Comparative Efficacy of Linaclotide Versus Other Oral Constipation Treatments in Chronic Constipation: a Network Meta-analysis

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Abstract
This systematic literature review and network meta-analysis (NMA) indirectly compared the Japanese standard dose of linaclotide 500 μg with other oral chronic constipation (CC) treatments. PubMed, Cochrane-CENTRAL, Ichushi-Web, and ClinicalTrials.gov were systematically searched for eligible randomized controlled trials of 43 oral drugs approved globally for CC, including irritable bowel syndrome with constipation (IBS-C) and opioid-induced constipation (OIC). The mean difference (95% credible interval) in change from baseline in weekly number of spontaneous bowel movements (SBM) was compared between linaclotide 500 μg (unapproved in OIC) and other treatments using Bayesian methodology. Fifty-two publications (54 trials) involving 47 treatments (16 drugs, different doses of the same drug treated as different treatments) were included in the NMA. Despite including various drugs/doses, for the mean difference in weekly SBM change, linaclotide 500 μg was statistically significantly more efficacious than other drugs/doses (vs 500 μg linaclotide) including the following: placebo (−1.907; −2.568, −1.237); lubiprostone 16 μg (−2.090; −3.226, −0.968); methylaltrexone 150 mg (−1.807; −3.126, −0.491), 300 mg (−1.411; −2.722, −0.096), and 450 mg (−1.405; −2.708, −0.097); naloxegol 5 mg (−2.074; −4.001, −0.131) and 12.5 mg (−1.329; −2.347, −0.318); and tegaserod 4 μg (−1.133; −2.059, −0.207) and 12 mg (−1.024; −1.822, −0.228), and statistically significantly less effective than linaclotide 600 μg non-approved dose (1.159; 0.123, 2.199) and bisacodyl 10 mg (2.979; 1.723, 4.233). These findings provide relative efficacy data for linaclotide 500 μg vs other constipation drugs/doses regarding improving weekly SBM in CC and IBS-C and may inform clinical decision-making for constipation treatments.

Keywords Constipation · Linaclotide · Network meta-analysis · Systematic literature review

Introduction
Chronic constipation (CC), including functional constipation and irritable bowel syndrome with constipation (IBS-C), affects approximately 14% of adults globally [1], negatively impacts the quality of life of patients, and increases healthcare costs [2–5]. Chronic constipation is characterized by infrequent bowel movements, hard stools, feeling of incomplete evacuation, abdominal discomfort or pain, and bloating sensation [6]. The initial treatment strategy for constipation usually includes non-pharmacological approaches such as dietary fiber, changes in life habits, or exercise, followed by pharmaceutical agents in non-responsive individuals [7, 8]. Several classes of pharmaceutical agents are available for treatment of different types of constipation such as bulking agents (e.g., ispaghula, wheat), osmotic laxatives (polyethylene glycol [PEG], lactulose), stimulant laxatives (e.g., bisacodyl), stool...
softeners and lubricants, prokinetic agents (e.g., prucalopride), and secretagogues (e.g., lubiprostone) [7, 8]. Despite the abundance of treatment options available for the different constipation types, nearly 50% of patients are dissatisfied with current treatments because of lack of efficacy and unwanted side effects [9].

In Japan, the prevalence of CC, including IBS-C, is higher than global estimates (approximately 28%), but there is little epidemiological or humanistic information on CC currently available [10]. Currently, magnesium oxide, followed by stimulant laxatives, are widely used for treatment of CC in Japan [11]. Recently, linaclotide, a first-in-class, minimally absorbed oligo peptide with guanylate cyclase-C agonistic activity [12], was approved for IBS-C followed by CC in Japan [13]. Based on the results of dose-determining clinical studies conducted in Japan and the United States (US), the approved standard dose in Japan is higher (500 μg) than the doses approved for CC (72 μg and 145 μg) and IBS-C (290 μg) in the US [13, 14]. However, the relative efficacy of 500 μg linaclotide in comparison to the available treatment modalities for CC in Japan and globally is unknown because of a lack of head-to-head comparison trials.

In clinical practice, selection of the most appropriate therapy for CC is challenging due to the lack of direct comparisons between the available constipation drugs. Most published trials on constipation treatments are placebo-controlled studies, limiting the ability to compare active treatments [15, 16]. A valid statistical estimate of the comparative efficacy of different treatment modalities can be achieved using a network meta-analysis (NMA) that combines direct head-to-head evidence and indirect comparative evidence [17–20]. An NMA of different treatments for CC has recently been published [21]; however, it did not include patients with IBS-C, was limited to evidence primarily from Western countries, and included a limited number of constipation treatments. The objective of this study was to perform a systematic literature review (SLR) and NMA to compare the efficacy of linaclotide 500 μg to other available treatment modalities (including other linaclotide doses) for CC, including IBS-C.

Methods

Study Design

An SLR and NMA of global (including Japanese) clinical trials on CC was conducted to compare 500 μg linaclotide with other constipation treatments. The conduct of the study was based on a protocol that has been published (Registration Number: CRD42018111737) in the PROSPERO International prospective register of systematic reviews [22]. Identification of studies on CC treatments, the literature search strategy, and the analysis of risk of bias of included studies were performed using the Cochrane Handbook for Systematic Reviews of Intervention [23]. The results have been reported according to the guidelines on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for reporting systematic reviews incorporating an NMA [24].

Search Strategy

The SLR was conducted using the databases PubMed, Ichushi-Web (a Japanese bibliographic database maintained by Japan Medical Abstracts Society), Cochrane-CENTRAL, and ClinicalTrials.gov up to August 8, 2017. The majority of the Cochrane-CENTRAL records were taken from MEDLINE and EMBASE, but records were also derived from other published and unpublished sources [25].

To establish a broad network among constipation treatments, approximately 43 oral drug treatments for constipation were considered for inclusion in the analysis. The comparator drugs, which were identified from the World Health Organization Anatomical Therapeutic Chemical classification system, World Gastroenterology Organisation Global Guidelines, and Japanese guidelines for the treatment of constipation, included the following: linaclotide, liquid paraffin, docusate sodium (sodium diostyl sulfosuccinate), oxyphenasitine, bisacodyl, dantron, phenolphthalein, castor oil, senna glycosides (sennosides), cascara (casanthranol), sodium picosulfate, bisoxatin, ispaghula (psylla seeds), ethulose, sterculia, linseed, methylcellulose, Triticum (wheat fiber), polycarbophil calcium, magnesium carbonate, magnesium oxide, magnesium peroxide, magnesium sulfate, magnesium hydroxide, lactulose, lactitol, sodium sulfate, pentaerithrity, macrocol (or PEG), mannitol, sorbitol, sodium phosphate, magnesium citrate, sodium taartrate, methylalteoxone bromide, alvimopan, naloxegol, naloxone, lubiprostone, prucalopride, tegaserod, plecanatide, and mosapride. The common search terms used were constipation, IBS-C, opioid-induced constipation (OIC), along with the generic and brand names of the above 43 selected treatments, and were searched in all fields. The term OIC was included because some pre-determined drug therapies were approved for OIC in addition to CC and IBS-C (e.g., lubiprostone). Therefore, in addition to treatments for CC and IBS-C, the network was expanded to include studies that also had an OIC treatment arm. Multiple different combinations of these treatments using “and/or” were used. No limits were applied for language, publication date, or publication status; foreign-language publications were translated. The detailed search strategy used for PubMed is shown in Table S1. The search strategies for all databases were similar and were adapted for each database.

Study Selection and Data Extraction

The eligibility criteria involved limiting all searches to randomized controlled trials (RCTs) and quasi-randomized trials
with data for the primary outcome and including all trials conducted in Japan and other countries that included patients > 18 years with CC including IBS-C and OIC. The following studies were excluded: observational studies and studies other than clinical trials or without a control group, studies on patients with organic constipation, any studies assessing constipation treatments other than the 43 selected oral drugs, treatments administered rectally, studies on diagnosis and prevention of constipation, and any studies not reporting the primary outcome measure or with incomplete outcomes.

All studies retrieved from the literature search were assessed for inclusion by two independent reviewers (WT and KI). Reference lists of retrieved studies were also manually searched to identify studies not retrieved by the electronic literature search. After removal of duplicates, studies were screened for eligibility first using titles and abstracts and second using the full text. Any disagreements were resolved by consensus, and resolution of disagreements was finally confirmed by HO. Extraction of data from the eligible trials was conducted by WT and KI. Only published data were used for this analysis. Missing data for any study endpoint were not included in the analysis. Besides the study endpoint, the time point of endpoint data reported, patient characteristics, and the constipation type reported in the eligible studies were also extracted.

Assessment of Risk of Bias

Risk of bias of each trial was conducted in accordance with the Cochrane Handbook for Assessing the Risk of Bias [26]. The risk of bias was categorized as high, low, or unclear.

Outcomes Assessed

The primary endpoints for this study were the change from baseline in weekly number of spontaneous bowel movements (SBM), complete spontaneous bowel movements (CSBM), change in severity scores for abdominal bloating and abdominal discomforts, and change in scores for stool characteristics and patient quality of life. The secondary endpoint was treatment-related adverse events. However, only SBM is reported here because of insufficient or poor-quality data for the other outcomes in the selected studies.

Network Meta-analysis

Outcome data extracted from each of the eligible clinical trials were used to conduct the NMA to indirectly compare the different constipation interventions, including placebo, with linaclotide 500 μg. The treatment modalities included in the NMA were placebo, linaclotide, lubiprostone, plecanatide, PEG, prucalopride, lactulose, bisacodyl, ispaghula, wheat, lactitol, methylnaltrexone, alvimopan, naloxegol, naloxone, and tegaserod. Trials on combination therapies were not included. Trials studying different doses of a single treatment (e.g., 16, 32, and 48 μg lubiprostone; 1, 2, and 4 mg prucalopride; and 0.5 and 1 mg alvimopan) or non-approved treatment dosages (e.g., 1 mg linaclotide 1000 μg) were included in the treatment network. In general, different doses of a single treatment were considered as separate treatment modalities in the network. However, to simplify the network, small differences in drug dosages considered to be clinically equivalent (e.g., 10 and 10.35 g PEG; 579 and 600 μg linaclotide) were pooled into the same drug group [27, 28]. For linaclotide, the following doses were assessed, and those considered clinically equivalent were pooled (with assistance from Ironwood Pharmaceuticals): 72 and 75 μg, 145 and 150 μg, 290 and 300 μg, and 579 and 600 μg. Similarly, for PEG, the 10-g and 10.35-g doses were considered clinically equivalent and were pooled.

An NMA based on the methodology proposed by White et al. [29] using Bayesian modeling was used to analyze the efficacy of all treatments in the network simultaneously. An arm-based approach (as proposed in the methodology by White et al.) was used, whereby for each trial, a model with a baseline treatment outcome, with other treatment outcomes as comparisons to the baseline treatment, was assessed. Non-informative prior distributions were used for the analyses using the Bayesian model. The main outcome parameter of the NMA was the mean difference and 95% credible interval (CrI) for the change in weekly number of SBM before and after linaclotide 500 μg compared with each constipation treatment. Linaclotide 500 μg was considered statistically significantly better than other treatments when the 95% CrI of the treatments was less than 0 and was considered statistically significantly worse than other treatments when the 95% CrI of the treatments was greater than 0.

First, the network of different interventions including placebo was plotted in the NMA. Then, the NMA was conducted by fitting an inconsistency model. Consistency was defined as when the contrast effect of the same set of comparators did not change among different paths in the network. If the contrast effect changed, then inconsistency was considered to exist. Parameters of inconsistency were included in the inconsistency model and the null hypothesis of consistency was checked by globally testing all the inconsistency parameters using the global Wald test. If the consistency was not rejected by the global Wald test, then the NMA was conducted by fitting the consistency model without inconsistency parameters. Both inconsistency and consistency models were fitted by hierarchical Bayesian methodology. All NMA analyses were conducted using WinBUGS (version 1.4.3, MRC Biostatistics Unit, University of Cambridge, UK). The results of the NMA were assessed by two reviewers (HO and SS).

Sensitivity Analyses

The following sensitivity analyses were conducted: NMA limited to trials without high risk of bias, limited to CC (i.e.,
excluding trials of IBS-C and OIC), limited to CC and IBS-C (i.e., excluding trials of OIC), and trials with average baseline weekly SBM less than 3 (severe constipation, i.e., excluding trials with mild-to-moderate constipation).

Results

Study Inclusion

Of the 1577 publications/trial articles retrieved and screened for inclusion, 52 publications (54 trials) were eligible and included in the NMA (Fig. 1). Manual searching identified 4 trials (phase 2 and 3 results of linaclotide in Japan, ClinicalTrials.gov identifiers: NCT01714843, NCT02316899, NCT02425722, and NCT02809105) that were accepted for publication at the time of this study and have since been published [30–33]. After removal of duplicates, trials were excluded if they were not aimed at studying the treatment effects of CC, had interventions not included in the predetermined 43 oral drug list, did not report change in SBM before and after treatment as the endpoint, included patients below the age of 18 years, were evaluating organic constipation, or were non-randomized trials or pre-clinical studies.

Trial and Patient Characteristics

An overview of the study characteristics of the 52 publications (54 trials) for which outcome data were collected is shown in Table 1. Most included studies were placebo-controlled studies; only 3 studies compared active treatments [38, 60, 68] and 2 others compared different doses of the same active treatments [40, 65]. Of the 52 publications, 23 compared different dosages of the same active treatment with placebo as a control group [32–34, 40, 43, 47, 49, 51, 53, 55, 57–59, 61, 62, 64, 65, 67, 72, 73, 75, 76, 78]. The sample size in the trials ranged from 20 patients to 1519 patients. A total of 22,733 patients with constipation (including CC, IBS-C, and OIC) were included across all trials. Although traditional treatments such as magnesium oxide were initially selected, they were not included for analysis in the NMA either due to limited and low-quality evidence or not meeting the inclusion criteria for age.

Overall, there was a low risk of bias within each of the included trials (Fig. S1) and across all trials (Fig. 2). Of the 54 trials, the risk of bias for one trial could not be assessed because the full text could not be obtained [71]. Randomization sequences were adequate and clearly reported in the remaining 53 trials (100%), and blinding of participants and personnel were reported in approximately 94.3% of trials. A high risk of bias was evident for a relatively small proportion of the included trials, primarily because of a lack of blinding of outcome assessments (3 trials, 5.7%). There was an unclear risk of bias for allocation concealment (39 trials, 73.6%) and selective reporting (31 trials, 58.5%).

The patient characteristics across the included studies are shown in Table S2. The average patient age in the studies ranged from 33.7 to 76.4 years, and the baseline SBM ranged from 0.9 to 7.1. Patient age was not reported in 2 studies [45, 49].

Fig. 1 Flow chart for study selection. Exclusion criteria for the first level of screening were no outcome data for effectiveness, safety, satisfaction, or quality of life of patients. The exclusion criterion for the second level of screening was no data for the change in SBM number before and after treatment. SBM, spontaneous bowel movement.
| Reference        | Disease | Arm | Drug          | Dose/day | Patient number | Change from baseline in SBM | Time point of extracted data | Baseline weekly SBM | Baseline weekly SBM (≥ 3:1; < 3:0; unknown: N) |
|------------------|---------|-----|---------------|----------|---------------|-----------------------------|-----------------------------|-------------------|----------------------------------|
| Andresen V, et al. [34] | IBS-C | Arm 1 | Linaclotide | 100 μg | 12 | 0.52/day | 5 days | 1 |
|                  |        | Arm 2 | Linaclotide | 1000 μg | 12 | 0.9/day | 5 days | |
|                  |        | Arm 3 | Placebo     | NA      | 12 | 0.22/day | 5 days | |
| Awad RA, et al. [35] | IBS-C | Arm 1 | PEG         | 10.35 g | 20 | 2.5/week | 30 days | 0 |
|                  |        | Arm 2 | Placebo     | NA      | 22 | 2.8/week | 30 days | 0 |
| Badiali D, et al. [36] | CC    | Arm 1 | Triticum    | 20 g    | 12 | 3.8/week | 4 weeks | 0 |
|                  |        | Arm 2 | Placebo     | NA      | 12 | 2.5/week | 4 weeks | 0 |
| Barish CF, et al. [37] | CC    | Arm 1 | Lubiprostone | 48 μg | 119 | 4.61/week | 1 week | 0 |
|                  |        | Arm 2 | Placebo     | NA      | 118 | 2.49/week | 1 week | 0 |
| Bouchnik Y, et al. [38] | CC    | Arm 1 | PEG         | 20 g    | 32 | 0.28/day | 4 weeks | 1 |
|                  |        | Arm 2 | Lactulose   | 20 g    | 33 | 0.06/day | 4 weeks | 0 |
| Chapman RW, et al. [39] | IBS-C | Arm 1 | PEG         | 26 g    | 67 | 3.12/week | 4 weeks | 0 |
|                  |        | Arm 2 | Placebo     | NA      | 70 | 1.74/week | 4 weeks | 0 |
| Chaussade S, et al. [40] | CC    | Arm 1 | PEG         | 5.9 g   | 67 | 5/week | 4 weeks | 0 |
|                  |        | Arm 2 | PEG         | 10 g    | 66 | 4.4/week | 4 weeks | 0 |
|                  |        | Arm 3 | PEG         | 11.8 g  | 69 | 5.8/week | 4 weeks | 0 |
|                  |        | Arm 4 | PEG         | 20 g    | 67 | 4.8/week | 4 weeks | 0 |
| Chey WD, et al. [41] | IBS-C | Arm 1 | Linaclotide | 290 μg | 401 | 4/week | 12 weeks | 0 |
|                  |        | Arm 2 | Placebo     | NA      | 403 | 1.3/week | 12 weeks | 0 |
| Chey WD, et al. [42] | IBS-C | Arm 1 | Tegaserod   | 12 mg   | 172 | 2.31/week | 4 weeks | 1 |
|                  |        | Arm 2 | Placebo     | NA      | 164 | 1.49/week | 4 weeks | 0 |
| Chey WD, et al. [43] | OIC   | Arm 1 | Naloxegol   | 12.5 mg | 211 | 2.56/week | 12 weeks | 0 |
|                  |        | Arm 2 | Naloxegol   | 25 mg   | 212 | 3.02/week | 12 weeks | 0 |
|                  |        | Arm 3 | Placebo     | NA      | 211 | 2.02/week | 12 weeks | 0 |
|                  |        | Arm 4 | Placebo     | NA      | 231 | 2.1/week | 12 weeks | 0 |
| Christie J, et al. [44] | CC    | Arm 1 | Lubiprostone | 48 μg | 37 | 3.59/week | 4 weeks | 0 |
|                  |        | Arm 2 | Placebo     | NA      | 39 | 2.45/week | 4 weeks | 0 |
| Emmanuel AV, et al. [45] | CC    | Arm 1 | Prucalopride | 1 mg | 37 | 1.8/week | 4 weeks | 0 |
|                  |        | Arm 2 | Placebo     | NA      | 36 | 0.7/week | 4 weeks | 0 |
| Fukudo S, et al. [46] | CC    | Arm 1 | Lubiprostone | 48 μg | 62 | 2.74/week | 2 weeks | 0 |
|                  |        | Arm 2 | Placebo     | NA      | 62 | 1.33/week | 2 weeks | 0 |
| Irving G, et al. [47] | OIC   | Arm 1 | Alvimopan   | 0.5 mg  | 161 | 3.19/week | 12 weeks | 0 |
|                  |        | Arm 2 | Alvimopan   | 1 mg    | 160 | 3.05/week | 12 weeks | 0 |
|                  |        | Arm 3 | Placebo     | NA      | 164 | 2.18/week | 12 weeks | 0 |
| Jamal MM, et al. [48] | OIC   | Arm 1 | Lubiprostone | 48 μg | 212 | 3.2/week | 12 weeks | 0 |
|                  |        | Arm 2 | Placebo     | NA      | 212 | 2.4/week | 12 weeks | 0 |
| Jansen JP, et al. [49] | OIC   | Arm 1 | Alvimopan   | 0.5 mg  | 174 | 3.42/week | 12 weeks | 0 |
|                  |        | Arm 2 | Alvimopan   | 1 mg    | 172 | 3.51/week | 12 weeks | 0 |
|                  |        | Arm 3 | Placebo     | NA      | 172 | 2.01/week | 12 weeks | 0 |
| Johanson JF, et al. [50] | CC    | Arm 1 | Lubiprostone | 48 μg | 120 | 3.69/week | 2 weeks | 0 |
|                  |        | Arm 2 | Placebo     | NA      | 122 | 1.71/week | 2 weeks | 0 |
| Johanson JF, et al. [51] | CC    | Arm 1 | Tegaserod   | 4 mg    | 450 | 1.9/week | 12 weeks | 1 |
|                  |        | Arm 2 | Tegaserod   | 12 mg   | 451 | 1.9/week | 12 weeks | 0 |
|                  |        | Arm 3 | Placebo     | NA      | 447 | 0.9/week | 12 weeks | 0 |
| Johnston JM, et al. [52] | CC    | Arm 1 | Linaclotide | 100 μg | 12 | 6.18/week | 2 weeks | N |
|                  |        | Arm 2 | Placebo     | NA      | 10  | 2.76/week | 2 weeks | N |
### Table 1 (continued)

| Reference               | Disease Arm | Drug     | Dose/day | Patient number | Change from baseline in SBM\(^a\) | Time point of extracted data | Baseline weekly SBM\(^b\) (≥ 3:1; < 3:0; unknown: N) |
|-------------------------|-------------|----------|----------|----------------|----------------------------------|------------------------------|-------------------------------------------------|
| Johnston JM, et al. [53] | IBS-C       | Arm 1    | Linaclotide 75 μg | 79          | 4.62/week                       | 12 weeks                     | Differ by groups                                |
|                         |             | Arm 2    | Linaclotide 150 μg | 82          | 4.36/week                       | 12 weeks                     |                                                 |
|                         |             | Arm 3    | Linaclotide 300 μg | 84          | 4.97/week                       | 12 weeks                     |                                                 |
|                         |             | Arm 4    | Linaclotide 600 μg | 89          | 5.64/week                       | 12 weeks                     |                                                 |
|                         |             | Arm 5    | Placebo NA        | 85          | 1.68/week                       | 12 weeks                     |                                                 |
| Kamm MA, et al. [54]    | CC          | Arm 1    | Placebo NA        | 121         | 0.8/week                        | 4 weeks                      | 1                                               |
|                         |             | Arm 2    | Bisacodyl 10 mg   | 247         | 5.4/week                        | 4 weeks                      |                                                 |
| Kamm MA, et al. [55]    | CC          | Arm 1    | Tegaserod 4 mg    | 417         | 1.6/week                        | 12 weeks                     | 1                                               |
|                         |             | Arm 2    | Tegaserod 12 mg   | 431         | 2/week                          | 12 weeks                     |                                                 |
|                         |             | Arm 3    | Placebo NA        | 416         | 0.9/week                        | 12 weeks                     |                                                 |
| Kienzle-Horn S, et al. [56] | CC        | Arm 1    | Bisacodyl 10 mg   | 27          | 1.13/day                        | 3 days                       | 1                                               |
|                         |             | Arm 2    | Placebo NA        | 27          | 0.28/day                        | 3 days                       |                                                 |
| Lacy BE, et al. [57]    | CC          | Arm 1    | Linaclotide 145 μg | 153         | 3.5/week                        | 12 weeks                     | 0                                               |
|                         |             | Arm 2    | Linaclotide 290 μg | 159         | 3.6/week                        | 12 weeks                     |                                                 |
|                         |             | Arm 3    | Placebo NA        | 171         | 1.5/week                        | 12 weeks                     |                                                 |
| Lembo AJ, et al. [58]   | CC          | Arm 1    | Linaclotide 75 μg | 59          | 2.6/week                        | 4 weeks                      | 0                                               |
|                         |             | Arm 2    | Linaclotide 150 μg | 56          | 3.3/week                        | 4 weeks                      |                                                 |
|                         |             | Arm 3    | Linaclotide 300 μg | 62          | 3.6/week                        | 4 weeks                      |                                                 |
|                         |             | Arm 4    | Linaclotide 600 μg | 62          | 4.3/week                        | 4 weeks                      |                                                 |
|                         |             | Arm 5    | Placebo NA        | 68          | 1.5/week                        | 4 weeks                      |                                                 |
| Lembo AJ, et al. [59]   | CC          | Arm 1    | Linaclotide 145 μg | 217         | 3/week                          | 12 weeks                     | 0                                               |
|                         |             | Arm 2    | Linaclotide 290 μg | 216         | 3/week                          | 12 weeks                     |                                                 |
|                         |             | Arm 3    | Placebo NA        | 209         | 1.1/week                        | 12 weeks                     |                                                 |
| Lembo AJ, et al. [59]   | CC          | Arm 1    | Linaclotide 145 μg | 213         | 3.4/week                        | 12 weeks                     | 0                                               |
|                         |             | Arm 2    | Linaclotide 290 μg | 202         | 3.7/week                        | 12 weeks                     |                                                 |
|                         |             | Arm 3    | Placebo NA        | 215         | 1.1/week                        | 12 weeks                     |                                                 |
| Heitland W, et al. [60] | CC          | Arm 1    | Lactulose 20 g    | 20          | 0.36/day                        | 2 weeks                      | Differ by groups                                |
|                         |             | Arm 2    | Lactitol 20 g     | 30          | 0.49/day                        | 2 weeks                      |                                                 |
| Hongo M, et al. [61]    | CC          | Arm 1    | Lubiprostone 16 μg | 41          | 2.3/week                        | 1 week                       | N                                               |
|                         |             | Arm 2    | Lubiprostone 32 μg | 43          | 3.5/week                        | 1 week                       |                                                 |
|                         |             | Arm 3    | Lubiprostone 48 μg | 44          | 6.8/week                        | 1 week                       |                                                 |
|                         |             | Arm 4    | Placebo NA        | 42          | 1.5/week                        | 1 week                       |                                                 |
| Sanders M, et al. [62]  | OIC         | Arm 1    | Naloxone 2.5 mg   | 8           | 2.21/week                       | 3 weeks                      | 0                                               |
|                         |             | Arm 2    | Naloxone 5 mg     | 8           | 2.36/week                       | 3 weeks                      |                                                 |
|                         |             | Arm 3    | Naloxone 10 mg    | 8           | 4.1/week                        | 3 weeks                      |                                                 |
|                         |             | Arm 4    | Naloxone 20 mg    | 7           | 5.19/week                       | 3 weeks                      |                                                 |
|                         |             | Arm 5    | Placebo NA        | 8           | 1.38/week                       | 3 weeks                      |                                                 |
| Shroff S, et al. [63]   | CC          | Arm 1    | Lubiprostone 48 μg | 34          | 4.12/week                       | 4 weeks                      | N                                               |
|                         |             | Arm 2    | Placebo NA        | 36          | 2.48/week                       | 4 weeks                      |                                                 |
| Sloots CE, et al. [64]  | OIC         | Arm 1    | Placebo NA        | 66          | 1.5/week                        | 4 weeks                      | 0                                               |
|                         |             | Arm 2    | Prucalopride 2 mg | 66          | 2.2/week                        | 4 weeks                      |                                                 |
|                         |             | Arm 3    | Prucalopride 4 mg | 64          | 2.5/week                        | 4 weeks                      |                                                 |
| Sobhani I, et al. [65]  | CC          | Arm 1    | Lactulose 10 g    | 99          | 5.09/week                       | 3 weeks                      | 0                                               |
|                         |             | Arm 2    | Lactulose 20 g    | 99          | 4.88/week                       | 3 weeks                      |                                                 |
| Tomás-Ridocci M, et al. [66] | CC | Arm 1    | Ispaghula 20 g    | 10          | 5.5/week                        | 4 weeks                      | 0                                               |
|                         |             | Arm 2    | Placebo NA        | 10          | 1.15/week                       | 4 weeks                      |                                                 |
|                         |             | Arm 1    | Naloxegol 5 mg    | 31          | 1.3/week                        | 4 weeks                      | 0                                               |
|                         |             | Arm 2    | Naloxegol 25 mg   | 29          | 3/week                          | 4 weeks                      |                                                 |
| Reference | Disease | Arm | Drug | Dose/day | Patient number | Change from baseline in SBM | Time point of extracted data | Baseline weekly SBM ($\geq 3:1; < 3:0; \text{unknown: N}$) |
|-----------|---------|-----|------|----------|-----------------|-----------------------------|-----------------------------|---------------------------------|
| Webster L, et al. [67] |  | Arm 3 | Naloxegol | 50 mg | 30 | 3.5/week | 4 weeks |  |
|  |  | Arm 4 | Placebo | NA | 95 | 1.3/week | 4 weeks |  |
| Xu Z, et al. [68] | CC | Arm 1 | Lactitol | 10 g | 63 | 4.29/week | 7 days | 0 |
|  |  | Arm 2 | Lactulose | 10 g | 66 | 4.29/week | 7 days | 0 |
| Fenn GC, et al. [69] | CC | Arm 1 | Ispaghula | 10.8 g | 91 | 4.7/week | 14 days | 0 |
|  |  | Arm 2 | Placebo | NA | 84 | 2.2/week | 14 days | 0 |
| Lin SR, et al. [70] | CC | Arm 1 | Tegaserod | 12 mg | 304 | 1.57/week | 4 weeks | N |
|  |  | Arm 2 | Placebo | NA | 303 | 0.89/week | 4 weeks | 0 |
| Mareya S, et al. [71] | OIC | Arm 1 | Lubiprostone | 48 µg | 572 | 3.2/week | 12 weeks | N |
|  |  | Arm 2 | Placebo | NA | 568 | 2.7/week | 12 weeks | 0 |
| Miner PB, et al. [72] | CC | Arm 1 | Plecanatide | 3 mg | 453 | 3.2/week | 12 weeks | 0 |
|  |  | Arm 2 | Plecanatide | 6 mg | 441 | 3.1/week | 12 weeks | 0 |
|  |  | Arm 3 | Placebo | NA | 452 | 1.3/week | 12 weeks | 0 |
| Müller-Lissner S, et al. [73] | CC | Arm 1 | Prucalopride | 1 mg | 76 | 2.4/week | 4 weeks | 1 |
|  |  | Arm 2 | Prucalopride | 2 mg | 75 | 1.9/week | 4 weeks | 1 |
|  |  | Arm 3 | Prucalopride | 4 mg | 79 | 1.9/week | 4 weeks | 1 |
|  |  | Arm 4 | Placebo | NA | 70 | 0.9/week | 4 weeks | 1 |
| Novick J, et al. [74] | IBS-C | Arm 1 | Tegaserod | 12 mg | 767 | 2.45/week | 12 weeks | 1 |
|  |  | Arm 2 | Placebo | NA | 752 | 1.65/week | 12 weeks | 1 |
| Paulson DM, et al. [75] | OIC | Arm 1 | Alvimopan | 0.5 mg | 58 | 1.6/week | 3 weeks | 1 |
|  |  | Arm 2 | Alvimopan | 1 mg | 56 | 2.9/week | 3 weeks | 1 |
|  |  | Arm 3 | Placebo | NA | 54 | 1.2/week | 3 weeks | 1 |
| Rauck R, et al. [76] | OIC | Arm 1 | Methylnaltrexone | 150 mg | 201 | 2/week | 12 weeks | 0 |
|  |  | Arm 2 | Methylnaltrexone | 300 mg | 201 | 2.4/week | 12 weeks | 0 |
|  |  | Arm 3 | Methylnaltrexone | 450 mg | 201 | 2.4/week | 12 weeks | 0 |
|  |  | Arm 4 | Placebo | NA | 201 | 1.9/week | 12 weeks | 0 |
| NCT02291679 [77] | CC | Arm 1 | Linaclootide | 72 µg | 411 | 2.366/week | 12 weeks | 0 |
|  |  | Arm 2 | Placebo | NA | 401 | 1.329/week | 12 weeks | 0 |
| NCT00402337 [78] | CC | Arm 1 | Linaclootide | 72 µg | 54 | 2.59/week | 4 weeks | N |
|  |  | Arm 2 | Linaclootide | 145 µg | 51 | 3.25/week | 4 weeks | N |
|  |  | Arm 3 | Linaclootide | 290 µg | 58 | 3.57/week | 4 weeks | N |
|  |  | Arm 4 | Linaclootide | 579 µg | 51 | 4.29/week | 4 weeks | N |
|  |  | Arm 5 | Placebo | NA | 61 | 1.45/week | 4 weeks | N |
| NCT00948818 [79] | IBS-C | Arm 1 | Linaclootide | 290 µg | 405 | 3.898/week | 12 weeks | N |
|  |  | Arm 2 | Placebo | NA | 395 | 1.13/week | 12 weeks | N |
| NCT01880424 [80] | IBS-C | Arm 1 | Linaclootide | 290 µg | 417 | 2.96/week | 12 weeks | N |
|  |  | Arm 2 | Placebo | NA | 422 | 1.51/week | 12 weeks | N |
| NCT00380250 [81] | IBS-C | Arm 1 | Lubiprostone | 16 µg | 390 | 1.59/week | 2 months | N |
|  |  | Arm 2 | Placebo | NA | 193 | 1.41/week | 2 months | N |
| Fukudo S, et al. [33] | IBS-C | Arm 1 | Linaclootide | 62.5 µg | 103 | 2.81/week | 2 months | 0 |
|  |  | Arm 2 | Linaclootide | 125 µg | 103 | 3.43/week | 2 months | 0 |
|  |  | Arm 3 | Linaclootide | 250 µg | 103 | 3.15/week | 2 months | 0 |
|  |  | Arm 4 | Linaclootide | 500 µg | 98 | 3.11/week | 2 months | 0 |
|  |  | Arm 5 | Placebo | NA | 103 | 1.77/week | 2 months | 0 |
| Fukudo S, et al. [32] | CC | Arm 1 | Linaclootide | 62.5 µg | 78 | 3.47/week | 2 weeks | 0 |
|  |  | Arm 2 | Linaclootide | 125 µg | 69 | 2.86/week | 2 weeks | 0 |
|  |  | Arm 3 | Linaclootide | 250 µg | 72 | 3.73/week | 2 weeks | 0 |
and baseline SBM values were unknown in 9 studies \[52, 61, 63, 70, 71, 78–81\]. The distribution of male and female patients across the included studies was non-uniform, with significantly more female patients than male patients in most studies (Table S2). The average treatment duration across the trials ranged from 3 days to 12 weeks (Table 1).

**Treatment Network**

A total of 47 treatments for 16 constipation oral drugs was plotted in the network for the primary analysis (Fig. 3). For all treatment arms, placebo was a common reference comparator treatment arm. The most frequently studied agents were linaclotide (trials = 16, patients = 4656) and lubiprostone (trials = 9, patients = 1674). The most frequently used comparisons were linaclotide versus placebo (trials = 16) and lubiprostone versus placebo (trials = 9). There were 3 direct head-to-head comparisons between 2 active treatments (lactulose 20 g versus lactitol 20 g, lactulose 10 g versus lactitol 10 g, and PEG 20 g versus lactulose 20 g) and 25 comparisons between different dosages of the same treatment (Table 1 and Fig. 3). Each treatment in the NMA pooled data was from trials of different durations. There were no significant inconsistencies for the indirect evidence within the NMA. Therefore, a consistency model was applied for the NMA.

**NMA Results**

Indirect comparison of the 47 selected constipation treatments with linaclotide 500 μg showed that linaclotide 500 μg was more effective in terms of the change in weekly SBM before and after treatment than most other treatments (Table 2 and Fig. 4). When the mean difference in the change in weekly SBM with other constipation treatments was compared with that of linaclotide 500 μg, linaclotide 500 μg was statistically significantly more effective than placebo (−1.907; −2.568 to −1.237); lubiprostone 16 μg (−2.090; −3.226 to −0.968); methylnaltrexone 150 mg (−1.807; −3.126 to −0.491), 300 mg (−1.411; −2.722 to −0.096), and 450 mg (−1.405; −2.708 to −0.097); naloxegol 5 mg (−2.074; −4.001 to −0.131) and 12.5 mg (−1.329; −2.347 to −0.318); tegaserod 4 mg (−1.133; −2.059 to −0.207); and tegaserod 12 mg (−1.024; −1.822 to −0.228). Linaclotide 500 μg was statistically significantly less effective than placebo.

**Fig. 2** Overall risk of bias across all selected studies

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**Table 1** (continued)

| Reference          | Disease | Arm | Drug   | Dose/day | Patient number | Change from baseline in SBM | Time point of extracted data | Baseline weekly SBM (≥3:1; <3:0; unknown: N) |
|--------------------|---------|-----|--------|----------|----------------|-----------------------------|-----------------------------|---------------------------------|
| Arm 4 Linaclotide | IBS-C   | Arm 1 | Linaclotide | 500 μg  | 74             | 3.97/week                   | 2 weeks                      | 2 weeks |
| Arm 5 Placebo     |         | Arm 2 | Placebo | NA       | 80             | 1.53/week                   | 2 weeks                      | 2 weeks |
| Fukudo S, et al.  | CC      | Arm 1 | Linaclotide | 500 μg  | 249            | 3.14/week                   | 12 weeks                     | 0 |
| Fukudo S, et al.  | CC      | Arm 2 | Placebo | NA       | 251            | 1.49/week                   | 12 weeks                     | 0 |

CC chronic constipation, IBS-C irritable bowel syndrome with constipation, NA not applicable, OIC opioid-induced constipation, SBM spontaneous bowel movement.
Fig. 3  Treatment network for the network meta-analysis. The size of each node represents the number of patients pooled for each treatment and the thickness of the edges represents the number of trials for each comparison. Altogether, 47 treatments/16 drugs were included in the NMA. Different doses of the same drug were treated as separate treatments. Clinically equivalent doses of the same treatment were pooled together. CC, chronic constipation; IBS-C, irritable bowel syndrome with constipation; NMA, network meta-analysis; OIC, opioid-induced constipation; PEG, polyethylene glycol.

effective than the non-approved dose of linaclotide 600 μg (1.159; 0.123 to 2.199) and bisacodyl 10 mg (2.979; 1.723 to 4.233). The differences in efficacy between linaclotide 500 μg and other doses of linaclotide were not statistically significant.

**Sensitivity Analysis Results**

Sensitivity analyses were conducted on trials involving only CC (26 trials; Fig. 5a), trials with only CC and IBS-C (43 trials; Fig. 5b), trials with only severe constipation (30 trials; Fig. 6a), and trials with only a low risk of bias (48 trials; Fig. 6b). The effects of linaclotide 500 μg were mostly consistent across each of the sensitivity analyses conducted. Linaclotide 500 μg remained significantly more effective than each of the comparators identified in the primary analysis and was significantly less effective than bisacodyl 10 mg. Additionally, linaclotide 500 μg was significantly more effective than lubiprostone 16 μg when the sensitivity analysis included trials involving only CC (Fig. 5a), trials involving CC and IBS-C (Fig. 5b), and trials with a low risk of bias (Fig. 6b). However, the sensitivity analysis of trials involving only CC showed that there was no significant difference between linaclotide 500 μg and the non-approved dose of linaclotide 600 μg (Fig. 5a), which is in contrast to the findings from the primary analysis (Fig. 4).

**Discussion**

This is the first study to compare the approved standard dose of linaclotide 500 μg in Japan with other constipation treatments available worldwide. While lower doses of linaclotide are approved for CC (72 μg, 145 μg) in the US and IBS-C (290 μg) in the US and European Union [14, 82], dose-ranging studies conducted in Japan showed that the 500-μg dose was the optimal dose in this population in terms of efficacy and safety [30, 32, 33]. The reasons for the higher dose of linaclotide in Japan may be due to a weaker responsiveness to linaclotide in Japanese patients than in Western patients due to
Table 2  Efficacy of constipation treatments in terms of mean change from baseline in weekly SBM in relation to linaclotide 500 μg

| Treatment                        | Number of patients | Treatment durations in included studiesa | Mean difference from linaclotide 500 μg | 95% credible interval |
|----------------------------------|--------------------|------------------------------------------|------------------------------------------|-----------------------|
| Linaclotide 500 μg              | 511                | 2 weeks, 12 weeks, 2 months              | 0                                        | -1.907 - 2.568 - 1.237 |
| Placebo                          | 8554               |                                         | -1.383 - 0.538                           |
| Linaclotide 62.5 μg              | 181                | 2 weeks, 2 months                       | -0.420 - 1.385                           |
| Linaclotide 72/75 μg             | 603                | 4 weeks, 12 weeks                       | -0.481 - 1.355                           |
| Linaclotide 100 μg               | 24                 | 5 days, 2 weeks                         | 0.835 - 3.485                            |
| Linaclotide 125 μg               | 172                | 2 weeks, 2 months                       | -0.337 - 1.310                           |
| Linaclotide 145/150 μg           | 772                | 4 weeks, 12 weeks                       | 0.115 - 0.720                            |
| Linaclotide 250 μg               | 175                | 2 weeks, 2 months                       | -0.120 - 1.094                           |
| Linaclotide 290/300 μg           | 2004               | 4 weeks, 12 weeks                       | 0.363 - 0.400                            |
| Linaclotide 579/600 μg           | 202                | 4 weeks, 12 weeks                       | 1.159 - 0.123                            |
| Linaclotide 1000 μg              | 12                 | 5 days                                  | 3.181 - 0.175                            |
| Lubiprostone 16 μg               | 431                | 1 week, 2 months                        | -2.090 - 3.226                           |
| Lubiprostone 32 μg               | 43                 | 1 week                                  | -1.539 - 3.311                           |
| Lubiprostone 48 μg               | 1200               | 1 week, 2 weeks, 4 weeks, 12 weeks      | -0.431 - 1.278                           |
| PLEVYURATIDE 3 mg                | 453                | 12 weeks                                | 0.000 - 1.173                            |
| PLEVYURATIDE 6 mg                | 441                | 12 weeks                                | -0.096 - 1.275                           |
| PEG 5.9 g                        | 67                 | 4 weeks                                 | -1.686 - 4.826                           |
| PEG 10/10.35 g                   | 86                 | 30 days, 4 weeks                        | -2.267 - 4.966                           |
| PEG 11.8 g                       | 69                 | 4 weeks                                 | -0.879 - 4.000                           |
| PEG 20 g                         | 99                 | 4 weeks                                 | -1.888 - 5.008                           |
| PEG 26 g                         | 67                 | 4 weeks                                 | -0.532 - 2.265                           |
| Penecloridine 1 mg               | 113                | 4 weeks                                 | -0.155 - 1.517                           |
| Penecloridine 2 mg               | 141                | 4 weeks                                 | -0.963 - 2.287                           |
| Penecloridine 4 mg               | 143                | 4 weeks                                 | -0.823 - 2.111                           |
| Lactulose 10 g                   | 165                | 7 days, 3 weeks                         | -3.213 - 7.287                           |
| Lactulose 20 g                   | 152                | 2 weeks, 3 weeks, 4 weeks               | -3.424 - 7.259                           |
| Bisacodyl 10 mg                  | 274                | 3 days, 4 weeks                         | 2.979 - 7.123                            |
| Ispaghula 10.8 g                 | 91                 | 14 days                                 | 0.593 - 1.037                            |
| Ispaghula 20 g                   | 10                 | 4 weeks                                 | 2.465 - 7.195                            |
| Wheat (Triticum) 20 g            | 12                 | 4 weeks                                 | 4.139 - 3.023                           |
| Lactitol 10 g                    | 63                 | 7 days                                  | -3.210 - 7.602                           |
| Lactitol 20 g                    | 30                 | 2 weeks                                 | -2.505 - 7.091                           |
| Methylaltrexone 150 mg           | 201                | 12 weeks                                | -1.807 - 3.126                           |
| Methylaltrexone 300 mg           | 201                | 12 weeks                                | -1.411 - 2.722                           |
| Methylaltrexone 450 mg           | 200                | 12 weeks                                | -1.405 - 2.708                           |
| Alvimopan 0.5 mg                 | 393                | 3 weeks, 12 weeks                       | -0.843 - 1.857                           |
| Alvimopan 1 mg                   | 388                | 3 weeks, 12 weeks                       | -0.611 - 1.620                           |
| Nalfinoxel 5 mg                  | 31                 | 4 weeks                                 | -2.074 - 4.001                           |
| Nalfinoxel 12.5 mg               | 439                | 12 weeks                                | -1.329 - 2.347                           |
| Nalfinoxel 25 mg                 | 467                | 4 weeks, 12 weeks                       | -0.787 - 1.768                           |
| Nalfinoxel 50 mg                 | 30                 | 4 weeks                                 | 0.122 - 1.828                            |
| Naloxone 2.5 mg                  | 8                  | 3 weeks                                 | -1.081 - 2.584                           |
| Naloxone 5 mg                    | 8                  | 3 weeks                                 | -0.942 - 2.526                           |
| Naloxone 10 mg                   | 8                  | 3 weeks                                 | 0.809 - 3.441                            |
| Naloxone 20 mg                   | 7                  | 3 weeks                                 | 1.891 - 2.547                            |
| Tegaserod 4 mg                   | 867                | 12 weeks                                | -1.133 - 2.059                           |
| Tegaserod 12 mg                  | 2125               | 4 weeks, 12 weeks                       | -1.024 - 1.822                           |

PEG polyethylene glycol, SBM spontaneous bowel movement

a Different studies of a particular treatment had different treatment durations

Findings from the SLR and NMA demonstrated that, in terms of the mean difference in the change in weekly SBM between the Japanese standard dose of linaclotide 500 μg and other constipation treatments, the Japanese standard dose was significantly more effective than lubiprostone 16 μg; methylaltrexone 150, 300, and 450 mg; nalfinoxel 5 and 12.5 mg; and tegaserod 4 and 12 mg. The standard dose was significantly less effective than the non-approved dose of

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Linaclotide 600 μg and bisacodyl 10 mg. However, interpretation of these findings should take into account that some of the treatments analyzed in the NMA included those approved for OIC (e.g., naxlegol, naloxone, alvimopan, methylnaltrexone, lubiprostone). Therefore, although our findings showed that the opioid receptor antagonists methylnaltrexone and naloxegol were less effective than linaclotide 500 μg, the NMA was not conducted solely in patients with OIC, and linaclotide is not an approved treatment for patients with OIC. In addition, the relatively greater efficacy of bisacodyl compared with linaclotide 500 μg should take into account that the analyses only included two bisacodyl trials: one of 3 days duration [56] and the other of 4 weeks duration [54]. In comparison, the treatment durations for the four trials on linaclotide 500 μg ranged from 2 to 12 weeks [30, 32, 33]. Moreover, bisacodyl, being a stimulant laxative, is more suitable for short-term use in temporary constipation and is not usually recommended in CC [83].
Sensitivity analyses for all comparisons except linaclotide 600 µg showed that these results were consistent when trials with a high risk of bias, trials with mild-to-moderate constipation, trials involving OIC, and trials involving IBS-C and OIC were excluded. For the sensitivity analysis involving trials on CC only, there was no significant difference in the efficacy of linaclotide 500 µg and linaclotide 600 µg. This is consistent with the findings from previous dose-determining studies in Japanese patients in which similar efficacy was observed between different linaclotide doses for patients with CC [31, 32]. The reason for the similar efficacy between linaclotide 500 and 600 µg that was observed in CC trials only may be attributed to a difference in linaclotide reactivity in CC and IBS-C patients.

In contrast to the current study, findings from the SLR and NMA of treatments for CC conducted by Nelson et al. in 2016 showed that most pharmacological therapies for chronic functional constipation featured similar efficacy [21]. However, similar to the current study, Nelson et al. also found superior efficacy for bisacodyl in terms of an increase in SBM compared with all other constipation treatments. There were several differences between the Nelson study and this study in terms of overall objectives and study design that may have contributed to the different outcomes. The focus of the current NMA was to compare all constipation treatments, including those approved for CC, IBS-C, and OIC, with the recently approved dose of linaclotide 500 µg in Japan, while the Nelson study compared the efficacy between drugs for CC only and did not include patients with IBS-C or OIC. In addition, the Nelson et al. study included only 21 studies and 8 constipation treatments in the NMA, whereas the current study included 52 studies and 47 treatments (16 drugs with approved dose of linaclotide 500 µg).

An additional finding from this study was that linaclotide 500 µg was significantly more effective than lubiprostone 16 µg (and 32 and 48 µg in point estimate terms, Table 2), a chloride channel activator [84]. Lubiprostone 48 µg was approved for CC in Japan in 2012 [85]. This finding suggests that linaclotide may be a suitable alternative for patients in whom lubiprostone is ineffective or contraindicated in Japanese healthcare settings. Further, in point estimate terms, linaclotide 500 µg was also more effective than plecanatide 3 and 6 mg (Table 2), which has the same pharmacological properties (guanylate cyclase-C agonistic activity) as linaclotide [86]. Together, these results suggest that head-to-head clinical trials on linaclotide active comparators, both...
The main strength of this study is that it was an NMA of RCTs on constipation treatments that provides a valid statistical alternative to direct head-to-head studies. This study used Bayesian NMA modeling, which allows for indirect comparison of treatments by combining evidence from multiple RCTs while retaining the randomization element. To minimize publication bias, both published studies and abstracts were included. In addition, the included studies were found to be consistent; hence, a consistency model could be applied to the NMA. By including drugs commonly used for constipation in clinical practice and different doses of the same drug as separate treatments, this NMA has provided a comprehensive analysis of the constipation treatment landscape. In addition, the inclusion of studies conducted globally and in Japan provides results that are useful for clinical treatment decisions globally and specifically in the Japanese context.

This study was subject to several limitations. First, conventional treatments such as magnesium oxide that are commonly used in Japan were not included in the NMA due to the limited amount and low quality of the available information. Additionally, constipation treatments administered rectally and newer agents in development were not included. Therefore, the influence of traditional treatments, treatments with modes of administration other than orally, and newer agents on the overall results of this study is unknown. Second, although CSBM and abdominal pain are the US Food and Drug Administration-recommended primary endpoints for assessment of constipation treatment efficacy for IBS-C [87, 88], weekly SBM was the primary endpoint for this analysis because it was the most commonly reported measure among the selected studies, which allowed us to increase the number of studies in the NMA and expand the network. Safety endpoints were also not assessed in this study. Therefore, interpretation of these results should take into consideration that assessment of only one endpoint (SBM) may not elucidate all the benefits of a particular constipation treatment, and other factors such as CSBM, abdominal symptoms, and adverse events such as diarrhea should be taken into account. Third, although linaclotide is not approved for use in OIC, studies on OIC were included in this analysis to expand the network to include all studies on target CC and IBS-C treatments that also have OIC as an approved indication (e.g., lubiprostone). Although linaclotide has been used off-label for the treatment of OIC [89, 90], the use of linaclotide 500 µg for patients with OIC is not currently approved or licensed.

Within and between drug classes, for the treatment of chronic constipation are warranted.

The main strength of this study is that it was an NMA of RCTs on constipation treatments that provides a valid statistical alternative to direct head-to-head studies [17–19]. This study used Bayesian NMA modeling, which allows for indirect comparison of treatments by combining evidence from multiple RCTs while retaining the randomization element. To minimize publication bias, both published studies and articles with results accepted for publication were included. In addition, the included studies were found to be consistent; hence, a consistency model could be applied to the NMA. By including drugs commonly used for constipation in clinical practice and different doses of the same drug as separate treatments, this NMA has provided a comprehensive analysis of the constipation treatment landscape. In addition, the inclusion of studies conducted globally and in Japan provides results that are useful for clinical treatment decisions globally and specifically in the Japanese context.

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Within and between drug classes, for the treatment of chronic constipation are warranted.
Linaclotide 500 μg was also significantly more effective than placebo, lubiprostone 16 mg, and tegaserod 4 and 12 mg and less effective than bisacodyl 10 mg and the non-approved dose of linaclotide 600 μg. Linaclotide 500 μg was also significantly more effective than methylnaltrexone 150, 300, and 450 mg and naloxone 12.5 mg; however, these agents are used in OIC, which is not an approved indication for linaclotide. The results of this NMA provide relative efficacy data that are particularly useful for clinical decision-making for treatment of CC and IBS-C until head-to-head clinical trials on constipation treatments become available.

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Role of the Sponsor Astellas Pharma Inc. was involved in the study design, data collection, data analysis, and preparation of the manuscript. Access to anonymized individual participant level data will not be provided for this study as it meets one or more of the exceptions described on www.clinicalstudydatarequest.com under “Sponsor Specific Details for Astellas.”

Authors Contribution All authors participated in the interpretation of study results and in the drafting, critical revision, and approval of the final version of the manuscript. HO was involved in the study design/concept, data collection, analysis, and interpretation. WT and KI were involved in the acquisition of data and statistical analysis. SS was involved in the study design, statistical analysis, and interpretation. TO and AN were involved in the analysis and interpretation.

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Compliance with Ethical Standards

Conflict of Interest H. Okumura and S. Shoji are employees of Astellas Pharma Inc. K. Iwasaki is an employee of Milliman and W. Tang was an employee of Milliman at the time of the study and received funding from Astellas Pharma Inc. T. Odaka and A. Nakajima received an advisory contract fee from Astellas Pharma Inc.

Ethical Approval This study protocol was reviewed by Astellas Medical Affairs Japan Protocol Review Committee and approved. The conduct of the study was based on a protocol that has been published (Registration Number: CRD42018111737) in the PROSPERO International prospective register of systematic reviews [22].

Informed Consent Not available because this study is categorized into secondary data collection based on published data.

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