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MEDICINE

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); methylnaltrexone 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 mg (− 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 pharmacological 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

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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 dioctyl sulfosuccinate), oxyphenisatine, 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, pentaerithrityl, macrogol (or PEG), mannitol, sorbitol, sodium phosphate, magnesium citrate, sodium tartrate, methylnaltrexone 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., 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 pre-determined 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,

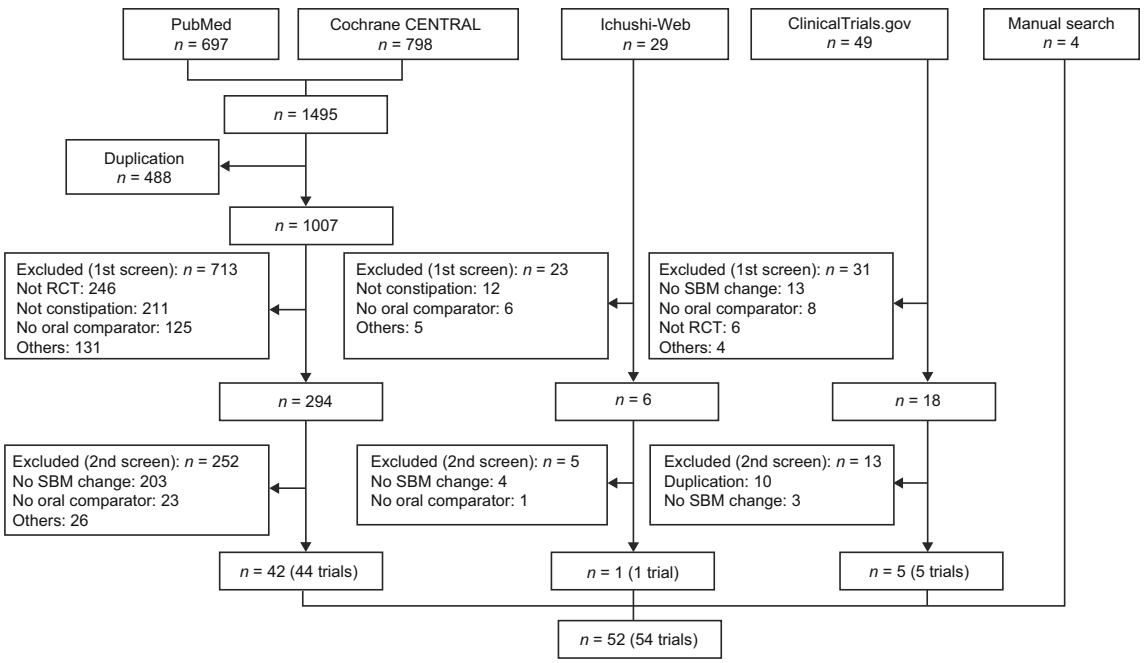

Fig. 1 Flow chart for study selection. Exclusion criteria for the first level of screening were no outcome data for effectiveness, safety, satisfaction, or quality of life of patients. The exclusion criterion for the second level of screening was no data for the change in SBM number before and after treatment. SBM, spontaneous bowel movement

Table 1 Study characteristics of the included 52 studies (54 trials)

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)
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	
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	
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	
Bouhnik 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	
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	
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	
		Arm 3	PEG	11.8 g	69	5.8/week	4 weeks	
		Arm 4	PEG	20 g	67	4.8/week	4 weeks	
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	
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	
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	
		Arm 3	Placebo	NA	211	2.02/week	12 weeks	
Chey WD, et al. [43]	OIC	Arm 1	Naloxegol	12.5 mg	228	2.62/week	12 weeks	0
		Arm 2	Naloxegol	25 mg	226	3.14/week	12 weeks	
		Arm 3	Placebo	NA	231	2.1/week	12 weeks	
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	
Emmanuel AV, et al. [45]	CC	Arm 1	Prucalopride	1 mg	37	1.8/week	4 weeks	1
		Arm 2	Placebo	NA	36	− 0.7/week	4 weeks	
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	
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	
		Arm 3	Placebo	NA	164	2.18/week	12 weeks	
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	
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	
		Arm 3	Placebo	NA	172	2.01/week	12 weeks	
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	
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	
		Arm 3	Placebo	NA	447	0.9/week	12 weeks	
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	

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	
	OIC	Arm 1	Naloxegol	5 mg	31	1.3/week	4 weeks	0
		Arm 2	Naloxegol	25 mg	29	3/week	4 weeks	

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)
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	
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	
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	
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	
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	
		Arm 3	Placebo	NA	452	1.3/week	12 weeks	
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	
		Arm 3	Prucalopride	4 mg	79	1.9/week	4 weeks	
		Arm 4	Placebo	NA	70	0.9/week	4 weeks	
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	
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	
		Arm 3	Placebo	NA	54	1.2/week	3 weeks	
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	
		Arm 3	Methylnaltrexone	450 mg	200	2.4/week	12 weeks	
		Arm 4	Placebo	NA	201	1.9/week	12 weeks	
NCT02291679 [77]	CC	Arm 1	Linaclotide	72 µg	411	2.366/week	12 weeks	0
		Arm 2	Placebo	NA	401	1.329/week	12 weeks	
NCT00402337 [78]	CC	Arm 1	Linaclotide	72 µg	54	2.59/week	4 weeks	N
		Arm 2	Linaclotide	145 µg	51	3.25/week	4 weeks	
		Arm 3	Linaclotide	290 µg	58	3.57/week	4 weeks	
		Arm 4	Linaclotide	579 µg	51	4.29/week	4 weeks	
		Arm 5	Placebo	NA	61	1.45/week	4 weeks	
NCT00948818 [79]	IBS-C	Arm 1	Linaclotide	290 µg	405	3.898/week	12 weeks	N
		Arm 2	Placebo	NA	395	1.13/week	12 weeks	
NCT01880424 [80]	IBS-C	Arm 1	Linaclotide	290 µg	417	2.96/week	12 weeks	N
		Arm 2	Placebo	NA	422	1.51/week	12 weeks	
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	
Fukudo S, et al. [33]	IBS-C	Arm 1	Linaclotide	62.5 µg	103	2.81/week	2 months	0
		Arm 2	Linaclotide	125 µg	103	3.43/week	2 months	
		Arm 3	Linaclotide	250 µg	103	3.15/week	2 months	
		Arm 4	Linaclotide	500 µg	98	3.11/week	2 months	
		Arm 5	Placebo	NA	103	1.77/week	2 months	
Fukudo S, et al. [32]	CC	Arm 1	Linaclotide	62.5 µg	78	3.47/week	2 weeks	0
		Arm 2	Linaclotide	125 µg	69	2.86/week	2 weeks	
		Arm 3	Linaclotide	250 µg	72	3.73/week	2 weeks	

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)
		Arm 4	Linaclotide	500 μg	74	3.97/week	2 weeks	
		Arm 5	Placebo	NA	80	1.53/week	2 weeks	
Fukudo S, et al. [30]	IBS-C	Arm 1	Linaclotide	500 μg	249	3.14/week	12 weeks	0
		Arm 2	Placebo	NA	251	1.49/week	12 weeks	
Fukudo S, et al. [31]	CC	Arm 1	Linaclotide	500 μg	90	3.78/week	2 weeks	0
		Arm 2	Placebo	NA	88	1.25/week	2 weeks	

CC chronic constipation, *IBS-C* irritable bowel syndrome with constipation, *NA* not applicable, *OIC* opioid-induced constipation, *SBM* spontaneous bowel movement

[a] Change from baseline in daily or weekly number of SBM after treatment

[b] Weekly SBM of enrolled patients at the start of each respective trial

71], 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

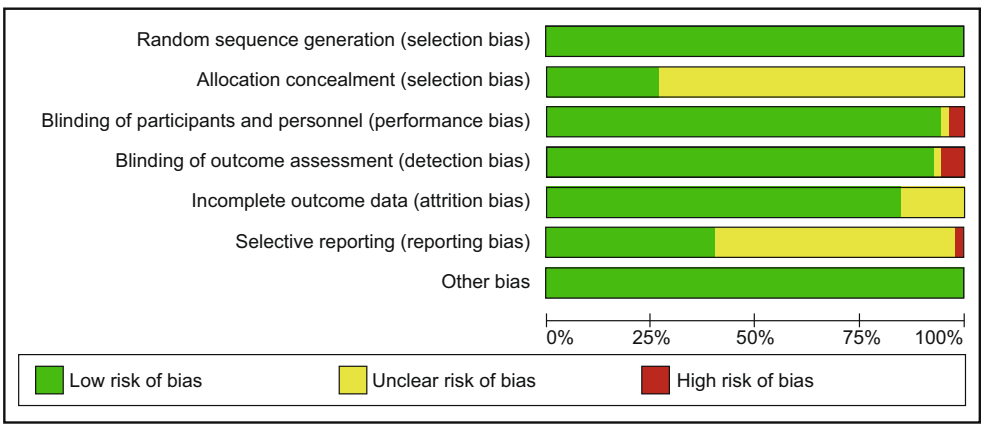

Fig. 2 Overall risk of bias across all selected studies

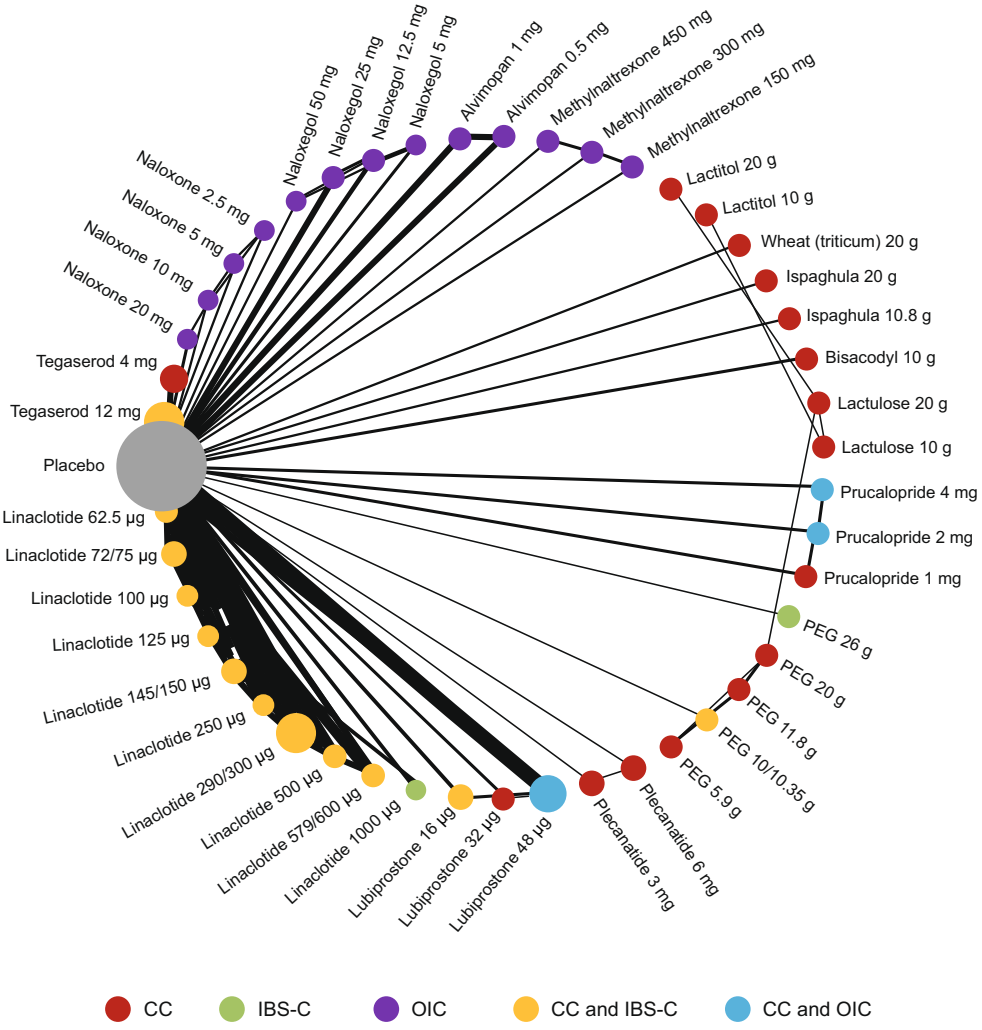

Fig. 3 Treatment network for the network meta-analysis. The size of each node represents the number of patients pooled for each treatment and the thickness of the edges represents the number of trials for each comparison. Altogether, 47 treatments/16 drugs were included in the NMA. Different doses of 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 studies[a]	Mean difference from linaclotide 500 μg	95% credible interval	
Linaclotide 500 μg	511	2 weeks, 12 weeks, 2 months	0	0	0
Placebo	8554		−1.907	−2.568	−1.237
Linaclotide 62.5 μg	181	2 weeks, 2 months	−0.420	−1.383	0.538
Linaclotide 72/75 μg	603	4 weeks, 12 weeks	−0.481	−1.385	0.424
Linaclotide 100 μg	24	5 days, 2 weeks	0.835	−1.789	3.485
Linaclotide 125 μg	172	2 weeks, 2 months	−0.337	−1.310	0.645
Linaclotide 145/150 μg	772	4 weeks, 12 weeks	0.115	−0.720	0.949
Linaclotide 250 μg	175	2 weeks, 2 months	−0.120	−1.094	0.857
Linaclotide 290/300 μg	2004	4 weeks, 12 weeks	0.363	−0.400	1.136
Linaclotide 579/600 μg	202	4 weeks, 12 weeks	1.159	0.123	2.199
Linaclotide 1000 μg	12	5 days	3.181	−0.175	6.537
Lubiprostone 16 μg	431	1 week, 2 months	−2.090	−3.226	−0.968
Lubiprostone 32 μg	43	1 week	−1.539	−3.311	0.228
Lubiprostone 48 μg	1200	1 week, 2 weeks, 4 weeks, 12 weeks	−0.431	−1.278	0.450
Plecanatide 3 mg	453	12 weeks	0.000	−1.173	1.176
Plecanatide 6 mg	441	12 weeks	−0.096	−1.275	1.077
PEG 5.9 g	67	4 weeks	−1.686	−4.826	1.462
PEG 10/10.35 g	86	30 days, 4 weeks	−2.267	−4.966	0.438
PEG 11.8 g	69	4 weeks	−0.879	−4.000	2.242
PEG 20 g	99	4 weeks	−1.888	−5.008	1.225
PEG 26 g	67	4 weeks	−0.532	−2.265	1.207
Prucalopride 1 mg	113	4 weeks	−0.155	−1.517	1.209
Prucalopride 2 mg	141	4 weeks	−0.963	−2.257	0.329
Prucalopride 4 mg	143	4 weeks	−0.823	−2.111	0.483
Lactulose 10 g	165	7 days, 3 weeks	−3.213	−7.287	0.843
Lactulose 20 g	152	2 weeks, 3 weeks, 4 weeks	−3.424	−7.259	0.429
Bisacodyl 10 mg	274	3 days, 4 weeks	2.979	1.723	4.233
Ispaghula 10.8 g	91	14 days	0.593	−1.037	2.230
Ispaghula 20 g	10	4 weeks	2.465	−1.395	6.352
Wheat (*Triticum*) 20 g	12	4 weeks	−0.589	−4.139	3.023
Lactitol 10 g	63	7 days	−3.210	−7.602	1.198
Lactitol 20 g	30	2 weeks	−2.505	−7.091	2.133
Methylnaltrexone 150 mg	201	12 weeks	−1.807	−3.126	−0.491
Methylnaltrexone 300 mg	201	12 weeks	−1.411	−2.722	−0.096
Methylnaltrexone 450 mg	200	12 weeks	−1.405	−2.708	−0.097
Alvimopan 0.5 mg	393	3 weeks, 12 weeks	−0.843	−1.857	0.168
Alvimopan 1 mg	388	3 weeks, 12 weeks	−0.611	−1.620	0.403
Naloxegol 5 mg	31	4 weeks	−2.074	−4.001	−0.131
Naloxegol 12.5 mg	439	12 weeks	−1.329	−2.347	−0.318
Naloxegol 25 mg	467	4 weeks, 12 weeks	−0.787	−1.768	0.200
Naloxegol 50 mg	30	4 weeks	0.122	−1.828	2.095
Naloxone 2.5 mg	8	3 weeks	−1.081	−5.384	3.240
Naloxone 5 mg	8	3 weeks	−0.942	−5.262	3.397
Naloxone 10 mg	8	3 weeks	0.809	−3.441	5.111
Naloxone 20 mg	7	3 weeks	1.891	−2.547	6.365
Tegaserod 4 mg	867	12 weeks	−1.133	−2.059	−0.207
Tegaserod 12 mg	2125	4 weeks, 12 weeks	−1.024	−1.822	−0.228

PEG polyethylene glycol, *SBM* spontaneous bowel movement

[a] Different studies of a particular treatment had different treatment durations

differences in the genes encoding the guanylate cyclase-C pathway, differences in the presence of endogenous or bacterial proteases, and differences in external factors (e.g., diet) between the two populations. The findings from this NMA provide clinically relevant information on the use of linaclotide for the management of CC and IBS-C in Japan and the relative efficacy of linaclotide 500 μg compared with other constipation treatments.

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; methylnaltrexone 150, 300, and 450 mg; naloxegol 5 and 12.5 mg; and tegaserod 4 and 12 mg. The standard dose was significantly less effective than the non-approved dose of

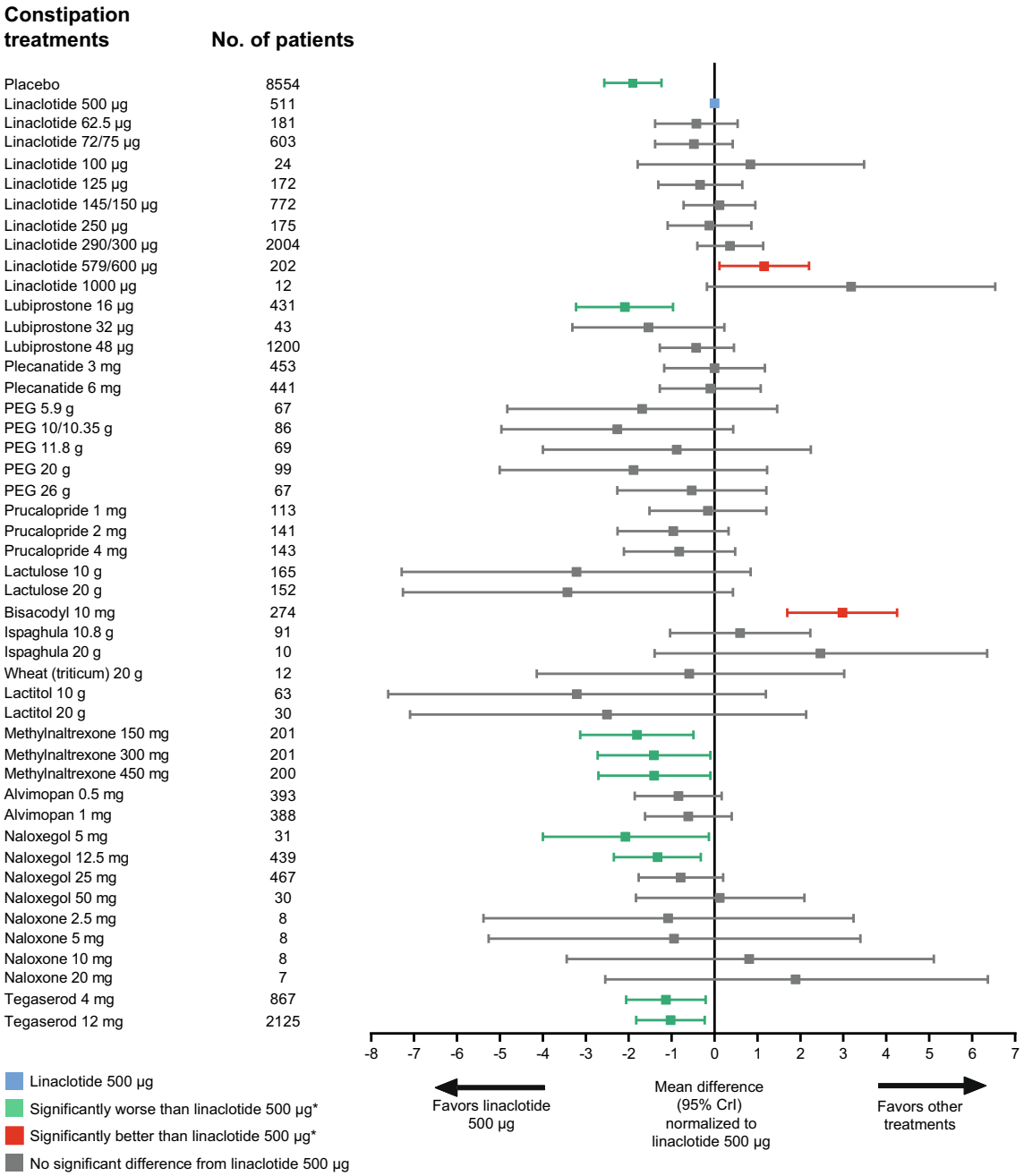

Fig. 4 Overall mean difference in the number of weekly SBM before and after treatment compared with linaclotide 500 µg. The asterisk indicates mean differences were considered significantly different from linaclotide 500 µg when the 95% credible intervals (CrI) was more or less than 0. PEG, polyethylene glycol; SBM, spontaneous bowel movement

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., nalexegol, 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].

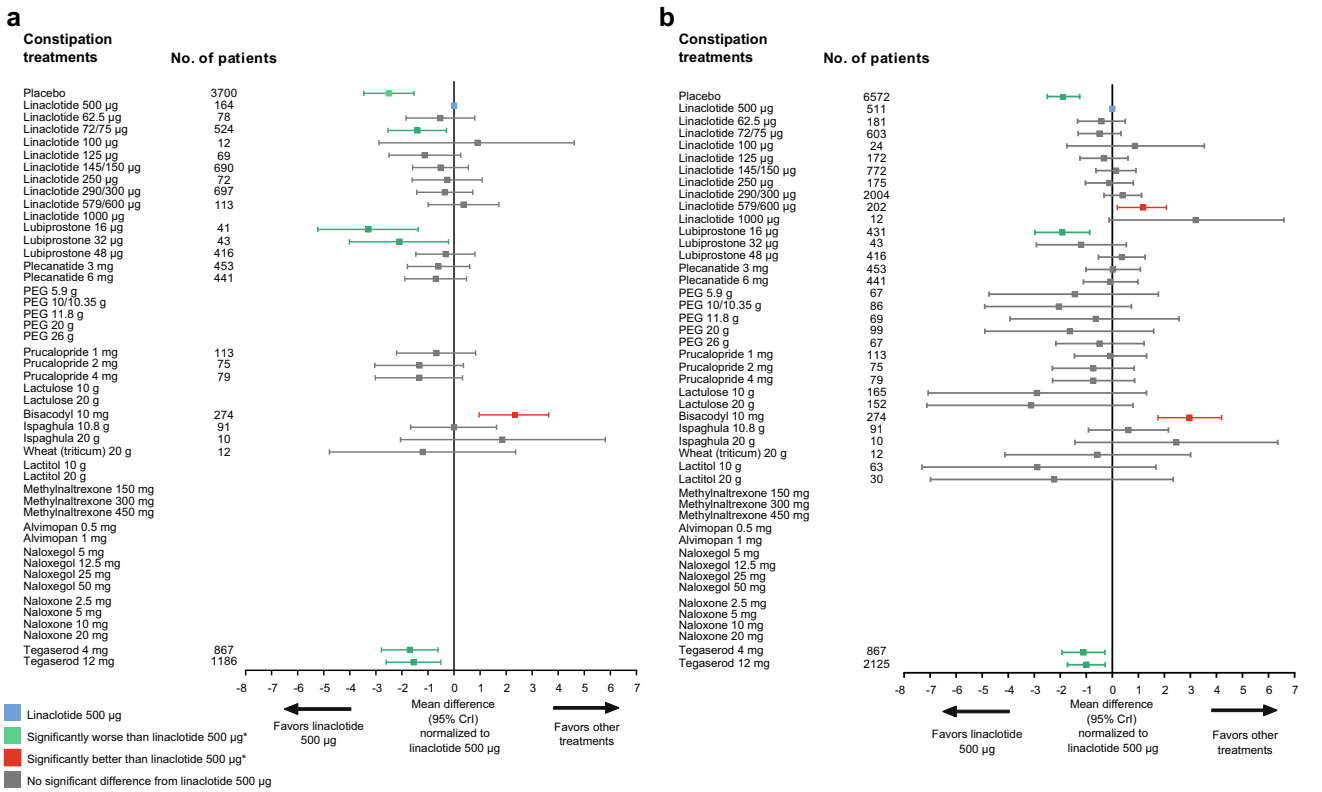

Fig. 5 Sensitivity analyses for **a** 26 trials of patients with only chronic constipation (i.e., 28 trials involving patients with IBS-C and OIC were excluded) and **b** 43 trials of patients with only chronic constipation and IBS-C (i.e., 11 trials involving patients with OIC were excluded). Data are the mean difference in weekly SBM compared with linaclotide 500 µg. 95% CrI, 95% credible interval; IBS-C, irritable bowel syndrome with constipation; OIC, opioid-induced constipation; PEG, polyethylene glycol; SBM, spontaneous bowel movement

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 different dosages considered as separate treatments) in the NMA.

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

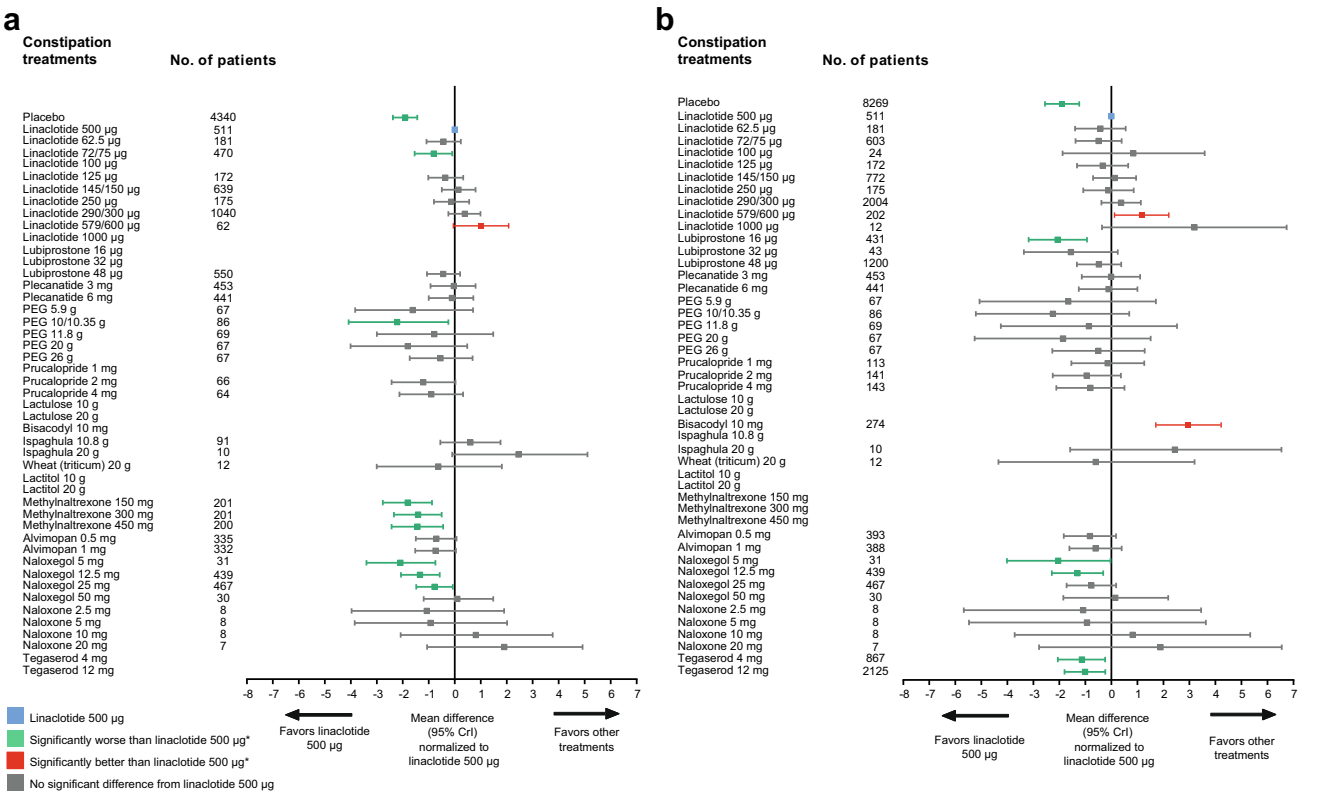

Fig. 6 Sensitivity analyses for **a** 30 trials of patients with average baseline SBM < 3 (i.e., 22 trials on mild-to-moderate constipation [≥ 3 SBM/week] and 2 trials that could not be connected in the network were excluded) and **b** 48 trials without a high risk of bias (i.e., 4 trials with high risk of bias and 2 trials that could not be connected in the network were excluded). 95% CrI, 95% credible interval; PEG, polyethylene glycol; SBM, spontaneous bowel movement

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 studies 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.

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

recommended. Fourth, this NMA featured several different doses of the included constipation treatments, as well as unapproved doses, pooling of data from different constipation indications, pooling of clinically equivalent doses, and a wide range of follow-up periods, all of which may have influenced the overall results. The criterion for statistically significant differences was based on whether the 95% CrI crossed 0, because minimally important differences that are clinically relevant for SBM were not found in the literature. Therefore, these results should be interpreted carefully in clinical settings. Lastly, as potential heterogeneity in study designs, trial procedures, patients, and settings between the included studies may have influenced results, sensitivity analyses were conducted to address the potential effects of including different constipation types (CC, IBS-C, and OIC) and patients with different disease severities. However, other differences across the studies, including the wide range of study durations (3 days to 12 weeks) and pooling of clinically equivalent doses of linaclotide and PEG, may have contributed to the heterogeneity and should be taken into account when interpreting the results.

In conclusion, linaclotide 500 μg, which is the approved dose in Japan for CC and IBS-C, was found to be significantly more effective than placebo, lubiprostone 16 μg, 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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