.22, 1.83] 5 8 cable = 0.84 (P = 0.40)

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3.7.4.6 Balsalazide dosing

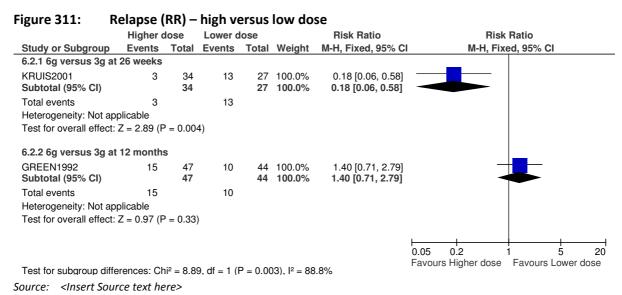
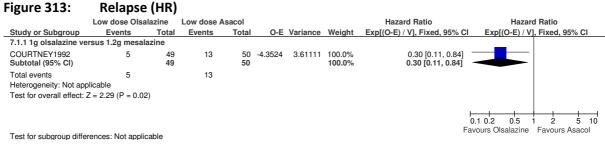


Figure 312: Withdrawals – high versus low

0							
	Higher of	dose	Lower of	lose		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
6.3.1 3.0g balsalazide	e vs. 6.0g l	balsala	zide				
GREEN1992	7	54	10	54	34.4%	0.70 [0.29, 1.70]	
KRUIS2001	6	40	21	48	65.6%	0.34 [0.15, 0.77]	
Subtotal (95% CI)		94		102	100.0%	0.47 [0.26, 0.84]	
Total events	13		31				
Heterogeneity: Chi ² = ²	1.36, df = 1	(P = 0.	24); l ² = 2	7%			
Test for overall effect: 2	Z = 2.55 (F	P = 0.01)				
							0.1 0.2 0.5 1 2 5 10
							Favours Higher dose Favours Lower dose
Test for subgroup diffe	rences: No	ot applic	able				

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3.7.4.7 Low dose olsalazine versus low dose Asacol



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Figure 314: Withdrawals

	Low dose Olsa	alazine	Low dose A	Asacol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
COURTNEY1992	8	49	10	50	100.0%	0.82 [0.35, 1.89]	
Total (95% CI)		49		50	100.0%	0.82 [0.35, 1.89]	-
Total events	8		10				
Heterogeneity: Not appli	icable						0.01 0.1 1 10 100
Test for overall effect: Z	= 0.47 (P = 0.64	4)				F	0.01 0.1 1 10 100 Favours Low olsalazine Favours Low Asacol

Source: <Insert Source text here>

3.7.4.8 Low dose olsalazine versus low dose sulphasalazine

Figure 315:	Relap	se (H	IR)						
•	Low dose Olsa	lazine	Low dose Sulpha	salzine				Hazard Ratio	Hazard Ratio
Study or Subgroup	Events	Total	Events	Total	O-E	Variance	Weight	Exp[(O-E) / V], Fixed, 95% CI	Exp[(O-E) / V], Fixed, 95% CI
8.1.1 1g olsalazine ve	ersus 2g SASP								
IRELAND1988	16	82	10	82	3.74239	6.15385	17.8%	1.84 [0.83, 4.05]	
NILSSON1995	59	161	55	161	6.99227	28.4649	82.2%	1.28 [0.89, 1.85]	
Subtotal (95% CI)		243		243			100.0%	1.36 [0.98, 1.90]	◆
Total events	75		65						
Heterogeneity: Chi ² =	0.66, df = 1 (P = 0	.41); l ² =	0%						
Test for overall effect:	Z = 1.82 (P = 0.07	7)							
								0.1	0.2 0.5 1 2 5 10
									Irs Low Olsalazine Favours Low SASP
Test for subaroup diffe	erences: Not appli	cable							
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Figure 316: Withdrawals Olsalazine Sulphasalazine **Risk Ratio Risk Ratio** Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% Cl M-H, Fixed, 95% Cl 8.3.1 1g olsalazine versus 2g SASP IRELAND1988 19 82 11 82 39.3% 1.73 [0.88, 3.40] NILSSON1995 60.7% 14 161 17 161 0.82 [0.42, 1.61] Subtotal (95% CI) 243 100.0% 1.18 [0.74, 1.88] 243 Total events 33 28 Heterogeneity: Chi² = 2.32, df = 1 (P = 0.13); l² = 57% Test for overall effect: Z = 0.69 (P = 0.49) Total (95% CI) 243 243 100.0% 1.18 [0.74, 1.88] Total events 33 28 Heterogeneity: Chi² = 2.32, df = 1 (P = 0.13); l² = 57% 0.01 0.1 10 100 Test for overall effect: Z = 0.69 (P = 0.49) Favours Olsalazine Favours SASP Test for subgroup differences: Not applicable Source: <Insert Source text here>

3.7.4.9 Low dose sulphasalazine versus high dose olsalazine



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Figure 318: Withdrawals

0							
	Sulphasal	azine	Olsalaz	zine		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
9.3.2 2g sulphasalazi	ine versus 2	g olsala	zine				
KRUIS1995	4	40	5	34	100.0%	0.68 [0.20, 2.33]	
Subtotal (95% CI)		40		34	100.0%	0.68 [0.20, 2.33]	
Total events	4		5				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.61 (P =	- 0.54)					
Total (95% CI)		40		34	100.0%	0.68 [0.20, 2.33]	
Total events	4		5				
Heterogeneity: Not ap	plicable						0.01 0.1 1 10 100
Test for overall effect:	Z = 0.61 (P =	0.54)					Favours SASP Favours Olsalazine
Test for subgroup diffe	erences: Not a	applicab	le				
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3.7.4.10 High dose sulphasalazine versus high dose olsalazine

Figure 319: Relapse (RR)

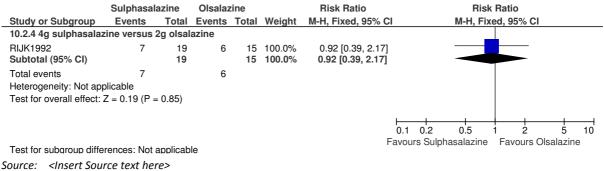
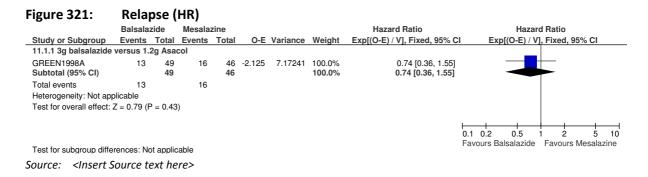


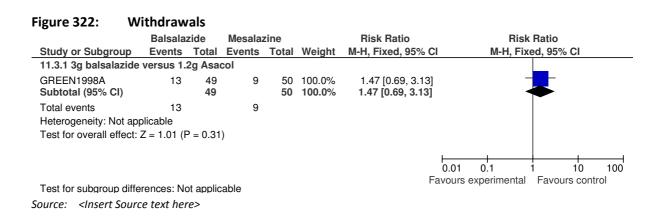
Figure 320: Withdrawals

1 igui e 320.	witharaw	uis				
	Sulphasala	zine Olsala	zine		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total Events	Total	Weight	M-H, Fixed, 95%	CI M-H, Fixed, 95% CI
10.3.3 4g sulphasal	azine versus 2	g olsalazine				
RIJK1992 Subtotal (95% CI)	4	23 8 23	23 23	100.0% 100.0%	0.50 [0.17, 1.43 0.50 [0.17, 1.43	
Total events Heterogeneity: Not a Test for overall effec		8 (0.20)				
Total (95% CI)		23	23	100.0%	0.50 [0.17, 1.43	
Total events Heterogeneity: Not a Test for overall effec Test for subgroup dil	t: Z = 1.29 (P =	,				0.01 0.1 1 10 100 Favours Sulphasalazine Favours Olsalazine

Source: <Insert Source text here>

3.7.4.11 Low balsalazide versus low Asacol





3.7.4.12 High Salofalk versus low balsalazide

Figure 323:	Relapse (RF	R)				
	Salofalk	Balsala	zide		Risk Ratio	Risk Ratio
Study or Subgro	up Events T	otal Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
12.2.1 1.5g Salofa	alk versus 3g ba	alsalazide				
KRUIS2001 Subtotal (95% CI	6	29 13 29	27 27	100.0% 1 00.0%	0.43 [0.19, 0.97] 0.43 [0.19, 0.97]	
Total events Heterogeneity: No Test for overall eff		13 = 0.04)				
Test for subgroup	differences: Not	applicable				0.01 0.1 1 10 100 Favours Salofalk Favours Balsalazide

Test for subgroup differences: Not applicable Source: <Insert Source text here>

Figure 324: Withdrawals

	Salofalk	Balsala	zide		Risk Ratio	Risk Ratio
Study or Subgroup	Events Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl
12.3.2 1.5g Salofalk v	ersus 3g balsala	azide				
KRUIS2001 Subtotal (95% CI)	15 44 44	21	48 48	100.0% 100.0%	0.78 [0.46, 1.31] 0.78 [0.46, 1.31]	
Total events Heterogeneity: Not app	15 blicable	21				
Test for overall effect: 2	Z = 0.94 (P = 0.3	5)				
						0.01 0.1 1 10 100
Test for subgroup diffe	rences: Not appl	icable				Favours Salofalk Favours Balsalazide
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3.7.4.13 High balsalazide versus high Salofalk

Figure 325:	Rel	apse (R	R)					
		Balsala	zide	Salofa	alk		Risk Ratio	Risk Ratio
Study or Subgrou	цр	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
13.2.2 6g balsalaz	zide v	/ersus 1.	5g Salo	falk				
KRUIS2001		3	34	6	29	100.0%	0.43 [0.12, 1.56]	
Subtotal (95% CI))		34		29	100.0%	0.43 [0.12, 1.56]	
Total events		3		6				
Heterogeneity: Not	t appl	licable						
Test for overall effe	ect: Z	. = 1.29 (F	P = 0.20)				
								0.01 0.1 1 10 100
-							F	avours Balsalazide Favours Salofalk
Test for subgroup	differ	ences: No	ot applic	able				
Source Insert Su	ource	tovt hor	0					

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igure 326: W	/ithdraw	als					
	Balsala	zide	Salofa	alk		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
13.3.3 6g balsalazide	e versus 1.	5g Salo	ofalk				
KRUIS2001	6	40	15	44	100.0%	0.44 [0.19, 1.02]	
Subtotal (95% CI)		40		44	100.0%	0.44 [0.19, 1.02]	\bullet
Total events	6		15				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 1.91 (F	P = 0.06	5)				
						0.01	0.1 1 10 100
						Favou	rs Balsalazide Favours Salofalk
Test for subgroup diff	erences: No	ot applic	able				

Test for subgroup differences: Not applicable Source: <Insert Source text here>

4 Appendix K: Costs of drugs used in the treatment of ulcerative colitis

The costs of drugs reviewed in the guideline are presented below.

Table 33: Costs of topical aminosalicylates

Drug	Form	Strength	Pack size	Cost per pack	Unit costs
Asacol	suppositories	250mg	20	£4.82	£0.24
Asacol	suppositories	500mg	10	£4.82	£0.48
Asacol	foam enema	1g/metered application	14 applications	£26.72	£1.91
Pentasa	suppositories	500mg	28	£40.01	£1.43
Pentasa	retention enema	1g/100mL	28	£17.73	£0.63
Salazopyrin	suppositories	500mg	10	£3.30	£0.33
Salofalk	suppositories	500mg	30	£14.81	£0.49
Salofalk	enema	2g/59mL	7	£29.92	£4.27
Salofalk	rectal foam	1g/metered application	14 applications	£30.17	£2.16

Source: BNF 61⁶³

Table 34: Costs of topical corticosteroids

Drug	Form	Strength	Pack size	Cost per pack	Unit costs
Budenofalk	rectal foam	2 mg budenoside/met ered application	14 applications	£57.11	£4.08
Entocort	enema	2 mg budenoside/100 mL	7	£39.60	£4.71
Hydrocortisone	foam	hydrocortisone acetate 10%	14 applications	£9.33	£0.66
Prednisolone	rectal foam	20mg prednisolone /metered application,	14 applications	£48.00	£3.43
Predsol	retention enema	20mg prednisolone /100-mL	7	£7.50	£1.07
Predsol	suppositories	prednisolone 5 mg	10	£1.35	£0.14

Source: BNF 61⁶³

Form	Strength	Pack size	Cost per pack	Unit costs
tablets	5mg	30	£56.56	£1.89
tablets	5mg	28	£0.96	£0.05
enteric coated tablets	5mg	28	£3.79	£0.17
	tablets tablets enteric coated	tablets 5mg tablets 5mg enteric coated	tablets5mg30tablets5mg28enteric coated	tablets5mg30£56.56tablets5mg28£0.96enteric coated

Table 35: Costs of oral corticosteroids

Source: BNF 61⁶³

Table 36: Costs of oral aminosalicylates

Cost item	Form	Strength	Pack size	Cost per pack
Pentasa	SR tablets	500mg	100	£30.74
Pentasa	M/R granules	1g	50	£30.74
Pentasa	M/R granules	2g	60	£73.78
Pentasa	M/R tablets	1g	60	£36.89
Mezavant XL	G/R tablets	1.2g	60	£62.44
Mesalazine	E/C tablets	400mg	120	£41.62
Salofalk	G/R tablets	500mg	100	£32.38
Salofalk	G/R, M/R granules	1.5g	60	£48.85
Salofalk	G/R, M/R granules	500mg	100	£28.74
Salofalk	E/C tablets	250mg	100	£16.19
Asacol	E/C, M/R tablets	400mg	90	£29.41
Asacol	E/C, M/R tablets	800mg	180	£117.62
Sulfasalazine	E/C tablets	500mg	100	£10.14
Sulazine	E/C tablets	500mg	112	£14.83
Sulfasalazine	tablets	500mg	112	£7.83
Salazopyrin En_Tab	E/C tablets	500mg	112	£8.43
Salazopyrin	tablets	500mg	112	£6.97
Dipentum	tablets	500mg	60	£21.18
Dipentum	capsules	250mg	112	£19.77
Balsalazide	capsules	750mg	130	£30.42

Note: Drugs that have different strengths but the same form and costs have been excluded from this table. Source: BNF 61⁶³

Table 37: Costs of immunomodulators	
---	--

Cost item	Form	Strength	Pack size	Cost per pack	
Azathioprine					
Azathioprine	tablets	25mg	28	£4.41	
Azathioprine	tablets	50mg	56	£4.36	
Imuran	tablets	25mg	100	£10.99	
Imuran	tablets	50mg	100	£7.99	
Ciclosporin					

Cost item	Form	Strength	Pack size	Cost per pack
Capimune	capsules	25mg	30	£13.50
Capsorin	capsules	25mg	30	£13.11
Deximune	capsules	25mg	30	£13.80
Neoral	capsules	25mg	30	£18.59
Tacrolimus				
Adoport	capsules	500 micrograms	50	£50.50
Capexion	capsules	500 micrograms	50	£52.50
Modigraf	granules	200 micrograms	50 sachets	£71.30
Prograf	capsules	500 micrograms	50	£61.88
Tacni	capsules	500 micrograms	50	£50.48
Vivadex	capsules	500 micrograms	50	£46.41
Advagraf	M/R capusles	500 micrograms	50	£35.79
Methotrexate				
Methotrexate	tablets	2.5mg	28	£4.61
Source: BNF 61 ⁶³				

Table 38: Costs of drugs for severe ulcerative colitis

Cost item	Farmer	Cture weth	Dealy size	Continues no als
Cost item	Form	Strength	Pack size	Cost per pack
Ciclosporin				
Sandimmun	concentrate for intravenous infusion	50mg/ml	• 1-mL ampoule	• £1.94
			• 5-mL ampoule	• £9.17
Hydrocortisone				
Solu-Cortef	powder for reconstitution	100mg	one vial	£1.16
Methylprednisolon	e			
Solu-Medrone	powder for reconstitution	40mg	one vial	£1.58

Source: BNF 61⁶³

5 Appendix L: Cost-effectiveness analyses

5.1 Induction of remission

5.1.1

Please note that evidence on treatments for inducing remission in people with mild-to-moderate ulcerative colitis was reviewed in 2019. The updated evidence review and full current recommendations can be found on the NICE website.

Table 59. Relevant economic	studies on induction of remiss	
Study	Description	Comments
Brereton ¹⁰	2.4g/day MEZAVANT XL	MEZAVANT XL was found to be
	mesalazine (Mezavant) versus	more effective and more
	2.4g/day mesalazine (Asacol)	costly with an incremental
		cost-effectiveness ratio of
		£749 per QALY.
Buckland	High dose (4.8g/day) versus	High dose is less costly and
	standard dose (2.4g/day)	more effective than standard
	(mesalazine (Asacol)	dose.
Mackowiak	Balsalazide (6.75g/day) versus)	Balsalazide dominates
WIACKOWIAN	mesalazine delayed tablets	(mesalazine as it costs less per
	(2.4g/day or 4.8g/day)	symptom or steroid free day.
	2.16/00/01/106/00/p	Symptom of steroid nee days
Connolly	Oral mesalazine (4g/day)	Combination therapy is
	versus oral mesalazine	cheaper and more effective.
	(4g/day) and mesalazine	
	enema (1g/100ml)	

These studies help to highlight the cost-effectiveness of specific aminosalicylates (ASAs) or ASA doses. However, other ASAs are available which have not been addressed. In addition, the studies have modelled different treatment sequences after failure of first line treatment. The GDG considered that there are other clinically relevant sequences that have not been captured and hence this topic was considered to be a top priority for original economic analysis. The treatment options available for patients with proctitis and proctosigmoiditis was deemed to be less variable and hence modelling for this subgroup was not identified as high priority by the GDG. The original economic model presented here sought to address the various treatment options available for the induction of remission in people with mild to moderate left sided or extensive ulcerative colitis.

(5.1.2) (Methods

.1.2.1 Model overview

A cost-utility analysis was undertaken in Microsoft Excel® where costs and quality-adjusted life years (OALYs) were considered from a UK NHS and personal social services perspective (PSS).

Comparators

- 10. 0

The comparators examined in the model are treatment sequences chosen by the GDG. The GDG considered the suitability of the drugs for use in patients with mild to moderate left sided or extensive UC and current clinical practice when compiling the treatment sequences.

Based on the studies reviewed in the induction of remission chapter, two network meta-analyses (NMAs) were conducted addressing the treatments for the induction of remission (Appendix I). A baseline NMA was conducted which addressed three outcomes; clinical remission, clinical improvement and withdrawals due to adverse events. The NMA showed that there was no clinically significant difference between individual oral ASAs in terms of their effectiveness in inducing clinical remission. However, a dose effect observed. A second NMA was conducted (combined NMA) which pooled trials reporting low dose oral ASAs into one treatment group, and trials reporting high dose oral ASAs into another treatment group. The oral ASAs were grouped into low and high doses based on the recommended doses in the BNF⁵³ and corroborated by GDG opinion. The dose ranges are shown in Table 40.

The clinical outcome of the combined NMA was clinical remission as it was considered by the GDG to be an important measure of disease activity. In addition, the majority of relevant studies reported this outcome so the results could be aggregated. The results of the combined NMA informed the clinical inputs in this economic analysis.

Table 40. (Oral ASA doses used in	in the combined network meta-an	arysis
Drug treatment	Lower dose of range stated in the BNF	Higher dose of the range stated in the BNF
Aminosalicylates	● (Mesalazine (≥1.6-2.4g)	 Mesalazine (>2.4g)
	 Sulphasalazine (4-6g) 	 Sulphasalazine (>6g)
	 Olsalazine (1-<1.5g) 	• Balsalazide ($\geq 6 \leq 6.75g$) ^(a)
		 Olsalazine (≥1.5g)

(a) The Balsalazide dose ranges from ≥ 6≤6.75g in order to include a study using a dose of 6.6g; this was considered to be √likely to have a similar efficacy to 6.75g.)

The following observations were made in the selection of drugs in the strategies:

- (A low dose oral ASA therapy could be followed by a regimen containing a high dose oral ASA but (not vice versa. The GDG considered this to be a logical step in the treatment pathway as a dose) (effect was observed in the clinical review.)
- For first line treatment, the following drugs were compared low dose oral ASA, high dose oral (ASA, high dose ASA + beclometasone and high dose oral ASA + topical ASA. In the clinical review) (section, a dose effect was not observed for topical ASAs; therefore doses in the model are based) (on standard BNF doses. Prednisolone was not considered as a first line option based on GDG) (opinion that use of steroids would be delayed in clinical practice to avoid steroid associated side) (effects.)
- The GDG elected to exclude monotherapy with topical preparations from the model for several (reasons:)
 - Limited studies were identified in the clinical review that trialled these drugs in a cohort that had predominantly left sided or extensive ulcerative colitis.
 - In these studies, the dose and preparation of the topical ASAs did not appear to affect clinical or endoscopic outcomes.
 - (o) In addition, the GDG felt that using a topical treatment with limited local release would not be appropriate to treat extensive disease.
- The use of high dose oral ASA administered alone or in combination with either a topical ASA or beclometasone was considered in patients who failed first line treatment with low dose oral ASA.

The use of high dose oral ASA with either topical ASA or beclometasone was considered for those who failed first line treatment with high dose oral ASA.

- Patients who had failed ASA therapy altogether were switched to prednisolone. The GDG noted (that in clinical practice patients, prednisolone could be added on to existing ASA therapy.)
 (However this could not be modelled due to lack of clinical data for the use of ASA and) (prednisolone in combination.)
- The final stage in all strategies following prednisolone failure was admission to hospital as patients are assumed to have progressed to severe UC. The treatment sequence for severe disease was not explicitly modelled as this was beyond the scope of this question. Therefore the simplifying assumption was made that inpatients received intravenous drugs which would lead to remission in most patients. Those who failed to respond required surgery to induce remission.

The ten treatment strategies compared are summarised in Table 41.

	in cathlene strategies in the model						
Strategy	1st line	2nd line	(3rd line)	4th line	5th line		
		high dose oral ASA +					
1	High dose oral ASA	(topical ASA)	prednisolone	inpatient			
2	High dose oral ASA	prednisolone	(inpatient)				
3	Low dose oral ASA	prednisolone	inpatient				
		(high dose oral ASA +)					
4	Low dose oral ASA	(topical ASA)	(prednisolone)	(inpatient)			
5	Low dose oral ASA	high dose oral ASA	prednisolone	(inpatient)			
_			high dose oral +				
6	Low dose oral ASA	high dose oral ASA	topical ASA	prednisolone	inpatient		
	High dose oral ASA						
	+ topical ASA	prednisolone	inpatient				
	High dose oral ASA						
	+ oral						
8	beclometasone	prednisolone	(inpatient				
		high dose oral ASA +					
9	Low dose oral ASA	oral beclometasone	prednisolone	inpatient			
		high dose oral ASA +					
10	High dose oral ASA	oral beclometasone	prednisolone	(inpatient)			

(Table 41:) (Treatment strategies in the model)

5.1.2.3 (Population)

The population entering the model were adults with active mild to moderate left sided or extensive UC. Author reported definitions of disease activity were used, in line with the clinical review protocol. Left sided or extensive disease was defined as inflammation greater than 30-40cm (see Appendix C). Patients failing to respond to prednisolone were assumed to have progressed to more severe disease. The treatment sequence for severe disease was not explicitly modelled as this was beyond the scope of this question.

5.1.2.4 (Time horizon)

The time horizon considered in the base case model was 28 weeks. This was set to reflect the longest treatment sequence in the model which consists of five lines of treatment. The trials included in the NMA had varying durations as shown in Table 42. Data from oral ASA trials showed that the rate of remission or withdrawals tapered off as treatment time increased enabling an inference to be made that the trial durations were sufficient to capture health effects. Therefore, an average of the trial durations was used in the model following GDG approval. The trials addressing combination

treatments were of shorter duration than ASA only trials. It was noted that the shorter duration may unfairly favour combination treatments in terms of cost impact and QALY gain. In order to consider this uncertainty, a sensitivity analysis was conducted were the treatment duration was set to 8 weeks for all drugs.

Although prednisolone efficacy was based on a single 3 week trial, the GDG elected to model it over an 8 week period. This was done to reflect clinical practice as prednisolone is usually tapered off according to a recognized reducing dose schedule. The durations for the other drugs were agreed by the GDG and are shown in Table 42.

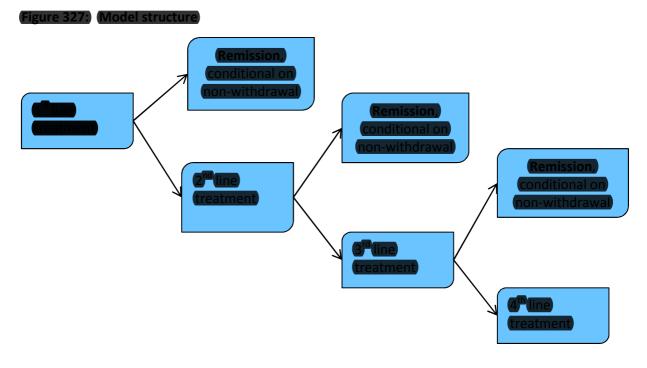
Table 42: Drug treatment durations

	Treatment duration	
Drug	reported in trials	(Treatment duration in model)
Low dose oral ASA	6-12 weeks	8 weeks
(High dose oral ASA)	6-12 weeks	8 weeks
(High dose oral ASA + topical ASA)	4 weeks	4 weeks
(High dose oral ASA + beclometasone)	4 weeks	4 weeks
Prednisolone	3 weeks	8 weeks

(5.1.2.5) (Approach to modelling)

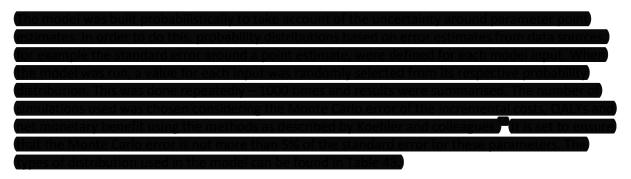
5.1.2.5.1 (Model structure)

A decision tree was constructed in which the QALY gain is driven by the proportion of people in whom remission is successfully induced. Author reported definitions of remission were used in line with the clinical review. Remission was conditional on not having withdrawn from therapy due to adverse events. People who withdrew or failed to respond to therapy at the end of a course of treatment moved on to the next treatment in the sequence. The GDG were aware that specific adverse events could be attributed to certain drugs included in the model. They however concluded that the reporting of adverse events in the RCTs was not sufficient to model specific treatment related adverse events. Withdrawal from treatment was therefore used as a proxy for adverse events. This implies that the costs and dis-utilities pertaining to adverse events for each treatment would be captured by the cost of treating withdrawals and the associated utility loss from remaining in active disease. To capture the benefits of inducing remission early, patients in whom remission is induced on the first line of treatment will gain more QALYs than those who respond on subsequent lines of treatment. The structure of the model is shown in Figure 327.



5.1.2.6 Uncertainty

5.1.2.6.1 (Probabilistic analysis)



Parameter	Type of distribution	Properties of distribution	Parameters for the distribution
Cost and resource use	Gamma	Bounded at 0. Derived from) (mean and standard error)	$\alpha = (mean/SEM)2$ $\lambda = mean/SEM2$
Resource use	Triangular	Derived from expert opinion or reported in data source.	(Min = minimum value) (Likeliest = mean) (Max = maximum value)
Treatment effects, utility weights and reference costs	Lognormal	Bounded at 0. Derived from log (mean) and standard error.	(μ = ln(RR)) (SD(μ) = (ln[UpperCl] — (ln[lowerCl])/1.96*2)

(Table 43:) (Distributions used in the model)

5.1.2.6.2 (Uni- and multi-variate sensitivity analysis)

Uni-variate (single variable) sensitivity analyses were conducted in order to test the robustness of model results to changes in key parameters. In one way sensitivity analysis, one parameter is varied while all other parameters are kept constant and the effects of changing this parameter on model results are explored. The analyses are described in Table 64. A multi-variate (multiple variable)

sensitivity analyses was also conducted where more than one parameter was varied while other parameters were kept constant. The analysis is described in Table 65.

(5.1.2.7) (Model inputs)

5.1.2.7.1 (Summary table of model inputs)

The relative effects of treatments on the baseline transition probabilities were derived from clinical evidence identified in the systematic review undertaken for the guideline, the results of the NMA and supplemented by additional data sources as required. Health utility data were obtained from the literature. Cost inputs were obtained from recognized national sources such as the drug tariff, NHS reference costs and Personal Social Services Research Unit (PSSRU) publications. All inputs were validated by the GDG. Summaries of the model inputs used in the base-case analysis are provided in Table 44, Table 45, Table 46 and Table 47. More details about sources, calculations and rationale for selection can be found in the sections following this summary table.

Table 44:) (Summary of model inputs: clinical probabilities of withdrawal and remission conditional)

on non-witharawan		
Variable	(Probability of withdrawal)	Probability of remission conditional on non-withdrawal
Low dose oral ASA	6.6%	31.6%
High dose oral ASA	5.2%	40.3%
High dose oral ASA + topical ASA	6.4%	48.0%
High dose oral ASA + beclometasone	1.2%	64.2%
Prednisolone	0%(3)	52.9%

Source: clinical review and NMA

(a) Based on GDG consensus as no withdrawals data from trial

(Table 45:) Summary of model inputs: proportions of inpatients going into remission

Variable	Proportion of inpatients	Source
Intravenous drug-induced remission	91%	GDG
Surgical-induced remission	9%	GDG

Table 46: Summary of model inputs: utility weights

Variable	Estimate	Range	Reference
Remission	0.94	0.937-0.943	(Poole et a) ¹⁰³
Active disease	0.775	0.751-0.800	Poole et al

Table 47: Summary of model inputs: costs

Variable	Cost	Source
Drugs		
Course of low dose oral ASA	£63.59	(MIMS ¹ , Drug tariff ⁹⁷
Course of high dose oral ASA	£126.06	(MIMS ¹ , Drug tariff ⁹⁷
Course of high dose oral ASA + topical	£167.57	(MIMS ¹ , Drug tariff ⁹⁷

Variable	Cost	Source
ASA		
Course of high dose oral ASA + oral		MIMS ¹ , Drug tariff ⁹⁷
beclometasone	£115.82	
Course of prednisolone	£21.38	MIMS ¹ , Drug tariff ⁹⁷
Inpatient treatment		
		NHS reference costs ²⁸ (code)
Intravenous therapy	£2464.20	(FZ37G, FZ37H, FZ37I, FZ37J)
Surgerv	£7404.44	(NHS reference costs ²⁸ (code) (FZ08A, FZ08B)
Tests	L7404.44	1200A, 1200D
		NHS reference costs ²⁸ (code)
Full blood count	£3.00	(DAP823)
		NHS reference costs ²⁸ (code)
Renal function test	£1.00	DAP841)
Consultations (per hour)		
Consultant Gastroenterologist	£137.00	PSSRU ²³
General practitioner	£127.00	(PSSRU ²³⁾
IBD nurse specialist	£53.00	PSSRU ²³
(Telephone consultation with IBD nurse)		Payments by results guidance
(specialist)	£23.00	(2009-10 ²⁹)
Specialist registrar	£59.00	(PSSRU ²³⁾
opecialist registral	253.00	(NHS reference costs ²⁸ (code)
Non consultant post-surgical visit	£56.84	(301S)
Weekly consultation costs for patients		
with relapse	£7.75	Calculation
Weekly consultation costs for patients		
(in remission)	£1.38	Calculation

5.1.2.8 (Baseline events (withdrawal and remission)

Baseline risks were pooled from the placebo arms of RCTS included in the clinical review by using the generic inverse variance method. This provided the baseline log odds of withdrawals due to adverse) events and spontaneous remission conditional on non-withdrawal. The results are presented in Table 48.

(Table 48: Baseline events)

		Odds of remission conditional on non-
Treatment	Odds of withdrawal (log scale)	withdrawal (log scale)
No treatment		
(Placebo)	-2.406	-1.525

5.1.2.9 (Relative treatment effects (withdrawal and remission)

Treatment-specific probabilities for withdrawal and remission conditional on non-withdrawal were obtained from the combined NMA conducted. A brief outline of the methods can be found below with the full methodology reported in Appendix I.

A conditional logistic regression NMA was conducted to take into account the negative correlation between withdrawals and remission. This is because it is assumed that people who withdraw cannot go into remission, and similarly people counted as being in remission have not withdrawn due to adverse events. In other words, the two events are mutually exclusive. Therefore, treatment effects for the model had to be accounted for such that the number of withdrawals and remissions could not exceed the number of people in the trial. This was captured by removing the number of withdrawals from the denominator when entering data for remission into WinBUGS. The calculation is described in Equation 1. The NMA produced estimates of treatment effects measured on the log odds scale. The results are shown in Table 49.

Equation 1: Calculating probability of remission conditional on non-withdrawal



Where:

(P(R|W^c) = probability of remission conditional on non-withdrawal

P(R) = probability of remission

P(W) = probability of withdrawal

Table 49: Estimates of treatment effects from NMA

(freatment)	Odds of withdrawal (log scale)	Odds of remission conditional) on non-withdrawal (log scale)
Low dose oral ASA	-0.239	0.754
High dose oral ASA	-0.498	1.132
High dose oral ASA + topical ASA	-0.283	1.447
High dose oral ASA + beclometasone	-1.979	2.108
Prednisolone	•	1.641

Withdrawals were assumed to occur at the end of a treatment cycle. People who withdrew due to adverse events while on any dose of oral ASA moved to the next non-ASA treatment in the sequence. The GDG noted that in reality, clinicians may elect to try another type of ASA before switching patients to other therapies. However, a simplifying assumption was made that patients who had an adverse reaction to one ASA might have an adverse reaction to all ASAs. Therefore in the model they were switched to a non-ASA therapy if they withdrew.

In the model, there were no withdrawals due to adverse events while on prednisolone treatment. This is because withdrawal data could not be obtained from the trial included in the NMA. The GDG considered that rarely would a side effect be observed that would necessitate withdrawal from treatment. In addition, due to disease severity at this stage, the primary aim would be to induce remission and delay use of intravenous therapy.

Relative treatment effects were calculated by adjusting the baseline log odds shown in Table 48 by the treatment specific log odds shown in Table 49. The symbols used to denote the variables in the calculation are described in Table 50.

Table 50: Explanation of symbols from equations

Symbol for equation Explanation

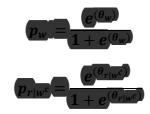
Ulcerative colitis Appendix L: Cost-effectiveness analyses

Symbol for equation	Explanation
BOw	Baseline odds for withdrawa
$\mathbf{BO}_{r w^c}$,	Baseline odds for remission conditional on non-withdrawal
θ_w	Treatment specific odds for withdrawal
$\theta_{r w^c}$	Treatment specific odds for remission conditional on non-withdrawal
ORw	(Treatment specific log odds ratio for withdrawal)
$OR_{r w^c}$	Treatment specific log odds ratio for remission conditional on non-withdrawal
p _w	Probability of withdrawal
Date	Probability of remission conditional on non-withdrawa

The calculation is as follows:

 $\theta_w = Ln(OR_w) + Ln(BO_w)$ $\theta_{r|w^c} = Ln(OR_{r|w^c}) + Ln(BO_{r|w^c})$

And:



The calculation enabled baseline and relative treatment effects to be modelled on the same log odds scale. The final treatment-specific probabilities used in the model can be seen in Table 51.

	Probability of remission conditional on						ditional on	
	(Probability of withdrawa)			(non-withdrawa)				
	Probability of withdraway			(non-with				
Variable	mean	sa	median	C	mean	sd	median	O
				_				_
Low dose oral								
ASA	6.6%	0.22	6.6%	4.4%, 9.8%	31.6%	0.14	31.5%	26.0%, 37.9%
(High dose oral)			_			_		
ASA	5.2%	0.24	5.2%	3.3%, 8.0%	40.3%	(0.15)	40.2%)	(<u>33.3%, 47.9%</u>)
High dose oral								
(ASA + topical)								
ASA	6.4%	0.63	6.3%	2.0%. 19.2%	48.0%	0.42	47.9%	(29.0%, 67.8%)
High dose oral								
ASA +						_		
beclometasone	1.2%	(1.46)	(1.4%)	0.0%, 12.8%	64.2%	0.42	64.0%	44.4%, 80.6%
Prednisolone					52.9%	0.83	52.1%	19.5%, 86.2%)
Teamsolone				•	52.570	0.00	52.170	19.970, 00.270
Combination trea	tment wi	th high o	dose oral <i>i</i>	ASA +beclome	tasone wa	as associ	ated with	the highest
probability of rem	nission co	nditiona	l on non-v	withdrawal. Po	ssible inc	onsister	cies with	the withdrawal
data were noted.	Firstly, w	ithdraw	al rates w	ere higher for	low dose	oral ASA	compare	d to high dose
oral ASA. In addit	ional with	drawal	from high	dose oral ASA	+ beclom	etasone	e was lowe	er than the high

Table 51: Absolute probabilities in the model

dose oral ASA + topical ASA or high dose oral ASA alone. The high dose oral ASA + beclometasone data was based on a single study however which could explain this inconsistency.

Inpatient treatment and surgery

Patients who failed to respond to prednisolone in each strategy were assumed to have progressed to more severe disease and were hospitalised. Based on clinical practice as described by the GDG, inpatients would typically start on a course of intravenous steroids and failing response to that would be administered intravenous ciclosporin. Infliximab could be administered in line with the NICE technological appraisal recommendation^{93,95}. As this model however was concerned with the pathway for mild to moderate disease, the specific treatments for severe disease were not explicitly modelled. Therefore the simplifying assumption was made that inpatients received intravenous drugs which would lead to remission in most patients. Those who failed to respond required surgery to induce remission. The GDG provided estimates on the proportion of inpatients that would have drug-induced remission and surgically-induced remission. The estimates are shown in Table 52.

(Table 52:) Probabilities of inpatient remission)	
Variable	(Proportion of inpatients)
Intravenous drug-induced remission	91%
Surgical-induced remission	9%

5.1.2.10 Utilities

For economic evaluation, a specific measure of Health Related Quality of Life (HRQoL) known as utility is required to calculate Quality Adjusted Life Years (QALYs). Utilities indicate the preference for health states on a scale from 1 (perfect health) to negative infinity. Death in this model is considered to have a utility of 0. The NICE reference case⁹⁴ specifies that the preferred utility assessment tool is the EQ-5D instrument.

A systematic search identified studies with appropriate utility weights to use in the model. A description of the studies is shown in Table 53.

(Table 53: (Relevant utility data)

Study	Description	Values
Poole	Ulcerative colitis disease activity index	Remission: 0.940
	(UCDAI) scores and EQ5D scores were	Mild/moderate disease:
	collected from 126 patients enrolled in a trial	0.775
	comparing oral and topical mesalazine with	Severe relapse: 0.660
	oral mesalazine alone. 92% of patients have	
	mild/moderate UC while 8% had severe UC. A	
	model was developed to predict EQ5D scores	
	based on individual abbreviated-UCDAI items.	
	(The algorithm was used to predict EQ5D)	
	scores for patients with differing UC severities	
	enrolled in the Phase IV PODIUM (Pentasa)	
	once daily in ulcerative colitis for	
	maintenance of remission) study.	
Prenzler	The health states modelled in this paper were	Remission: 0.845
	assigned utilities based on disease severity.	Active UC: 0.589
	The utility data used in the paper was based	Severe relapse: 0.317
	on two studies. The utility scores were	
	obtained via a time trade off approach and	
	the EQ5D from a sample of 151 patients with	

Study	Description	Values
	UC.	
Yen ¹³⁷	(The health states modelled were assigned)	Remission: 0.919
	utilities based on disease severity. The utilities were derived from various studies	Outpatient flare: 0.770
	using the time trade off method. Some	Inpatient flare: 0.608
	assumptions were made based on similarities (with Crohn's disease.)	

Utility weights estimated by Poole¹⁰³were used in the base case analysis because the data was obtained from a UK population which had similarities with the cohort modelled in this analysis. In addition, EQ5D was estimated which is in line with the NICE reference case and utilities were based on clinical severity as defined by the UCDAI. UCDAI scores have been reviewed in the clinical review section of this guideline.

A sensitivity analysis was conducted to test the robustness of the model results and is described in Table 64.

5.1.2.11 (Resource use and cost

Consultations

The GDG provided estimates on the number of consultations and the average length of consultation time that people with active UC would receive, regardless of the treatment they are taking. Unit costs were obtained from the PSSRU²³ and adjusted by the consultation time to estimate average weekly costs of consultations. The inputs are summarised in Table 54.

Table 54: Consultations for people with active disease

Type of consultation	(Frequency (every 4 weeks)	(Length of consultation) (minutes)	(Cost per (nour ^(a)
(Consultant) (gastroenterologist)	10 visits per 100 patients	20	£137
(General practitioner)	40 visits per 100 patients	(17.2 ⁽²⁾	£127.00
(IBD nurse specialist) (Telephone consultation)	30 visits per 100 patients	20	(£53.00 ^(b)
with IBD nurse specialist	20 calls per 100 patients	10	£23.00
(Average weekly costs of co	(10 visits per 100 patients)	(20) (£7.75)	(£59.00)

(b) (Payments by results guidance 2009-10)²⁹

The GDG also provided estimates of the nature and frequency of contacts that people in remission) would have with the health service. The frequencies are shown in Table 55. It was assumed the length of consultations would be the same as for people with active disease but at a reduced frequency. In addition, it was also assumed that only 80% of patients would utilise these services.

Ulcerative colitis Appendix L: Cost-effectiveness analyses

Table 55: (Frequency of consultations for people in remission)

Type of consultation	(Annual frequency)
Consultant gastroenterologist	One per year (half of all people)
General practitioner	One per year (all people)
BD nurse specialist	One per year (half of all people)
Telephone consultation with IBD nurse specialist	One per year (half of all people)
Specialist registrar	One per year (half of all people)
Based on these frequencies and cost data provid	ed in the Table 54, an average weekly consultation

cost of £1.38 was calculated for a person in remission.

Drugs

Mesalazines, such as Ipocol and Octasa have not been included in this analysis as they are not named in the studies identified in the clinical review. The GDG were unable to comment on their relative efficacy. Therefore, for mesalazine preparations, only those addressed in the clinical review were used to inform drug costs in the model. The average costs of low dose and high dose oral ASAs were based on costs of the individual drugs and dose ranges described in Table 40 and the BNF⁶³. Unit costs were obtained from the drug tariff⁹² and MIMS^T. Average costs of drugs were calculated if more than one preparation was identified from these sources. These costs are presented in Table 56, Table 57, Table 58, Table 59 and Table 60.

Table 56: Low dose oral ASA costs in the model

Cost item	Pack size	(Cost per pack (£)	Daily dose (grams)
Pentasa SR Tab 500mg	100	30.74	2
Pentasa Gran Sach 1g M/R	50	30.74	2
Pentasa Gran Sach 2g M/R	60	73.78	2
Pentasa Tab 1g M/R	60	36.89	2
Mezavant XL Tab G/R 1.2g	60	62.44	2.4
(Ipocol Tab E/C 400mg)	120	41.62	2.4
Salofalk Tab G/R 500mg	100	32.38	1.5
Salofalk Gran Sach G/R 1.5g M/R	60	48.85	1.5
Salofalk Gran Sach G/R 1g M/R	50	28.74	2
Salofalk Gran Sach G/R 500mg M/R	100	28.74	1.5
Salofalk Tab E/C 250mg	100	16.19	1.5
Asacol MR Tab E/C 400mg	90	29.41	2.4
Asacol MR Tab E/C 800mg	180	117.62	2.4
Sulfasalazine Tab E/C 500mg	100	10.14	4
Sulazine EC Tab 500mg	112	14.83	4
Sulfasalazine Tab 500mg	112	7.83	4
Salazopyrin En_Tab 500mg	112	8.43	4
Salazopyrin Tab 500mg	112	6.97	4
Dipentum Tab 500mg	60	21.18	1
Dipentum Cap 250mg	112	19.77	1
Average cost per 8 week course		£63.59	

(Source: (MIMS¹ and GDG

Based on the costs and doses in Table 56, an average cost of £63.59 was calculated for an 8 week course of low dose oral ASA in the base case. The total cost including consultations was £125.59.

Table 57: High dose oral ASA costs in the model

Cost item	(Pack size)	(Cost per pack (£)	Daily dose (grams)
Pentasa SR Tab 500mg	100	30.74	4
Pentasa Gran Sach 1g M/R	50	30.74	4
Pentasa Gran Sach 2g M/R	60	73.78	4
Pentasa Tab 1g M/R	60	36.89	4
Mezavant XL Tab G/R 1.2g	60	62.44	4.8
Mesalazine Tab E/C 400mg	120	41.62	4.8
Salofalk Tab G/R 500mg	100	32.38	8
Salofalk Gran Sach G/R 1.5g M/R	60	48.85	8
Salofalk Gran Sach G/R 1g M/R	50	28.74	4
Salofalk Gran Sach G/R 500mg M/R	100	28.74	3
Salofalk Tab E/C 250mg	100	16.19	3
Asacol MR Tab E/C 400mg	<u>90</u>	29.41	4.8
Asacol MR Tab E/C 800mg	180	117.62	4.8
Sulfasalazine Tab E/C 500mg	100	10.14	8
Sulazine EC Tab 500mg	112	14.83	8
Sulfasalazine Tab 500mg	112	7.83	8
Salazopyrin En_Tab 500mg	112	8.43	8
Salazopyrin Tab 500mg	112	6.97	8
Dipentum Tab 500mg	60	21.18	8
Dipentum Cap 250mg	112	19.77	8
Balsalazide 750mg	130	30.42	6.75
Average cost per 8 week course		£126.06	

Source: MIMS¹ and GDG

Based on the costs and doses in Table 57, an average cost of £126.06 was calculated for an 8 week course of high dose oral ASA in the base case. The total cost including consultations was £188.05.

Table 58: Topical ASA costs in the model			
Cost item	Pack size	Cost per pack (£)	(Daily dose (grams)
Asacol 1g foam enema	14	26.72	
Pentasa 1g retention enema		17.73	
Salofalk 2g liquid enema		29.92	2
Salofalk 1g rectal foam	14	30.17	2
Source:) (MIMS [®] (and GDG)			

Based on the average costs of high dose oral ASA shown in Table 57, and the data in Table 58, an average cost of £167.57 was calculated for a 4 week combination therapy of high dose oral ASA + topical ASA in the base case. The total cost including consultations was £198.57.

Table 59: Beclometasone costs in the model

Drug	Pack size	Cost per pack (£)	Daily Dose (mg)
Beclometasone 5mg tablets	30	56.56	5

(Source:) (MIMS¹

Based on the average cost of high dose oral ASA shown in Table 57, and the data in Table 59, an average cost of £115.82 was calculated for a 4 week combination therapy of high dose oral ASA + beclometasone in the base case. The total cost including consultations was £146.82.

Table 60: Prednisolone costs in the model

Costitem	Pack size	Cost per pack(£)	Dose
Prednisolone 5 mg	28	0.96	40 mg initially then tapered by
Prednisolone e/c 5 mg	28	3.79	5mg weekly
Average cost per 8 week course		£21	1.38

(Source:) (MIMS¹ and GDG)

Based on the data in Table 60, an average cost of £21.38 was calculated for an 8 week course of prednisolone in the base case. The total cost including consultations was £83.37.

Drug-specific tests

Drug-specific tests were based on the recommendations in the BNF⁶³ and were verified by the GDG. People were assumed to have renal function and blood tests after being on an ASA for 3 months, then once annually. The frequency of tests over a strategy is therefore based on amount of time spent receiving oral ASA therapy. Consequently only patients in strategies 1,4,5,6,9 and 10 who completed oral ASA courses (regardless of treatment outcome) were assumed to have one renal and one blood test. The unit costs of tests are summarised in Table 61.

Table 61: Tests for people on oral ASAs

Tests	Cost per test	Source
Full blood count	E1	NHS reference costs ²⁸ (code DAP823)
Renal function	E3	NHS reference costs ²⁸ (code DAP841)

Cost of inpatient drug treatment

The cost of in-patient drug treatment was estimated from NHS reference costs²⁸. As the reference costs are populated by taking into consideration all the care a patient would receive while admitted, drug costs have not been calculated separately. Average weighted costs were calculated based on procedures listed under the HRG codes shown in Table 62. The overall cost of inpatient drug treatment was assumed to be £2,464 in the model.

(Table 62: Inpatient costs)

Description	HRG	Weight	Cost
Inflammatory Bowel Disease with length of stay 2 days or more			
with Major CC with Interventions	FZ37G	8.1%	£3,566
Inflammatory Bowel Disease with length of stay 2 days or more			
with Major CC without Interventions	FZ37H	14.6%	£2,516
Inflammatory Bowel Disease with length of stay 2 days or more			
without Major CC with Interventions	(FZ371)	34.2%	£2,318
Inflammatory Bowel Disease with length of stay 2 days or more			
without Major CC without Interventions	FZ37J	43.1%	£2,355

Description	HRG	Weight	Cost
Average inpatient costs		£2,464	
(Source:) (NHS reference costs)			

Cost of surgery

Average weighted costs were calculated based on surgical procedures such as total colectomy, panproctocolectomy and ileostomy. The procedures were identified in the NHS reference costs²⁸ under 2 HRG codes – FZ08A and FZ08B (Table 63) and were verified by the GDG. Patients who had surgery were assumed to have a post-operative consultation which was costed at £56.84 (Table 47). The overall cost of surgery was assumed to be £7,460 in the model.

(Table 63: Surgery costs in model)

Description	HRG	Weight	Cost
Complex Large Intestine Procedures with Major CC	FZ08A	31%	£9,606
Complex Large Intestine Procedures without Major CC	FZ08B	69%	£6,411
Average surgery cost		£7,460	
A			

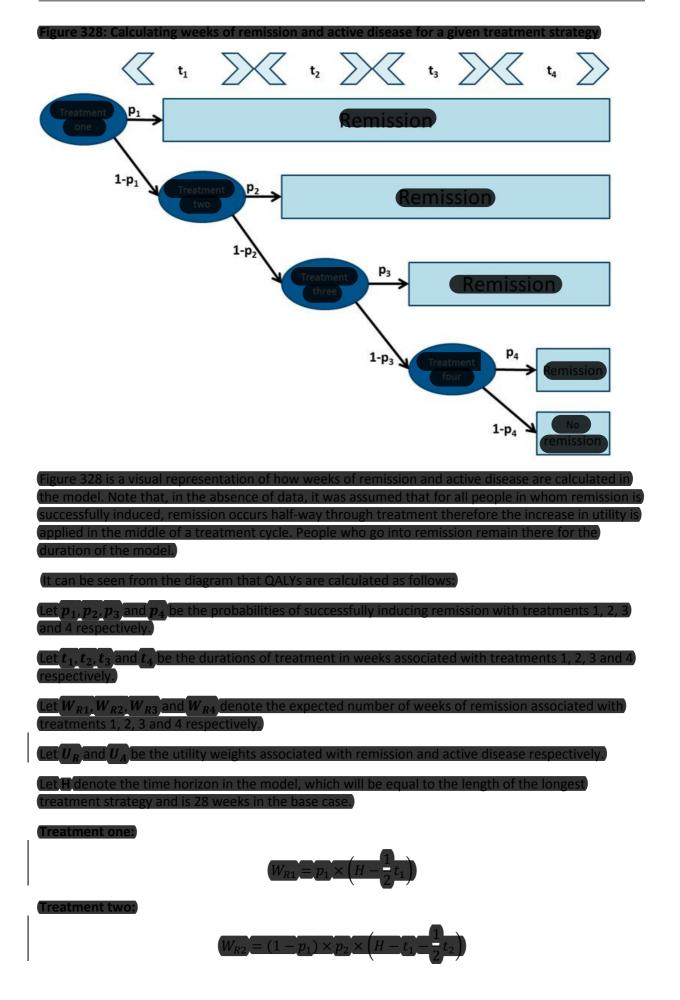
(Source:) (NHS reference costs²⁸)

5.1.2.12 Computations

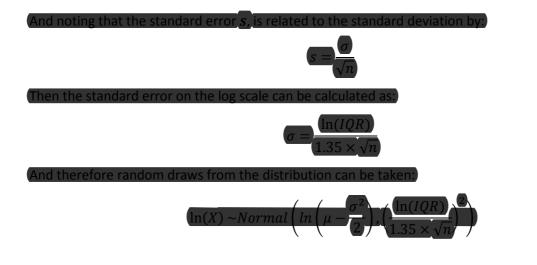
The mean cost and effectiveness of the competing strategies were calculated using Microsoft Office Excel 2007.

5.1.2.13 Calculating QALYs

In order to calculate the QALYs associated with a given treatment strategy, we consider both the probability of inducing remission for each individual treatment, and the time spent in remission over the course of the model. To do this, we partition the treatment strategy into individual treatments and calculate the number of weeks of remission and active disease that occur as a direct result of each treatment. These are then aggregated over the duration of the strategy and QALYs for a given strategy are calculated by multiplying the number of weeks of remission and active disease by the appropriate utility weights.



I	Treatment three:
	$W_{R3} = (1 - p_1) \times (1 - p_2) \times p_3 \times \left(H - t_1 - t_2 - \frac{1}{2}t_3\right)$
I	Treatment four:
	$W_{R4} = (1 - p_1) \times (1 - p_2) \times (1 - p_3) \times p_4 \times \left(H - t_1 - t_2 - t_3 - \frac{1}{2}t_4\right)$
	Note that the term $p_4 \times (H - t_1 - t_2 - t_3 - t_4)$ is added to the equation for cases when the overall length of the treatment strategy is less than the time horizon. In the event that the duration of the treatment strategy is equal to the time horizon this term is equal to zero, since $H = t_1 + t_2 + t_3 + t_4$.
	Then the total number of weeks of remission, W_R and number of weeks of active disease W_A are given by:
	$W_R = W_{R1} + W_{R2} + W_{R3} + W_{R4}$
	$W_A = H - W_R$
	And the total treatment specific QALYs, Q, are calculated as:
	$Q = \frac{1}{52} \times (W_R \times U_R + W_A \times U_A)$
5.1.2.14	Probabilistic analysis in the model
	In the probabilistic analysis, distributions were assigned to treatment effects, utilities and where possible, costs as described in Table 43. This was done to account for the uncertainty in model inputs and capture the effect of this uncertainty on model outputs.
	Treatment effects:
	To capture the uncertainty in treatment effects, a sample of 1000 random sets of treatment effects was taken from the NMA using the CODA function in WinBUGS. This has the advantage of preserving the correlation between variables, which would not be accounted for if they were sampled from their individual distributions. For the probabilistic analysis, in each simulation, a random set of treatment effects was chosen from the sample using random number generation.
	Reference costs:
	Costs of tests, in-patient treatment and surgery were obtained from NHS reference costs.in order to assign a distribution to reference costs, it was assumed that they followed a lognormal distribution and used the inter-quartile range to calculate an approximate standard error on the log scale.
	Let X be the cost we seek to assign a distribution to, i.e. $\ln(X) \sim Normal(\mu, \sigma^2)$
	Let M be the mean associated with the cost.
	Let IQR be the inter-quartile range associated with the cost.
	Note that for normally distributed data:
	$IQR \approx 1.35\sigma$

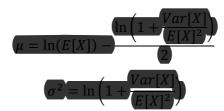


Utilities:

Utilities were sampled probabilistically by assigning lognormal distributions to utility decrements as described in (ref Briggs). Normal distribution parameters were converted to lognormal parameters by method of moments, as defined below:

Let E[X] and Var[X] be the mean and variance respectively, of the utility decrement U

Then the parameters of the lognormal distribution, μ and σ^2 are found by:



5.1.2.15 Calculating cost-effectiveness

It is possible, for a particular cost-effectiveness threshold, to express cost-effectiveness results in terms of net monetary benefit (NMB). This is calculated by multiplying the total QALYs for a comparator by the threshold cost per QALY value (e.g. £20,000) and then subtracting the total costs. The decision rule then applied is that the comparator with the highest NMB is the cost-effective option at the specified threshold. That is the option that provides the highest number of QALYs at an acceptable cost. For ease of computation NMB is used to identify the optimal strategy in the probabilistic-analysis simulations.

Let C_t and Q_t denote the mean costs and mean QALYs respectively, associated with a given treatment. Then the mean net monetary benefit NMB_t is calculated as:

 $NMB_{t} = (\pounds 20,000 \times Q_{t}) - C_{t}$

Where £20,000 per QALY represents the cost-effectiveness threshold in the NICE reference case.

This net benefit is calculated for each of the 1000 simulations in the probabilistic analysis. This means that the probability that a given treatment would be optimal can be estimated based on the number of times it has the highest net monetary benefit.

However, the strategy that is optimal overall is the one that has the highest net monetary benefit calculated using the mean costs and QALYs, where means were the average of the 1,000 simulated estimates.

5.1.2.16 Sensitivity analyses

The sensitivity of the results to changes to inputs and assumptions was tested by conducting seven uni-variate analyses as described in Table 64. SA1, SA2, SA3 and SA4 were conducted deterministically while SA5, SA6 and SA7 were conducted probabilistically.

Table 64: Uni-variat	e sensitivity analyses in the m	odel	
Sensitivity analysis	Description	Value in base case	Value in sensitivity analysis
SA1: Utility weights	The sensitivity of results to utility weights was tested by using estimates of utility from Prenzler ¹⁰⁸ . This paper had (the lowest values for utility) data out of relevant studies) identified. It was not used in (the base case as the data was) based on 2 abstracts.)	Remission = 0.94 Active disease = 0.775	Remission = 0.845 Active disease = 0.589
SA2: Trial durations	In the base case, the combination treatments had durations of 4 weeks. This SA was conducted assuming (these drugs were) administered for 8 weeks to capture the effect of (increased treatment costs.	 High dose oral ASA + (beclometasone given) (for 4 weeks.) High dose oral ASA + (topical ASA given for) (4 weeks.) 	 High dose oral ASA + (beclometasone given) (for 8 weeks.) High dose oral ASA + (topical ASA given for 8 weeks.)
SA3: GP contacts	It was decided to vary the frequency of visits to a GP due to a view that more patients may be treated in the community.	40 visits per 100 patients every 4 weeks	60 visits per 100 patients every 4 weeks
SA4: Prednisolone withdrawal	The withdrawal rate from prednisolone was set as zero in the base case by the GDG due to lack of data. This rate was varied to test impact on the results of the model.	Prednisolone withdrawal	Prednisolone withdrawal
SA5: Efficacy of non-1 ^{ef} line treatments	In the model, the efficacy data (for 2 nd and 3 rd line treatments) was from studies that trialled (them as 1 st line treatments. In) this SA, the efficacy of these (drugs was reduced when used) as 2 nd or 3 rd line treatments. This was to reflect the fact that these treatments may not be as efficacious in this context.	As described in Table 44.	Assumed that drugs were 30% less efficacious when used as non-1 St line treatments.
SA6: Low withdrawal rates for oral ASAs	The withdrawal rates used in (the model were obtained) from the NMA. In order to assess if ASAs are better (tolerated than the base case) analysis suggests, lower) (withdrawal rates were used in)	 Low dose ASA (withdrawal = 6.6%) (High dose ASA) (withdrawal = 5.2%) 	 Low dose ASA (withdrawal = 6.4%) (High dose ASA) (withdrawal = 4.4%)

SA7: High (individual ASA preparations) (included in the NMA and using the lowest estimate available.Cow dose ASA (withdrawal = 6.6%)SA7: High (individual ASAs)The withdrawal rates used in the model were obtained (for oral ASAs)The withdrawal rates used in the model were obtained (for oral ASAs)• Low dose ASA (withdrawal = 5.2%)• Low dose ASA (withdrawal = 5.2%)SA7: High (withdrawal rates)• The withdrawal rates used in the model were obtained (for oral ASAs)• Low dose ASA (withdrawal = 5.2%)• Low dose ASA (withdrawal = 5.2%)SA7: High (withdrawal rates)• The withdrawal rates were used in the model were obtained (for oral ASAs)• Low dose ASA (withdrawal = 5.2%)• Low dose ASA (withdrawal = 5.2%)SA7: High (withdrawal rates)• Cow dose ASA (withdrawal = 5.2%)• Low dose ASA (withdrawal = 5.2%)• Low dose ASA (withdrawal = 5.4%)	Sensitivity analysis	Description	Value in base case	Value in sensitivity analysis
Included in the NMA and Using the highest estimate available.	SA7: High withdrawal rates	 (this SA. This data was) (obtained by reviewing the) (estimates of withdrawal for) (individual ASA preparations) (included in the NMA and) (using the lowest estimate) (available,) The withdrawal rates used in) (the model were obtained) (from the NMA. In order to) (assess if ASAs are more poorly) (tolerated than the base case) (analysis suggests, higher) (withdrawal rates were used in) (this SA. This data was) (obtained by reviewing the) (estimates of withdrawal for) (individual ASA preparations) (included in the NMA and) (using the highest estimate) 	 (Low dose ASA) withdrawal = 6.6% (High dose ASA) 	 Low dose ASA withdrawal = 33.1% High dose ASA

One multi-variate sensitivity analysis was conducted deterministically to address the effects of ASA costs on the model results. The analysis is described in Table 65.

Sensitivity analysis	Description	Value in base case	Value in sensitivity analysis
Drug costs	In the base case, the daily costs of oral ASAs were based on an average of individual	• (Daily cost of low dose) oral ASA = £1.14	(The daily costs of ASAs) (were varied from in) (£0.50 increments.)
	(ASA preparations. The GDG) (was aware of the costs) (differences between different)	 Daily cost of high dose oral ASA = £2.33 	
	ASA preparations. This SA was conducted to capture the		
	effect of ASA drug costs on the model results.		

(5.1.2.17) (Model validation)

The model was developed in consultation with the GDG. The model structure, inputs and results were presented to and discussed with the GDG for clinical validation and interpretation.

The model was systematically checked by the health economist undertaking the analysis; this included inputting null and extreme values and checking that results were plausible given inputs. The model was peer reviewed by a second experienced health economist from the NCGC; this included systematic checking of the model formulae and calculations. The model parameters and results were also assessed against the content of this appendix.

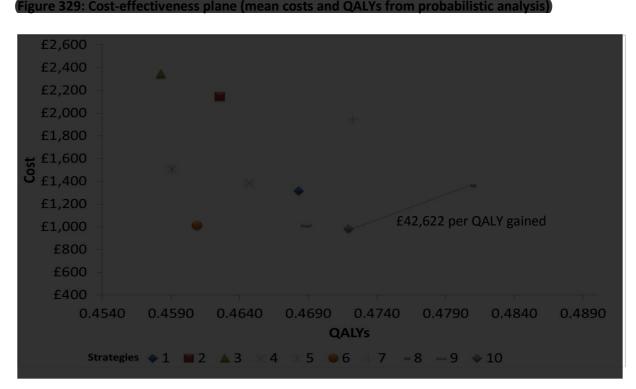
5.1.2.18 (Interpreting results)

The strategy with the highest mean net monetary benefit is the one that should be recommended,³⁵ though the uncertainty around costs and QALYs should also be taken into consideration. Due to lack of data we were unable to explicitly capture the disutility of treatment-specific adverse events. This should be taken into consideration when interpreting the results.

(5.1.3) (Results)

5.1.3.1 (Base case results)

In the base case, model inputs were set as shown in section 5.1.2.7 and the model was run probabilistically. Figure 329 shows the cost-effectiveness plane, depicting the mean costs and QALYs associated with each treatment strategy. Although strategy 8 yields better outcomes than strategy 10, it is more expensive. The QALY gained by moving from strategy 10 to strategy 8 does not justify the increased costs as an incremental cost-effectiveness ratio of £42,622 was calculated. This is significantly greater than the £20,000 per QALY cost-effectiveness threshold defined by NICE. Therefore the cost effective option is strategy 10. The strategy comprises of first line treatment with a high dose oral ASA with therapy escalated in the following sequence in the event of treatment failure; high dose oral ASA + beclometasone, prednisolone, inpatient drug treatment and surgery.



Cost-effectiveness in the base case (per patient)

The probabilistic results allowed a ranking of the net monetary benefit to be developed and also showed the probability of an intervention being cost effective out of 1000 simulations. The cumulative ICERs for the 1000 simulations were plotted to check the stability of the ICERs. The ICERs were stable after approximately 200 simulations. Table 66 shows the breakdown of results. Strategy 10 had the highest NMB and was cost-effective in 54% of the simulations. This shows that although strategy 10 is likely to be cost effective, there is uncertainty in the results. This was highlighted by the confidence intervals around the ranking of the net monetary benefit which ranged from 1 to 4.

Strategy	Treatment sequence	Costs	QALYS	Cost per QALY gained (non- (dominated)		(NIMB rank) (95%) confidence (interval) ^(a)	Probability of being most cost- effective strategy
10	High dose oral ASA, high dose oral ASA + beclometasone, prednisolone	£984	0.472	£42,622 versus strategy 8	£8,454	(1 (1,4))	54%
9	Low dose oral ASA, high dose oral ASA + beclometasone, prednisolone	£1,012	0.469	Dominated	£8,364	2 (1,6)	5%
8	High dose oral ASA +) beclometasone, prednisolone	£1,364)	0.481	Dominated	£8,253	3 (1,7)	26%)
6	Low dose oral ASA, high dose oral ASA high dose oral ASA + topical ASA,	£1,013)	0.461	Dominated	£8,205	(4 (1,6)	12%)

(Strategy)	(Treatment sequence)	Costs	QALYS	Cost per QALY gained (non- (dominated)	(NIMB ^(B)	(NMB rank) (95%) confidence (interval) ⁽⁶⁾	(Probability) (of being) (most cost-) (effective) (strategy)
	(High dose oral ASA) (high dose oral ASA +) (topical ASA,) (prednisolone)	£1,316	0.468	Dominated	£8,050	5 (1,6)	6%
0	Low dose oral ASA, high dose oral ASA + topical ASA, prednisolone	£1,386	0.465	Dominated	£7,908	6 (3,7)	0%
6	Low dose oral ASA,) High dose oral ASA, prednisolone High dose oral ASA +	£1,509	0.459	(Dominated)	£7,673	(7 (5,9))	0%
2	(topical ASA, prednisolone) (High dose oral ASA) prednisolone	£1,953 £2,144	0.472	Dominated	£7,492	(8 (3,9) (9 (8,9)	0%
3	Low dose oral ASA, prednisolone	£2,345	0.458	Dominated	£6,820	10 (9,10)	0%

In order to better understand the above results, a further break down can be found below.

Costs

Table 67 shows the total costs attributed to each strategy in the model. The total costs are calculated based on costs of drugs, tests, consultations, inpatient treatment and surgery. The cheapest treatment sequence is strategy 10 at a cost of £984. The strategy comprises of first line treatment with a high dose oral ASA with therapy escalated in the following sequence in the event of treatment failure; high dose oral ASA + beclometasone, prednisolone, inpatient drug treatment and surgery.

Table 67:	Mean costs in the ba	se case (p	per patie	nt)			
Strategy	Treatments	Drug	Tests	Consultations (active)	Inpatient + surgery	Consultations (remission)	Total Costs
•	High dose oral ASA, high dose oral ASA + topical ASA, prednisolone	<u>£713</u>	62	£102	£477		£1,316
2	High dose oral ASA, prednisolone	£1,085	£D	£100	£939	£20	£2,144
8	Low dose oral ASA, prednisolone	£1,152	ED	£105	£1,070	E18	£2,345
•	Low dose oral ASA high dose oral ASA + topical ASA prednisolone	£720	62	£107	£536	620	£1,386

				Consultations	(Inpatient)	Consultations	Total
Strategy	Treatments	Drug	Tests	(active)	+ surgery	(remission)	costs
6	Low dose oral ASA, high dose oral ASA, prednisolone	<u>£760</u>	£2	E130	£599	E18	£1,509
6	Low dose oral ASA) (high dose oral ASA) (high dose oral ASA) (+ topical ASA) (prednisolone)	£540	•	£130	(322)	E19	£1,013
	(High dose oral ASA) (+ topical ASA, prednisolone)	£1,023	£D	£65	£841	£24	£1,953
8	(High dose oral ASA) (+ beclometasone, prednisolone)	£705	ED	£54	£577	627	£1,364
9	Low dose oral ASA, high dose oral ASA + beclometasone, prednisolone	<u>£518</u>	62	(EIOI)	£369		£1,012
10	High dose oral ASA, high dose oral ASA + beclometasone, prednisolone	£534	62	696	£328	624	£984)

Outcomes

Table 68 shows the amount of time spent in remission and active disease for each strategy. This information was used to calculate the total QALYs for each strategy as described in section 5.1.2.13. Strategy 8 was the most effective option as it yielded 20.05 weeks of remission and 7.95 weeks in active disease. This resulted in 0.481 QALYs. This is because the first treatment in the strategy which is high dose oral ASA + beclometasone is the most effective first line treatment enabling more patients to go into remission earlier.

Table 68: N			the tile of		
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Strategy	Treatments	Weeks of remission	(Weeks of non remission)	QALYS
	High dose oral ASA, high dose oral ASA + topical ASA, prednisolone	16.09	11.91	0.468
2	High dose oral ASA, prednisolone	14.28	13.72	0.463
8	(Low dose oral ASA, prednisolone)	12.92	15.08	0.458
	Low dose oral ASA, high dose oral ASA + topical ASA, prednisolone	14.97	13.03	0.465
6	Low dose oral ASA, high dose oral ASA, prednisolone	13.18	14.82	0.459
6	Low dose oral ASA , high dose oral) ASA, high dose oral ASA + topical)	13.76	14.24	0.461

Strategy	Treatments	Weeks of remission	Weeks of non remission	QALYS
	ASA , prednisolone			
0	(High dose oral ASA + topical ASA,) (prednisolone)	17.34	10.66	0.472
8	(High dose oral ASA +) (beclometasone, prednisolone)	20.05	7.95	0.481
	(Low dose oral ASA, high dose oral) (ASA + beclometasone,) (prednisolone)	16.26	11.74	0.469
10	(High dose oral ASA, high dose oral) (ASA + beclometasone,) (prednisolone)	(17.23	(10.77)	0.472

Strategy 10 is the cheapest option but it is not the most effective. However, it comes out as cost effective when compared with strategy 8 (the most effective option). This is because the additional gain of 0.009 QALYs is not worth the additional £380 that would have to be spent to achieve that gain. This gives a cost per additional QALY gained of £42,622 which is well above the NICE £20,000 threshold.

(5.1.3.2) (Sensitivity analyses)

5.1.3.2.1 (Uni-variate sensitivity analysis)

One-way sensitivity analyses as described in Table 64 were conducted in order to test the robustness of model results. SA1 – SA2 were conducted deterministically, while SA3 - SA7 were conducted probabilistically and the results are presented in Table 69. Strategy 10 (high dose oral ASA followed by high dose oral ASA + beclometasone, prednisolone, inpatient drug treatment and surgery) was the most cost effective strategy (highest NMB) across all the analyses with the exception of SA5. As strategy 8 had only two lines of treatment (one of which was the most effective treatment choice), reducing the efficacy of non-1st line treatments had less of an effect on the NMB. Hence in SA5, it was the most cost effective strategy.

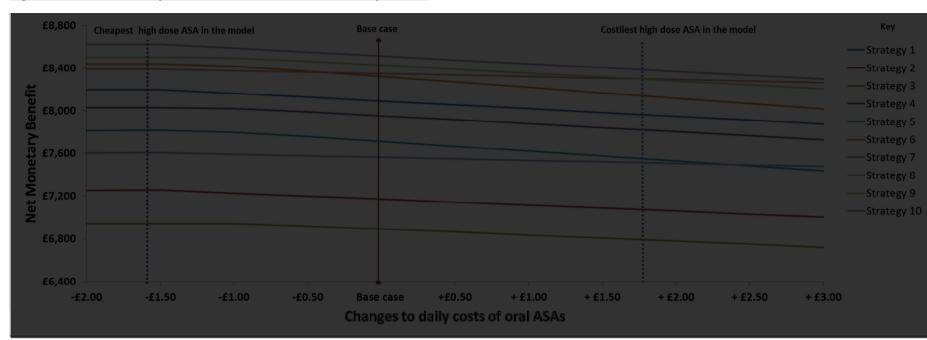
Table 69:	One-way sensit	ivity anal	sis results	-mean n	et monet	tary bene	f <mark>it per</mark> pa	tient*	
Strategy	Treatments	Base Case	SA1	SA2	SA3	SA4	SA5	SA6	SA7
	(High oral ASA , (High oral ASA + (topical ASA) (Prednisolone)	(£8,050)	£6,654)	£9,303	E8.044	£7,993	(£6,123)	(£8,041)	(£8,071)
2	High oral ASA , Prednisolone	£7,107	£5,671	£8,538	£7,131	£7,013	£5,496	£7,122	£7,147
8	Low oral ASA, Prednisolone	£6,820	£5,344	£8,248	£6,848	£6,719	£4,983	£6,824	£6,533
4	(Low oral ASA,) (High oral ASA +) (topical ASA,) (Prednisolone)	£7,908	£6,475	£9,134	£7,902	£7,848	£5,730	£7,903	£8,141

Strategy	freatments	Base case	SA1	SA2	SA3	SA4	SA5	SAG	SA7
6	Low oral ASA) (High oral ASA, (Prednisolone)	£7,673	£6,172	£9,099	£7,676	£7,614	£5,626	<u>£7,678</u>	<u>£7,970</u>
	Low oral ASA, (High oral ASA, (High oral ASA + (topical ASA,)								
6	(Prednisolone) (High oral ASA +) (topical ASA) (Prednisolone)	(£8,205)	(£6,803)	£9,610	€8,201) €7,502	(£8,188) (£7,397)	(£5,996)	(£8,204)	(£7,533)
	(High oral ASA +) oral) (Beclometasone,)								
8	(Prednisolone) (Low oral ASA,) (High oral ASA +) (oral)	(<u>£8,253</u>)	£7,057	£9,470	£8,271	(18,203)	±7,231	18,252	±8,270
9	(Beclometasone,) (Prednisolone) (High oral ASA,) (High oral ASA +	£8,364	£6,998	£9,656	£8,365	<u>£8,333</u>	£5,975	£8,364	£8,458
10	(night of all ASA +) (ora) (Beclometasone,) (Prednisolone)	(£8,454)	£7,117	£9,766				1111 58	- 8 4 6 3

*Using a willingness to pay threshold of £20,000 per QALY.

(5.1.3.2.2) (Multi-variate sensitivity analysis)

One multi-variate deterministic analysis as described in Table 65 was conducted to assess the effect of daily costs of oral ASA on the model results. Figure 330 shows the change to the NMB for each strategy as daily costs of ASAs are decreased or increased in £0.50 increments. The NMB decreased across all strategies, as the daily costs of ASAs increased. However, strategy 10 remained the cost effective strategy irrespective of the daily cost of ASA.



igure 330: Effect of daily costs of oral ASAs on net monetary benefit

(5.1.4) (Discussion)

5.1.4.1 (Summary of results)

The cost-effectiveness analysis shows that the most cost effective treatment strategy to induce remission in patients with mild to moderate left sided and extensive disease is high dose oral ASA followed by high dose oral ASA + beclometasone followed by prednisolone. This analysis was based on a conditional logistic regression network meta-analysis conducted using RCT data, acquisition costs, PSSRU costs and NHS reference costs. The results were robust to sensitivity analysis conducted.

5.1.4.2 Limitations & interpretation

The model is based on findings from RCTs and therefore any issues concerning interpretation of the clinical review also apply to interpretation of the economic analysis. Limitations of the model which impact on the interpretation of the results are as follows:

- Oral ASAs have been grouped into low and high doses. It is plausible that particular brands of ASAs may be slightly more or less efficacious than others but the differences were not considered (to be clinically significant based on the NMA results. This uncertainty could mean that the effectiveness of ASAs may be under or over-estimated however the magnitude is unknown.
- Mesalazines, such as Ipocol and Octasa have not been included in this analysis as they are not named in the studies identified in the clinical review. The GDG were unable to comment about (the relative efficacy of these mesalazines hence caution should be exercised when generalising) (the results of this model.)
- Patients who had failed ASA therapy altogether were switched to prednisolone. The GDG noted (that in clinical practice patients, prednisolone could be added on to existing ASA therapy.)
 (However this could not be modelled due to lack of clinical data for the use of ASA and) (prednisolone in combination.)
- The costs and dis-utilities of drug-specific adverse events were not explicitly modelled due to lack of robust data; however withdrawal from treatment was used as a proxy for adverse events. This means that the cost-effectiveness of all treatments strategies may have been over-estimated although the magnitude is unknown as each drug is likely to have a specific side-effect profile. The overestimation of the ICER would be greater for treatments that have more serious side effects compared to those with less serious side effects. This introduces uncertainty around interpretation of the results.
- The clinical data informing non-first line treatments were obtained from studies that had trialled (the drugs as first line. This means that the effectiveness of certain treatments may have been) (over-estimated when used as a non-first line treatment options. Consequently, this would impact (on the cost-effectiveness of the overall strategy. A sensitivity analysis was conducted to address) (this issue. All the treatment strategies compared became less cost effective however the most) (cost effective option was strategy 8 which comprises of first line combination treatment with a) (high dose oral ASA and oral becometasone and switching to prednisolone in the event of treatment) (failure)

5.1.4.3 Generalisability to other populations / settings

The analysis was based on data obtained from an adult population hence may not be generalizable to paediatric populations. This is especially important as the dose ranges of ASAs were based on adult doses. A model relevant to the paediatric population could not be constructed due to paucity of clinical data.

The model applies to patients with mild to moderate left sided or extensive disease. Other extents of UC such as proctitis have not been addressed and as such treatment options used in the model may not be applicable. Similarly, in terms of disease activity, treatment of severe UC has not been explicitly modelled. There may be other treatment options for this population not captured in the model.

5.1.4.4 Comparisons with published studies

The results of relevant economic studies addressing this topic area have been summarised briefly in Table 39.

In the model, oral ASAs were addressed as a class based on the clinical review findings that there was no clinically significant difference between the individual ASA preparations. Hence, the model results cannot be compared to the Brereton¹⁰ and Mackowiak⁸⁶ studies.

The study by Buckland¹¹ found a higher dose of ASA to be cost effective compared to a lower dose. This is supported by the model result. All strategies where the only difference was the use of either a low dose ASA or a high dose ASA first line that is, strategies 1 versus 4, 2 versus 3 and 10 versus 9, high dose ASA was always cost effective.

The study by Connolly¹⁹ (found combination treatment of oral and topical mesalazine was found to) be more cost effective than oral mesalazine. This is supported by the model results as strategy 7) (high dose oral ASA + topical ASA followed by prednisolone) has a higher NMB than strategy 2(high) dose oral ASA followed by prednisolone).

5.1.4.5 (Conclusion and evidence statement)

The original economic analysis suggests that high dose oral ASA followed by high dose oral ASA + beclometasone followed by prednisolone is the most cost effective treatment strategy to induce remission in patients with mild to moderate left sided or extensive ulcerative colitis.

5.2 Maintenance of remission

5.2.1 Introduction

This economic analysis explores the cost-effectiveness of different doses of aminosalicylates (ASAs) for the maintenance of remission in patients who have previously had a mild to moderate inflammatory exacerbation of left sided or extensive ulcerative colitis (UC). This analysis incorporated results of the induction model described above therefore it does not address patients with proctitis and proctosigmoiditis. In addition the GDG identified that the treatment options for patients with proctitis and proctosigmoiditis was deemed to be less variable and hence modelling for this subgroup was not identified as high priority.

A study by Yen¹³⁷ assessed the cost-effectiveness of no maintenance therapy versus 5-ASA maintenance therapy in patients with mild to moderate UC. 5-ASA therapy was shown to increase the discounted QALYs per person yielding an incremental cost-effectiveness ratio (ICER) of £146,000/QALY. This figure was highly dependent on the daily cost of ASAs as a sensitivity analysis showed that the ICER was £10,306/QALY when cheaper drug costs of sulfasalazine were used. The GDG noted that there were issues surrounding the applicability of this study as some health state utilities were inferred from a Crohn's disease and the model was based on a non-UK population. The full study details can be found in Appendix G.

The network meta-analysis (described in Appendix I) conducted on oral ASA maintenance treatments provided effectiveness data for low dose oral ASAs and high dose oral ASAs. The GDG felt that

majority of patients would be on maintenance therapy after successful induction of remission and therefore considered this topic to be a top priority for original economic analysis. Hence, the original economic model presented here sought to address the question about the cost-effectiveness of different doses of ASAs for maintaining remission in people with ulcerative colitis.

5.2.2 Methods

5.2.2.1 Model overview

A cost-utility analysis was undertaken in Microsoft Excel[®] where costs and quality-adjusted life years (QALYs) were considered from a UK NHS and personal social services perspective (PSS). Both costs and QALYs were discounted at a rate of 3.5% per annum in line with NICE methodological guidance⁹⁶.

5.2.2.1.1 Comparators

Two network meta-analyses (NMAs) were conducted addressing the use of oral ASAs for maintenance of remission in people who have previously had a mild to moderate inflammatory exacerbation of left sided or extensive UC (Appendix I). A baseline NMA was conducted which addressed two outcomes; rate of relapse and withdrawals from treatment. The NMA didn't demonstrate any clinically significant differences between the lower doses of oral ASAs in terms of their effectiveness in maintaining remission. This was the same for the higher doses of oral ASAs. In the NMA, a dose effect was not observed between lower and higher doses of oral ASAs but in the clinical review a dose relationship was suggested. It was thought that the same groupings should be used as in the induction NMAs due to small event rates. It was also felt that because there was large uncertainty in the results, grouping the oral ASAs into low and high doses could strengthen the power to demonstrate an effect.

A second NMA (combined NMA) was therefore conducted which combined trials reporting low dose oral ASAs into one treatment group, and trials reporting high dose oral ASAs into another treatment group. The grouping was based on doses identified in the clinical review, recommended doses in the BNF⁶³ and GDG opinion. The dose ranges are shown in Table 70. The results of this NMA informed the clinical inputs in this economic analysis.

Drug treatment	Low maintenance dose oral ASA	High maintenance dose oral ASA
Aminosalicylates	Mesalazine (≤1.5g) ^(a)	Mesalazine (>1.5g) ^(a)
	Salofalk (≤1.5g)	Salofalk (>1.5g)
	Pentasa (≤2g)	Pentasa (>2g)
	Asacol (≤1.2g)	Asacol (>1.2g)
	Olsalazine (≤1g)	Olsalazine (>1g)
	Balsalazide (≤3g)	Balsalazide (>3g)
	Sulfasalazine (≤2g)	Sulfasalazine (>2g)

Table 70: Oral ASA doses used in the combined network meta-analysis

(a) For trials that do not specify the brand of mesalazine

The six comparators examined in the model were chosen by the GDG. The comparators explored the use of different doses of aminosalicylates (ASA) and are as follows:

- o **No maintenance, returning to no maintenance strategy:** starting patients on no maintenance and returning to no maintenance after treating an outpatient flare.
- o **No maintenance, returning to low dose ASA strategy:** starting patients on no maintenance and moving to a low maintenance dose ASA after treating an outpatient flare.
- **No maintenance, returning to high dose ASA strategy:** starting patients on no maintenance and moving to a high maintenance dose ASA after treating an outpatient flare.

- o **Low dose ASA, returning to low dose ASA strategy:** starting patients on low maintenance dose ASA and returning to a low maintenance dose ASA after treating an outpatient flare.
- o **Low dose ASA, returning to high dose ASA strategy:** starting patients on low maintenance dose ASA and moving to a high maintenance dose ASA after treating an outpatient flare.
- o **High dose ASA, returning to high dose ASA strategy:** starting patients on high maintenance dose ASA and returning to a high maintenance dose ASA after treating an outpatient flare.

5.2.2.1.2 Population

The population entering the model are adults in remission who have previously had a mild to moderate inflammatory exacerbation of left sided or extensive ulcerative colitis. Author reported definitions of disease activity were used, in line with the clinical review protocol. Left sided or extensive disease was defined as inflammation greater than 30-40cm (see Appendix C). The cohort starting age was chosen as 18 years as the GDG felt this represented a typical age of onset. The risk of mortality was assumed to be the same as that of the general UK population.

5.2.2.1.3 Time horizon

The time horizon considered in the base case model was two years. This time horizon was chosen to reflect the duration of the longest trial explored in the clinical review for maintenance of remission. In addition, the GDG considered that other treatment pathways not captured in the model could arise over a longer time horizon time, for example when treating patients that have frequent relapses. Hence, interpreting the results based on a longer time horizon could be inappropriate. However, the effect of a longer time horizon on the model results was explored in a sensitivity analysis.

5.2.2.2 Approach to modelling

5.2.2.2.1 Model structure

A Markov model was constructed in which, the QALY gain is driven by the amount of time people spend in the remission and active disease (relapse) states.

The trials included in the clinical review reported data on the number of relapses while on maintenance treatment. In addition, some of the trials reported data on the number of withdrawals from treatment. The available data informed the combined NMA, which provided estimates of probabilities of withdrawing from treatment and relapsing from maintenance treatment. The probability of relapse was conditional on not having withdrawn from maintenance treatment. Treatment effects in this economic model were based on these two outcomes - withdrawals and relapses.

A cycle length of two months was chosen to reflect the duration of the treatment of patients who are undergoing induction treatment for a flare. In any 2-month cycle, patients could remain in remission or experience a relapse. Patients who experienced a relapse were treated with the cost effective treatment strategy derived from the induction of remission economic model, described in section 5.1. Briefly, the strategy involved outpatient treatment with a high induction dose of oral ASA. In the event of failure to respond to this therapy, treatment was escalated as follows: high induction dose of oral ASA + beclometasone, followed by prednisolone. If the flare persisted, patients were treated as inpatients and received intravenous drug therapy which could be with either steroids or ciclosporin. Finally, lack of response to intravenous therapy resulted in patients having surgery.

There were three options modelled for patients who went into remission after an outpatient flare. They could receive no treatment or they could be placed on either a low dose oral ASA or high dose oral ASA maintenance therapy as outlined in section 5.2.2.1.1. Inpatients that went into druginduced remission were placed on azathioprine maintenance therapy while inpatients that had surgically-induced remission remained in remission for the rest of the model and were not on any maintenance treatment. All patients in remission (except surgical remission) had a probability of relapsing.

Two Markov model structures were developed to describe the pathway of treatment. This was necessary as the treatment pathway varied depending on what maintenance treatment patients received after a flare. For all comparators, it was assumed that patients who withdrew from treatment remained in remission for the duration of the cycle. In the next cycle however, their risk of relapse was similar to those on no maintenance treatment.

The first model structure shown in Figure 331 is relevant for comparators 1, 4 and 6 as described in section 5.2.2.1.1. Based on this, patients entered the model on one of the following options - no maintenance, low dose oral ASA or high dose oral ASA. In the event of a flare, they were treated as described above and following remission, they returned to the same maintenance regimen with which they entered the model.

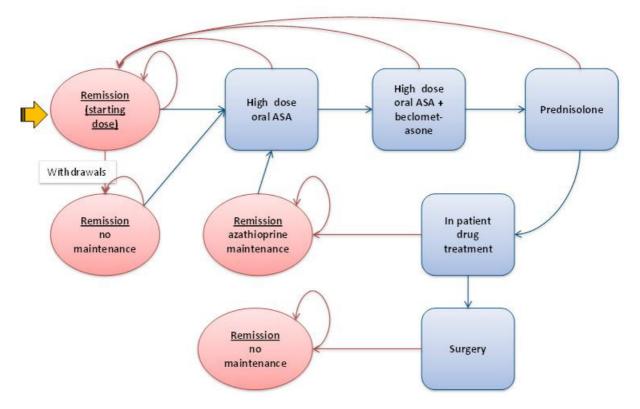


Figure 331: Markov model structure for comparators 1, 4 and 6

The second model structure shown in Figure 332 is relevant for comparators 2, 3 and 5 as described in section 5.2.2.1.1. Based on this, patients entered the model on either no maintenance or low dose oral ASA. In the event of a flare, they were treated as described above but returned to a maintenance regimen different to that with which they entered the model.

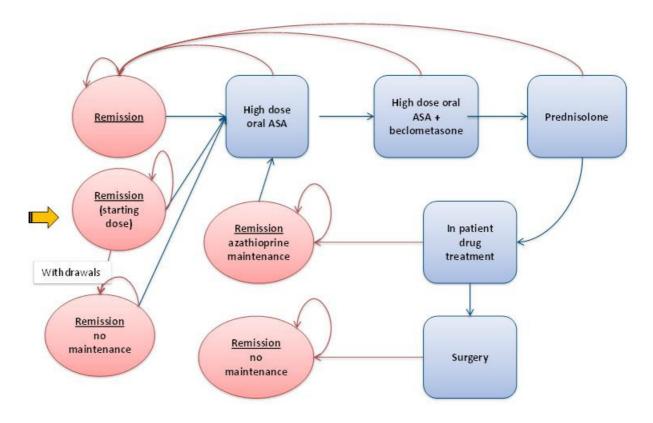


Figure 332: Markov model structure for comparators 2, 3 and 5

5.2.2.3 Uncertainty

5.2.2.3.1 Probabilistic analysis

The model was built probabilistically to take account of the uncertainty around parameter point estimates. In order to do this, probability distributions based on error estimates from data sources, for example the standard error around a point estimate, were defined for each model input. When the model was run, a value for each input was randomly selected from its respective probability distribution. This was done repeatedly – 1000 times and results were summarised. The number of simulations used was chosen considering the Monte Carlo error of the incremental costs, QALYs and net monetary benefit using the methods as described by Koehler and colleagues⁶⁹. It is set to ensure that the Monte Carlo error is not more than 5% of the standard error for these parameters. The types of distribution used in the model are described in Table 71.

Parameter	Type of distribution	Properties of distribution	Parameters for the distribution
Cost and resource use	Gamma	Bounded at 0. Derived from mean and standard error	α = (mean/SEM)2 λ = mean/SEM2
Resource use	Triangular	Derived from expert opinion or reported in data source.	Min = minimum value Likeliest = mean Max = maximum value
Treatment effects, utility weights and reference costs	Lognormal	Bounded at 0. Derived from log (mean) and standard error.	μ = ln(meanRR) SD(μ) = (ln[UpperCl] – ln[lowerCl])/1.96*2

Table 71: Distributions used in the model

5.2.2.3.2 Uni- and multi-variate sensitivity analysis

Uni-variate (single variable) sensitivity analyses were conducted in order to test the robustness of model results to changes in key parameters. In one way sensitivity analysis, one parameter is varied while all other parameters are kept constant and the effects of changing this parameter on model results are explored. The analyses are described in Table 89. A multi-variate (multiple variable) sensitivity analysis was also conducted where more than one parameter was varied while other parameters were kept constant. The analysis is described in Table 90.

5.2.2.4 Model inputs

5.2.2.4.1 Summary table of model inputs

People in remission

The relative effects of treatments on the baseline transition probabilities were derived from clinical evidence identified in the systematic review undertaken for the guideline, the results of the NMA and supplemented by additional data sources as required. Health utility data were obtained from the literature. Cost inputs were obtained from recognized national sources such as the BNF⁶³, drug tariff, NHS reference costs and Personal Social Services Research Unit (PSSRU) publications. All inputs were validated by the GDG. Summaries of the model inputs used in the base-case analysis are provided in Table 72, Table 73 and Table 74. More details about sources, calculations and rationale for selection can be found in the sections following this summary table.

Table 72: Summary of model inputs: clinical probabilities of withdrawal and relapse conditional on non-withdrawal (per cycle)

Variable	Probability of withdrawal	Probability of relapse conditional on non-withdrawal
No treatment	6.2%	13.3%
Low dose oral ASA	9.7%	6.8%
High dose oral ASA	7.4%	5.1%
Azathioprine	-	5.9%

Source: clinical review and NMA

Table 73: Summary of model inputs: utility weights

Variable	Estimate	Range	Reference
Remission on no maintenance treatment	0.940	0.937-0.943	Assumption
Remission on maintenance treatment	0.940	0.937-0.943	Poole et al ¹⁰³
Active disease (outpatient)	0.775	0.751-0.800	Poole et al ¹⁰³
Active disease (inpatient)	0.660	0.595-0.725	Poole et al ¹⁰³
Post-surgery	0.840	0.800-0.930 ^(a)	Yen et al ¹³⁷

(a) Different from value used in the study. Value was chosen to ensure consistency with other utility scores used in the model.

Table 74: Summary of model inputs: cost inputs

Variable	Cost	Source
Drugs (per 2 month cycle)		

Variable	Cost	Source
Low dose oral ASA	£49.41	MIMS ¹ , Drug tariff ⁹⁷
High dose oral ASA	£100.11	MIMS ¹ , Drug tariff ⁹⁷
Azathioprine	£40.88	MIMS ¹ ,
Tests		
Full blood count	£3.00	NHS reference costs ²⁸ (code DAP823)
Renal and liver function tests	£1.00	NHS reference costs ²⁸ (code DAP841)
ТРМТ	£26.00	Crohn's guideline ⁹³
Patient weight to calculate drug costs	77.9kg	National average body weight for UK (Crohn's guideline) ⁹³
Consultations (per hour)		
Consultant Gastroenterologist	£137.00	PSSRU ²³
General practitioner	£127.00	PSSRU ²³
IBD nurse specialist	£53.00	PSSRU ²³
Telephone consultation with IBD nurse specialist	£23.00	Payments by results guidance 2009-10 ²⁹
Specialist registrar	£59.00	PSSRU ²³
Weekly consultation costs for patients in remission	£1.38	Calculation

People in relapse

The costs and probabilities associated with induction treatments for people in relapse are those associated with the optimal strategy in the induction of remission model and can be found in the induction of remission model write-up (section 5.1).

5.2.2.4.2 Baseline events (withdrawal and relapse)

Baseline risks were pooled from the placebo arms of RCTS included in the clinical review by using the generic inverse variance method. This provided the baseline log odds of withdrawals and log hazard of relapse conditional on non-withdrawal. The results are presented in Table 75.

Table 75:Baseline events

Treatment	Odds of withdrawal (log scale)	risk of relapse conditional on non-withdrawal (log hazard)
No treatment (Placebo)	-0.749	0.016

5.2.2.4.3 Relative treatment effects (withdrawal and relapse)

Treatment-specific probabilities for withdrawal and relapse conditional on non-withdrawal were obtained from the combined NMA conducted. A brief outline of the methods can be found below with the full methodology reported in Appendix I.

A logistic regression NMA was conducted to obtain estimates on the probability of withdrawal associated with a particular treatment. For estimates of relapse conditional on non-withdrawal, a specific NMA methodology termed a multi-statistic evidence synthesis¹³⁵ was conducted. This was used as relevant trials that reported relapse data presented them as either hazard ratios or

cumulative count statistics. The methodology allowed both of these outputs to be combined in a single analysis and for the treatment effects to be produced on a log hazard scale.

As relapse was made conditional on non-withdrawal, treatment effects for the model had to be accounted for such that the number of withdrawals and relapses could not exceed the number of people. This was relevant for trials reporting cumulative count statistics. The calculation was done by removing the number of withdrawals from the denominator when entering data for relapses into WinBUGS. The calculation is described in Equation 1. The NMA results are shown in Table 76.

Equation 2- Calculating probability of relapse conditional on non-withdrawal

$$P(R|W^c) = \frac{P(R)}{1 - P(W)}$$

Where:

P(R|W^c) = probability of relapse conditional on non-withdrawal

P(R) = probability of relapse

P(W) = probability of withdrawal

Table 76: Estimates of treatment effects from NMA

Treatment	Odds of withdrawal (log scale)	risk of relapse conditional on non- withdrawal (hazard ratio)
Low dose ASA	0.580	0.490
High dose ASA	0.214	0.366

The baseline effects shown in Table 6 were transformed to 2-month cycle probabilities. In addition, the baseline effects were adjusted by the treatment effects in Table 7 and transformed to 2-monthly probabilities as shown in Note: 2 months was expressed in terms of weeks to give a value of 8.66

Table 77. The transformation to two-month probabilities is described in Equation 3.

Equation 3: Transformation to two-month probabilities

$$p_{2month} = 1 - \exp[-(-\ln(1 - p_{1week})) * (8.66)]$$

Note: 2 months was expressed in terms of weeks to give a value of 8.66

Treatment	Probability of withdrawal	Probability of relapse conditional on non-withdrawal
No treatment	6.3%	13.3%
Low dose ASA	9.7%	6.8%
High dose ASA	7.4%	5.1%

Table 77: Absolute probabilities per two-month cycle

People who did not withdraw from treatment relapsed according to the probabilities shown in Table 77 and moved into the active disease health states where they received treatment to induce remission.

People who withdrew from treatment remained in remission for the duration of the cycle. In the next cycle, they could remain in remission or have a probability of relapse similar to people on no treatment as shown in Table 77. This pathway is shown in Figure 333.

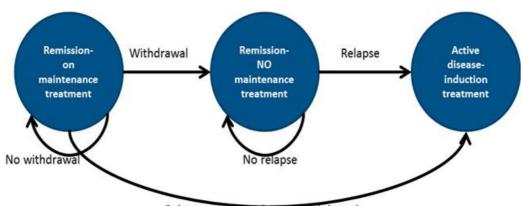


Figure 333: Pathway for patients withdrawing from treatment

Relapse conditional on no withdrawal

Possible inconsistencies with the withdrawal data were noted. There was a higher probability of withdrawals from low dose oral ASA compared to high dose oral ASA. This could be due to people withdrawing from treatment for reasons other than adverse events. A sensitivity analysis was conducted where the probability of withdrawal from both low and high dose oral ASAs were set to the same value. This is described in Table 89.

Azathioprine maintenance

The clinical data on having a relapse while on azathioprine was obtained from Hawthorne 1992⁵⁵. In the study, patients were randomised to either azathioprine (10-150mg) or placebo and followed up for 1 year. No withdrawals due to adverse events were reported. The GDG considered that since azathioprine maintenance was a secondary health state in the model, this paucity in data would not have a major influence on the results. The probability of relapse over a 2-month cycle was 5.9%.

5.2.2.4.4 Utilities

For economic evaluation, a specific measure of Health Related Quality of Life (HRQoL) known as utility is required to calculate Quality Adjusted Life Years (QALYs). Utilities indicate the preference for health states on a scale from 1 (perfect health) to negative infinity. Death in this model is considered to have a utility of 0. The NICE reference case⁹⁴ specifies that the preferred utility assessment tool is the EQ-5D instrument. The utilities used in the model were obtained from two studies¹⁰³,¹³⁷ described in Table 78.

Name	Description	Values				
Poole ¹⁰³	Ulcerative colitis disease activity index (UCDAI) scores and EQ5D scores were collected from 126 patients enrolled in a trial comparing oral and topical mesalazine with oral mesalazine alone. 92% of patients have mild/moderate UC while 8% had severe UC. An algorithm was developed to predict EQ5D scores based on individual abbreviated-UCDAI items. The algorithm was used to predict EQ5D scores for patients with differing UC severities enrolled in	Remission: 0.940 Mild/moderate disease: 0.775 Severe relapse: 0.660				

Table 78: Utilities in the model

Name	Description	Values
	the Phase IV PODIUM (Pentasa once daily in ulcerative colitis for maintenance of remission) study. In the PODIUM study, 359 patients were in remission at baseline. At 12 months, 73.8% were in remission, 22.6% were in mild to moderate relapse and 3.6% were in severe relapse.	
Yen ¹³⁷	The health states modelled were assigned utilities based on disease severity. The utilities were derived from various studies using the time trade off method. Some assumptions were made based on similarities with Crohn's disease.	Post-colectomy = 0.840

In order to capture the change in quality of life between the different health states modelled, utility scores were assigned as shown in Table 79. It was assumed that the utilities of being in remission on no maintenance treatment and on maintenance treatment were the same due to lack of relevant data.

Table 79: Health state utilities

Variable	Estimate	Range	Source
Remission on no maintenance treatment	0.940	0.937-0.943	Assumption
Remission on maintenance treatment	0.940	0.937-0.943	Poole et al ¹⁰³
Active disease (outpatient)	0.7750	0.751-0.800	Poole et al ¹⁰³
Active disease (inpatient)	0.660	0.595-0.725	Poole et al ¹⁰³
Post-surgery	0.840	0.800-0.930 ^(a)	Yen et al ¹³⁷

(a) Different from value used in the study. Value was chosen to ensure consistency with other utility scores used in the model.

5.2.2.4.5 Resource use and cost

People in relapse

The drug and consultation costs for patients in relapse are show in Table 80. For more detailed information pertaining to induction of remission, see the induction of remission model write-up (section 5.1).

Variable	Cost	Source
Course of high dose oral ASA ^(a)	£188.05	MIMS ¹ , PSSRU ²³
Course of high dose oral ASA + oral beclometasone ^(a)	£146.82	MIMS ¹ , PSSRU ²³
Course of prednisolone ^(a)	£83.37	MIMS ¹ , PSSRU ²³
Inpatient treatment	£2464.20	NHS reference costs ²⁸ (code FZ37G, FZ37H, FZ37I, FZ37J)
		NHS reference costs ²⁸
Surgery	£7404.44	(code FZ08A, FZ08B)

Please note that the detailed information in the section below is applicable to people in remission health states.

People in remission

1. Consultations

The GDG provided estimates on the frequency of consultations and the average length of consultation time that people in remission would receive on an annual basis. These consultations are regardless of the treatment patients are taking. Unit costs were obtained from the PSSRU²³ and adjusted by the consultation time to estimate average weekly costs of consultations. It was assumed that only 80% of patients would utilise these services. The inputs are summarised in Table 81.

Table 81:	Consultations	for p	eople in	remission
Table of.	consultations	iui p	eopie ii	16111331011

Type of consultation	Annual frequency	Length of consultation (minutes)	Cost per hour ^(a)		
Consultant					
gastroenterologist	One per year (HALF of all people)	20	£137		
General practitioner	One per year (all people)	17.2 ^(a)	£127.00		
IBD nurse specialist	One per year (HALF of all people)	20	£53.00 ^(b)		
Telephone consultation with IBD					
nurse specialist	One per year (HALF of all people)	10	£23.00		
Specialist registrar	One per year (HALF of all people)	20	£59.00		
(a) Source: PSSRU ²³					

(b) Payments by results guidance 2009-10²⁹

2. Drugs

Mesalazines, such as Mesren and Octasa have not been included in this analysis as they are not named in the studies identified in the clinical review. The GDG were unable to comment on their relative efficacy. Therefore, for mesalazine preparations, only those addressed in the clinical review were used to inform drug costs in the model. The average costs of low dose and high dose oral ASAs were based on costs of the individual drugs and dose ranges described in described in Table 70. Unit costs were obtained from the drug tariff⁹⁷ and BNF⁶³. The drugs included in the cost calculations are listed in Table 82, Source: MIMS¹ and GDG

Table 83 and Source: MIMS¹ and GDG

Table 84.

Table 82:	Low dose oral ASA costs in the model
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Cost item	Daily dose (grams)	Pack size	Cost per pack (£)	Cost per day (£)	Weekly cost (£)
Pentasa SR Tab 500mg	2	100	30.74	1.23	8.61
Mezavant XL G/R Tab 1.2g	1.2	60	62.44	2.08	14.57
Salofalk G/R Tab 500mg	1.5	100	32.38	0.97	6.80
Salofalk M/R G/R Granules 1.5g	1.5	60	48.85	0.81	5.70
Asacol M/R E/C Tab 400mg	1.2	90	29.41	0.98	6.86
Sulfasalazine E/C Tab 500mg	2	100	20.54	0.82	5.75
Sulazine E/C Tab 500mg	2	112	14.83	0.53	3.71

Cost item	Daily dose (grams)	Pack size	Cost per pack (£)	Cost per day (£)	Weekly cost (£)
Sulfasalazine Tab 500mg	2	112	8.16	0.29	2.04
Salazopyrin En-Tab 500mg	2	112	6.97	0.25	1.74
Salazopyrin Tab 500mg	2	112	8.43	0.30	2.11
Dipentum Tab 500mg	1	60	21.18	0.71	4.94
Colazide Capsules 750mg	3	130	30.42	0.94	6.55
		130		0.01	0.00
Average costs per cycle			£49.41		

Source: MIMS¹ and GDG

Table 83: High dose oral ASA costs in the model

Drug name	Daily dosage (grams)	Pack size	Cost per pack(£)	Cost per day(£)	Weekly cost(£)
Pentasa SR Tab 500mg	4	100	30.74	2.46	17.21
Mezavant XL G/R Tab 1.2g	2.4	60	62.44	2.08	14.57
Salofalk G/R Tab 500mg	3	100	32.38	1.94	13.60
Salofalk M/R G/R Granules 1.5g	3	60	48.85	1.63	11.40
Salofalk M/R G/R Granules 1g	3	50	28.74	1.72	12.07
Asacol M/R E/C Tab 400mg	2.4	90	29.41	1.96	13.72
Sulfasalazine E/C Tab 500mg	4	100	20.54	1.64	11.50
Sulazine E/C Tab 500mg	4	112	14.83	1.06	7.42
Sulfasalazine Tab 500mg	4	112	8.16	0.58	4.08
Salazopyrin En-Tab 500mg	4	112	6.97	0.50	3.49
Salazopyrin Tab 500mg	4	112	8.43	0.60	4.22
Dipentum Tab 500mg	2	60	21.18	1.41	9.88
Colazide Capsules 750mg	6	130	30.42	1.87	13.10
Average costs per cycle			£100.11		
Source: MIMS ¹ and GDG					

Table 84: Azathioprine costs in the model

Drug name	Daily dosage (mg/kg)	Pack size	Cost per pack(£)	Cost per day ^(a) (£)	Weekly cost(£)	
Azathioprine 25mg Tab	2.5	28	6.02	1.67	11.72	
Azathioprine 50mg Tab	2.5	56	5.04	0.35	2.45	
Imuran 25mg Tab	2.5	100	10.99	0.86	5.99	

Drug name	Daily dosage (mg/kg)	Pack size	Cost per pack(£)	Cost per day ^(a) (£)	Weekly cost(£)
Imuran 50mg Tab	2.5	100	7.99	0.31	2.18
Average costs per cycle			£40.88		

Average costs per cycle Source: MIMS¹ and GDG

Source: IVIIVIS and GDG

(a) calculated based on an average patient weight of 77.9kg

Drug-specific tests

Drug-specific tests were based on the recommendations in the BNF⁶³ and were verified by the GDG. Patients on maintenance treatment on either low dose or high dose oral ASA had 2 renal function tests and 2 full blood counts in the first year and then one set of tests annually. Patients on maintenance with azathioprine were assumed to have one thiopurine methyltransferase (TPMT) assay prior to initiation of treatment, as well as full blood counts, liver and renal function tests on a regular basis. The frequency of tests while on azathioprine decreased after the first year. These tests are summarised in Table 85 and Table 86.

Table 85: Tests for people on low dose or high dose oral ASAs

Type of test	Unit cost	Year one	Year 2	Source
Full blood count	£3	2 tests	1 test	NHS reference costs ²⁸ (code DAP823)
Renal function test	£1	2 tests	1 test	NHS reference costs ²⁸ (code DAP841)

Table 86: Tests for people on azathioprine

Type of test	Unit cost	Year one	Year 2	Source
Full blood count	£3	12 tests	4 tests	NHS reference costs ²⁸ (code DAP823), BNF 61 ⁶³
Renal function test	f1	12 tests	4 tests	NHS reference costs ²⁸ (code DAP841), BNF 61 ⁶³
Liver function test	f1	12 tests	4 tests	NHS reference costs ²⁸ (code DAP823), BNF 61 ⁶³
TPMT assay	£26	1 test	-	Crohn's guideline ⁹³

Summary of health state costs

The total costs attributed to each health state comprised of the costs of drugs, tests and consultations. The costs per two-month cycle are shown in Table 87.

Table 87:	Health	state	costs
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Health state	Costs	Source
Remission on no maintenance treatment	£11.91	Calculations
Remission on low dose oral ASA maintenance treatment	£62.65	Calculations
Remission on high dose oral ASA maintenance treatment	£113.35	Calculations
Remission on azathioprine maintenance treatment	£67.11	Calculations

5.2.2.4.6 Computations

The mean cost and effectiveness of the competing strategies were calculated using Microsoft Office Excel 2007.

5.2.2.4.7 Calculating QALYs

In order to calculate the QALYs associated with a given treatment, in each cycle, the number of people in each health state was multiplied by the utility weight associated with that health state and divided by an adjustment factor to reflect the cycle length. A worked example of the utility calculation is shown In Table 88; please note this is a simplified calculation as the full calculation would take account of all the health states shown in Table 79.

Table 88: Example calculation of QALYs

	Remission	Active disease (outpatient)
Number of people in health state	720	280
Utility weight	0.94	0.775
QALYs per patient (over a 2 month cycle)	$\frac{720 \times 0.94}{1000} \times \frac{2}{12} = 0.113$	$\frac{280 \times 0.775}{1000} \times \frac{2}{12} = 0.036$

The total QALYs for the 2 month cycle described above would be 0.113 + 0.036 = 0.149. These QALY contributions are then aggregated over the two-year model time horizon to calculate the total number of QALYs associated with each treatment.

5.2.2.4.8 Probabilistic analysis in the model

In the probabilistic analysis, distributions were assigned to treatment effects, utilities and where possible, costs as described in Table 71. This was done to account for the uncertainty in model inputs and capture the effect of this uncertainty on model outputs. Please see the induction of remission model write-up for more details on how inputs pertaining to induction of remission were made probabilistic.

Treatment effects:

To capture the uncertainty in treatment effects, a sample of 1000 random sets of treatment effects was taken from the NMA using the CODA function in WinBUGS. This has the advantage of preserving the correlation between variables, which would not be accounted for if they were sampled from their individual distributions. For the probabilistic analysis, in each simulation, a random set of treatment effects was chosen from the sample using random number generation.

Reference costs:

Costs of tests, in-patient treatment and surgery were obtained from NHS reference costs. In order to assign a distribution to reference costs, it was assumed that they followed a lognormal distribution and the interquartile range was used to calculate an approximate standard error on the log scale. The calculation is explained below.

Let **X** be the cost assigned to a distribution to, i.e. $\ln(X) \sim Normal(\mu, \sigma^2)$

Let M be the mean associated with the cost.

Let *IQR* be the interquartile range associated with the cost.

Note that for normally distributed data:

$$IQR \approx 1.35\sigma$$

And noting that the standard error s, is related to the standard deviation by:

$$s = \frac{\sigma}{\sqrt{n}}$$

Then the standard error on the log scale can be calculated as:

$$\sigma = \frac{\ln(IQR)}{1.35 \times \sqrt{n}}$$

And therefore random draws from the distribution can be taken:

$$\ln(X) \sim Normal\left(ln\left(\mu - \frac{\sigma^2}{2}\right), \left(\frac{\ln(IQR)}{1.35 \times \sqrt{n}}\right)^2\right)$$

Utilities:

Utilities were sampled probabilistically by assigning lognormal distributions to utility decrements as described in (ref Briggs). Normal distribution parameters were converted to lognormal parameters by method of moments, as defined below:

Let E[X] and Var[X] be the mean and variance respectively, of the utility decrement U

Then the parameters of the lognormal distribution, μ and σ^2 are found by:

$$\mu = \ln(E[X]) - \frac{\ln\left(1 + \frac{Var[X]}{E[X]^2}\right)}{2}$$
$$\sigma^2 = \ln\left(1 + \frac{Var[X]}{E[X]^2}\right)$$

5.2.2.4.9 Calculating cost-effectiveness

It is possible, for a particular cost-effectiveness threshold, to express cost-effectiveness results in terms of net monetary benefit (NMB). This is calculated by multiplying the total QALYs for a comparator by the threshold cost per QALY value (for example, £20,000) and then subtracting the total costs. The decision rule then applied is that the comparator with the highest NMB is the most cost-effective option at the specified threshold. That is the option that provides the highest number of QALYs at an acceptable cost. For ease of computation NMB is used to identify the optimal strategy in the probabilistic analysis simulations.

Let C_t and Q_t denote the mean costs and mean QALYs respectively, associated with a given treatment. Then the mean net monetary benefit NMB_t is calculated as:

$NMB_t = (20,000 \times Q_t) - C_t$

Where £20,000 per QALY represents the cost-effectiveness threshold in the NICE reference case.

This net benefit is calculated for each of the 1000 simulations in the probabilistic analysis. This means that the probability that a given treatment would be optimal can be estimated based on the number of times it has the highest net monetary benefit.

However, the strategy that is optimal overall is the one that has the highest net monetary benefit calculated using the mean costs and QALYs, where means were the average of the 1,000 simulated estimates.

5.2.2.5 Sensitivity analyses

The sensitivity of the results to changes to inputs and assumptions was tested by conducting four uni-variate sensitivity analyses as described in Table 89. The analyses were conducted deterministically.

		Value in base	Value or range in
Sensitivity analysis	Description	case	sensitivity analysis
SA1: Time horizon	Time horizon increased	Two years	Five years
SA2: QALY discount rate	QALY discount rate decreased	3.5%	1.5%
SA3: High baseline risk	It was decided to increase the baseline risk for relapse to reflect a cohort that was more prone to flares. The aim was to determine what treatment sequence would be appropriate in this scenario.	14.2%	90%
SA4: Low baseline risk	It was decided to decrease the baseline risk for relapse to reflect a cohort less prone to flares. The aim was to determine what treatment sequence would be appropriate in this scenario.	14.2%	10%
SA5: Withdrawal rates	The withdrawal rates from low dose and high dose ASA were set to the same values to account for uncertainty in the withdrawals data.	Low dose ASA: 7.4% High dose ASA: 9.7%	Low dose ASA: 9.7% High dose ASA: 9.7%

Table 89: Uni-variate sensitivity analyses in the model

One multi-variate sensitivity analysis was conducted deterministically to address the effects of ASA costs on the model results. The analysis is described in Table 90.

Table 90:	Multi-variate sensitivity analysis in the model
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Sensitivity analysis	Description	Value in base case	Value in sensitivity analysis
Drug costs	In the base case, the daily costs of oral ASAs were based on an average of individual ASA preparations. The GDG was aware of the costs differences between different ASA preparations. This SA was conducted to capture the effect of ASA drug costs on the model results.	Daily cost of low dose oral ASA = £0.82 Daily cost of high dose oral ASA = £1.65	The daily costs of ASAs were varied from in £0.20 increments.

5.2.2.6 Model validation

The model was developed in consultation with the GDG; model structure, inputs and results were presented to and discussed with the GDG for clinical validation and interpretation.

The model was systematically checked by the health economist undertaking the analysis; this included inputting null and extreme values and checking that results were plausible given inputs. The model was peer reviewed by a second experienced health economist from the NCGC; this included systematic checking of the model formulae and calculations. The model parameters and results were also assessed against the content of this appendix.

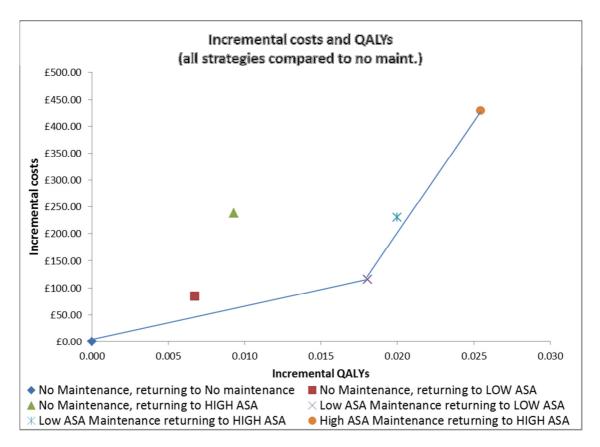
5.2.2.7 Interpreting results

The strategy with the highest mean net monetary benefit is the one that should be recommended³⁵ though the uncertainty around costs and QALYs should also be taken into consideration. Due to lack of data we were unable to explicitly capture the disutility of treatment-specific adverse events. This should be taken into consideration when interpreting the results.

5.2.3 Results

5.2.3.1 Base case results

In the base case, model inputs were set as shown in section 5.2.2.4 and the model was run probabilistically. Figure 334 shows the incremental increase in costs and QALYs when all strategies are compared to the no maintenance returning to no maintenance strategy. Note that the line on the graph represents the non-dominated options, this means the options that are more costly but also more effective and under the £20,000 per QALY gained threshold. The graph shows that the low maintenance returning to low maintenance strategy is the cost effective option because while it is more costly than no treatment it is also considerably more cost effective. The high maintenance returning to high maintenance returning to low maintenance strategy is not considered cost effective because, while it is more effective than the low maintenance returning to low maintenance strategy, this gain does not justify the increased cost as incremental cost-effectiveness ratio of £42,574 was calculated. This is significantly greater than the £20,000 per QALY cost-effectiveness threshold defined by NICE.





Cost-effectiveness in the base case (per patient)

The probabilistic results allowed a ranking of the net monetary benefit to be developed and also showed the probability of an intervention being cost effective out of 1000 simulations. The cumulative ICERs for the 1000 simulations were plotted to check the stability of the ICERs. The ICERs were stable after approximately 200 simulations. Table 91 shows the breakdown of the results. The low maintenance returning to low maintenance strategy had the highest NMB and was cost effective in 61% of the simulations. The high maintenance returning to high maintenance strategy was cost effective in 30% of cases. This shows that while the low maintenance returning to low maintenance strategy is likely to be cost effective there is uncertainty about this result and there is a good possibility that high maintenance returning to high maintenance strategy could be cost effective. The uncertainty between these two options can be found in Figure 335. This figure shows that while in the majority of cases, the low maintenance returning to low maintenance strategy is in the top right hand quadrant of the cost-effective ness plane and under the cost-effectiveness threshold, it is occasionally less cost effective than the high maintenance returning to high maintenance strategy (in the top left quadrant – more costly and less effective).

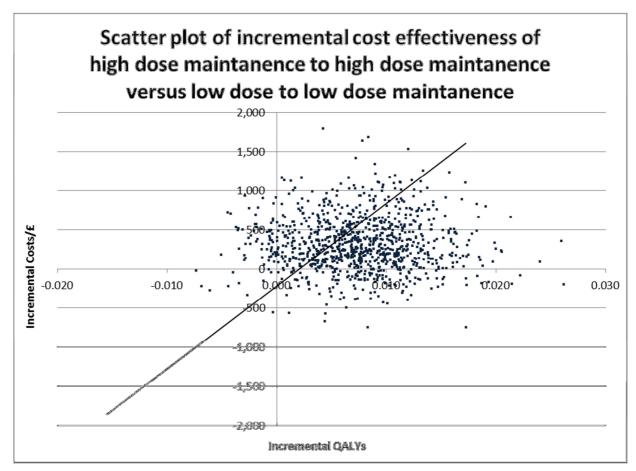
Comparator	Costs	QALYs	NMB ^(a)	NMB rank (95% confidence interval) ^(a)	Probability of being most cost-effective strategy	ICER compared to no maintenance
No maintenance returning to no maintenance strategy	£926	1.780	£34,670	5(1,6)	9%	comparator
No maintenance returning to low dose	£1,011	1.787	£34,720	4(2,6)	0%	£12,526

Table 91: Cost-effectiveness in the base case (per patient)	Table 91:	Cost-effectiveness	in the base case	(per patient)
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Comparator	Costs	QALYs	NMB ^(a)	NMB rank (95% confidence interval) ^(a)	Probability of being most cost-effective strategy	ICER compared to no maintenance
oral ASA strategy						
No maintenance returning to high dose oral ASA strategy	£1,165	1.789	£34,618	6(2,6)	0%	£25,596
Low dose oral ASA returning to low dose oral ASA strategy	£1,041	1.798	£34,916	1(1,6)	61%	£6,382
Low dose oral ASA returning to high dose oral ASA strategy	£1,157	1.800	£34,839	2(2,5)	0%	£11,534
High dose oral ASA returning to high dose oral ASA strategy	£1,356	1.805	£34,749	3(1,6)	30%	£16,909

(a) Using a willingness to pay threshold of £20,000 per QALY

Figure 335: Scatter plot to show the uncertainty around the incremental costs and effect between the high dose ASA returning to high dose ASA strategy and low dose ASA returning to low dose ASA strategy



In order to better understand the above results, a further break down can be found below.

Costs

Table 92 shows the total costs attributed to each comparator in the model. The total costs are calculated based on costs of drugs, tests, consultations, inpatient treatment and surgery. Over a two year horizon, the no maintenance retuning to no maintenance strategy has the lowest costs at £926.24 per patient. This is because the costs of maintenance treatment with ASAs are not a factor in this comparator.

Comparator	Drugs	Tests	Consultations	Inpatient	Surgery	Total
No maintenance returning to no maintenance strategy	£389.57	£1.30	£261.86	£219.93	£53.59	£926.24
No maintenance returning to low dose oral ASA strategy	£506.38	£3.42	£249.16	£202.02	£49.70	£1,010.69
No maintenance returning to high dose oral ASA strategy	£673.11	£3.56	£244.31	£195.39	£48.29	£1,164.66
Low dose oral ASA returning to low dose oral ASA strategy	£610.31	£6.33	£228.82	£157.90	£38.03	£1,041.38
Low dose oral ASA returning to high dose oral ASA strategy	£735.16	£6.43	£225.13	£153.08	£37.03	£1,156.83
High dose oral ASA returning to high dose oral ASA strategy	£969.86	£6.71	£215.22	£132.81	£31.83	£1,356.43

Table 92: Mean costs in the base case (per patient)

Outcomes

Table 93 shows the amount of time spent in remission and active disease for each comparator. Time in remission is made up of time spent while on no drug treatment and maintenance treatment. Time with active disease is made up of time spent while on induction treatment and surgery. This information was used to calculate the total QALYs for each strategy as described in section 5.2.2.4.7. The most effective comparator was the high maintenance returning to high maintenance strategy as 20.68 weeks were spent in remission and 3.31 weeks in active disease. This resulted in 1.805 QALYs over a two year time horizon.

Comparator	Time on no maintenance treatment	Time on drug maintenance treatment	Total time in remission	Time on induction treatment	Time in Surgery	Total time with active disease	Total QALYs
No maintenance returning to no maintenance strategy	17.33	1.36	18.68	5.27	0.04	5.31	1.780
No maintenance returning to low dose oral ASA strategy	12.14	7.17	19.31	4.65	0.03	4.68	1.787

Comparator	Time on no maintenance treatment	Time on drug maintenance treatment	Total time in remission	Time on induction treatment	Time in Surgery	Total time with active disease	Total QALYs
No maintenance returning to high dose oral ASA strategy	12.62	6.74	19.36	4.60	0.03	4.63	1.789
Low dose oral ASA returning to low dose oral ASA strategy	5.67	14.92	20.59	3.38	0.02	3.40	1.798
Low dose oral ASA returning to high dose oral ASA strategy	5.97	14.66	20.63	3.34	0.02	3.36	1.800
High dose oral ASA returning to high dose oral ASA strategy	7.45	13.23	20.68	3.29	0.02	3.31	1.805

5.2.3.2 Sensitivity analyses

5.2.3.2.1 Uni-variate sensitivity analysis

One-way sensitivity analyses as described in Table 89 were conducted in order to test the robustness of model results. The analyses were conducted deterministically and the results are presented in Table 94. SA1 shows that over a 5 year time horizon, the low dose oral ASA returning to low dose oral ASA strategy remained the cost effective option. This was also the same result in SA2 which looked at the impact of a 1.5% QALY discount rate on the analysis. SA3 looked at the impact of a higher baseline risk on the base case results. A higher baseline risk suggests that patients are more likely to have a relapse. In this scenario, the high dose oral ASA returning to high dose oral ASA strategy was the cost effective option. This can be interpreted to mean that it is cost effective to maintain patients who are more prone to relapses on a high dose ASA due to it being more efficacious than other comparators. Cost gains are made by preventing downstream costs of more expensive drug treatment and hospitalisations. SA4 looked at the impact of a lower baseline risk on the base case results. A lower baseline risk suggests that patients are less prone to relapses. In this scenario, the no maintenance returning to no maintenance strategy was the cost effective option. This means that for patients who do not frequently relapse, it is cost effective to treat them only when they have a flare. SA5, which addressed the uncertainty in withdrawal rates did not change the conclusions of the base case analysis.

Comparator	Base case	SA1	SA2	SA3	SA4	SA5
No maintenance returning to no maintenance strategy	£34,675	£82,207	£35,009	£32,839	£36,450	£34,675
No maintenance returning to low dose oral ASA strategy	£34,751	£82,579	£35,086	£33,240	£36,425	£34,751

Table 94: Uni-variate sensitivity analyses-mean net monetary benefit per patient*

Comparator	Base case	SA1	SA2	SA3	SA4	SA5
No maintenance returning to high dose oral ASA strategy	£34,640	£82,294	£34,975	£33,211	£36,391	£34,645
Low dose oral ASA returning to low dose oral ASA strategy	£34,988	£82,827	£35,325	£33,592	£36,226	£34,988
Low dose oral ASA returning to high dose oral ASA strategy	£34,906	£82,573	£35,242	£33,561	£36,204	£34,909
High dose oral ASA returning to high dose oral ASA strategy	£34,807	£82,473	£35,143	£33,626	£35,839	£34,809

5.2.3.2.2 Multi-variate sensitivity analysis

One multi-variate deterministic analysis as described in Table 90 was conducted to assess the effect of daily costs of oral ASA on the model results. Figure 336 shows the change to the NMB for each comparator as daily costs of ASAs are decreased or increased in £0.20 increments. The no maintenance returning to no maintenance strategy remained unchanged as it is not influenced by the costs of ASA maintenance treatment. Overall, the NMB for all comparators decreased as the costs of daily ASAs increased. If the cheapest high dose ASA identified in the model was used, the high dose oral ASA returning to high dose oral ASA strategy became the cost effective option. If the costliest high dose ASA identified in the model was used, the no maintenance to no maintenance strategy becomes favourable. These results are to be interpreted with caution as other ASAs are available whose costs have not been included in this analysis.

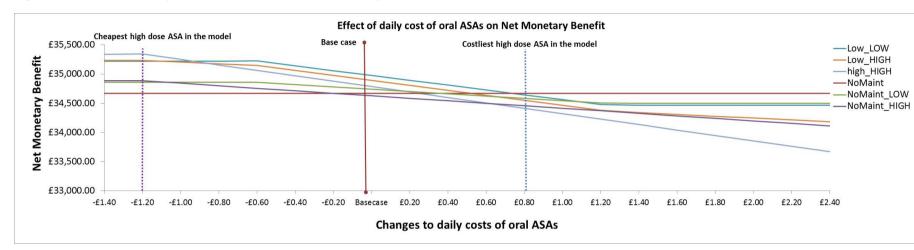


Figure 336: Effect of daily cost of oral ASAs on net monetary benefit

5.2.4 Discussion

5.2.4.1 Summary of results

The cost-effectiveness analysis shows that it is cost effective to use a low dose oral ASA to maintain remission in patients who have previously had a mild to moderate inflammatory exacerbation of left sided or extensive ulcerative colitis. This analysis was based on a multi-statistic network metaanalysis conducted using RCT data, acquisition costs, PSSRU costs and NHS reference costs. The results were robust to sensitivity analysis conducted.

5.2.4.2 Limitations and interpretations

The model is based on findings from RCTs and therefore any issues concerning interpretation of the clinical review also apply to interpretation of the economic analysis. Limitations of the model which impact on the interpretation of the results are as follows:

- The costs and dis-utilities of drug-specific adverse events were not explicitly modelled due to lack of robust data. This means that the cost-effectiveness of oral ASAs may have been over-estimated although the magnitude is unknown as each individual ASA is likely to have a specific side-effect profile. The overestimation of the ICER would be greater for ASAs that have more serious side effects compared to those with less serious side effects. This introduces uncertainty around interpretation of the results.
- In the model, it is assumed that all relapses have the same severity. It is possible therefore that the induction treatment sequence may not be appropriate for all patients. This assumption may overestimate the cost-effectiveness of all comparators.
- Mesalazines, such as Mesren and Octasa have not been included in this analysis as they are not named in the studies identified in the clinical review. The GDG were unable to comment on their relative efficacy. The GDG were unable to comment about the relative efficacy of these mesalazines hence caution should be exercised when generalising the results of this model.
- Patients who withdraw from treatment were assumed to still be in remission. This is a conservative approach. If withdrawal from treatment results in flare of disease, the cost-effectiveness of all comparators may have been overestimated in the model.
- Treatment adherence was assumed to be 100% in the model. The GDG however noted that this may not be the case in reality and measures to improve adherence are discussed elsewhere in the guideline.

5.2.4.3 Generalisability to other populations/settings

The analysis was based on data obtained from an adult population hence may not be generalizable to paediatric populations. This is especially important as the dose ranges of ASAs were based on adult doses. A model relevant to the paediatric population could not be constructed due to paucity of clinical data.

Relapses in the model are assumed to be mild to moderate initially. In reality, patients may experience greater severities of relapse which may necessitate treatment options different to those captured in the model. Similarly, other extents of UC such as proctitis have not been addressed and as such treatment options used in the model may not be applicable.

5.2.4.4 Comparisons with published studies

The results of relevant economic studies addressing this topic area have been summarised briefly in section 5.2.1.

Yen¹³⁷ assessed the cost-effectiveness of no maintenance therapy versus 5-ASA maintenance therapy in patients with mild to moderate UC. In the study, 5-ASA therapy was shown to increase the discounted QALYs per person yielding an incremental cost-effectiveness ratio (ICER) of £146,000/QALY. This result was sensitive to costs of ASA as the ICER decreased to £10,306/QALY when cheaper drug costs of sulfasalazine were used.

The comparators modelled in the study are similar to two comparators in this original economic analysis -the no maintenance, returning to no maintenance and low dose oral ASA returning to high dose oral ASA strategies. A major difference between two analyses is the cost of drug treatment. An ICER of £11,534/QALY was calculated when the two strategies were compared in our model. This is taking into account the fact that drug costs used in our model were closer to the sensitivity analysis values used in the Yen study. In addition, post-operative complications and costs have been modelled in the Yen study which could explain the differences in the results.

5.2.4.5 Conclusion and evidence statements

The original cost-effectiveness analysis conducted for this guideline suggests that low dose oral ASA is the most cost effective option to maintain remission in patients with left sided or extensive ulcerative colitis, although there is considerable uncertainty related to interpretation of the withdrawals data.

6 Appendix M: Research recommendations

The Guideline Development Group has made the following recommendations for research, based on its review of evidence, to improve NICE guidance and patient care in the future.

6.1 Key future research recommendations (FRR)

6.1.1 FRR1 Induction of remission for people with moderate ulcerative colitis: prednisolone compared with aminosalicylates

Research question:

What is the clinical and cost effectiveness of prednisolone compared with aminosalicylates for the induction of remission for people with moderate ulcerative colitis?

Why this is important:

Currently, people with moderate active ulcerative colitis most frequently receive either aminosalicylates or prednisolone as treatment, but there is no direct trial evidence comparing these treatments. Therefore people may receive treatment that is either less effective (in terms of symptom reduction or resolution, quality of life or healing of the colonic mucosa) or associated with greater side effects (especially with prednisolone). This is an important question in children, but the use of steroids is more contentious in children and there may be greater reluctance to use them because of possible effects on growth and development. People with moderate exacerbations of ulcerative colitis would be recruited and randomised to receive either prednisolone plus a boneprotecting agent or high-dose aminosalicylates. Primary end-points should be clinical remission and endoscopic remission.

	, ,		
PICO question	 Population – children and adults with moderate active ulcerative colitis. Intervention – prednisolone Comparison – aminosalicylates Outcome – critical outcomes would include: clinical remission (time to remission); endoscopic remission; clinical improvement; quality of life. 		
Importance to patients or the population	Currently, patients with moderate active ulcerative colitis most frequently receive either aminosalicylates or prednisolone as treatment, but there is no direct trial evidence comparing these treatments. Therefore there is potential for patients to receive treatment that is either less effective in terms of symptom reduction or resolution, quality of life or healing of the colonic mucosa, or associated with greater side-effects – particularly when receiving prednisolone.		
Relevance to NICE guidance	Future guidelines would be able to give clear guidance, based on direct evidence of which treatment is more appropriate.		
Relevance to the NHS	Improved symptom control may reduce hospital attendances and GP and specialist nurse consultations. Reduced steroid use would result in reduced steroid related morbidity including those relating to osteoporosis.		
National priorities	Appropriate use of systemically available corticosteroids, such as prednisolone, will help in the approach to growth and development in children and young people and reducing risks relating to osteoporosis.		
Current evidence base	No direct comparisons between aminosalicylates and prednisolone exist. Guideline recommendations have been made on the basis of clinical experience, consensus, network meta-analysis and economic analysis (see chapter 5 and appendices I and L). The evidence base also lacks a way of differentiating		

Criteria for selecting high-priority research recommendations:

	between those with differing severity of attacks, but which still fall in the 'moderate' category as defined by Truelove and Witts, and described in chapter 5 of the guideline.				
Equality	No current equality issues identified.				
Study design	Randomised controlled, double blind trial, in which patients with moderate flares of ulcerative colitis are randomised to receive either prednisolone plus a bone protecting agent or high dose aminosalicylates. The effect of disease severity within this cohort should also be evaluable (for example by stratification using clinical or laboratory parameters). Clinical and endoscopic remission should be considered as co-primary end-points, and adverse events (particularly related to systemic corticosteroid effect), quality of life and cost-effectiveness should also be evaluated, including non-invasive measures of mucosal healing.				
Feasibility	This would be feasible in a reasonable time frame and at a reasonable cost.				
Other comments	There are additional issues (for example relating to growth and development) which would determine the place of corticosteroids in children and so a trial needs to take this into account. However, this remains an important question in children, as well as adults, and so children have been included in this research question and recommendation. The guideline comments on two additional areas of weakness in the evidence base. Firstly, Evidence for drugs used for maintenance of remission is not generally based on studies where people are randomised following an acute flare of the condition – which is the usual clinical situation in which such treatment is prescribed. Secondly, the guideline recommendations on second- line treatment uses information from studies where the drugs have actually been used first line. The study described above could therefore be usefully run in such a way that additional studies addressing these two, additional gaps could be run.				
Importance	High: the research is essential to inform future updates of key recommendations in the guideline.				

6.1.2 FRR2 Induction of remission for people with moderate ulcerative colitis: prednisolone compared with beclometasone

Research question:

What is the clinical and cost effectiveness of prednisolone plus an aminosalicylate compared with beclometasone plus an aminosalicylate for induction of remission for people with moderate ulcerative colitis?

Why this is important:

Evidence exists about the effectiveness of beclometasone plus an aminosalicylate for induction of remission in people with moderate ulcerative colitis. It seems likely that any corticosteroid would have a similar effect to beclometasone (in combination with an aminosalicylate), but no evidence was available to confirm this. Prednisolone is cheap and readily available. Evidence to show comparable or better clinical and cost effectiveness of prednisolone plus an aminosalicylate compared with beclometasone plus an aminosalicylate would represent a significant cost benefit and potentially increased or at least similar clinical efficacy. The research should take the form of a double-blind randomised controlled trial. The outcomes should include patient satisfaction measures.

Criteria for selecting high-priority research recommendations:

PICO question	Population – people with moderate ulcerative colitis.
	Intervention – prednisolone+ ASA.
	Comparison – beclometasone + ASA.

	Outcome – critical outcomes would include: clinical remission (time to remission); endoscopic remission; clinical improvement; quality of life.
Importance to patients or the population	The importance of effective induction of remission is high due to the debilitating nature of the condition. Future guidance may recommend prednisolone + ASA as a clinically effective as well as cost effective option: the research is essential to inform future updates of key recommendations in the guideline.
Relevance to NICE guidance	Future NICE guidance may recommend prednisolone+ASA ahead of other combinations for induction in moderate ulcerative colitis
Relevance to the NHS	Prednisolone is approximately 50x cheaper than beclometasone (BNF Nov 12 equivalent doses).
	There would be a requirement to disseminate any updated guidance to stakeholders.
National priorities	If prednisolone is at least as effective in combination with ASA as beclometasone people would have an effective treatment. If it is more effective people would experience the benefit of better induction of remission either in terms of time to resolution and/or an extended period of remission
Current evidence base	The NICE Ulcerative Colitis Guideline Development Group systematic review found no evidence available regarding prednisolone+ASA as a treatment option.
Equality	The research has no equality issues.
Study design	The research to take the form of a double blind randomised controlled trial. The outcomes should include patient satisfaction measures.
Feasibility	No issues noted.
Other comments	None.
Importance	High: the research is essential to inform future updates of key recommendations in the guideline.

6.1.3 FRR3 Induction of remission for people with subacute ulcerative colitis that is refractory to systemic corticosteroids

Research question:

What are the benefits, risks and cost effectiveness of methotrexate, ciclosporin, tacrolimus, adalimumab and infliximab compared with each other and with placebo for induction of remission for people with subacute ulcerative colitis that is refractory to systemic corticosteroids?

Why this is important:

The best drug treatment for people with subacute ulcerative colitis whose condition fails to respond to treatment with oral prednisolone (a systemic corticosteroid) is unclear. Without effective treatment the condition may deteriorate, and may lead to the person requiring hospital admission for intravenous corticosteroid treatment or even surgery. It is common clinical practice to offer treatment with methotrexate or a calcineurin inhibitor (ciclosporin or tacrolimus), but high-quality evidence to guide clinicians is lacking. The use of infliximab in such cases was not recommended by NICE in technology appraisal guidance 140. This question should be investigated by a multicentre randomised, placebo-controlled trial in adults in secondary care. Outcomes should include patient-centred outcome measures.

Criteria for selecting high-priority research recommendations:

PICO question	Population – people with subacute ulcerative colitis refractory to systemic steroids.
	Intervention – methotrexate, ciclosporin, tacrolimus, adalimumab, infliximab. Comparison – to each other and placebo.

	Outcome – critical outcomes would include: clinical remission (time to remission); endoscopic remission; clinical improvement; quality of life.
Importance to patients or the population	At present, individuals may be offered treatment with an ineffective drug and be exposed to significant adverse effects. Moreover, the underlying disease may progress decreasing quality of life and possibly leading to hospital admission or surgery.
Relevance to NICE guidance	The answer to this research question will determine future NICE guidance and change clinical practice. The research findings will generate new knowledge that will be of value to gastroenterologists throughout the UK.
Relevance to the NHS	The results may improve the out-patient management of individuals with subacute ulcerative colitis or proctitis and possibly avoid surgery. If these drugs are effective people would have fewer days off work or be admitted to hospital. There would be health benefits and cost benefits to the NHS and the wider economy.
National priorities	This question involves improving the care of individuals with a chronic illness in keeping with the National Service Framework for Long Term Conditions.
Current evidence base	The current evidence base is very small; there are only two low quality RCTs of tacrolimus as induction treatment. There are no RCTs for the use of methotrexate or ciclosporin in subacute ulcerative colitis or proctitis.
Equality	The research question has no particular equality issues.
Study design	Multi-centre randomised, placebo-controlled trial in adults in secondary care. Outcomes should include patient-centred outcome measures.
Feasibility	Strict entry criteria will be required. A clear definition of subacute colitis or proctitis will be needed. In view of the risks associated with these drugs (increased risk of infection; lung, liver and kidney damage; bone marrow suppression) pre-trial screening and close monitoring (including drug levels) will be essential.
Other comments	There will be limited interest from pharmaceutical industry as none of these drugs are licensed for ulcerative colitis.
Importance	High: the research is essential to inform future updates of key recommendations in the guideline.

6.1.4 FRR4 Maintenance treatment for people with mild to moderate ulcerative colitis

Research question:

What is the clinical and cost effectiveness of regular maintenance treatment compared with no regular treatment (but rapid standard treatment if a relapse occurs) in specific populations with mild to moderate ulcerative colitis?

Why this is important:

Maintenance treatment reduces the chance of relapses occurring, but for much of the time a drug is being taken with no obvious benefit, and it may have side effects. An exacerbation of ulcerative colitis can usually be effectively treated or stopped if treatment is given when the first symptoms or signs of a relapse appear. It may be both clinically and cost effective to manage ulcerative colitis in this way, with people receiving episodic treatment rather than taking a drug continuously. This form of treatment may be appropriate if relatively few (for example 1 or 2) mild relapses occur per year. The study population would be people in whom mild to moderate ulcerative colitis of any extent is in remission and who are not taking immunomodulator or biological drugs.

Criteria for selecting high-priority research recommendations:

PICO question Population – people who have just had amild to moderate exacerbation of ulcerative colitis who are now in remission.

	Intervention – regular maintenance treatment (daily dosing).
	Comparison – no regular treatment (eg intermittent, tapering down, or no treatment at all).
	Outcome – critical outcomes would include: clinical relapse (time to relapse); health-related quality of life.
Importance to patients or the population	For patients who have a low risk of relapse, answering this question could potentially reduce unnecessary medication, and its associated side effects and cost, if no maintenance treatment is found to be a clinically and cost effective option for this specific subgroup of patients.
Relevance to NICE guidance	Future NICE guidance may recommend no maintenance treatment for people with mild to moderate ulcerative colitis.
Relevance to the NHS	Potential cost-saving on unnecessary drugs taken continuously for no benefit.
National priorities	If no maintenance treatment is at least as effective in maintaining remission as regular maintenance treatment people would not have to take unnecessary drugs continuously.
Current evidence base	The NICE Ulcerative Colitis Guideline Development Group systematic review found little evidence available to indicate that no maintenance is a clinically effective and cost effective option to maintain remission.
Equality	The research has no equality issues.
Study design	Studies to investigate this would be with patients in whom mild to moderate ulcerative colitis of any extent is in remission and who are not taking immunomodulator or biological drugs.
Feasibility	No issues noted.
Other comments	None.
Importance	High: the research is essential to inform future updates of key recommendations in the guideline.

6.1.5 FRR5 Risk tool for predicting the likelihood of needing surgery for adults with acute severe ulcerative colitis

Research question:

To develop and validate a risk tool that predicts the likelihood of needing surgery for adults admitted to hospital with acute severe ulcerative colitis.

Why this is important:

Acute severe ulcerative colitis is a life-threatening emergency. About 30% of people admitted to hospital with acute severe ulcerative colitis will require colectomy to avoid colonic perforation during the emergency admission. The Truelove and Witts' severity index is used to define the clinical severity of disease on admission but has not been validated as a predictor of the need for colectomy during treatment. The Travis (Oxford) criteria are used to predict the likelihood of colectomy after 3 days of treatment with intravenous steroids, but may be less useful later in the course. No tools have been developed and validated in patients receiving rescue therapy with anti-tumour necrosis factor (TNF) antibodies or ciclosporin. A validated tool that can reliably predict a person's likelihood of needing a colectomy over the course of an admission to hospital for treating acute severe ulcerative colitis would allow the medical and surgical teams and the person to prepare for colectomy and potentially inform decisions about introducing rescue therapy with ciclosporin or infliximab and when continued medical therapy is unlikely to be successful. There may also be psychological and nutritional benefits to the person and cost benefits to the NHS (for example, shorter length of inpatient stay; decreased risk of infection; less use of rescue therapy). The tool would be developed by a derivation study using a prospective cohort. The tool would be validated using a different prospective cohort from that of the derivation study.

PICO question	Derivation study			
	Population – adults with acute severe ulcerative colitis.			
	Prognostic factors – defined a priori to specify the variables to include in the model on the basis of traditional risk scores and other factors thought to affect the outcome:			
	 risk factors - stool frequency, pyrexia, tachycardia, colonic dilatation, low albumin, low haemoglobin, high platelet count, CRP>45mg/l 			
	other factors, rescue therapy.			
	Outcome – colectomy during hospital admission.			
Importance to patients or the population	It would be of great help to patients if they could be advised at different stages of their hospital admission about the chance of requiring surgery or escalation of medical therapy. This would inform the decision as to whether to continue current treatment, escalate medical treatment or proceed to colectomy.			
Relevance to NICE guidance	The answer to this question will provide new knowledge and evidence and is very likely to change the management of people admitted to hospital with acute severe ulcerative colitis. The result will add to the NICE guidance.			
Relevance to the NHS	There may be cost benefits to the NHS eg shorter length of inpatient stay; decrease risk of infection; less use of "rescue therapy".			
National priorities	None.			
Current evidence base	The current evidence base is limited by lack of blinding, assessment at different points in each study, variable availability of validation studies and appropriately designed studies have not been undertaken in patients receiving optimised rescue therapy.			
Equality	Not applicable.			
Study design	Derivation study - a prospective cohort study to develop the tool. Validation study - a different prospective cohort from that of the derivation study to validate the tool.			
Feasibility	The proposed research can be carried out in a realistic timescale and at an acceptable cost. There are no specific ethical or technical issues.			
Other comments	This study could be run from a single centre – with multi-centre participation. A research fellow would be required to design a database to collate and analyse data. Clinicians could be invited to identify cases and to complete an online database. Similar methodology to audit used to produce Rockall score for patients with acute upper GI bleeding.			
Importance	High: the research is essential to inform future updates of key recommendations in the guideline.			

Criteria for selecting high-priority research recommendations:

6.2 Other future research recommendations

- 1. In children and young people with ulcerative colitis receiving steroid treatment, what are the clinical benefits of routine monitoring of bone density, what tests should be done and how frequently?
- 2. A registry to collect data to answer 'What are the potential harms or benefits of drug treatments in pregnant women with ulcerative colitis?'.
- 3. What are the information needs of people with ulcerative colitis when they are considering surgery?

- 4. What is the clinical and cost effectiveness of sulphasalazine compared to high-dose branded mesalazine for induction of remission for people with mild moderate ulcerative colitis?
- 5. What is the validity, reliability and accuracy of available adult risk tools as a predictor for the need for surgery in people admitted into hospital with acute severe ulcerative colitis?
- 6. What is the validity, reliability and accuracy of the paediatric ulcerative colitis activity index (PUCAI) as a predictor for surgery for children and young people admitted to hospital with acute severe colitis?
- 7. In people with mild to moderate ulcerative colitis, what are the best second-line treatment strategies for induction of remission after people have failed to respond to ASA mono or combination therapies?
- 8. In people with subacute ulcerative colitis, what are the best second-line treatment strategies for induction of remission after people have failed to respond to oral prednisolone?
- 9. In people with mild to moderate ulcerative colitis, what are the best strategies for the induction of remission after people have failed to respond to tacrolimus?
- 10.Establish a national registry to identify the incidence of growth failure and/or pubertal delay in ulcerative colitis and the relationship with treatment (to record treatment [steroids, ASA, immunomodulators] and growth [z scores]).

7 Appendix N: Author definitions

7.1 Remission and improvement definitions

Table 95: Study definitions of remission and improvement for the induction of remission

Study reference	Clinical remission	Endoscopic remission	Clinical and endoscopic remission	Clinical improvement
ANDUS2008/AN DUS2010	DAI<4	≥1 point decrease in DAI from baseline to final visit (LOCF)	EI<4	
ARDIZZONE1999	CAI<4		EI<6	CAI<4, EI<6
BARMEIR2003	DAI≤3 at the end of treatment			
Baron 1962			Clinical and endoscopic remission (no symptoms; inactive or normal mucosa). Patient reported bleeding or mucus in the stool, sense of well being, sigmiodoscopy- grade. According to Lennard-Jones et al (1960)- active, moderately active, inactive or normal.	
BIANCONE2007		Response: a reduction in DAI score of≥1 point		
BINDER1987	Change in disease activity according to the Binder scale (Grade 0).	Change in disease activity according to the Binder scale (Grade 0).		Change in disease activity according to the Binder scale (Grade 0 or 1).
BOSSA2007	Stool frequency < 3/day on day 7 and no visible blood			
CAMPIERI1988	When symptoms (such as motions, blood, mucus) had completely disappeared	A reduction of at least one grade of activity according to the adopted evaluation scale	Repaired rectal mucosa	
CAMPIERI1990	Symptomless, with no more than 2 bowel movements/day without visible	A decrease in the severity of symptoms and signs, not meeting the criteria for	According to Baron's criteria	

	blood	remission, plus those in remission		
CAMPIERI1990A	Complete disappearance of symptoms	A reduction of at least one grade from the baseline value according to the adopted evaluation scale	Rectal mucosa was repaired	
CAMPIERI1991	Symptoms of active disease had resolved	At least one grade of reduction in activity according to the criteria adopted	Rectal mucosa was repaired with the appearance of a vascular pattern	
CAMPIERI1991A	Symptoms of active disease (such as bleeding or mucus) had disappeared	Reduction of at least one grade of activity according to the adopted scale	Repaired rectal mucosa	
CAMPIERI1993	Physician's clinical global evaluation of disease activity. Return to normal stool frequency, no visible blood in the stools, no abdominal symptoms	Decrease in the severity of symptoms not meeting the criteria for remission) – figures include those classed as improved and those in remission	Grade 0, normal mucosa. Modified Baron's criteria	
CAMPIERI2003	DAI score <3			Reduction of at least 3 points in DAI score from baseline
CORTOT2008	CAI ₁₋₄ ≤2		Endoscopic score <4 (according to Rachmilewitz)	
CORTOT2008	CAI ₁₋₄ ≤2		Endoscopic score <4 (according to Rachmilewitz)	
D'HAENS2010				CAI reduction by at least 50% of the baseline value (Rachmilewitz) or remission (CAI<4)
DANIELSSON198 7			Score of 0 on endoscopy (Truelove & Richards)	

DHAENS2001				Improvement in the clinical-activity score. Response was defined as a score of < 10 on days 7 and 8 with a drop in the score from day 1 to day 8 of at least 3 points and the possibility to discharge the patient
DHAENS2006	UCDAI score of ≤1, with a score of 0 for rectal bleeding and stool frequency and at least a 1 point reduction from baseline.			
DICK1964				'Improved or much improved' based on patients wellbeing, decrease in stool frequency, and return to normal consistency, decrease / disappearance in pus, mucus and blood.
FARUP1995	Complete response DAI ≤2.			
FARUP2001	Enhanced UCDAI (includes the PFA) score of 0-1			Enhanced UCDAI reduction of ≥2. This is added to those in remission to give all those that improved.
FERRY1993	Asymptomatic- free from all symptoms, formed bowel movements, no visible blood (all of the above for at least 7 days)	Normal mucosa	Normal mucosa and asymptomatic.	
FRIEDMAN1986 A	According to author defined scale (max 6). Clinical score of 1.	According to author defined scale (max 6). Score of 0.		Decrease in clinical score of ≥1
GIBSON2006	CAI≤4	EI<4		Clinical remission or improved CAI≥3 from baseline.
GIONCHETTI199 8	DAI=0 on clinical section	DAI=0 on the sigmoidoscopic section		Much improved, PGA score of 1

GREEN1998	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.		Complete remission (symptomatic remission with no use of relief medication in the previous 4 days and grade 0 or 1 UC on sigmoidoscopy)	
GROSS2006	CAI≤4 at the final/ withdrawal visit in the PPA population	Based on the CAI, no further information given	According to Rachmilewitz	
GROSS2011	CAI score ≤4 with a stool frequency <18/week and 0- 1blood stool/ week	EI≤3		Complete or marked or slight improvement of symptoms on the Physician's Global Assessment
HANAUER1993	PGA score of 1: complete relief of symptoms	Sigmoidoscopic score of 0-4 out of 15		Treatment benefit (complete relief of symptoms, marked, moderate or slight improvement of symptoms, PGA score of 1, 2, 3 & 4)
HANAUER1996	According to the number of bowel movements and the amount of blood in the stool. This definition was taken from the Cochrane systematic review on oral ASAs.	A 5 point scale where remission was a score of 0 or 1.		
HANAUER1998	Physician's Global Assessment score of 1, complete resolution of symptoms	PGA score of 1 or 2	Score of <4	

HANAUER1998A			Sigmoidoscopic grade 0	≤3 stools/day, no blood, no urgency, no abdominal pain or painful evacuations and a sigmoidoscopic score of 0. This had to be achieved in the preceding 2 days to the visit.
HANAUER2005			Complete remission (complete resolution of stool frequency (normal), rectal bleeding (none), PFA score (generally well), endoscopy (normal) and a PGA score of 0.	Treatment success (complete remission or a clinical response to therapy (improvement in the baseline PGA score and improvement in ≥1 clinical assessment (stool frequency, rectal bleeding, PFA, endoscopy findings) and no worsening in any other clinical assessment.
HANAUER2007			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)	Overall improvement (complete remission or response to therapy.
HARTMANN201 0	CAI <4	EI <2 at week 8		
HETZEL1986				A change of at least two grades in symptomatic wellbeing to good or very good by week 6
HIWATASHI2011	0-1 in total score (UCDAI)			Efficacy was defined as a reduction over 2 scores (UCDAI)
ITO2010A	UCDAI≤2 and a bloody stool score of 0 at the final assessment			Patients with a decrease in UCDAI by ≥2 points except patients who experienced a remission. For our analysis the remission figures were combined to give an overall number of those who had

National Clinical Guideline Centre, 2013.

				improved.
JEWELL1974	Not meeting the mild/moderate/sev ere Truelove and Witts criteria	Normal appearances (score of 0)		
JIANG2004	Defecation 0-2 times/day, no gross blood or microscopic red cells in stool.	Among the 7 items, 5 or more lowered by a grade after treatment	Subsidence of clinical symptoms with relative normal mucous membrane in colonoscopy.	Defecation 3-4 times per day with no gross blood in stool but less than 10 RBC per high power microscopic field.
KAMM2007	Score of 0 points for stool frequency and rectal bleeding (UCDAI)	Modified sigmoidoscopy score of ≤1, with no mucosal friability.	Modified UCDAI≤1 with rectal bleeding and stool frequency of 0, no mucosal friability and ≥1 point reduction in sigmoidoscopy score from baseline.	Decrease of ≥3 points from baseline in the total modified UCDAI score.
KOLKMAN2004	CAI <u><</u> 4 or 30% decrease			CAI decrease greater than 30%
KRUIS2003	CAI≤4	EI<4		CAI decreased by at least 3 points.
KRUIS2009	CAI≤4	EI<4		Decrease in CAI by at least 1 point from baseline to the individual study end.
LAMET2011	DAI<3			
LAURITSEN1986	Based on a diary in which the number of bowel movements and presence of absence of blood.		Assessed using Binder 4-point scale, E ₀ = inactive, C ₀ = inactive	
LEE1996	<3 stools per day with no blood.	Grade 1 – normal findings including minor abnormalities in vascular pattern		
LEE1996	≤3 stools per day with no blood.	Grade 1 – normal findings including minor abnormalities in vascular pattern		
LÉMANN1995	No blood (score =0) and little or no mucus (score =0 to	Score =0 on pre- defined 4 point scale.		

	1) judged on 3 point scale.			
LENNARD JONES1960			Remission of the disease is defined as freedom from symptoms combined with the finding of an inactive or, rarely, normal mucosa on sigmoidoscopy.	
LEVINE2002			Normal stool frequency and no blood in stool for 48hrs before visit. PGA score of 'quiescent' and a sigmoidoscopic score of mild or normal.	Improvement by at least one category in the four category disease activity score i.e. normal, mild, moderate, severe
LICHTENSTEIN20 07	Scores of 0 for total stool frequency and total rectal bleeding.		Modified UCDAI score of ≤1, with a score of 0 for rectal bleeding and stool frequency, and at least a 1 point reduction in sigmoidoscopy score.	Decrease of ≥3 points from baseline in the overall modified UCDAI.
LICHTIGER1994				A clinical-activity score of less than 10 on two consecutive days
LINDGREN2002				Absence of clinical symptoms (no blood in stools, and <3 bowel movements/24hrs) and an endoscopic score of 0-1
LOFBERG1996		Endoscopic remission (score of 0) after 4 weeks. Normal =0, Granularity, oedema and lack of normal vascular pattern= 1, Hyperemia, friability and petechiae and all of score 1 =2, Ulcerations(and all of score 1 and 2)=3.		

National Clinical Guideline Centre, 2013.

LOFBERG1994			Score of 0 on endoscopy (Truelove & Richards)	Score of 0 on endoscopy and ≤3 stools/day without blood
MARAKHOUSKI2 005	CAI≤4			
MARTEAU2005	UCDAI≤1			decrease in UCDAI >2 points
MEYERS1987				Reduction in the global clinical colitis activity that allowed reclassification into a milder category or if there was a lower overall sigmoidoscopic score or both.
MIGLIOLI1990	No more than two bowel movements per day with no visible blood in the stool in the symptom less patient			Clear decrease in severity of symptoms and signs not satisfying remission criteria.
MULDER1988				Decrease of ≥2 according to Van der Heide
OGATA2006	DAI≤2, with no individual score >1	Mucosal healing, score of 0 or 1		Partial and complete response base on DAI >4 points all categories improved).
OGATA2012	DAI score ≤2	Mucosal appearance subscore of 0 or 1)		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).
OREN1996	Mayo score (including sigmoidoscopy results) of ≤3 with the condition that the patient was not being administered steroids or a score of ≤2 without sigmoidoscopy results			
POKROTNIEKS20 00	CAI≤4, associated with a decrease of at least 2 points from baseline	Investigator's global assessment: complete relief, marked or slight	EI≤3	

		improvement (therapeutic benefit)		
POWELLTUCK19 78	Remission, activity score =0			A reduction in score by two or more points
POWELLTUCK19 86			Non friable rectal mucosa (grade 0)	Non friable rectal mucosa (grade 0) and a score of -0 for all clinical variables (malaise, bowel frequency, stool consistency, rectal bleeding)
PRANTERA2005	CAI≤4, according to Rachmilewitz	El≤2		
PRUITT2002	PFA score of normal or mild and absence of rectal bleeding.		Symptomatic remission plus a sigmoidoscopic evaluation score of normal or mild.	
RAEDLER2004	CAI ₁₋₄ ≤2	El≤2	CAI ₁₋₇ ≤4 and EI≤2	
RIJK1991			No definition was given, but the Cochrane systematic review included it as an 'author defined outcome' – assessment based on clinical and endoscopic criteria.	
RIZELLO2002	DAI score <3	Based on Baron's criteria		Reduction of at least 3 points in DAI score from baseline
RIZZELLO2003				Disease activity Index - > reduced by at least 1 point from baseline
ROBINSON1988				Unknown definition- The inclusion criteria for the Cochrane Systematic review was 'author defined' definition'
ROMANO2010	Score <10 on PUCAI score	Baron score 0-1		
SANDBORN2009 A	Stool frequency score of 0 and rectal bleeding score of 0.		Complete response (PGA score of 0, i.e. complete resolution of or normalization of stool frequency,	Treatment success/overall improvement (partial response: improvement from baseline in the PGA score and no

			bleeding and sigmoidoscopy with CFT assessment score)	worsening in any of the 3 component scores) and complete response (those that have improved or gone into remission)
SANDBORN2012 B	Score of 0 for both rectal bleeding and stool frequency subscores from the UCDAI		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 no missing 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.	≥3 point reduction in the UCDAI score.
SCHERL2009	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	Mucosal healing (sigmoidoscopy score of 0 or 1)	Complete remission (MMDAI score of ≤1)	
SCHROEDER198 7	Complete response (complete resolution of all symptoms, all assessment scores 0 (stool frequency, rectal bleeding and PGA)			Partial response (substantial but incomplete improvement in the assessment scores). The value has been added to those in remission to give the total number of patients who improved.
SELBY1985				Improvement in the clinical factors measured was judged

				to represent a positive response
SNINSKY1991	Complete resolution of symptoms, with all assessment scores determined to be 0.			A reduction in the PGA score and in at least one other component score with no score increased in severity.
SOOD2002	<150 (activity index ,Seo 1992)			
TARPILA1994			Score of 0 or 1 after 4 weeks	
TRUELOVE1995	Indicted by all of 1 or 2 stools a day without blood, no fever, no tachycardia, Hb normal,ESR normal or returning to normal, gaining weight.			Improved but not reached remission
VAN2003				A score of less than 10 on day 8 with a drop of \ge 3 as compared with baseline
VECCHI2001	CAI<4	EI <4		Reduction in CAI of 50% from baseline
WILLIAMS1987				DAI score of 0
ZINBERG1990				Unknown definition- The inclusion criteria for the Cochrane Systematic review was 'author defined' definition'

7.2 Relapse definitions

Table 96: Study definitions of relapse for the maintenance of remission

Study reference	Remission	Relapse
ANDREOLI1987	Unknown. Included in the Cochrane systematic review.	The development of a new acute phase within 12 months from the beginning of the survey was considered a negative result
ANDREOLI1994	Clinical remission achieved and microscopic inflammation cleared from biopsy specimens	Endoscopic grade >0
ARDIZZONE1999C	Absence of active disease symptoms and no signs of active inflammation on sigmoidoscopy	Increased stool frequency with blood or mucus and evidence of active disease on sigmoidoscopy

AZADKHAN1980	Absence of colitis symptoms and the absence of signs of inflammation on sigmoidoscopy and on histological examination of rectal biopsy specimens as defined by Truelove & Richards	Most relapses were associated with clinical symptoms of colitis but some patients remained free from symptoms but with inflammation on sigmoidoscopy and histology
BARDAZZI1994	Mild symptoms and normal mucosa (endoscopically)	Erythematous and friable mucosa even in the absence of symptoms
COURTNEY1992	Absence of symptoms or the presence of only mild stable symptoms of colitis	Development of new symptoms of colitis sufficiently severe to warrant the introduction of systemic steroid therapy (by an investigator unaware of study treatment)
DALBASIO 1998	Clinical: absence of visible blood in the stools and no more than 2 bowel movements per day. Endoscopic: Score of 0 (Baron's criteria).	Development of symptoms together with evidence of endoscopic activity (grade >1 of Baron's classification)
DALBASIO1990	Mild symptoms and normal mucosa	Erythematous and friable mucosa, even in the absence of symptoms
DALBASIO1997	Mild symptoms and normal endoscopic appearance of the mucosa.	Presence erythematous and friable mucosa even in the absence of symptoms.
DARIENZO1990	Clinical: Absence of blood in the stools and absence of diarrhoea, abdominal pain and tenesmus. Endoscopic: Grade 0 or 1.	Identified by clinical activity endoscopically (grade2-4) and histologically (grade2 or3) confirmed, or in the absence of clinical manifestations, by endoscopic and histological evidence of activity.
DHAENS2012	Endoscopic remission withno or mild symptoms	Withdrawal due to lack of efficacy
DIGNASS2009	UCDAI score <2 at enrolment	UCDAI score of 3-8 is a mild/moderate relapse and >8 is severe
DISSANAYAKE1973	Symptom free and normal mucosa on sigmoidoscopy with no significant inflammation on rectal biopsy	Patient reports colitis symptoms and there is definite evidence of inflammation
GREEN1992	Not specified. Clinical and sigmoidoscopic remission.	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
GREEN1998A	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)	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
HANAUER1996A	Endoscopic appearance of the bowel (score of 0) and by the passage of five or fewer bloodless stools/day	Score of ≥1 on endoscopy at any time (score was from 0-3)

HAWKEY1997	Normal sigmoidoscopic appearances with no rectal bleeding during the week before entry and stools that were not liquid	Sigmoidoscopic score of ≥1 or experienced 3 consecutive days of rectal bleeding caused by UC or liquid stools for 1 week
HAWTHORNE1992	Absence of symptoms of active disease in patients not taking corticosteroids and with a sigmoidoscopic appearance of grade 0 or 1 (Baron et al.).	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.
HAWTHORNE2012		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.
IRELAND1988	Absence of colitis symptoms together with an absence of inflammation on sigmoidoscopy	Increased stool frequency with or without blood or mucus and with evidence of inflammation on sigmoidoscopy
ITO2010B		Bloody stool score of 1 or more and UCDAI of 3 or more.
JEWELL1974	Defined by severity of disease using the criteria of Truelove and Witts (1995)	Occurrence of diarrhoea with blood in the motion and with sigmoidoscopic evidence of inflammation
KAMM2008	Clinical and endoscopic remission (UCDAI score≤1), with rectal bleeding and 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 (from first part of the trial)	A requirement for alternative treatment for UC, including surgery or an increase in the dose of MEZAVANT XL mesalazine above 2.4g/day.
KANE2003	Absence of blood in the stools, urgency or cramping	>3 on the Harvey-Bradshaw index
KANE2008	Absence of blood in the stools, urgency or cramping. UCDAI score <3	UCDAI score >3 or an increase of more than 3 points during the preceding time interval
KIILERICH1992	No visible blood in the stools for >3 days within the last week and/or <3 stools/day for ≥4 days of the last week and sigmoidoscopy grade 1-2 at admission (no spontaneous bleeding without or with distinct vessels in the mucosa)	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)
KRUIS1995	Required normal endoscopic grading	Patients with a change in their normal endoscopic grading to at least moderate activity

KRUIS2001	Clinical remission: CAI<6. Endoscopic remission: CI<4. Remission of UC was both clinical and endoscopic remission	Both clinical and endoscopic relapse: CAI≥6 and EI>4 at completion of the study.
KRUIS2011	CAI≤4 and EI≤3	CAI>4 and an increase of ≥3 from baseline
MANTZARIS1994	Full clinical, endoscopic and histological remission (indexes not described)	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.
MANTZARIS2004	Absence of symptoms of colitis in view of a normal sigmoidoscopy with biopsies (UCDAI 0-1).	Development of new symptoms sufficiently severe to warrant treatment with steroids in view of an abnormal sigmoidoscopy (UCDAI>3)
MARTEAU1998	Clinical remission: No rectal bleeding, no mucus in the stools, no diarrhoea, no pain, and no tenesmus	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 > twice a day.
MATEJIMENEZ2000	Mayo Clinic score <7	Mayo Clinic score of ≥7
MINER1995	Sigmoidoscopic index of <5, mean of <5 stools per day, absence of rectal bleeding	 Three definitions: Sigmoidoscopic index of ≥5 and ≥1 of the following: mean of ≥5 trips to the toilet for 3 of 7 continuous days or the presence of rectal bleeding for 3 of 7 continuous days. Sigmoidoscopic index of ≥5 with missing data for trips to the toilet or rectal bleeding at the end of the study/final visit Missing data for the final Sigmoidoscopic index and early termination from the trial due to insufficient therapeutic effect
MISIEWICZ1965	Absence of symptoms. If the patient remained symptom free, the finding of a haemorrhagic mucosa on sigmoidoscopy did not constitute a relapse.	Recurrence of symptoms.
NILSSON1995	Grade 1 or 2 on endoscopy and no symptoms indicating relapse, such as diarrhoea or rectal bleeding	Suspected if there are >3 stools/day for >5 days and/or visible blood in stool for >4 consecutive days. Confirmed by endoscopy – macroscopic changes of grade 3 or 4 in the rectum.
OREN1996	Mayo score (including sigmoidoscopy results) of ≤ 3 with the condition that the patient was not being administered steroids or a score of ≤ 2 without sigmoidoscopy results	≥3 points in Mayo Clinic score (not including sigmoidoscopy) and/or reintroduction of steroids at a dose of ≥300mg/month
PAOLUZI2005	Absence of symptoms and endoscopic /histological changes typical of active UC	As per the Truelove & Witts criteria.

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.	UCDAI score >1
Free from symptoms	If rectal bleeding occurred for >3 successive days or the patients had had \geq 3 defecations daily for >5 successive day.
Absence of clinical signs of inflammation i.e. 3 stools or less per day without blood and a normal mucus membrane on sigmoidoscopy	Blood in stools, with or without diarrhoea and signs of inflammation on endoscopy. Also if at 48 weeks there was endoscopic inflammation but no presence of complaints.
Absence of blood in the stool	Symptomatic deterioration resulting in a sigmoidoscopy which confirms the macroscopic grading to be worse
<4 bowel movements per day without visible blood or mucus and with no signs of active disease at sigmoidoscopy	Occurrence of diarrhoea with macroscopic blood together with the finding of active inflammation on sigmoidoscopy.
Simple Clinical Colitis Activity Index (SCCAI) score of ≤2	Simple Clinical Colitis Activity Index score of ≥5
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)	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.
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.	Remission followed by worsening of symptoms, recognized by the patient as active disease (such as loose stools/ bowel frequency or rectal bleeding) wit the sigmoidoscopic appearance of active colitis.
	activity index, supported by a rectal sigmoidoscopy in the preceding 3 months or colonoscopy in the preceding 6 months. Free from symptoms Absence of clinical signs of inflammation i.e. 3 stools or less per day without blood and a normal mucus membrane on sigmoidoscopy Absence of blood in the stool <4 bowel movements per day without visible blood or mucus and with no signs of active disease at sigmoidoscopy Simple Clinical Colitis Activity Index (SCCAI) score of ≤2 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) 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

SOOD2003	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.	Worsening of symptoms (bowel bleeding, increased frequency, loose stools) with sigmoidoscopic evidence of active colitis (granularity, friability, spontaneous bleeding).
TRAVIS1994	No clinical symptoms of active disease and no signs of active inflammation on sigmoidoscopy (grade0: normal, 1: pink mucosa of quiescent colitis without visible vessels)	Increase in bowel frequency with blood or mucus and evidence of active disease on sigmoidoscopy
WRIGHT1993	Inactive UC diagnosed by the Truelove & Witts criteria	Relapse of diarrhoea (with or without blood and mucus) thought by the attending physician to warrant introduction of rectal or oral corticosteroids.
ΥΟΚΟΥΑΜΑ2007	Absence of symptoms and a score of <4 on the CAI.	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, antidiarrhoeal 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.

8 References

- 1 MIMS Online. 2013. Available from: http://www.mims.co.uk/ [Last accessed: 3 March 2013]
- 2 Andus T, Kocjan A, Muser M, Baranovsky A, Mikhailova TL, Zvyagintseva TD et al. Clinical trial: a novel high-dose 1 g mesalamine suppository (Salofalk) once daily is as efficacious as a 500-mg suppository thrice daily in active ulcerative proctitis. Inflammatory Bowel Diseases. 2010; 16(11):1947-1956
- 3 Ardizzone S, Doldo P, Ranzi T, Sturniolo GC, Giglio LA, Annese V et al. Mesalazine foam (Salofalk (R) foam) in the treatment of active distal ulcerative colitis. A comparative trial vs Salofalk (R) enema. Italian Journal of Gastroenterology and Hepatology. 1999; 31(8):677-684
- 4 Azad Khan AK, Howes DT, Piris J, Truelove SC. Optimum dose of sulphasalazine for maintenance treatment in ulcerative colitis. Gut. 1980; 21(3):232-240
- 5 Bar-Meir S, Fidder HH, Faszczyk M, Bianchi PG, Sturniolo GC, Mickisch O et al. Budesonide foam vs. hydrocortisone acetate foam in the treatment of active ulcerative proctosigmoiditis. Diseases of the Colon and Rectum. 2003; 46(7):929-936
- 6 Bardazzi G, d'Albasio G, Bonanomi AG, Trallori G, Messori A, Amorosi A et al. Intermittent versus continuous 5-aminosalicylic acid treatment for maintaining remission in ulcerative colitis. Italian Journal of Gastroenterology. 1994; 26(7):334-337
- 7 Baron JH, Connell AM, Kanaghinis TG, Lennard-Jones JE, Jones AF. Out-patient treatment of ulcerative colitis. Comparison between three doses of oral prednisone. BMJ. 1962; 2(5302):441-443
- 8 Biancone L, Gionchetti P, Blanco GDV, Orlando A, Annese V, Papi C et al. Beclomethasone dipropionate versus mesalazine in distal ulcerative colitis: A multicenter, randomized, doubleblind study. Digestive and Liver Disease. 2007; 39(4):329-337
- 9 Binder V, Bondesen S, Bonnevie O. Topical 5-aminosalicylic acid versus prednisolone in ulcerative proctosigmoiditis. A randomized, double-blind multicenter trial. Digestive Diseases and Sciences. 1987; 32(6):598-602
- 10 Brereton N, Bodger K, Kamm MA, Hodgkins P, Yan S, Akehurst R. A cost-effectiveness analysis of MMX mesalazine compared with mesalazine in the treatment of mild-to-moderate ulcerative colitis from a UK perspective. Journal of Medical Economics. 2010; 13(1):148-161
- 11 Buckland A, Bodger K. The cost-utility of high dose oral mesalazine for moderately active ulcerative colitis. Alimentary Pharmacology and Therapeutics. 2008; 28(11-12):1287-1296
- 12 Campieri M, Adamo S, Valpiani D, D'Arienzo A, d'Albasio G, Pitzalis M et al. Oral beclometasone dipropionate in the treatment of extensive and left-sided active ulcerative colitis: a multicentre randomised study. Alimentary Pharmacology and Therapeutics. 2003; 17(12):1471-1480
- 13 Campieri M, Defranchis R, Porro GB, Ranzi T, Brunetti G, Barbara L. Mesalazine (5-Aminosalicyclic Acid) Suppositories in the Treatment of Ulcerative Proctitis Or Distal Proctosigmoiditis - A Randomized Controlled Trial. Scandinavian Journal of Gastroenterology. 1990; 25(7):663-668

- 14 Campieri M, Gionchetti P, Belluzzi A, Brignola C, Tabanelli GM, Miglioli M et al. 5-Aminosalicylic Acid As Enemas Or Suppositories in Distal Ulcerative-Colitis. Journal of Clinical Gastroenterology. 1988; 10(4):406-409
- 15 Campieri M, Gionchetti P, Belluzzi A, Brignola C, Tampieri M, Iannone P 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 Colorectal Disease. 1990; 5(2):79-81
- 16 Campieri M, Gionchetti P, Belluzzi A, Brignola C, Tampieri M, Iannone P et al. Optimum Dosage of 5-Aminosalicylic Acid As Rectal Enemas in Patients with Active Ulcerative-Colitis. Gut. 1991; 32(8):929-931
- 17 Campieri M, Gionchetti P, Belluzzi A, Brignola C, Tampieri M, Iannone P et al. Sucralfate, 5-Aminosalicylic Acid and Placebo Enemas in the Treatment of Distal Ulcerative-Colitis. European Journal of Gastroenterology and Hepatology. 1991; 3(1):41-44
- 18 Campieri M, Paoluzi P, Dalbasio G, Brunetti G, Pera A, Barbara L. 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. 1993; 38(10):1843-1850
- 19 Connolly MP, Nielsen SK, Currie CJ, Marteau P, Probert CS, Travis SP. An economic evaluation comparing concomitant oral and topical mesalazine versus oral mesalazine alone in mild-tomoderately active ulcerative colitis based on results from randomised controlled trial. Journal of Crohn's and Colitis. 2009; 3(3):168-174
- 20 Connolly MP, Poole CD, Currie CJ, Marteau P, Nielsen SK. Quality of life improvements attributed to combination therapy with oral and topical mesalazine in mild-to-moderately active ulcerative colitis. Digestion. 2009; 80(4):241-246
- 21 Cortot A, Maetz D, Degoutte E, Delette O, Meunier P, Tan G et al. Mesalamine Foam Enema Versus Mesalamine Liquid Enema in Active Left-Sided Ulcerative Colitis. American Journal of Gastroenterology. 2008; 103(12):3106-3114
- 22 Courtney MG, Nunes DP, Bergin CF, O'Driscoll M, Trimble V, Keeling PW et al. Randomised comparison of olsalazine and mesalazine in prevention of relapses in ulcerative colitis. Lancet. 1992; 339(8804):1279-1281
- 23 Curtis L. Unit costs of social health care 2011. Canterbury: Personal Social Services Reseach Unit, University of Kent; 2011. Available from: http://www.pssru.ac.uk/project-pages/unitcosts/2011/index.php
- d'Albasio G, Pacini F, Camarri E, Messori A, Trallori G, Bonanomi AG et al. Combined therapy with
 5-aminosalicylic acid tablets and enemas for maintaining remission in ulcerative colitis: a
 randomized double-blind study. American Journal of Gastroenterology. 1997; 92(7):1143-1147
- 25 D'Haens G, Hommes D, Engels L, Baert F, van der Waaij L, Connor P et al. Once daily MMX mesalazine for the treatment of mild-to-moderate ulcerative colitis: a phase II, dose-ranging study. Alimentary Pharmacology and Therapeutics. 2006; 24(7):1087-1097
- 26 D'Haens G, Sandborn WJ, Barrett K, Hodgson I, Streck P. Once-Daily MMX Mesalamine for Endoscopic Maintenance of Remission of Ulcerative Colitis. American Journal of Gastroenterology. 2012; 107(7):1064-1077

- 27 Danielsson A, Hellers G, Lyrenas E, Lofberg R, Nilsson A, Olsson O et al. A controlled randomized trial of budesonide versus prednisolone retention enemas in active distal ulcerative colitis. Scandinavian Journal of Gastroenterology. 1987; 22(8):987-992
- 28 Department of Health. NHS reference costs 2010-11. 2012. Available from: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance /DH_131140 [Last accessed: 29 November 2012]
- 29 Department of Health Payment by Results Team. Payment by Results Guidance 2009-10. Leeds. Department of Health, 2009 Available from: www.dh.gov.uk/pbr
- 30 Dick AP, Grayson MJ, Carpenter RG, Petrie A. Controlled trial of sulphasalazine in the treatment of ulcerative colitis. Gut. 1964; 5:437-442
- 31 Dignass AU, Bokemeyer B, Adamek H, Mross M, Vinter-Jensen L, Borner N et al. Mesalamine Once Daily Is More Effective Than Twice Daily in Patients With Quiescent Ulcerative Colitis. Clinical Gastroenterology and Hepatology. 2009; 7(7):762-769
- 32 Dissanayake AS, Truelove SC. A controlled therapeutic trial of long-term maintenance treatment of ulcerative colitis with sulphazalazine (Salazopyrin). Gut. 1973; 14(12):923-926
- 33 Farup PG, Hinterleitner TA, Lukas M, Hebuterne X, Rachmilewitz D, Campieri M et al. Mesalazine 4 g 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 Diseases. 2001; 7(3):237-242
- 34 Farup PG, Hovde O, Halvorsen FA, Raknerud N, Brodin U. Mesalazine Suppositories Versus Hydrocortisone Foam in Patients with Distal Ulcerative-Colitis - A Comparison of the Efficacy and Practicality of 2 Topical Treatment Regimens. Scandinavian Journal of Gastroenterology. 1995; 30(2):164-170
- 35 Fenwick E, Briggs A. Cost-effectiveness acceptability curves in the dock: case not proven? Mecial Decision Making. 2007; 27(2):93-95
- 36 Ferry GD, Kirschner BS, Grand RJ, Issenman RM, Griffiths AM, Vanderhoof JA 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. 1993; 17(1):32-38
- 37 Feurle GE, Theuer D, Velasco S, Barry BA, Wordehoff D, Sommer A et al. Olsalazine Versus Placebo in the Treatment of Mild to Moderate Ulcerative-Colitis - A Randomized Double-Blind Trial. Gut. 1989; 30(10):1354-1361
- 38 Forbes A, Al-Damluji A, Ashworth S, Bramble M, Herbert K, Ho J et al. Multicentre randomizedcontrolled clinical trial of Ipocol, a new enteric-coated form of mesalazine, in comparison with Asacol in the treatment of ulcerative colitis. Alimentary Pharmacology and Therapeutics. 2005; 21(9):1099-1104
- 39 Gibson PR, Fixa B, Pekarkova B, Batovsky M, Radford-Smith G, Tibitanzl J 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 and Therapeutics. 2006; 23(7):1017-1026

- 40 Gionchetti P, Rizzello F, Venturi A, Ferretti M, Brignola C, Miglioli M et al. Comparison of oral with rectal mesalazine in the treatment of ulcerative proctitis. Diseases of the Colon and Rectum. 1998; 41(1):93-97
- 41 Green JR, Swan CH, Rowlinson A, Gibson JA, Brown P, Kerr GD et al. Short report: comparison of two doses of balsalazide in maintaining ulcerative colitis in remission over 12 months. Alimentary Pharmacology and Therapeutics. 1992; 6(5):647-652
- 42 Green JRB, Gibson JA, Kerr GD, Swarbrick ET, Lobo AJ, Holdsworth CD et al. Maintenance of remission of ulcerative colitis: A comparison between balsalazide 3 g daily and mesalazine 1.2 g daily over 12 months. Alimentary Pharmacology and Therapeutics. 1998; 12(12):1207-1216
- 43 Green JRB, Lobo AJ, Holdsworth CD, Leicester RJ, Gibson JA, Kerr GD et al. Balsalazide is more effective and better tolerated than mesalamine in the treatment of acute ulcerative colitis. Gastroenterology. 1998; 114(1):15-22
- 44 Gross V, Bar-Meir S, Lavy A, Mickisch O, Tulassay Z, Pronai L et al. Budesonide foam versus budesonide enema in active ulcerative proctitis and proctosigmoiditis. Alimentary Pharmacology and Therapeutics. 2006; 23(2):303-312
- 45 Gross V, Bunganic I, Belousova EA, Mikhailova TL, Kupcinskas L, Kiudelis G 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. 2011; 5(2):129-138
- 46 Hanauer S, Schwartz J, Robinson M, Roufail W, Arora S, Cello J et al. Mesalamine Capsules for Treatment of Active Ulcerative-Colitis - Results of A Controlled Trial. American Journal of Gastroenterology. 1993; 88(8):1188-1197
- 47 Hanauer SB. An oral preparation of mesalamine as long-term maintenance therapy for ulcerative colitis. A randomized, placebo-controlled trial. Annals of Internal Medicine. 1996; 124(2):204-211
- 48 Hanauer SB. Dose-ranging study of mesalamine (PENTASA) enemas in the treatment of acute ulcerative proctosigmoiditis: Results of a multicentered placebo-controlled trial. Inflammatory Bowel Diseases. 1998; 4(2):79-83
- 49 Hanauer SB, Barish C, Pambianco D, Sigmon R, Gannan R, Koval G. A multi-center, double-blind, placebo-controlled, dose-ranging trial of olsalazine for mild-moderately active ulcerative colitis. Gastroenterology. 1996; 110:A921
- 50 Hanauer SB, Robinson M, Pruitt R, Lazenby AJ, Persson T, Nilsson L et al. Budesonide enema for the treatment of active, distal ulcerative colitis and proctitis: A dose-ranging study. Gastroenterology. 1998; 115(3):525-532
- 51 Hanauer SB, Sandborn WJ, Dallaire C, Archambault A, Yacyshyn B, Yeh C et al. Delayed-release oral mesalamine 4.8 g/day (800 mg tablets) compared to 2.4 g/day (400 mg tablets) for the treatment of mildly to moderately active ulcerative colitis: The ASCEND I trial. Canadian Journal of Gastroenterology. 2007; 21(12):827-834
- 52 Hanauer SB, Sandborn WJ, Kornbluth A, Katz S, Safdi M, Woogen S et al. Delayed-release oral mesalamine at 4.8 g/day (800 mg tablet) for the treatment of moderately active ulcerative colitis: the ASCEND II trial. American Journal of Gastroenterology. 2005; 100(11):2478-2485
- 53 Hartmann F, Stein J, BudMesa-Study Group. Clinical trial: controlled, open, randomized multicentre study comparing the effects of treatment on quality of life, safety and efficacy of

budesonide or mesalazine enemas in active left-sided ulcerative colitis. Alimentary Pharmacology and Therapeutics. 2010; 32(3):368-376

- 54 Hawkey CJ, Dube LM, Rountree LV, Linnen PJ, Lancaster JF. A trial of zileuton versus mesalazine or placebo in the maintenance of remission of ulcerative colitis. The European Zileuton Study Group For Ulcerative Colitis. Gastroenterology. 1997; 112(3):718-724
- 55 Hawthorne AB, Logan RFA, Hawkey CJ, Foster PN, Axon ATR, Swarbrick ET et al. Randomized Controlled Trial of Azathioprine Withdrawal in Ulcerative-Colitis. BMJ. 1992; 305(6844):20-22
- 56 Hetzel DJ, Shearman DJC, Bochner F, Imhoff DM, Gibson GE, Fitch RJ et al. Azodisalicylate (Olsalazine) in the Treatment of Active Ulcerative-Colitis - A Placebo Controlled Clinical-Trial and Assessment of Drug Disposition. Journal of Gastroenterology and Hepatology. 1986; 1(3):257-266
- 57 Hiwatashi N, Suzuki Y, Mitsuyama K, Munakata A, Hibi T. Clinical trial: Effects of an oral preparation of mesalazine at 4 g/day on moderately active ulcerative colitis. A phase III parallel-dosing study. Journal of Gastroenterology. 2011; 46(1):46-56
- 58 Ireland A, Mason CH, Jewell DP. Controlled trial comparing olsalazine and sulphasalazine for the maintenance treatment of ulcerative colitis. Gut. 1988; 29(6):835-837
- 59 Ito H, Iida M, Matsumoto T, Suzuki Y, Aida Y, Yoshida T 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 Diseases. 2010; 16(9):1575-1582
- 60 Ito H, Iida M, Matsumoto T, Suzuki Y, Sasaki H, Yoshida T 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 Diseases. 2010; 16(9):1567-1574
- 61 Jewell DP, Truelove SC. Azathioprine in Ulcerative-Colitis Final Report on Controlled Therapeutic Trial. BMJ. 1974; 4(5945):627-630
- 62 Jiang XL, Cui HF. Different therapy for different types of ulcerative colitis in China. World Journal of Gastroenterology. 2004; 10(10):1513-1520
- 63 Joint Formulary Committee. British national formulary. 61st edition. London: British Medical Association and Royal Pharmaceutical Society; 2011. Available from: http://www.bnf.org.uk
- 64 Kamm MA, Lichtenstein GR, Sandborn WJ, Schreiber S, Lees K, Barrett K et al. Randomised trial of once- or twice-daily MMX mesalazine for maintenance of remission in ulcerative colitis. Gut. 2008; 57(7):893-902
- 65 Kamm MA, Sandborn WJ, Gassull M, Schreiber S, Jackowski L, Butler T et al. Once-daily, highconcentration MMX mesalamine in active ulcerative colitis. Gastroenterology. 2007; 132(1):66-75
- 66 Kane S, Holderman W, Jacques P, Miodek T. Once daily versus conventional dosing of pHdependent mesalamine long-term to maintain quiescent ulcerative colitis: Preliminary results from a randomized trial. Patient Preference and Adherence. 2008; 2:253-258
- 67 Kane S, Huo D, Magnanti K. A pilot feasibility study of once daily versus conventional dosing mesalamine for maintenance of ulcerative colitis. Clinical Gastroenterology and Hepatology. 2003; 1(3):170-173

- 68 Kiilerich S, Ladefoged K, Rannem T, Ranlov PJ. Prophylactic effects of olsalazine v sulphasalazine during 12 months maintenance treatment of ulcerative colitis. The Danish Olsalazine Study Group. Gut. 1992; 33(2):252-255
- 69 Koehler E, Brown E, Haneuse SJ. On the Assessment of Monte Carlo Error in Simulation-Based Statistical Analyses. American Statistician. 2009; 63(2):155-162
- 70 Kolkman JJ, Mollmann HW, Mollmann AC, Pena AS, Greinwald R, Tauschel HD et al. Evaluation of oral budesonide in the treatment of active distal ulcerative colitis. Drugs of Today. 2004; 40(7):589-601
- 71 Kruis W, Bar-Meir S, Feher J, Mickisch O, Mlitz H, Faszczyk M et al. The optimal dose of 5aminosalicylic acid in active ulcerative colitis: a dose-finding study with newly developed mesalamine. Clinical Gastroenterology and Hepatology. 2003; 1(1):36-43
- 72 Kruis W, Jonaitis L, Pokrotnieks J, Mikhailova TL, Horynski M, Batovsky M 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. 2011; 33(3):313-322
- 73 Kruis W, Judmaier G, Kayasseh L, Stolte M, Theuer D, Scheurlen C et al. Double-blind dose-finding study of olsalazine versus sulphasalazine as maintenance therapy for ulcerative colitis. European Journal of Gastroenterology and Hepatology. 1995; 7(5):391-396
- 74 Kruis W, Kiudelis G, Racz I, Gorelov IA, Pokrotnieks J, Horynski M et al. Once daily versus three times daily mesalazine granules in active ulcerative colitis: a double-blind, double-dummy, randomised, non-inferiority trial. Gut. 2009; 58(2):233-240
- 75 Kruis W, Schreiber S, Theuer D, Brandes JW, Schutz E, Howaldt S et al. Low dose balsalazide (1.5 g twice daily) and mesalazine (0.5 g three times daily) maintained remission of ulcerative colitis but high dose balsalazide (3.0 g twice daily) was superior in preventing relapses. Gut. 2001; 49(6):783-789
- 76 Lamet M. A multicenter, randomized study to evaluate the efficacy and safety of mesalamine suppositories 1 g at bedtime and 500 mg Twice daily in patients with active mild-to-moderate ulcerative proctitis. Digestive Diseases and Sciences. 2011; 56(2):513-522
- 77 Lamet M, Ptak T, Dallaire C, Shah U, Grace M, Spenard J et al. Efficacy and safety of mesalamine 1 g HS versus 500 mg BID suppositories in mild to moderate ulcerative proctitis: a multicenter randomized study. Inflammatory Bowel Diseases. 2005; 11(7):625-630
- 78 Lauritsen K, Laursen LS, Bukhave K, Rask-Madsen J. 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. 1986; 91(4):837-844
- 79 Lee FI, Jewell DP, Mani V, Keighley MRB, Kingston RD, Record CO et al. A randomised trial comparing mesalazine and prednisolone foam enemas in patients with acute distal ulcerative colitis. Gut. 1996; 38(2):229-233
- 80 Lemann M, Galian A, Rutgeerts P, Vanheuverzwijn R, Cortot A, Viteau JM et al. Comparison of Budesonide and 5-Aminosalicylic Acid Enemas in Active Distal Ulcerative-Colitis. Alimentary Pharmacology and Therapeutics. 1995; 9(5):557-562

- 81 Lennard-Jones JE, Longmore AJ, Newell AC, Wilson CWE, Jones FA. An Assessment of Prednisone, Salazopyrin, and Topical Hydrocortisone Hemisuccinate Used As Out-Patient Treatment for Ulcerative Colitis. Gut. 1960; 1(3):217-222
- 82 Levine DS, Riff DS, Pruitt R, Wruble L, Koval G, Sales D et al. A randomized, double blind, dose-response comparison of balsalazide (6.75 g), balsalazide (2.25 g), and mesalamine (2.4 g) in the treatment of active, mild-to-moderate ulcerative colitis. American Journal of Gastroenterology. 2002; 97(6):1398-1407
- 83 Lichtenstein GR, Kamm MA, Boddu P, Gubergrits N, Lyne A, Butler T 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 Hepatology. 2007; 5(1):95-102
- 84 Lindgren S, Lofberg R, Bergholm L, Hellblom M, Carling L, Ung KA et al. Effect of budesonide enema on remission and relapse rate in distal ulcerative colitis and proctitis. Scandinavian Journal of Gastroenterology. 2002; 37(6):705-710
- 85 Lofberg R, Ostergaard TO, Langholz E, Schioler R, Danielsson A, Suhr O et al. Budesonide versus prednisolone retention enemas in active distal ulcerative colitis. Alimentary Pharmacology and Therapeutics. 1994; 8(6):623-629
- 86 Mackowiak J, 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. Managed Care Interface. 2006; 19(10):39-46, 56
- 87 Marakhouski Y, Fixa B, Holoman J, Hulek P, Lukas M, Batovsky M et al. A double-blind doseescalating trial comparing novel mesalazine pellets with mesalazine tablets in active ulcerative colitis. Alimentary Pharmacology and Therapeutics. 2005; 21(2):133-140
- 88 Marteau P, Probert CS, Lindgren S, Gassul M, Tan TG, Dignass A 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. 2005; 54(7):960-965
- 89 Meyers S, Sachar DB, Present DH, Janowitz HD. Olsalazine sodium in the treatment of ulcerative colitis among patients intolerant of sulfasalazine. A prospective, randomized, placebo-controlled, double-blind, dose-ranging clinical trial. Gastroenterology. 1987; 93(6):1255-1262
- 90 Miglioli M, Brunetti G, Sturniolo GC, Bianchi PG, Campieri M, Cottone M et al. Oral 5-ASA (Asacol) in mild ulcerative colitis. A randomized double blind dose ranging trial. Italian Journal of Gastroenterology. 1989; 21(1 SUPPL.):7-8
- 91 Miner J, Hanauer S, Robinson M, Schwartz J, Arora S. Safety and efficacy of controlled-release mesalamine for maintenance of remission in ulcerative colitis. Digestive Diseases and Sciences. 1995; 40(2):296-304
- 92 Misiewicz JJ, Lennard-Jones JE, Connell AM, Baron JH, Avery Jones F. Controlled trial of sulphasalazine in maintenance therapy for ulcerative colitis. Lancet. 1965; 285(7378):185-188
- 93 National Clinical Guideline Centre. Crohn's disease: management in adults, children and young people. London. National Clinical Guideline Centre, 2012 Available from: http://guidance.nice.org.uk/CG152

- 94 National Institute for Health and Clinical Excellence. Guide to the methods of technology appraisal. London: National Institute for Health and Clinical Excellence; 2008. Available from: http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf
- 95 National Institute for Health and Clinical Excellence. Infliximab for acute exacerbations of ulcerative colitis (TA163). London. National Institute for Health and Clinical Excellence (NICE), 2008 Available from: http://guidance.nice.org.uk/TA163
- 96 National Institute for Health and Clinical Excellence. The guidelines manual. London: National Institute for Health and Clinical Excellence; 2009. Available from: http://www.nice.org.uk/aboutnice/howwework/developingniceclinicalguidelines/clinicalguidelin edevelopmentmethods/GuidelinesManual2009.jsp
- 97 NHS Business Services Authority. NHS electronic drug tariff. 2012. Available from: http://www.ppa.org.uk/edt/April_2012/mindex.htm [Last accessed: 15 April 2012]
- 98 Nilsson A, Danielsson A, Lofberg R, Benno P, Bergman L, Fausa O et al. Olsalazine versus sulphasalazine for relapse prevention in ulcerative colitis: a multicenter study. American Journal of Gastroenterology. 1995; 90(3):381-387
- 99 Ogata H, Matsui T, Nakamura M, Iida M, Takazoe M, Suzuki Y et al. A randomised dose finding study of oral tacrolimus (FK506) therapy in refractory ulcerative colitis. Gut. 2006; 55(9):1255-1262
- 100 Oren R, Arber N, Odes S, Moshkowitz M, Keter D, Pomeranz I et al. Methotrexate in chronic active ulcerative colitis: a double-blind, randomized, Israeli multicenter trial. Gastroenterology. 1996; 110(5):1416-1421
- 101 Paoluzi OA, Iacopini F, Pica R, Crispino P, Marcheggiano A, Consolazio A et al. Comparison of two different daily dosages (2.4 vs. 1.2 g) of oral mesalazine in maintenance of remission in ulcerative colitis patients: 1-year follow-up study. Alimentary Pharmacology and Therapeutics. 2005; 21(9):1111-1119
- 102 Pokrotnieks J, Marlicz K, Paradowski L, Margus B, Zaborowski P, Greinwald R. Efficacy and tolerability of mesalazine foam enema (Salofalk foam) for distal ulcerative colitis: A double-blind, randomized, placebo-controlled study. Alimentary Pharmacology and Therapeutics. 2000; 14(9):1191-1198
- 103 Poole CD, Connolly MP, Nielsen SK, Currie CJ, Marteau P. A comparison of physician-rated disease severity and patient reported outcomes in mild to moderately active ulcerative colitis. Journal of Crohn's and Colitis. 2010; 4(3):275-282
- 104 Porro GB, Prantera C, Campieri M, Petrillo M, Campanini MC, Gionchetti P et al. Comparative trial of methylprednisolone and budesonide enemas in active distal ulcerative colitis. European Journal of Gastroenterology and Hepatology. 1994; 6(2):125-130
- 105 Powell-Tuck J, Bown RL, Lennard-Jones JE. A comparison of oral prednisolone given as single or multiple daily doses for active proctocolitis. Scandinavian Journal of Gastroenterology. 1978; 13(7):833-837
- 106 Prantera C, Kohn A, Campieri M, Caprilli R, Cottone M, Pallone F 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. 2009; 30(9):908-918

- 107 Prantera C, Viscido A, Biancone L, Francavilla A, Giglio L, Campieri M. A new oral delivery system for 5-ASA: Preliminary clinical findings for MMx. Inflammatory Bowel Diseases. 2005; 11(5):421-427
- 108 Prenzler A, Yen L, Mittendorf T, von der Schulenburg JM. Cost effectiveness of ulcerative colitis treatment in Germany: a comparison of two oral formulations of mesalazine. BMC Health Services Research. 2011; 11:157
- 109 Pruitt R, Hanson J, Safdi M, Wruble L, Hardi R, Johanson J et al. Balsalazide is superior to mesalamine in the time to improvement of signs and symptoms of acute mild-to-moderate ulcerative colitis. American Journal of Gastroenterology. 2002; 97(12):3078-3086
- 110 Raedler A, Behrens C, Bias P. 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 and Therapeutics. 2004; 20(11-12):1353-1363
- 111 Riis P, Anthonisen P, Wulff HR, Folkenborg O, Bonnevie O, Binder V. The prophylactic effect of salazosulphapyridine in ulcerative colitis during long-term treatment. A double-blind trial on patients asymptomatic for one year. Scandinavian Journal of Gastroenterology. 1973; 8(1):71-74
- 112 Rijk MCM, Tongerson JHM. The efficacy and safety of sulphasalazine and olsalazine in patients with active ulcerative colitis. Gastroenterology. 1991; 100:A243
- 113 Rijk MCM, Van Lier HJJ, Van Tongeren JHM. Relapse-preventing effect and safety of sulfasalazine and olsalazine in patients with ulcerative colitis in remission: A prospective, double-blind, randomized multicenter study. American Journal of Gastroenterology. 1992; 87(4):438-442
- 114 Riley SA, Mani V, Goodman MJ, Herd ME, Dutt S, Turnberg LA. Comparison of delayed-release 5aminosalicylic acid (mesalazine) and sulfasalazine as maintenance treatment for patients with ulcerative colitis. Gastroenterology. 1988; 94(6):1383-1389
- 115 Rizzello F, Gionchetti P, D'Arienzo A, Manguso F, Di Matteo G, Annese V et al. Oral beclometasone dipropionate in the treatment of active ulcerative colitis: a double-blind placebocontrolled study. Alimentary Pharmacology and Therapeutics. 2002; 16(6):1109-1116
- 116 Rizzello F, Gionchetti P, Galeazzi R, Novelli G, Valpiani D, D'Arienzo A et al. Oral beclomethasone dipropionate in patients with mild to moderate ulcerative colitis: a dose-finding study. Advances in Therapy. 2001; 18(6):261-271
- 117 Robinson M, Gitnick G, Balart L, Das K, Turkin D. Olsalazine in the treatment of mild to moderate ulcerative colitis. Gastroenterology. 1988; 84:A381
- 118 Romano C, Famiani A, Comito D, Rossi P, Raffa V, Fries W. Oral beclomethasone dipropionate in pediatric active ulcerative colitis: a comparison trial with mesalazine. Journal of Pediatric Gastroenterology and Nutrition. 2010; 50(4):385-389
- 119 Sandberg-Gertzen H, Jarnerot G, Kraaz W. Azodisal sodium in the treatment of ulcerative colitis. A study of tolerance and relapse-prevention properties. Gastroenterology. 1986; 90(4):1024-1030
- 120 Sandborn WJ, Korzenik J, Lashner B, Leighton JA, Mahadevan U, Marion JF et al. Once-daily dosing of delayed-release oral mesalamine (400-mg tablet) is as effective as twice-daily dosing for maintenance of remission of ulcerative colitis. Gastroenterology. 2010; 138(4):1286-1296

- 121 Sandborn WJ, Regula J, Feagan BG, Belousova E, Jojic N, Lukas M et al. Delayed-release oral mesalamine 4.8 g/day (800-mg tablet) is effective for patients with moderately active ulcerative colitis. Gastroenterology. 2009; 137(6):1934-1943
- 122 Sandborn WJ, Travis S, Moro L, Jones R, Gautille T, Bagin R et al. Once-Daily Budesonide MMX[REGISTERED] Extended-Release Tablets Induce Remission in Patients With Mild to Moderate Ulcerative Colitis: Results From the CORE I Study. Gastroenterology. 2012; 143(5):1218
- 123 Scherl EJ, Pruitt R, Gordon GL, Lamet M, Shaw A, Huang S et al. Safety and efficacy of a new 3.3 g b.i.d. tablet formulation in patients with mild-to-moderately-active ulcerative colitis: a multicenter, randomized, double-blind, placebo-controlled study. American Journal of Gastroenterology. 2009; 104(6):1452-1459
- 124 Schroeder KW, Tremaine WJ, Ilstrup DM. Coated Oral 5-Aminosalicylic Acid Therapy for Mildly to Moderately Active Ulcerative-Colitis - A Randomized Study. New England Journal of Medicine. 1987; 317(26):1625-1629
- 125 Selby WS, Barr GD, Ireland A. Olsalazine in active ulcerative colitis. BMJ. 1985; 291(6506):1373-1375
- 126 Sninsky CA, Cort DH, Shanahan F, Powers BJ, Sessions JT, Pruitt RE et al. Oral Mesalamine (Asacol) for Mildly to Moderately Active Ulcerative-Colitis A Multicenter Study. Annals of Internal Medicine. 1991; 115(5):350-355
- 127 Sood A, Midha V, Sood N, Kaushal V, Awasthi G. Methylprednisolone acetate versus oral prednisolone in moderately active ulcerative colitis. Indian Journal of Gastroenterology. 2002; 21(1):11-13
- 128 Tarpila S, Turunen U, Seppala K, Aukee S, Pikkarainen P, Elomaa I et al. Budesonide enema in active haemorrhagic proctitis--a controlled trial against hydrocortisone foam enema. Alimentary Pharmacology and Therapeutics. 1994; 8(6):591-595
- 129 Travis SP, Tysk C, de Silva HJ, Sandberg-Gertzen H, Jewell DP, Jarnerot G. Optimum dose of olsalazine for maintaining remission in ulcerative colitis. Gut. 1994; 35(9):1282-1286
- 130 Truelove SC, Watkinson G, Draper G. Comparison of corticosteroid and sulphasalazine therapy in ulcerative colitis. BMJ. 1962; 2(5321):1708-1711
- 131 van Bodegraven AA, Boer RO, Lourens J, Tuynman HA, Sindram JW. Distribution of mesalazine enemas in active and quiescent ulcerative colitis. Alimentary Pharmacology and Therapeutics. 1996; 10(3):327-332
- 132 Vecchi M, Meucci G, Gionchetti P, Beltrami M, Di Maurizio P, Beretta L et al. Oral versus combination mesalazine therapy in active ulcerative colitis: a double-blind, double-dummy, randomized multicentre study. Alimentary Pharmacology and Therapeutics. 2001; 15(2):251-256
- 133 Williams CN, Haber G, Aquino JA. Double-Blind, Placebo-Controlled Evaluation of 5-Asa Suppositories in Active Distal Proctitis and Measurement of Extent of Spread Using Tc-99M-Labeled 5-Asa Suppositories. Digestive Diseases and Sciences. 1987; 32(12):S71-S75
- 134 Willoughby CP, Campieri M, Lanfranchi G. 5-Aminosalicylic acid (Pentasa) in enema form for the treatment of active ulcerative colitis. Italian Journal of Gastroenterology. 1986; 18(1):15-17

- 135 Woods BS, Hawkins N, Scott DA. Network meta-analysis on the log-hazard scale, combining count and hazard ratio statistics accounting for multi-arm trials: a tutorial. BMC Medical Research Methodology. 2010; 10:54
- 136 Wright JP, O'Keefe EA, Cuming L, Jaskiewicz K. Olsalazine in maintenance of clinical remission in patients with ulcerative colitis. Digestive Diseases and Sciences. 1993; 38(10):1837-1842
- 137 Yen EF, Kane SV, Ladabaum U. Cost-effectiveness of 5-aminosalicylic acid therapy for maintenance of remission in ulcerative colitis. American Journal of Gastroenterology. 2008; 103(12):3094-3105
- 138 Yokoyama H, Takagi S, Kuriyama S, Takahashi S, Takahashi H, Iwabuchi M et al. Effect of weekend 5-aminosalicylic acid (mesalazine) enema as maintenance therapy for ulcerative colitis: results from a randomized controlled study. Inflammatory Bowel Diseases. 2007; 13(9):1115-1120
- 139 Zinberg J, Molinas S, Das KM. Double-Blind Placebo-Controlled Study of Olsalazine in the Treatment of Ulcerative-Colitis. American Journal of Gastroenterology. 1990; 85(5):562-566