

Table Ib. The retrieval used in Embase

| | |
|-----|--|
| #1 | 'irritable colon'/exp |
| #2 | 'irritable bowel syndrome':ab,ti OR 'irritable bowel syndromes':ab,ti OR 'syndrome, irritable bowel':ab,ti OR 'syndromes, irritable bowel':ab,ti OR 'colitis, mucous':ab,ti OR 'colitides, mucous':ab,ti OR 'mucous colitides':ab,ti OR 'mucous colitis':ab,ti OR 'colon, irritable':ab,ti OR 'IBS':ab,ti OR 'IBS-C':ab,ti |
| #3 | #1 OR #2 |
| #4 | 'linaclotide'/exp OR 'tegaserod'/exp OR 'prucalopride'/exp OR 'lubiprostone'/exp OR 'macrogol 3350'/exp OR 'macrogol 4000'/exp OR 'lactulose'/exp OR 'plecanatide'/exp |
| #5 | "SDZ HTF 919":ab,ti OR "SDZ HTF-919":ab,ti OR "HTF 919":ab,ti OR "Zelnorm":ab,ti OR "Zelmac":ab,ti OR "tegaserod maleate":ab,ti OR "5-methoxyindol-3-carboxaldehyde amino(pentylamino)methylenehydrazone hydrogen maleate":ab,ti OR "4-amino-5-chloro-N-(1-(3-methoxypropyl)-4-piperidiny)-2,3-dihydro-1-benzofuran-7-carboxamide":ab,ti OR "R093877":ab,ti OR "R093877":ab,ti OR "Resolor":ab,ti OR "resotran":ab,ti OR "resotrans":ab,ti OR "motegrity":ab,ti OR "Prostan-1-oic acid, 16,16-difluoro-11-hydroxy-9,15-dioxo-, (11alpha)-":ab,ti OR "RU 0211":ab,ti OR "0211, RU":ab,ti OR "RU-0211":ab,ti OR "RU0211":ab,ti OR "SPI 0211":ab,ti OR "0211, SPI":ab,ti OR "SPI-0211":ab,ti OR "SPI0211":ab,ti OR "Amitiza":ab,ti OR "polyethylene glycol 3350":ab,ti OR "Polyethylene glycol 4000":ab,ti OR "PEG 3350":ab,ti OR "NuLytely":ab,ti OR "miralax":ab,ti OR "SF-ELS":ab,ti OR "sulfate-free electrolyte lavage solution":ab,ti OR "Duphalac":ab,ti OR "Normase":ab,ti OR "Amivalex":ab,ti OR "MD-1100 acetate":ab,ti OR "Linaclotide Acetate":ab,ti OR "Linzess":ab,ti OR "MD-1100":ab,ti OR "ASP-0456":ab,ti OR "ASP0456":ab,ti OR "Trulance":ab,ti OR "SP-304":ab,ti |
| #6 | #4 OR #5 |
| #7 | 'randomized controlled trial'/exp |
| #8 | 'clinical trials, randomized':ab,ti OR 'trials, randomized clinical':ab,ti OR 'controlled clinical trials, randomized':ab,ti OR 'randomized':ab,ti |
| #9 | #7 OR #8 |
| #10 | #3 AND #6 AND #9 |

Table Ic. The retrieval used in Cochrane library

| | |
|----|--|
| #1 | MeSH descriptor: [Irritable Bowel Syndrome] explode all trees |
| #2 | (Irritable Bowel Syndromes):ti,ab,kw OR (Syndrome, Irritable Bowel):ti,ab,kw OR (Syndromes, Irritable Bowel):ti,ab,kw OR (Colitis, Mucous):ti,ab,kw OR (Colitides, Mucous):ti,ab,kw OR (Mucous Colitides):ti,ab,kw OR (Mucous Colitis):ti,ab,kw OR (Colon, Irritable):ti,ab,kw OR (Irritable Colon):ti,ab,kw OR (IBS):ti,ab,kw OR (IBS-C):ti,ab,kw |
| #3 | #1 OR #2 |
| #4 | (Tegaserod):ti,ab,kw OR (SDZ HTF 919):ti,ab,kw OR (SDZ HTF-919):ti,ab,kw OR (HTF 919):ti,ab,kw OR (Zelnorm):ti,ab,kw OR (Zelmac):ti,ab,kw OR (tegaserod maleate):ti,ab,kw OR (maleate):ti,ab,kw OR (Prucalopride):ti,ab,kw OR (R 093877):ti,ab,kw OR (R093877):ti,ab,kw OR (Resolor):ti,ab,kw OR (resotran):ti,ab,kw OR (resotrans):ti,ab,kw OR (motegrity):ti,ab,kw OR (Lubiprostone):ti,ab,kw OR (RU 0211):ti,ab,kw OR (0211, RU):ti,ab,kw OR (RU-0211):ti,ab,kw OR (RU0211):ti,ab,kw OR (SPI 0211):ti,ab,kw OR (0211, SPI):ti,ab,kw OR (SPI-0211):ti,ab,kw OR (SPI0211):ti,ab,kw OR (Amitiza):ti,ab,kw OR (polyethylene glycol 3350):ti,ab,kw OR (Polyethylene glycol 4000):ti,ab,kw OR (PEG 3350):ti,ab,kw OR (NuLytely):ti,ab,kw OR (miralax):ti,ab,kw OR (SF-ELS):ti,ab,kw OR (sulfate-free electrolyte lavage solution):ti,ab,kw OR (Lactulose):ti,ab,kw OR (Duphalac):ti,ab,kw OR (Normase):ti,ab,kw OR (Amivalex):ti,ab,kw OR (Linaclotide):ti,ab,kw OR (MD-1100 acetate):ti,ab,kw OR (Linaclotide Acetate):ti,ab,kw OR (Linzess):ti,ab,kw OR (MD-1100):ti,ab,kw OR (ASP-0456):ti,ab,kw OR (ASP0456):ti,ab,kw OR (Plecanatide):ti,ab,kw OR (Trulance):ti,ab,kw OR (SP-304):ti,ab,kw |
| #5 | MeSH descriptor: [Randomized Controlled Trial] explode all trees |
| #6 | (Clinical Trials, Randomized):ti,ab,kw OR (Trials, Randomized Clinical):ti,ab,kw OR (Controlled Clinical Trials, Randomized):ti,ab,kw OR (Randomized):ti,ab,kw |
| #7 | #5 OR #6 |
| #8 | #3 AND #4 AND #7 |

Supplemental Table II. The characteristics of the 16 randomized controlled trials

| Author, year | Design | Sample size | Mean age (years) | Female (%) | Diagnostic criteria | Intervention | contrast | Treatment duration (days) | Outcomes |
|-------------------|-------------|-------------|------------------|------------|---------------------|---|----------|---------------------------|--|
| Rao, S 2012 | Multicenter | 802 | 43.5 | 90.5% | Rome II | Linacotide, 290ug qd | Placebo | 84 | Abdominal symptom Stool condition Safety |
| Tack, J 2005 | Multicenter | 2660 | 40.0 | 100% | Rome II | Tegaserod, 6mg bid | Placebo | 30 | Safety |
| Fukudo, S 2018 | Multicenter | 500 | 46.5 | 48.6% | Rome III | Linacotide, 500ug qd | Placebo | 84 | Safety |
| Novick, J 2002 | Multicenter | 1519 | 41.3 | 100% | Rome I | Tegaserod, 6mg bid | Placebo | 84 | Abdominal symptom Safety |
| Johanson, JF 2008 | Multicenter | 195 | 45.9 | 90.7% | Rome II | Lubiprostone, 8ug/16ug/24ug bid | Placebo | 90 | Safety |
| Fukudo, S 2016 | Multicenter | 559 | 41.0 | 91.1% | Rome III | Linacotide, 62.5ug/125ug/250ug/500ug qd | Placebo | 84 | Safety |

| | | | | | | | | | |
|----------------------|---------------|-----|------|-------|----------|--|---------|----|--|
| Chang, Lin 2021 | Single center | 614 | 46.5 | 81% | Rome III | Linacotide, 290ug qd | placebo | 84 | Abdominal symptom Stool condition Safety |
| Chey, William D 2021 | Multicenter | 593 | 45.4 | 82.1% | Rome III | Tenapanor, 50mg bid | placebo | 84 | Abdominal symptom Stool condition Safety |
| Chey, WD 2012 | Multicenter | 804 | 44 | 90% | Rome II | Linacotide, 290ug qd | placebo | 84 | Abdominal symptom Stool condition Safety |
| Johnston, JM 2010 | Multicenter | 420 | 44.4 | 92% | Rome II | Linacotide, 75ug/150ug/300ug/600ug qd | placebo | 84 | Abdominal symptom Stool condition Safety |
| Yang, YS 2018 | Multicenter | 839 | 41 | 82% | Rome III | Linacotide, 290ug qd | placebo | 84 | Abdominal symptom, Stool condition, Safety |

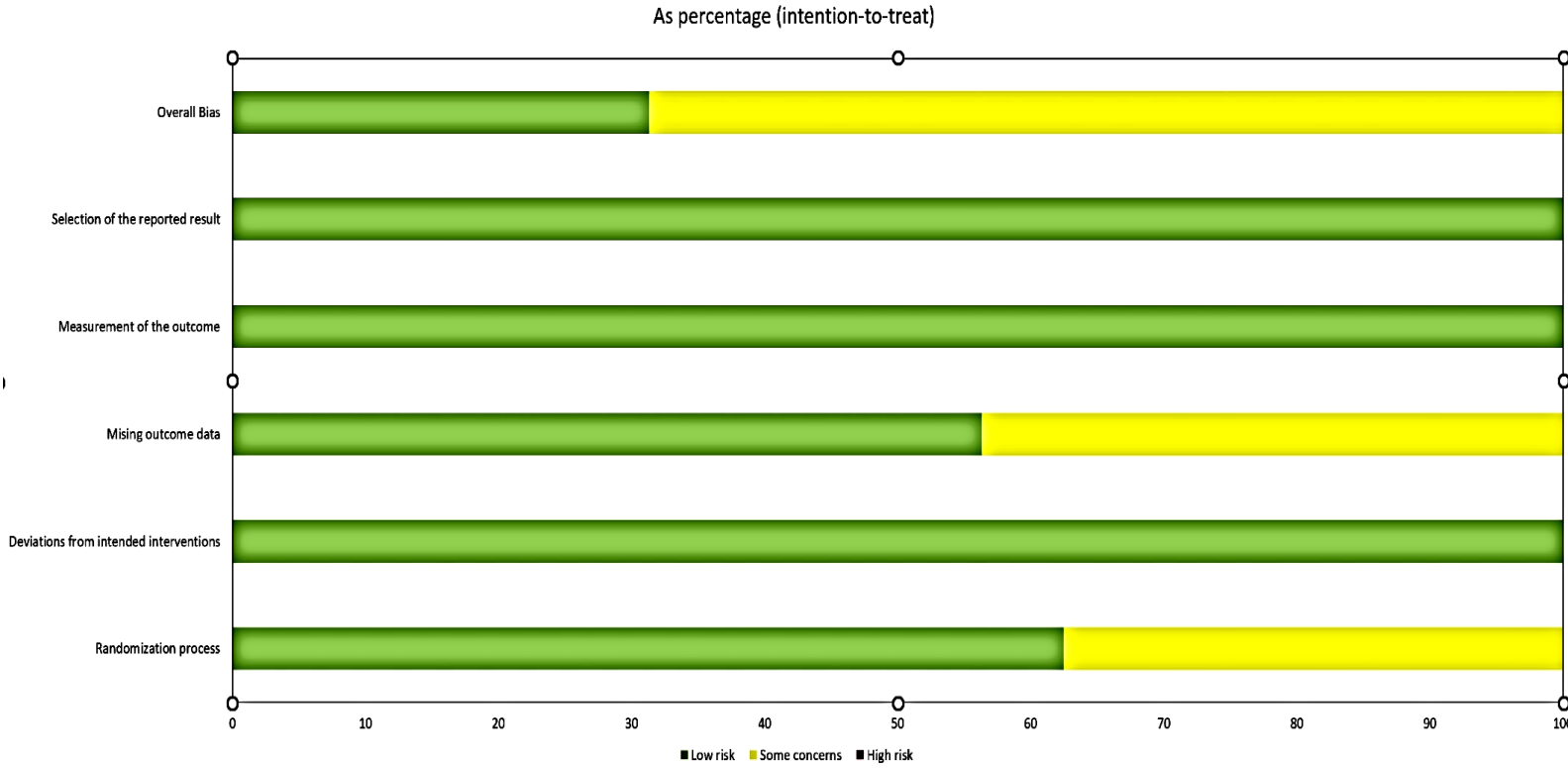
| | | | | | | | | | |
|-------------------------|---------------|-----|------|-------|----------|---------------------------------|---------|----|--|
| Whitehead, WE 2011 | Single center | 62 | 42.0 | 85.5% | Rome III | Lubiprostone 48ug qd | placebo | 14 | Abdominal symptom Stool condition |
| Rao, Satish SC 2020 | Single center | 39 | 42.2 | 97.4% | Rome III | Linacotide, 290ug qd | placebo | 70 | Abdominal symptom Stool condition Safety |
| Chapman, RW 2013 | Single center | 137 | 41.3 | 83.2% | Rome III | PEG 3350+E | placebo | 28 | Abdominal symptom Stool condition |
| Müller-Lissner, SA 2001 | Multicenter | 881 | 45.8 | 83% | Rome | Tegaserod, 2mg/6mg bid | placebo | 84 | Abdominal symptom |
| Chey, William D 2017 | Multicenter | 356 | 45.7 | 86.8% | Rome III | Tenapanor, 5mg/20mg/50mg bid | placebo | 84 | Abdominal symptom Stool condition Safety |

Eg: PEG 3350+E: Polyethylene glycol 3350 plus electrolytes

Supplemental Fig. 1. The risk of bias assessments for the eligible RCTs

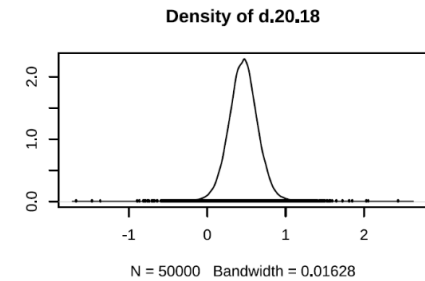
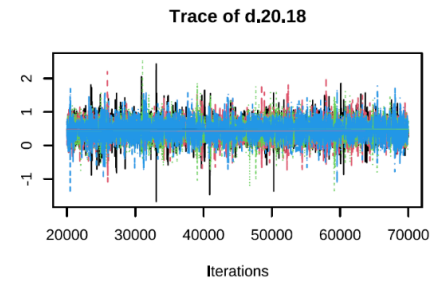
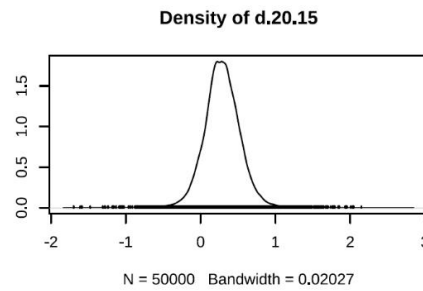
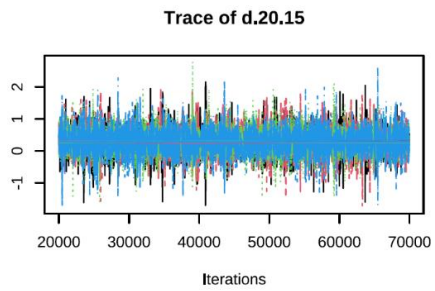
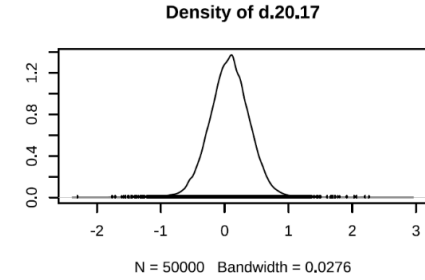
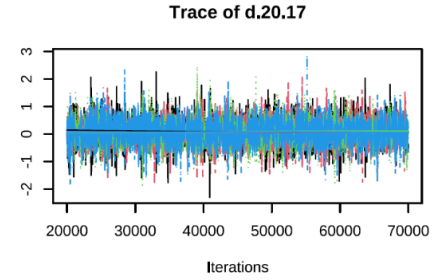
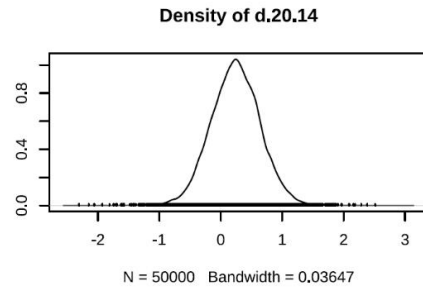
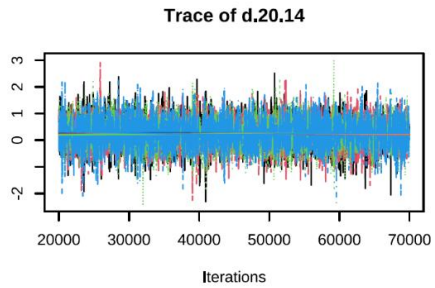
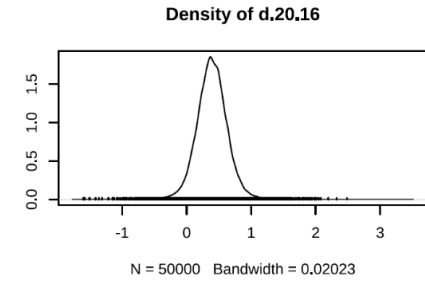
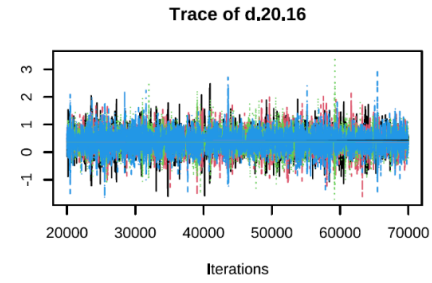
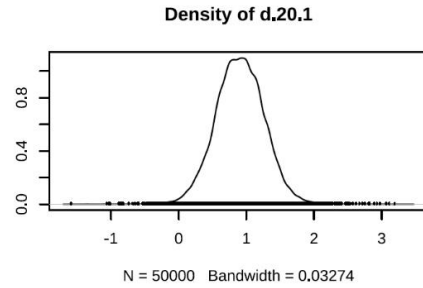
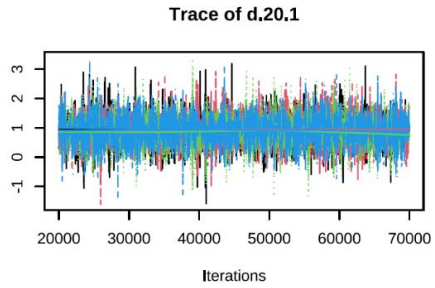
| Intention-to-treat | Unique ID | Study ID | Experimental | Comparator | Outcome | Weight | D1 | D2 | D3 | D4 | D5 | Overall | | |
|--------------------|-----------|-------------------------|--|------------|---|--------|----|----|----|----|----|---------|---|---|
| | 1 | Rao, S 2012 | Linaclotide, 290ug qd | Placebo | Abdominal symptom | 1 | ! | + | + | + | + | ! | + | Low risk |
| | 2 | Tack, J 2005 | Tegaserod, 6mg bid | Placebo | Safety | 1 | + | + | + | + | + | + | + | Some concerns |
| | 3 | Fukudo, S 2018 | Linaclotide, 500ug qd | Placebo | Safety | 1 | + | + | ! | + | + | ! | + | High risk |
| | 4 | Novick, J 2002 | Tegaserod, 6mg bid | Placebo | Abdominal symptom,Safety | 1 | + | + | ! | + | + | ! | + | |
| | 5 | Johanson, JF 2008 | Lubiprostone, 8ug/16ug/24ug bid | Placebo | Safety | 1 | ! | + | ! | + | + | ! | + | D1 Randomisation process |
| | 6 | Fukudo, S 2016 | Linaclotide, 62.5ug/125ug/250ug/500ug qd | Placebo | Safety | 1 | + | + | + | + | + | + | + | D2 Deviations from the intended interventions |
| | 7 | Chang, Lin 2021 | Linaclotide, 290ug qd | placebo | Abdominal symptom, Stool condition,Safety | 1 | + | + | + | + | + | + | + | D3 Missing outcome data |
| | 8 | Chey, William D 2021 | Tenapanor, 50mg bid | placebo | Abdominal symptom, Stool condition,Safety | 1 | ! | + | + | + | + | ! | + | D4 Measurement of the outcome |
| | 9 | Chey, WD 2012 | Linaclotide, 290ug qd | placebo | Abdominal symptom, Stool condition,Safety | 1 | ! | + | ! | + | + | ! | + | D5 Selection of the reported result |
| | 10 | Johnston, JM 2010 | Linaclotide, 75ug/150ug/300ug/600ug qd | placebo | Abdominal symptom, Stool condition,Safety | 1 | + | + | ! | + | + | ! | + | |
| | 11 | Yang, YS 2018 | Linaclotide, 290ug qd | placebo | Abdominal symptom, Stool condition,Safety | 1 | + | + | + | + | + | + | + | |
| | 12 | Whitehead, W E | Lubiprostone 48ug qd | placebo | Abdominal symptom, Stool condition | 1 | + | + | + | + | + | + | + | |
| | 13 | Rao, Satish S C | Linaclotide, 290ug qd | placebo | Abdominal symptom, Stool condition,Safety | 1 | + | + | ! | + | + | ! | + | |
| | 14 | Chapman, RW 2013 | PEG 3350+E | placebo | Abdominal symptom ,Stool condition | 1 | ! | + | + | + | + | ! | + | |
| | 15 | Müller-Lissner, SA 2001 | Tegaserod, 2mg/6mg bid | placebo | Abdominal symptom | 1 | ! | + | + | + | + | ! | + | |
| | 16 | Chey, William D 2017 | Tenapanor | placebo | Abdominal symptom, Stool condition,safety | 1 | + | + | ! | + | + | ! | + | |

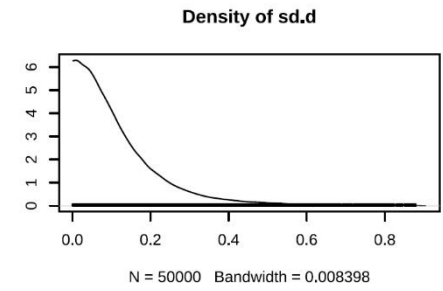
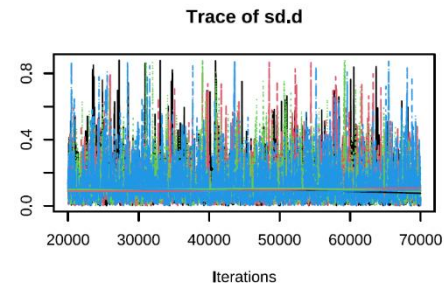
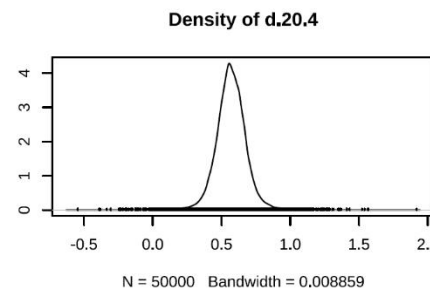
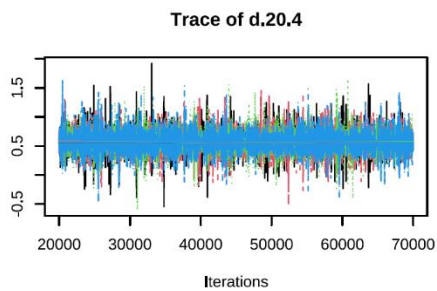
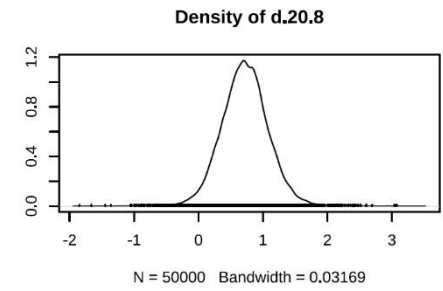
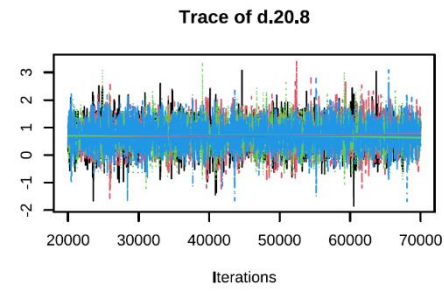
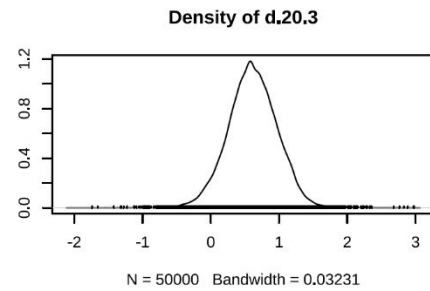
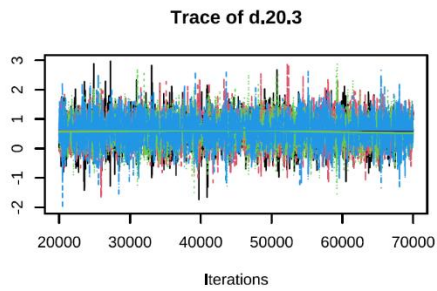
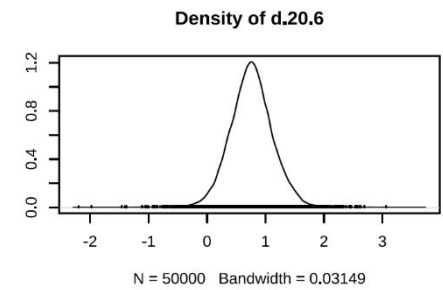
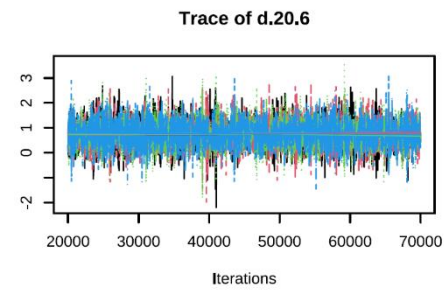
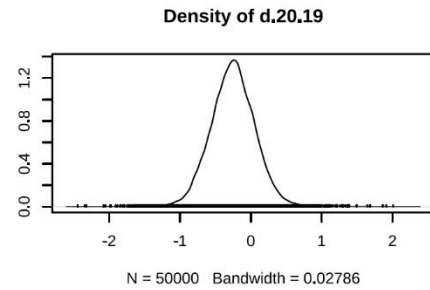
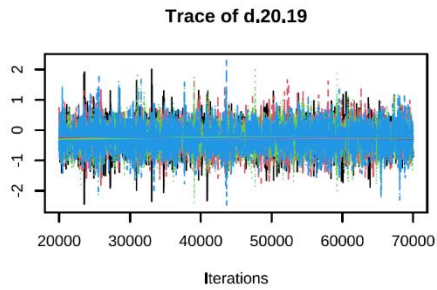
Supplemental Fig. 2. Proportion of items assessed for bias risk



Supplemental Figure 3

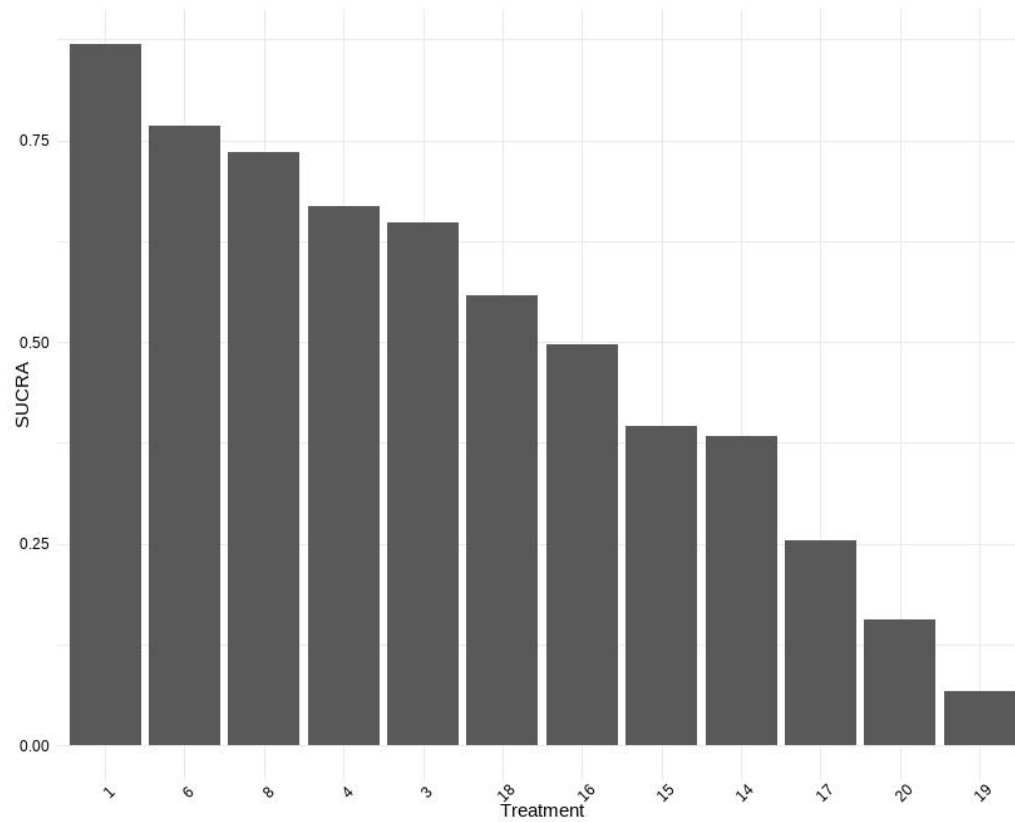
3a. Trace plots and density plots for abdominal pain





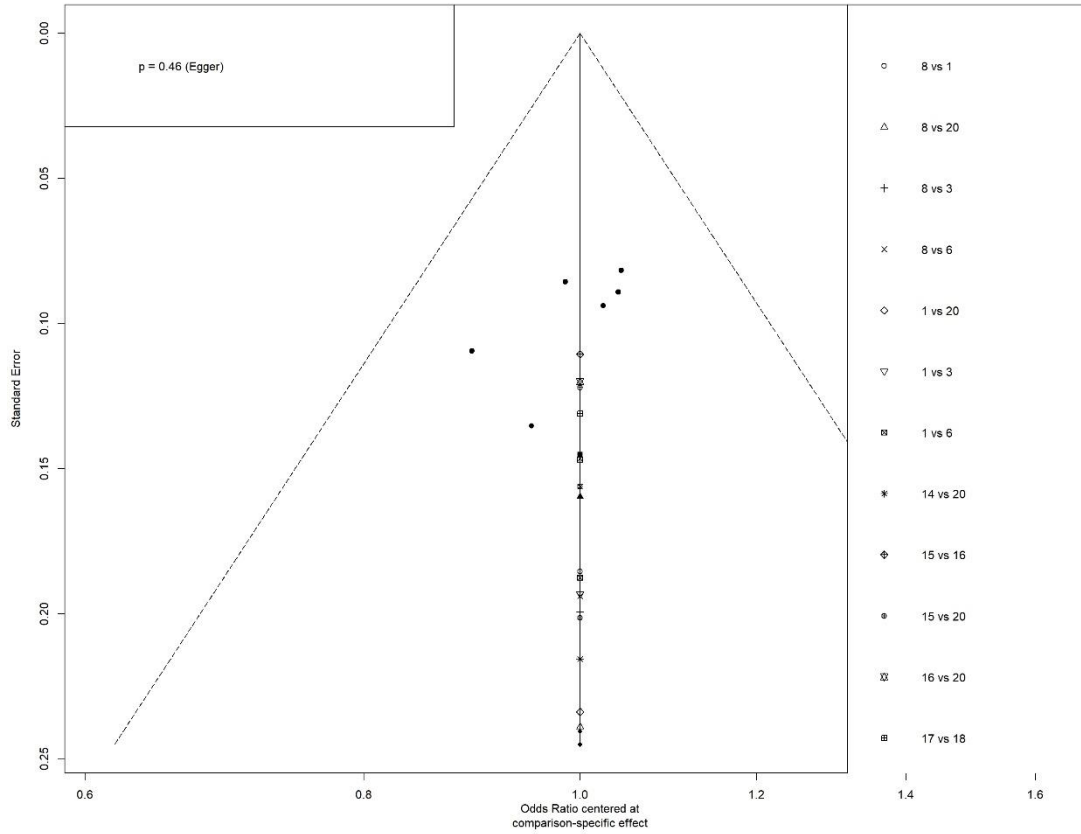
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3b. Efficacy ranking plot for abdominal pain



1, Linaclotide 125ug qd. 3, Linaclotide 250ug qd. 4, Linaclotide 290ug qd. 6, Linaclotide 500ug qd. 8, Linaclotide 62.5ug qd. 14, PEG 3350+E. 15, Tegaserod 2mg bid. 16, Tegaserod 6mg bid. 17, Tenapanor 20mg bid. 18, Tenapanor 50mg bid. 19, Tenapanor 5mg bid. 20, placebo.

3c. Funnel plot of bias assessment for abdominal pain

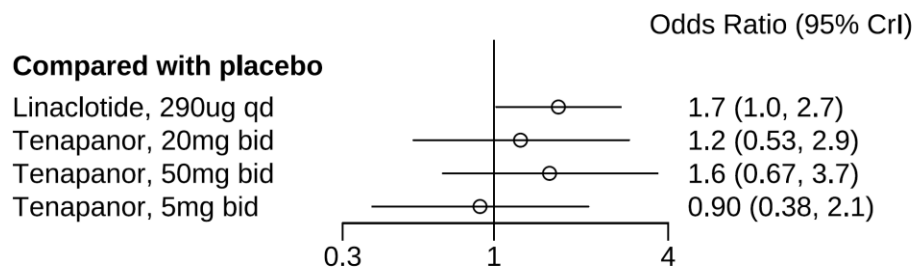


1, Linaclotide 125ug qd. 3, Linaclotide 250ug qd. 4, Linaclotide 290ug qd. 6, Linaclotide 500ug qd. 8, Linaclotide 62.5ug qd. 14, PEG 3350+E. 15, Tegaserod 2mg bid. 16, Tegaserod 6mg bid. 17, Tenapanor 20mg bid. 18, Tenapanor 50mg bid. 19, Tenapanor 5mg bid. 20, placebo.

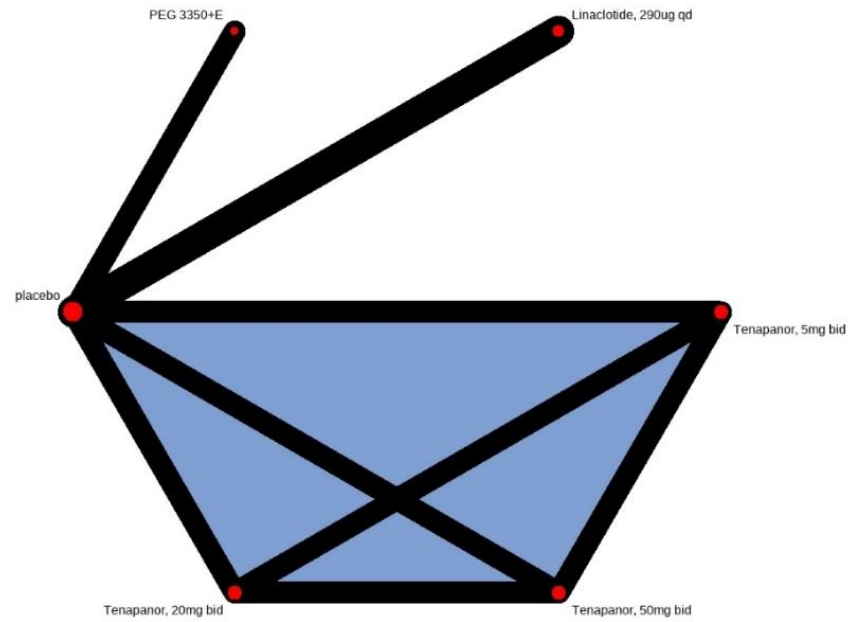
4b. League table for studies on abdominal cramping

| | | | | |
|------------------------|---------------------|---------------------|--------------------|---------|
| Linaclootide, 290ug qd | | | | |
| 1.35 (0.51, 3.6) | Tenapanor, 20mg bid | | | |
| 1.07 (0.4, 2.85) | 0.8 (0.34, 1.85) | Tenapanor, 50mg bid | | |
| 1.87 (0.7, 4.98) | 1.38 (0.59, 3.22) | 1.73 (0.74, 4.1) | Tenapanor, 5mg bid | |
| 1.67 (1.02, 2.74) | 1.24 (0.53, 2.92) | 1.56 (0.67, 3.67) | 0.9 (0.38, 2.12) | placebo |

4c. Forest plots for studies on abdominal cramping



Supplemental Figure 5

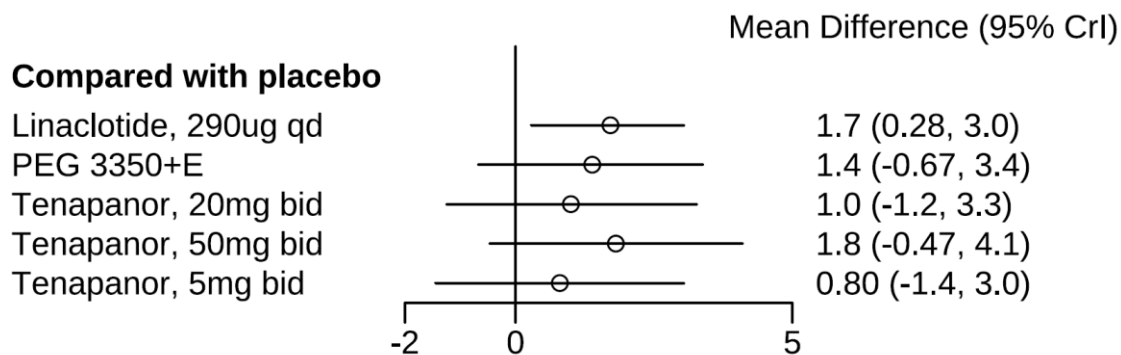


5a. Network diagram for studies on SBMs. Red circle sizes proportional to participant numbers in each intervention, and line thickness representing direct studies comparing two interventions.

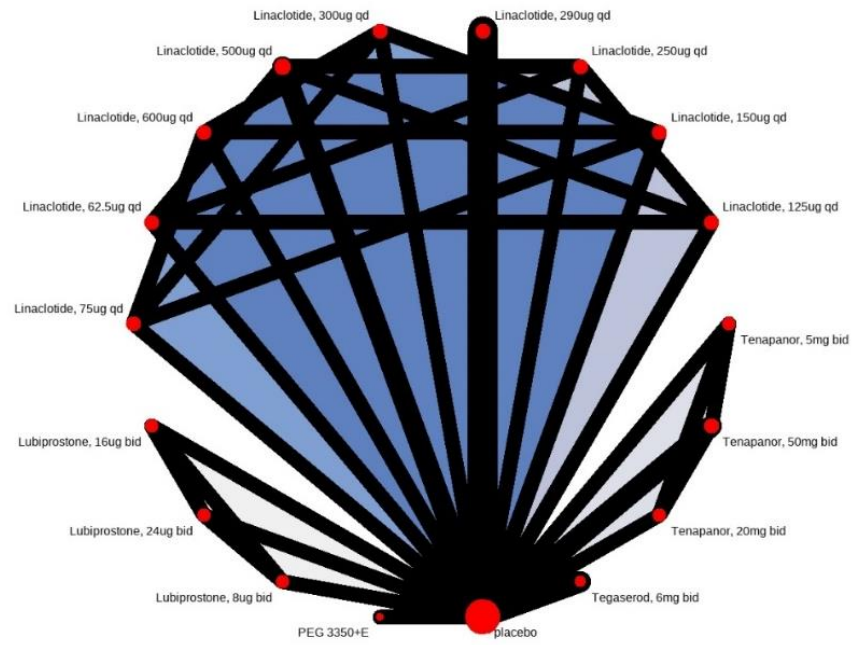
5b. League table for studies on SBMs

| | | | | | | | | | | |
|------------------------|---------------------|------------|---------------------|---------------------|---------------------|---------------------|--------------------|--------------------|-------------------|---------|
| Linaclootide, 290ug qd | 0.31 (-2.16, 2.74) | PEG 3350+E | 0.38 (-2.65, 3.38) | Tenapanor, 20mg bid | -0.81 (-3.06, 1.46) | Tenapanor, 50mg bid | 1.01 (-1.25, 3.28) | Tenapanor, 5mg bid | 0.8 (-1.45, 3.04) | placebo |
| | 0.69 (-1.98, 3.27) | | | | | | | | | |
| | -0.11 (-2.81, 2.49) | | -0.43 (-3.48, 2.59) | | | | | | | |
| | 0.89 (-1.77, 3.48) | | 0.58 (-2.46, 3.58) | | 0.2 (-2.04, 2.45) | | | | | |
| | 1.71 (0.28, 3.04) | | 1.38 (-0.67, 3.38) | | 1 (-1.24, 3.27) | | 1.81 (-0.47, 4.09) | | | |

5c. Forest plots for studies on SBMs



Supplemental Figure 6

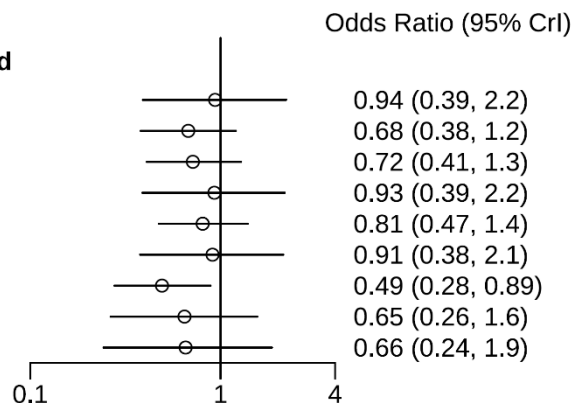


6a. Network diagram for Safety. Red circle sizes proportional to participant numbers in each intervention, and line thickness representing direct studies comparing two interventions.

6b. Forest plots for Safety

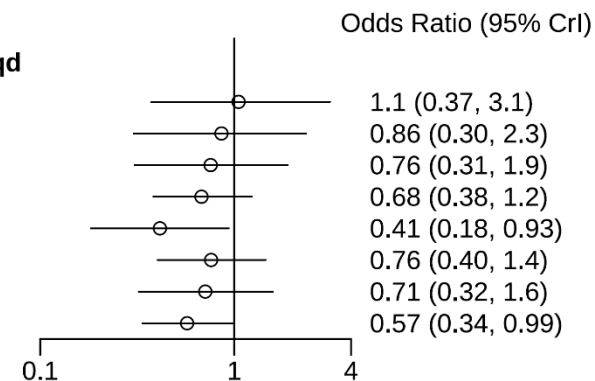
Compared with Linaclotide, 125ug qd

Linaclotide, 150ug qd
 Linaclotide, 250ug qd
 Linaclotide, 290ug qd
 Linaclotide, 300ug qd
 Linaclotide, 500ug qd
 Linaclotide, 600ug qd
 Linaclotide, 62.5ug qd
 Linaclotide, 75ug qd
 Lubiprostone, 16ug bid



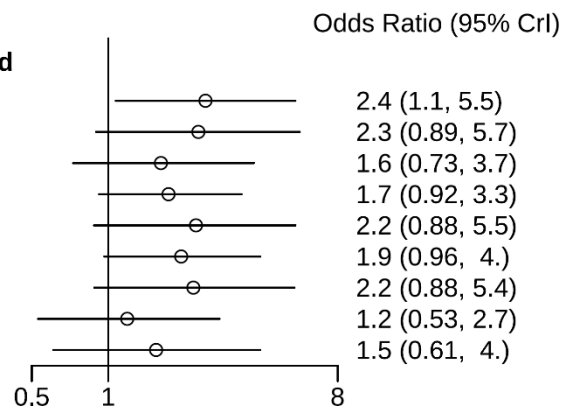
Compared with Linaclotide, 125ug qd

Lubiprostone, 24ug bid
 Lubiprostone, 8ug bid
 PEG 3350+E
 Tegaserod, 6mg bid
 Tenapanor, 20mg bid
 Tenapanor, 50mg bid
 Tenapanor, 5mg bid
 placebo



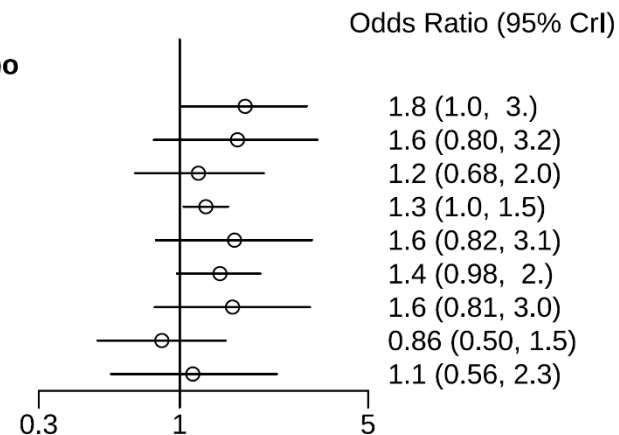
Compared with Tenapanor, 20mg bid

Linaclotide, 125ug qd
 Linaclotide, 150ug qd
 Linaclotide, 250ug qd
 Linaclotide, 290ug qd
 Linaclotide, 300ug qd
 Linaclotide, 500ug qd
 Linaclotide, 600ug qd
 Linaclotide, 62.5ug qd
 Linaclotide, 75ug qd

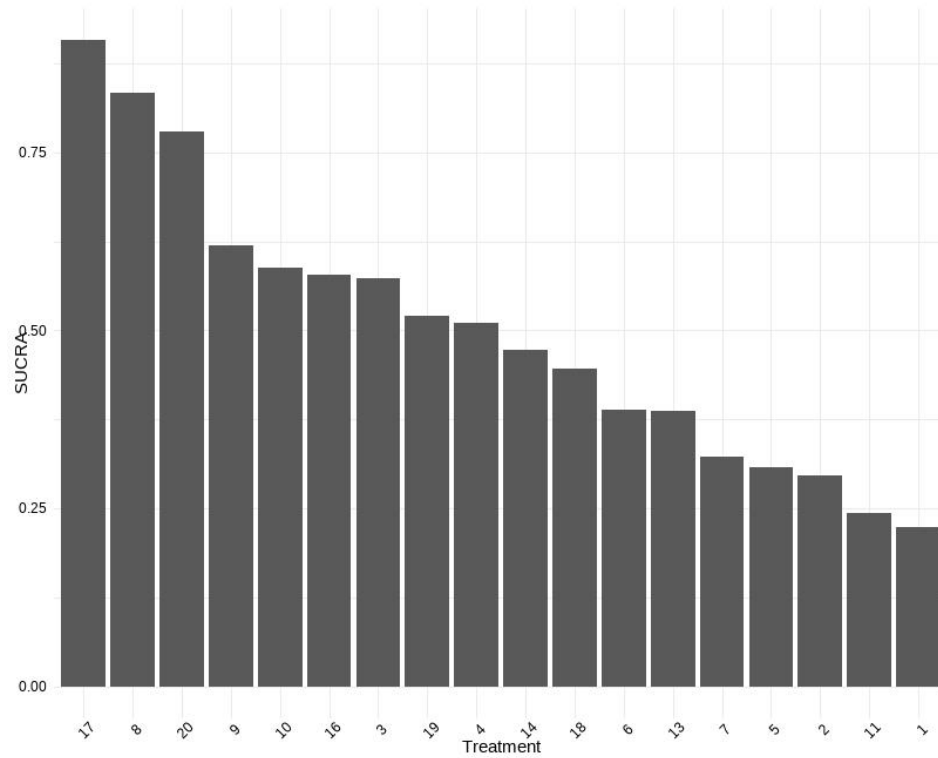


Compared with placebo

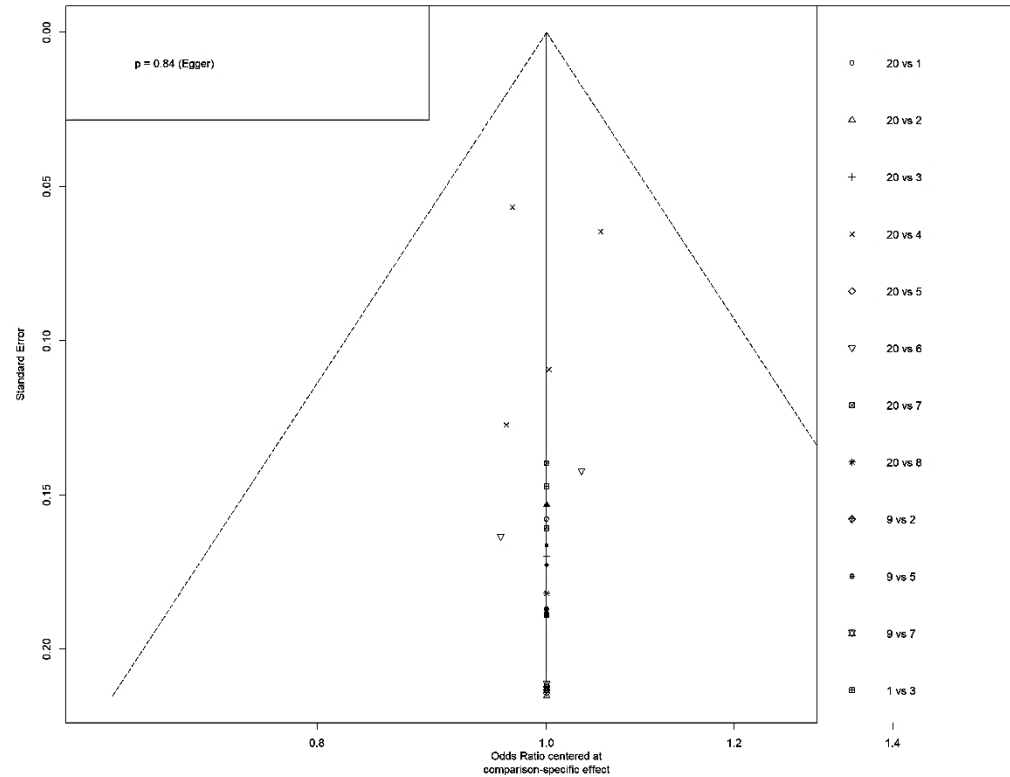
Linaclotide, 125ug qd
 Linaclotide, 150ug qd
 Linaclotide, 250ug qd
 Linaclotide, 290ug qd
 Linaclotide, 300ug qd
 Linaclotide, 500ug qd
 Linaclotide, 600ug qd
 Linaclotide, 62.5ug qd
 Linaclotide, 75ug qd



6c. Efficacy ranking plot for Safety



1, Linaclotide 125ug qd. 2, Linaclotide 150ug qd. 3, Linaclotide 250ug qd. 4, Linaclotide 290ug qd. 5, Linaclotide 300ug qd. 6, Linaclotide 500ug qd. 7, Linaclotide 600ug qd. 8, Linaclotide 62.5ug qd. 9, Linaclotide 75ug qd. 10, Lubiprostone 16ug bid. 11, Lubiprostone 24ug bid. 13, Lubiprostone 8ug bid. 14, PEG 3350+E. 16, Tegaserod 6mg bid. 17, Tenapanor 20mg bid. 18, Tenapanor 50mg bid. 19, Tenapanor 5mg bid. 20, placebo.



6d. Funnel plot of bias assessment for Safety. 1, Linaclotide 125ug qd. 2, Linaclotide 150ug qd. 3, Linaclotide 250ug qd. 4, Linaclotide 290ug qd. 5, Linaclotide 300ug qd. 6, Linaclotide 500ug qd. 7, Linaclotide 600ug qd. 8, Linaclotide 62.5ug qd. 9, Linaclotide 75ug qd. 10, Lubiprostone 16ug bid. 11, Lubiprostone 24ug bid. 13, Lubiprostone 8ug bid. 14, PEG 3350+E. 16, Tegaserod 6mg bid. 17, Tenapanor 20mg bid. 18, Tenapanor 50mg bid. 19, Tenapanor 5mg bid. 20, placebo.