APPENDIX

Risk of bias assessment: Methods

We assessed risk of bias (RoB) in included studies using the Cochrane Collaboration's evaluation tool, which addresses the following key domains: sequence generation; allocation concealment; blinding; incomplete outcome data; selective outcome reporting; and other sources of bias (e.g. extreme baseline imbalances in prognostic factors, etc). These particular items were considered for RoB assessment and were classified as "adequate" (low RoB), "inadequate" (high RoB), or "unclear" (uncertain RoB). Studies with adequate procedures in all domains were classified as low RoB; studies with inadequate procedures in at least one domain were classified as high RoB; and finally those with unclear procedures in one or more domains were considered to have uncertain RoB.

Discrepancies among reviewers were discussed and agreement was reached by consensus.

Risk of bias assessment: Results

Random sequence generation: 17 studies (55%) were judged to be at low RoB. For 14 studies (45%) information was insufficient to permit judgement (unclear RoB).

Allocation concealment: Eight studies (26%) were judged to be at low RoB. Information for 23 studies (74%) was insufficient.

Blinding of participants and personnel: the vast majority of studies (94%) were double-blind; two studies had a non-blinded design.

Incomplete outcome data: 16 studies (52%) were judged to be at high RoB because the rates of complete follow-up were low with significant imbalances (in numbers and/or reasons) across intervention groups. Four studies identified in regulatory authorities' drug assessment reports did not provide information to assess whether an important problem exists (unclear RoB). The remaining 11 studies (35%) were judged to be at low RoB.

Selective outcome reporting: the majority of studies (65%) were at low RoB. 11 studies (35%) were judged to be at high RoB because one or two outcomes of interest for this review were not reported, so they could not be entered in the meta-analysis.

Other potential threats to validity: One study was judged to be at high RoB because of a skewed allocation into the treatment groups regarding previous prednisone treatment. Four studies identified in regulatory authorities' drug assessment reports did not provide information to assess whether a problem exists (unclear RoB). The remaining 26 studies (84%) were judged to be at low RoB.

Overall, our assessment indicated low RoB in two studies (6%), which had short duration and reported high rates of complete follow-up without other threats to validity. 21 trials (68%) were rated as high-risk, and for the remaining eight (26%) RoB was unclear.

Quality assessment items (per trial) are presented in **Figure 2**.

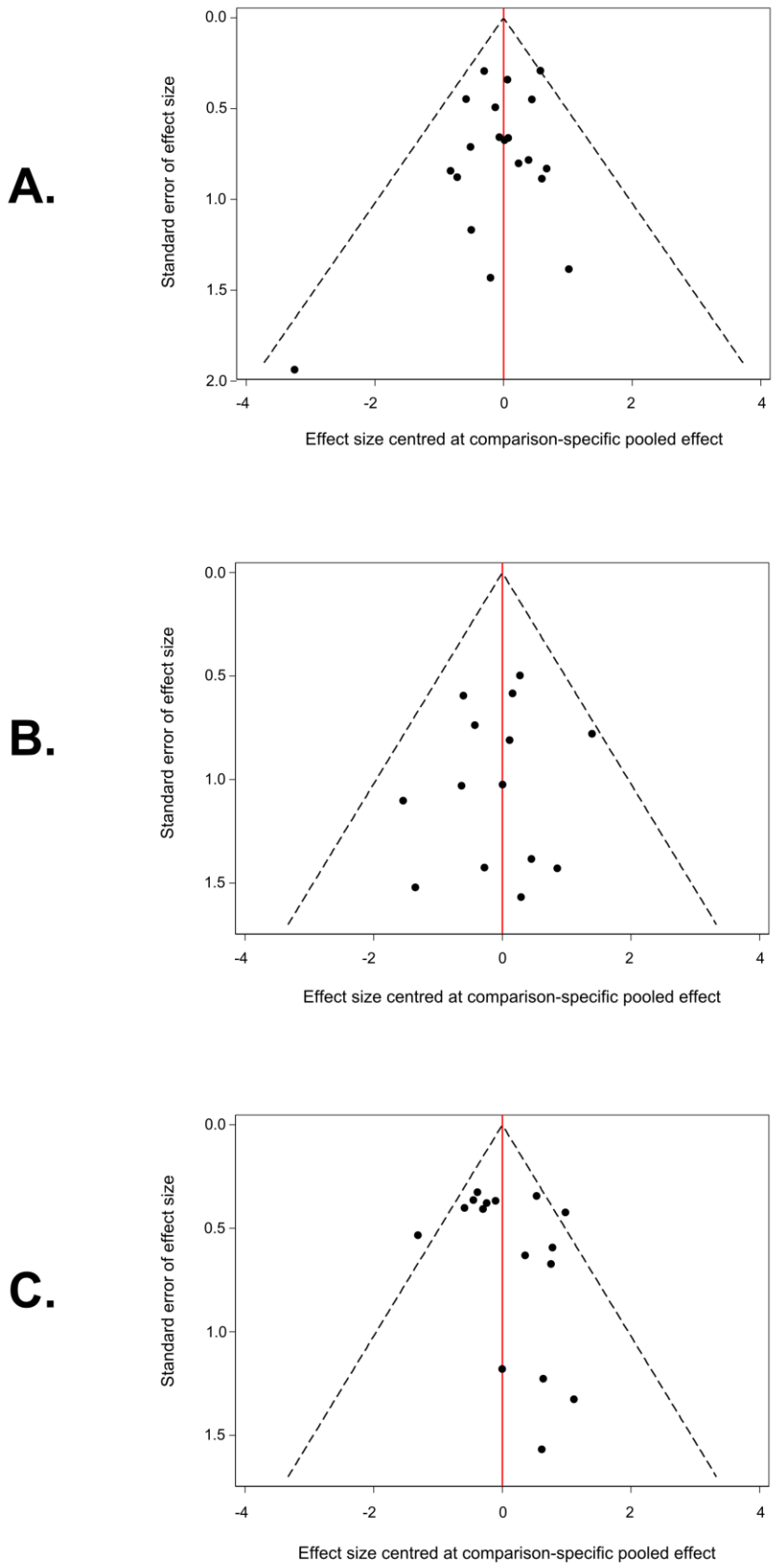

Figure S1. Funnel plots adjusted for inclusion of trials comparing different treatments against placebo.

A. Treatment discontinuation or withdrawal from the study due to adverse events

B. Serious adverse events

C. Corticosteroid-related adverse events

Table S1. Safety assessment of systemic and low-bioavailability steroids in IBD: **short-term group**.

A. Treatment discontinuations or withdrawals from the study due to adverse events

PBO				
0.95 (0.62–1.47)	**B-MMX**			
0.88 (0.52–1.50)	0.93 (0.51–1.67)	**BUD**		
2.22 (0.50–9.86)	2.33 (0.50–10.7)	2.51 (0.58–10.9)	**BDP**	
1.03 (0.33–3.18)	1.08 (0.34–3.45)	1.16 (0.41–3.28)	0.46 (0.13–1.69)	**PRED**

B. Serious adverse events

PBO				
0.71 (0.31–1.64)	**B-MMX**			
1.31 (0.55–3.15)	1.85 (0.56–6.12)	**BUD**		
0.30 (0.01–10.6)	0.42 (0.01–16.0)	0.23 (0.01–7.42)	**BDP**	
0.99 (0.25–3.89)	1.40 (0.30–6.54)	0.76 (0.25–2.33)	3.32 (0.12–89.8)	**PRED**

C. Corticosteroid-related adverse events

PBO				
1.11 (0.72–1.73)	**B-MMX**			
0.83 (0.54–1.28)	0.74 (0.42–1.31)	**BUD**		
0.48 (0.18–1.26)	0.43 (0.15–1.21)	0.58 (0.24–1.36)	**BDP**	
0.33 (0.19–0.60)	**0.30 (0.15–0.60)**	**0.40 (0.27–0.59)**	0.70 (0.32–1.51)	**PRED**

***Footnote**:* The column-defining treatment is compared with the row-defining treatment. The effect estimates in the cells are odds ratios (with 95% confidence intervals) from network meta-analysis. Because the outcomes are negative, ORs lower than 1.0 favour the treatment in the left upper square. Statistically significant results are shown in bold.

***Abbreviations**:* BDP, beclomethasone dipropionate; BUD, budesonide; B-MMX, budesonide MMX; IBD, inflammatory bowel disease; PBO, placebo; PRED, prednisone/prednisolone.

Table S2. Safety assessment of systemic and low-bioavailability steroids in IBD: **short-term group**.

A. Treatment discontinuations or withdrawals from the study due to adverse events

	SUCRA value (%)	Probability Best (%)	Mean Rank
PBO	47.4	6.6	3.1
B-MMX	40.6	6.0	3.4
BUD	30.4	2.7	3.8
BDP	86.8	77.1	1.5
PRED	44.8	7.7	3.2

B. Serious adverse events

	SUCRA value (%)	Probability Best (%)	Mean Rank
PBO	58.1	15.0	2.7
B-MMX	34.4	6.4	3.6
BUD	76.4	41.0	1.9
BDP	25.3	17.1	4.0
PRED	55.8	20.5	2.8

C. Corticosteroid-related adverse events

	SUCRA value (%)	Probability Best (%)	Mean Rank
PBO	76.1	25.3	2.0
B-MMX	87.3	64.0	1.5
BUD	55.8	7.0	2.8
BDP	26.2	3.7	4.0
PRED	4.7	0.0	4.8

***Footnote**:* Herein we present the SUCRA values providing the hierarchy of the competing treatments, the estimated probabilities of each treatment being the best, and the mean ranking of each treatment using 10,000 draws.

***Abbreviations**:* BDP, beclomethasone dipropionate; BUD, budesonide; B-MMX, budesonide MMX; IBD, inflammatory bowel disease; PBO, placebo; PRED, prednisone/prednisolone.

Table S3. Networks' assessment for homogeneity and consistency: **short-term group**.

Outcome	**Heterogeneity variance**	**Global Wald test for inconsistency**
Drug discontinuations or withdrawals due to AEs	tau-squared = 0.25	*p*-value = 0.20
Serious AEs	tau-squared = 0.31	*p*-value = 0.25
Corticosteroid-related AEs	tau-squared = 0.17	*p*-value = 0.27

Abbreviation: AEs, adverse events.

Table S4. Safety assessment of systemic and low-bioavailability steroids in IBD: **long-term group**.

A. Treatment discontinuations or withdrawals from the study due to adverse events

PBO				
2.06 (0.85–4.95)	**B-MMX**			
0.93 (0.54–1.61)	0.45 (0.16–1.28)	**BUD**		
1.42 (0.29–6.83)	0.69 (0.11–4.18)	1.52 (0.29–8.04)	**BDP**	
1.05 (0.46–2.38)	0.51 (0.15–1.69)	1.12 (0.46–2.77)	0.74 (0.13–4.36)	**PRED**

B. Serious adverse events

PBO				
1.03 (0.06–16.9)	**B-MMX**			
0.73 (0.36–1.48)	0.71 (0.04–12.6)	**BUD**		
–	–	–	**BDP**	
0.87 (0.39–1.94)	0.84 (0.05–15.4)	1.18 (0.72–1.94)	–	**PRED**

C. Corticosteroid-related adverse events

PBO				
0.78 (0.16–3.70)	**B-MMX**			
0.54 (0.30–0.99)	0.70 (0.13–3.72)	**BUD**		
0.32 (0.02–4.28)	0.42 (0.02–8.50)	0.60 (0.04–8.44)	**BDP**	
0.22 (0.08–0.63)	0.29 (0.04–1.87)	0.41 (0.15–1.12)	0.69 (0.04–11.1)	**PRED**

***Footnote**:* The column-defining treatment is compared with the row-defining treatment. The effect estimates in the cells are odds ratios (with 95% confidence intervals) from network meta-analysis. Because the outcomes are negative, ORs lower than 1.0 favour the treatment in the left upper square. Statistically significant results are shown in bold.

***Abbreviations**:* BDP, beclomethasone dipropionate; BUD, budesonide; B-MMX, budesonide MMX; IBD, inflammatory bowel disease; PBO, placebo; PRED, prednisone/prednisolone.

Table S5. Safety assessment of systemic and low-bioavailability steroids in IBD: **long-term group**.

A. Treatment discontinuations or withdrawals from the study due to adverse events

	SUCRA value (%)	Probability Best (%)	Mean Rank
PBO	36.3	0.5	3.5
B-MMX	85.1	58.6	1.6
BUD	29.5	1.7	3.8
BDP	57.9	32.0	2.7
PRED	41.2	7.1	3.4

B. Serious adverse events

	SUCRA value (%)	Probability Best (%)	Mean Rank
PBO	64.6	29.7	2.1
B-MMX	55.4	48.4	2.3
BUD	28.1	3.1	3.2
BDP	–	–	–
PRED	51.9	18.7	2.4

C. Corticosteroid-related adverse events

	SUCRA value (%)	Probability Best (%)	Mean Rank
PBO	85.0	48.4	1.6
B-MMX	66.9	33.6	2.3
BUD	48.9	1.3	3.0
BDP	35.7	16.5	3.6
PRED	13.5	0.1	4.5

***Footnote**:* Herein we present the SUCRA values providing the hierarchy of the competing treatments, the estimated probabilities of each treatment being the best, and the mean ranking of each treatment using 10,000 draws.

***Abbreviations**:* BDP, beclomethasone dipropionate; BUD, budesonide; B-MMX, budesonide MMX; IBD, inflammatory bowel disease; PBO, placebo; PRED, prednisone/prednisolone.

Table S6. Networks' assessment for homogeneity and consistency: **long-term group**.

Outcome	**Heterogeneity variance**	**Global Wald test for inconsistency**
Drug discontinuations or withdrawals due to AEs	tau-squared < 0.01	*p*-value = 0.09
Serious AEs	tau-squared < 0.01	*p*-value = 0.19
Corticosteroid-related AEs	tau-squared = 0.59	*p*-value = 0.89

Abbreviation: AEs, adverse events.