


ORIGINAL ARTICLE

A randomized controlled and long-term linaclotide study of irritable bowel syndrome with constipation patients in Japan

Shin Fukudo¹  | Hiroto Miwa² | Atsushi Nakajima³ | Ken Haruma⁴ | Masanori Kosako⁵ | Ayako Nakagawa⁵ | Hiraku Akiho⁵ | Yusuke Yamaguchi⁶ | Jeffrey M. Johnston⁷ | Mark Currie⁷ | Yoshikazu Kinoshita⁸

¹Department of Behavioral Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan

²Division of Gastroenterology, Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Japan

³Department of Gastroenterology and Hepatology, Yokohama City University, Yokohama, Japan

⁴General Internal Medicine 2, General Medical Center, Kawasaki Medical School, Kurashiki, Japan

⁵Japan-Asia Clinical Development 2, Development, Astellas Pharma Inc., Tokyo, Japan

⁶Japan-Asia Data Science, Development, Astellas Pharma Inc., Tokyo, Japan

⁷Ironwood Pharmaceuticals Inc., Cambridge, Massachusetts

⁸Department of Gastroenterology, Faculty of Medicine, Shimane University, Izumo, Japan

Correspondence: Shin Fukudo, Department of Behavioral Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan (sfukudo@med.tohoku.ac.jp).

Funding information

This research was funded by Astellas Pharma Inc., Tokyo, Japan.

Abstract

Background: Clinical testing was required to verify the effect of linaclotide 0.5 mg/d in patients with irritable bowel syndrome with constipation (IBS-C) in Japan.

Methods: This was a randomized, double-blind, placebo-controlled (Part 1) and long-term, open-label extension (Part 2) study of linaclotide at 60 hospitals and clinics in Japan. Patients with IBS-C diagnosed using Rome III criteria (n = 500) were randomly assigned to linaclotide 0.5 mg (n = 249) or placebo (n = 251) for a 12-week treatment period followed by open-label treatment with linaclotide (n = 324) for an additional 40 weeks. The primary endpoints were the responder rate of global improvement of IBS symptoms and complete spontaneous bowel movement (CSBM) during 12 weeks. The secondary endpoints included responder rates of SBM and abdominal pain/discomfort relief.

Key Results: Part 1: The responder rates for global improvement and for CSBM frequency were significantly higher for linaclotide compared to placebo ($P < 0.001$). Secondary endpoints including responder rates for SBM and abdominal pain/discomfort relief in the linaclotide group were also significantly greater than those in the placebo group. Part 2: Patients switched from placebo to linaclotide showed similar responder rates for global improvement and CSBM frequency to those in patients who continued to receive linaclotide, supporting sustained efficacy. Diarrhea was seen in 14.5% of patients; all cases were mild or moderate.

Conclusions and Inferences: This study suggests that a linaclotide dose of 0.5 mg is effective and safe for IBS-C patients in Japan.

KEYWORDS

FDA composite responder, guanylate cyclase C activator, multicultural aspects, phase 3 study, secretagogue

Abbreviations: 95% CI, 95% confidence interval; EMA, European Medicines Agency; FDA, Food and Drug Administration; GC-C, guanylate cyclase C; IBS, irritable bowel syndrome; IBS-C, irritable bowel syndrome with predominant constipation; IBS-QOL, irritable bowel syndrome-quality of life; PMDA, Pharmaceuticals and Medical Devices Agency; QOL, quality of life.

ClinicalTrials.gov number: NCT02316899, supported by Astellas Pharma, Inc.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2018 The Authors. *Neurogastroenterology & Motility* Published by John Wiley & Sons Ltd.

1 | INTRODUCTION

Irritable bowel syndrome (IBS) is a typical functional gastrointestinal (GI) disorder with a high worldwide prevalence.¹ According to the recent Rome IV criteria, IBS is characterized by persistent or recurrent abdominal pain which is associated with disturbed bowel movements.² Four subtypes are defined based on predominant stool consistency: IBS with predominant diarrhea, IBS with predominant constipation (IBS-C), IBS with mixed bowel habits, and IBS unclassified. Quality of life (QOL) is greatly reduced in patients with IBS.³ Direct and indirect costs of medical care in IBS patients in the US are 1.4 times more than in healthy subjects.⁴ Moreover, the costs of IBS and allied functional GI disorders are also substantial for both healthcare systems and society.^{5,6} Therefore, developing effective treatment for IBS is beneficial not only to individual patients but also to countries.

There are subtype-dependent and subtype-independent treatments for IBS, and the initial step is gut directed.⁷ The Food and Drug Administration (FDA) in the US⁸ and European Medicines Agency (EMA) in the EU⁹ have published guidelines for developing pharmacological treatment of IBS. The common strategies for initial IBS treatment are subtype dependent in both sets of guidelines.^{8,9} The Pharmaceuticals and Medical Devices Agency (PMDA) in Japan also reviews new agents for approval for the treatment of IBS.^{10,11} However, there was no approved treatment specific for IBS-C in Japan. In contrast, linaclotide has been developed for patients with IBS-C in the US and the EU.^{12,13}

Linaclotide is a 14-amino acid peptide which activates the guanylate cyclase C (GC-C) receptor expressed on the cell membrane of the luminal side of enterocytes.^{14,15} On activation of GC-C, cyclic guanosine monophosphate (cGMP) is produced in the epithelial cells of the gut and released into the extracellular space. Increased intracellular cGMP causes secretion of chloride and bicarbonate ions along with water into the intestinal lumen.¹⁶⁻¹⁸ Increased extracellular cGMP acts on the afferent neurons adjacent to the basolateral cell membrane of the enterocytes and inhibits firing of these intestinal nociceptors.¹⁹ Phase 3 studies conducted in North America and evaluated by the FDA and EMA established linaclotide 0.29 mg once per day as a safe and effective dose for patients with IBS-C.²⁰⁻²²

It is not always true that the most effective and safe dose is the same across different populations.²³ Differences in genes, diet, microbiota, and psychosocial stress may modify the effect of pharmacological agents for IBS-C.²³ A phase 2 study of linaclotide conducted before this present study in Japan supported the efficacy and safety of 0.5 mg linaclotide (1.7 times the approved dose in North America and Europe).²⁴ Therefore, clinical testing was performed to confirm the effect of linaclotide 0.5 mg/d for IBS-C patients in Japan. The aim of this study was to verify the hypothesis that the efficacy of linaclotide 0.5 mg is superior to placebo and to show acceptable safety in Japan.

Key Points

- Linaclotide has been approved in western countries for IBS with constipation (IBS-C) at a dose of 0.29 mg.
- A previous phase II trial in Japan reported that 0.5 mg/d of linaclotide was the most effective dose in IBS-C patients.
- This phase III trial in IBS-C patients in Japan revealed that 0.5 mg/d of linaclotide was effective on global improvement, complete spontaneous bowel movement, and abdominal pain/discomfort with enough safety.

2 | METHODS

2.1 | Patient population

This study was conducted in Japan from October 2014 to March 2016 at 60 hospitals and clinics with departments of gastroenterology. Male and female outpatients aged 20-79 years were diagnosed as having IBS-C based on the Rome III diagnostic criteria.²⁵ In brief, patients were eligible if they fulfilled the criteria for the last 3 months with IBS symptom onset at least 6 months prior to diagnosis. Patients had to have recurrent abdominal pain or discomfort for at least 3 days/month in the last 3 months associated with two or more of the following: improvement with defecation, onset associated with a change in frequency of stool, and/or onset associated with a change in form (appearance) of stool.²⁵ Patients had to have hard or lumpy stools at least 25% of the time, and loose (mushy) or watery stools with fewer than 25% of bowel movements.²⁵ Organic diseases were excluded by colonoscopy or double-contrast barium enema if these examinations had not been performed within 5 years. The study protocol was designed in accordance with the Declaration of Helsinki and was approved by institutional review boards at the all study sites. General Incorporated Association ICR Clinical Research Hospital Tokyo IRB, a representative ethic committee approved this clinical trial (Reference number: 0456-CL-0031) on 10 October 2014. All patients provided written informed consent prior to participating in the study.

Patients satisfying the inclusion criteria and not meeting any of the exclusion criteria regarding typical IBS-C symptoms during a 2-week bowel habit observation period were enrolled. The weekly mean abdominal pain/discomfort severity score was required to be 2.0 or more, assessed daily on a 5-point ordinate scale (1, none; 2, mild; 3, moderate; 4, severe; and 5, very severe).²⁴ A SBM was defined as defecation without laxatives, enema, or manual maneuvers.¹³ A complete SBM (CSBM) was defined as an SBM associated with a sensation of complete bowel emptying.^{8,13,20,21} Weekly mean CSBM frequency was required to be <3 and SBM frequency ≤5. Stool consistency was classified as type 1, separate hard lumps

like nuts (hard to pass); type 2, sausage shaped but lumpy; type 3, sausage like but with cracks on the surface; type 4, like a sausage or snake, smooth and soft; type 5, soft blobs with clear-cut edges (passed early); type 6, fluffy pieces with ragged edges (mushy stool); or type 7, watery, no solid pieces; all using the Bristol Stool Form Scale.²⁶ Patients had to report type 1 or 2 stools for $\geq 25\%$ of SBMs. Patients who had either type 7 for ≥ 1 SBM or type 6 for ≥ 2 SBMs were excluded. Patients who had not used drugs or undergone examinations that could affect the evaluation of study drug efficacy within 17 days prior to randomization, who recorded all items in the patient diary for 5 days or more during each week of the bowel habit observation period, and who were not judged ineligible for the study based on baseline clinical laboratory tests were randomized and successively administered treatment.

2.2 | Study design

This is a phase 3 study with a screening period, 2-week bowel habit observation period, and 52-week treatment period (Figure 1A). The treatment period included Part 1 (double-blind period; 12-week multicenter, double-blind, placebo-controlled, parallel-group, comparative study) and Part 2 (open-label period; 40-week multicenter, open-label, uncontrolled study). After the pretreatment period, eligible patients were randomly assigned to 12 weeks of oral treatment with placebo or linaclotide 0.5 mg once daily before breakfast. Randomization was performed in a 1:1 ratio using a block size of 6 using a web-based randomization system. For all patients, investigators and sponsors blinding was maintained until all observations and evaluations in Part 1 were completed, statistical analysis plans were finalized, and all data had been entered into the database. Visits were scheduled at weeks 2, 4, 8, and 12 (or at discontinuation) in Part 1 to assess treatment efficacy, drug compliance, and occurrence of adverse events. After Part 1, patients meeting transfer criteria (Table S1) were assigned to an additional 40 weeks of oral treatment with linaclotide 0.5 mg once daily before breakfast. To ensure that at least 100 patients received linaclotide for 1 year, approximately 320 patients were planned to be transitioned from Part 1 to Part 2. Visits for Part 2 were scheduled every 4 weeks (or at discontinuation) to assess treatment efficacy, drug compliance, and occurrence of adverse events. Dose reduction to 0.25 mg and optional re-escalation to 0.5 mg was allowed by the investigators from the week 12 visit of the treatment period until the week 24 visit of the treatment period in Part 2 (Table S1).

All authors had access to the study data and reviewed and approved the final manuscript.

2.3 | Data collection

During the bowel habit observation period and treatment period, patients recorded their IBS symptoms every day, using a paper diary at bedtime and at each bowel movement, and subsequently entered the data into an electronic database daily using an interactive voice response system to support daily completion of data

entry in the paper diary. This system of evaluating IBS symptoms has been previously reported as reliable and valid.^{10,11} In the paper diary, patients recorded stool frequency and, for each stool, Bristol Stool Form Scale type, straining severity, and sensation of incomplete evacuation. Straining was assessed on a 5-point ordinal scale (1, not at all; 2, a little bit; 3, a moderate amount; 4, a great deal; and 5, an extreme amount). Sensation of incomplete evacuation was assessed on a binary scale (0, absent or 1, present). Patients also scored the severity of their abdominal pain/discomfort and abdominal bloating on a 5-point ordinal scale. Every last day of 7 days during the treatment period, patients also recorded global assessment of relief of IBS symptoms, abdominal pain/discomfort relief, and abnormal bowel habits improvement compared to baseline (bowel habit observation period) using a 7-point balanced scale (1, completely relieved; 2, considerably relieved; 3, somewhat relieved; 4, unchanged; 5, somewhat worse; 6, considerably worse; and 7, as bad as I can imagine). Patients were also assessed for disease-specific health QOL²⁷ using the IBS-QOL Japanese version (IBS-QOL-J) measurement instrument²⁸ on the visits at week 0, 4, 8, 12, 16, 20, 24, 28, 40, 52, and time of discontinuation.

2.4 | Efficacy and safety endpoints

The coprimary endpoints, approved by PMDA, were the responder rate of the global assessment of relief of IBS symptoms during 12 weeks and the responder rate of CSBM during the same 12 weeks. Patients with a score of 1 or 2 at each weekly evaluation point were defined as weekly responders with respect to global assessment of relief of IBS symptoms and patients with ≥ 3 CSBM and an increase of ≥ 1 CSBM from baseline at each weekly evaluation point were defined as the weekly responder of CSBM. For each of the coprimary endpoints, patients who were weekly responders for at least 6 of the 12 weeks were considered to be overall responders.

Secondary endpoints included weekly abdominal pain/discomfort relief and of abnormal bowel habits improvement, and daily stool frequency (including CSBM and SBM), stool consistency, severity of straining, abdominal pain/discomfort and abdominal bloating, and IBS-QOL-J. Weekly responders of abdominal pain/discomfort relief or abnormal bowel habits improvement were defined as patients with a score of 1 or 2 at each weekly evaluation point and the patients who were weekly responders for at least 6 of the 12 weeks were considered to be overall responders. Weekly responders of SBM were defined as patients with ≥ 3 SBM and an increase of ≥ 1 SBM from baseline at each weekly evaluation point and patients who were weekly responders for at least 6 of the 12 weeks were considered to be overall responders.

As ad hoc additional endpoints, weekly responders of CSBM + 1 and abdominal pain/discomfort severity score were defined as patients with an increase of ≥ 1 CSBM and decrease in abdominal/discomfort of $\geq 30\%$ from baseline at each weekly evaluation point, respectively. Patients who were weekly responders for these endpoints for at least 6 of the 12 weeks were

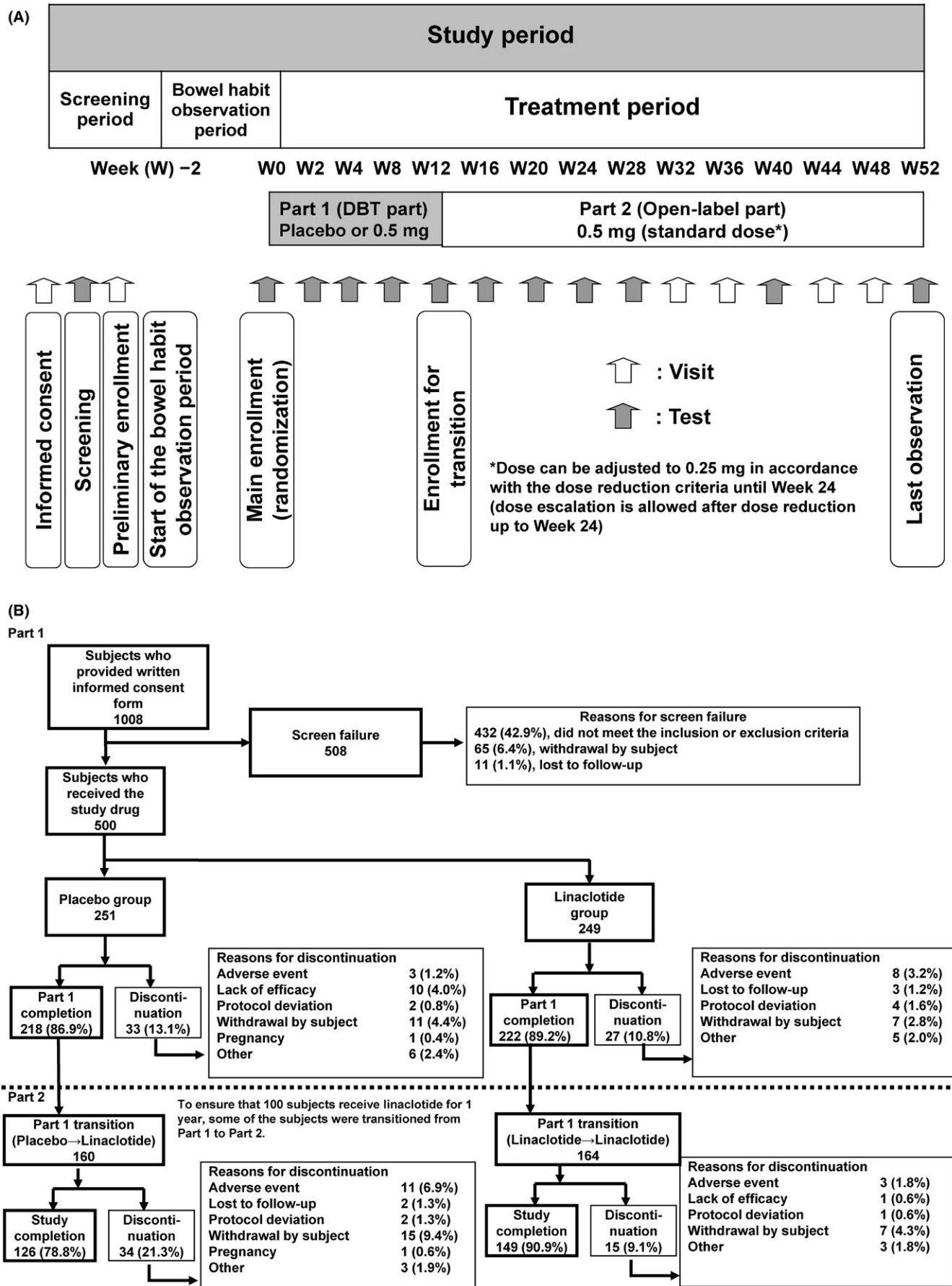


FIGURE 1 Flowchart of the study. A, Design of the study and schedule of assessments; B, Patient progress throughout the study

considered to be overall responders, with reference to the primary endpoints recommended by FDA guidelines.⁸ The composite responder rate was the proportion of patients who had a composite response of both CSBM + 1 and the abdominal pain/discomfort severity score, with reference to the composite responder definition recommended by FDA guidelines.⁸ The median time to first CSBM or SBM was calculated as the time from the initial administration of the first dose of the study drug to the first CSBM or SBM. In addition, the proportions of patients with first CSBM or SBM at 6, 12, 18, 24, 30, 36, 42, and 48 hours after the first dose were assessed.

All adverse events were recorded during the treatment period.

2.5 | Statistical analysis

Statistical analysis was performed using SAS Drug Development (ver. 3.4, SAS ver. 9.1.3 and ver. 4.5, SAS ver. 9.4) (SAS Institute Inc., Cary, NC, USA). Sample sizes estimated to provide more than 90% power to detect differences in both coprimary endpoints between placebo and linaclotide 0.5 mg were based on the phase II clinical study data,²⁴ using asymptotic normal approximation with a two-sided significance level of 0.05. In total, 480 patients (240 patients in each group) were selected for randomization.

Efficacy analyses were performed on the full analysis set, which was as complete as possible and as close as possible to the intention-to-treat (ITT) ideal of including all randomized subjects.²⁹ The full analysis set included all patients who received at least one dose of the study drug during the treatment period and in whom ≥ 1 endpoint could be evaluated. To determine the robustness of the results, primary analyses were performed according to the per-protocol set. Safety analyses were performed for all patients who received at least one dose of the study drug during the treatment period.

Responder rates for the coprimary endpoints are expressed as a percentage of patients, and 95% confidence intervals (95% CIs) are presented. The treatment groups were compared using Fisher's exact test with a two-sided significance level of 0.05 for each coprimary endpoint. Other responder rate parameters and percentages of subjects with CSBM or SBM within 24 hours after start of the initial administration of the study drug were similarly analyzed. To compare the linaclotide groups with placebo, analysis of covariance for change from baseline endpoints was performed with the treatment groups as a factor and baselines as covariates (weekly mean CSBM frequency, weekly mean SBM frequency, weekly mean stool form score, straining severity score, abdominal pain/discomfort severity score, abdominal bloating severity score, and the overall IBS-QOL and IBS-QOL subscale scores). In Part 2, overall IBS-QOL and subscale IBS-QOL scores obtained at baseline and at weeks 24 and 52 were compared to baseline using a paired *t* test. The median time to first CSBM or SBM was compared using the Kaplan-Meier method and log-rank test. Cumulative incidences of CSBM or SBM at specified time points after start of the initial administration were estimated by the Kaplan-Meier method.

3 | RESULTS

3.1 | Overall study population

Of the 1008 patients who provided written informed consent, 508 patients were excluded following the screening period and 500 patients were randomized into the placebo group (*n* = 251) or the linaclotide group (*n* = 249) in Part 1; of these, 218 patients in the placebo group and 222 patients in the linaclotide group completed the study (Figure 1B). After completion of Part 1, 324 patients were dosed with linaclotide in Part 2. Of these 324 patients, 126 patients from the placebo group who were transferred into the linaclotide group in Part 2 and 149 patients in the linaclotide group in Part 1 who continued to receive linaclotide in Part 2 completed the study. The reasons for discontinuation are shown in Figure 1B. The demographics and baseline characteristics were similar among all the patients allocated to each group in Part 1 and Part 2 (Table 1). The medication compliance rates were 98.65% in the placebo group and 97.21% in the linaclotide group in Part 1 and 98.90% in the placebo-linaclotide group and 99.05% in the linaclotide-linaclotide group in Part 2. Regarding linaclotide dosage, 27 (8.3%) patients reduced to 0.25 mg following the week 12 visit in Part 1 through the week 24 visit in Part 2 but no patients re-escalated based on the dose reduction criteria (Tables S1-S2).

3.2 | Primary endpoint

The responder rate of the global assessment of relief of IBS symptoms during 12 weeks in the linaclotide group (33.7%, 95% CI 27.9-40.0) was significantly higher than that in the placebo group (17.5%, 95% CI 13.0-22.8, Fisher's exact test, *P* < 0.001) (Figure 2A). The responder rate of CSBM during 12 weeks in the linaclotide group (34.9%, 95% CI 29.0-41.2) was significantly higher than that in the placebo group (19.1%, 95% CI 14.4-24.5, Fisher's exact test, *P* < 0.001) (Figure 2B). The difference between linaclotide and placebo groups with respect to responder rate of global assessment of relief of IBS symptoms was 16.2% (95% CI 8.3-24.1) with a relative risk (RR) of 1.92 (95% CI 1.40-2.65) and a number needed to treat (NNT) of 7 (95% CI 5-13). The difference for CSBM responder rates was 15.8% (95% CI 7.8-23.9) with a RR of 1.83 (95% CI 1.35-2.48) and a NNT of 7 (95% CI 5-13). (Table S3).

3.3 | Other endpoints in part 1

The responder rate of abdominal pain/discomfort relief during 12 weeks in the linaclotide group (29.3%, 95% CI 23.7-35.4) was significantly higher than that in the placebo group (15.5%, 95% CI 11.3-20.6, Fisher's exact test, *P* < 0.001) (Figure 3A). The responder rate of abdominal pain/discomfort severity score during 12 weeks in the linaclotide group (24.5%, 95% CI 19.3-30.3) was also significantly higher than that in the placebo group (15.1%, 95% CI 10.9-20.2, Fisher's exact test, *P* = 0.010) (Figure 3B). The difference between the linaclotide and placebo groups for abdominal

TABLE 1 Demographics and baseline characteristics of the treatment groups

Characteristic	Part 1			Part 2		Total
	Placebo (n = 251)	Linacotide (n = 249)	P value ^b	Placebo→Linacotide (n = 160)	Linacotide→Linacotide (n = 164)	
Age (y)	42.2 ± 11.3	41.6 ± 10.7	0.534	42.8 ± 11.7	42.2 ± 10.3	42.5 ± 11.0
Sex						
Male	24 (9.6%)	37 (14.9%)	0.077	12 (7.5%)	22 (13.4%)	34 (10.5%)
Female	227 (90.4%)	212 (85.1%)		148 (92.5%)	142 (86.6%)	290 (89.5%)
Duration of disease (mo) ^a	191.6 ± 146.7	191.0 ± 138.3	0.965	197.3 ± 148.8	192.3 ± 142.1	194.8 ± 145.3
CSBM frequency	0.39 ± 0.55	0.35 ± 0.56	0.480	0.34 ± 0.51	0.33 ± 0.55	0.33 ± 0.53
SBM frequency	2.39 ± 1.19	2.39 ± 1.11	0.964	2.47 ± 1.05	2.24 ± 1.09	2.36 ± 1.07
Weekly mean stool form score (1-7) ^b	2.01 ± 0.73	1.99 ± 0.70	0.711	1.98 ± 0.76	1.98 ± 0.69	1.98 ± 0.72
Weekly mean abdominal pain/discomfort severity score (1-5)	3.03 ± 0.67	3.02 ± 0.72	0.956	3.08 ± 0.65	3.01 ± 0.73	3.05 ± 0.69
Weekly mean abdominal bloating severity score (1-5)	3.11 ± 0.72	3.07 ± 0.78	0.593	3.17 ± 0.67	3.06 ± 0.78	3.11 ± 0.73
Weekly mean straining severity score (1-5) ^b	3.51 ± 0.74	3.55 ± 0.72	0.537	3.55 ± 0.73	3.59 ± 0.70	3.57 ± 0.72
IBS-QOL-J overall score	66.8 ± 19.1	69.5 ± 17.1	0.095	66.3 ± 19.5	69.5 ± 17.4	68.0 ± 18.5

CSBM, complete spontaneous bowel movement; SBM without a sensation of incomplete evacuation, SBM (spontaneous bowel movement); bowel movement without the use of a laxative, suppository, or enema, or taking measures for stool extraction on the day or prior to the day of this bowel movement.

^aNumber of subjects of placebo, linacotide, placebo→linacotide, and linacotide→linacotide are 249, 244, 158, and 162, respectively, because of unknown data.

^bNumber of subjects of placebo, linacotide, placebo→linacotide, and linacotide→linacotide are 233, 241, 156, and 157, respectively, because of missing data.

^cCalculated with t test except sex (evaluated by Fisher's exact test).

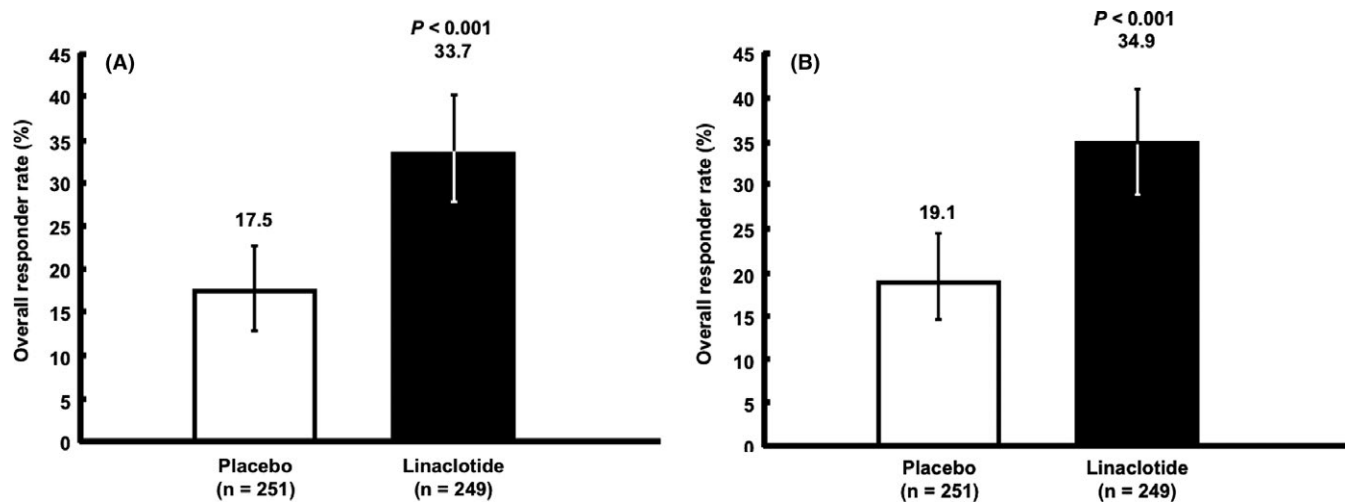


FIGURE 2 Primary endpoints expressing efficacy of linacotide. Column height: responder rate (%). Error bar: 95% CI. P values derived by Fisher's exact test, compared to placebo. A, Responder rate of global assessment of relief of IBS symptoms during 12 wk; B, Responder rate of CSBM during 12 wk

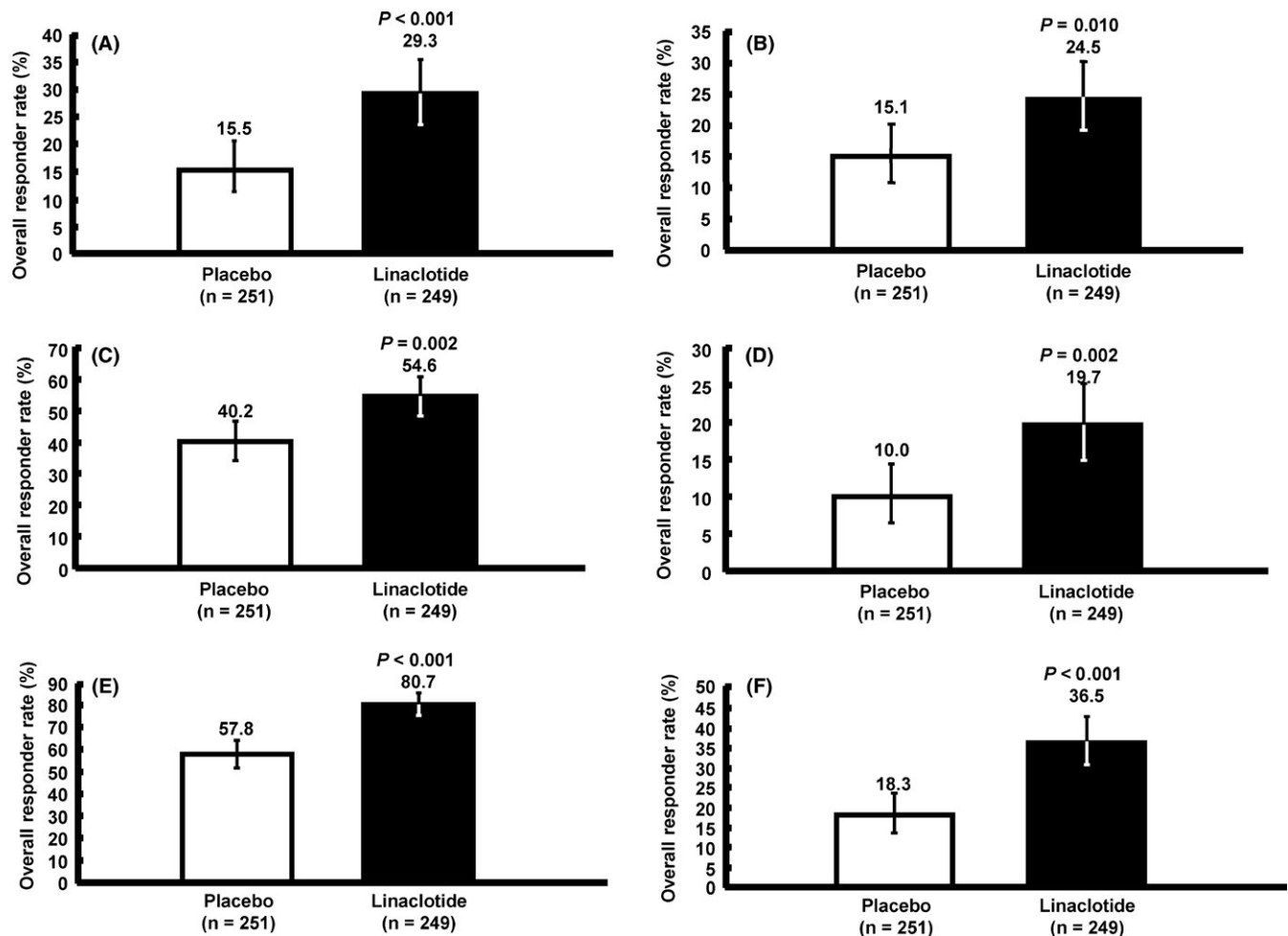


FIGURE 3 Secondary and ad hoc additional endpoints to support efficacy of linacotide. Column height: responder rate (%). Error bar: 95% CI. *P* values derived by Fisher's exact test, compared to placebo. A, Responder rate of abdominal pain/discomfort relief during 12 wk; B, Responder rate of abdominal pain/discomfort severity score during 12 wk; C, Responder rate of CSBM + 1 during 12 wk; D, Composite responder rate of CSBM + 1 and abdominal pain/discomfort severity score during 12 wk; E, Responder rate of SBM during 12 wk; F, Responder rate of abnormal bowel habits improvement during 12 wk

pain/discomfort severity score responder rates was 9.4% (95% CI 2.0-16.7) with a RR of 1.62 (95% CI 1.12-2.33) and a NNT of 11 (95% CI 6-50) (Table S3).

The responder rate of CSBM + 1 during 12 weeks in the linacotide group (54.6%, 95% CI 48.2-60.9) was also significantly higher than that in the placebo group (40.2%, 95% CI 34.1-46.6, Fisher's exact test, $P = 0.002$) (Figure 3C). The difference between the linacotide and placebo groups for CSBM + 1 responder rates was 14.4% (95% CI 5.3-23.4) with a RR of 1.36 (95% CI 1.12-1.64) and a NNT of 7 (95% CI 5-19) (Table S3).

The composite responder rates of CSBM + 1 and the abdominal pain/discomfort severity score during 12 weeks in the linacotide group (19.7%, 95% CI 14.9-25.2) was also significantly higher than that in the placebo group (10.0%, 95% CI 6.5-14.4, Fisher's exact test, $P = 0.002$) (Figure 3D). The difference between the linacotide and placebo groups for composite responder rates of CSBM + 1 and abdominal pain/discomfort responder was 9.7% (95% CI 3.1-16.3) with a RR of 1.98 (95% CI 1.26-3.09) and a NNT of 11 (95% CI 7-32) (Table S3).

The responder rates of SBM and abnormal bowel habits improvement during 12 weeks in the linacotide group (80.7%, 95% CI 75.3-85.4 for SBM; 36.5%, 95% CI 30.6-42.9 for abnormal bowel habits improvement) were significantly superior to those in the placebo group (57.8%, 95% CI 51.4-64.0, Fisher's exact test, $P < 0.001$ for SBM; 18.3%, 95% CI 13.7-23.7, Fisher's exact test, $P < 0.001$ for abnormal bowel habits improvement) (Figure 3E,F).

The median time to first CSBM in the linacotide group (89.33 hours, 95% CI 69.75-119.67) was significantly shorter than that in the placebo group (211.67 hours, 95% CI 160.88-291.62, log-rank test for comparison of cumulative incidence curves, $P < 0.001$) (Figure 4A). The median time to first SBM in the linacotide group (16.17 hours, 95% CI 10.00-19.17) was significantly shorter than that in the placebo group (26.40 hours, 95% CI 23.08-31.63, log-rank test for comparison of cumulative incidence curves, $P < 0.001$) (Figure 4B). Linacotide induced CSBM and SBM within 6 hours after the initial administration in 14.9% (95% CI 10.4-19.3) and 38.2% (95% CI 32.1-44.2) of patients, respectively, while placebo evoked CSBM

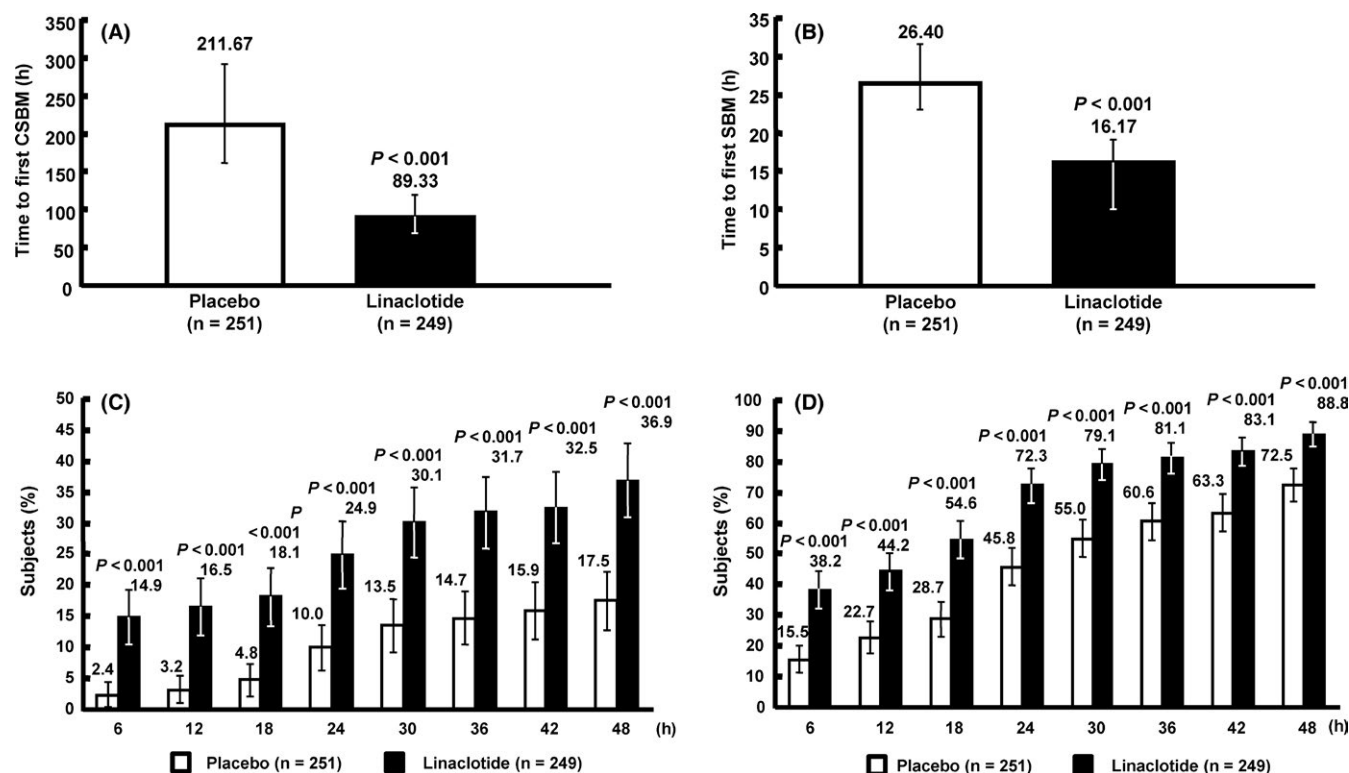


FIGURE 4 Ad hoc additional endpoints to support efficacy of linaclotide. (A,B), Column height: median time. Error bar: 95% CI. *P* values derived by log-rank test for comparison of cumulative incidence curve compared to placebo. (C,D), Column height: percentage (%). Error bar: 95% CI. *P* values derived by Wald test of difference of Kaplan-Meier estimates compared to placebo. A, Time to first CSBM; B, Time to first SBM; C, Cumulative incidence of CSBM after start of the initial administration; D, Cumulative incidence of SBM after start of the initial administration

and SBM within 6 hours after the initial administration in 2.4% (95% CI 0.5-4.3) and 15.5% (95% CI 11.1-20.0) of patients. Cumulative incidences of both SBM and CSBM after start of the initial administration of study drug were significantly higher in the linaclotide group than those in the placebo group at every time point (Wald test of differences on Kaplan-Meier estimates, $P < 0.001$) (Figure 4C,D).

The IBS-QOL overall score was significantly better for linaclotide compared with placebo at week 4 ($P = 0.022$), and numerically better, but not significant, at week 8, week 12, and the last evaluation (Figure S1). At the last evaluation time point, linaclotide performed significantly better on the subscale for body image ($P = 0.002$) and social reaction ($P = 0.040$) of the IBS-QOL compared to placebo, but not for the other subscales of the IBS-QOL (Figure S1). The linaclotide group also showed significantly better efficacy for other secondary endpoints compared to the placebo group (Figures S1 and S2).

3.4 | Efficacy endpoints in part 2

In Part 2, patients from Part 1 who continued to receive linaclotide and patients who switched from placebo in Part 1 to linaclotide in Part 2 showed efficacy as assessed by the weekly responder rate of global assessment of relief of IBS symptoms (Figure 5A) and by the weekly responder rate of CSBM (Figure 5B). The overall IBS-QOL scores in the linaclotide-linaclotide group increased from 69.5 (95% CI

66.8-72.2) at baseline ($n = 164$) to 88.3 (95% CI 86.2-90.4) at week 52 ($n = 150$). Long-term treatment of linaclotide significantly improved the overall and all subscale scores of IBS-QOL at week 24 and 52 compared with scores at baseline in Part 1 (paired *t* test, $P < 0.001$) (Figure 5C). Efficacy was also shown for other endpoints in Part 2 (Figure S3).

3.5 | Safety in part 1

Safety in Part 1 was evaluated in 500 patients. Adverse events were observed in 65 patients (25.9%) in the placebo group and 78 patients (31.3%) in the linaclotide group. The incidence of diarrhea was higher in the linaclotide group than that in the placebo group (9.6% vs 0.4%, Fisher's exact test, $P < 0.001$) (Table 2). All occurrences of diarrhea in Part 1 were mild or moderate. Drug-related serious adverse events included asthenic conditions (one patient) in the linaclotide group and white blood cell count decreased (one patient) in the placebo group. The magnitude of adverse events based on relative risks and numbers needed to harm was shown in Table S3.

3.6 | Safety in part 2

Safety in Part 2 was evaluated in 324 patients. Adverse events were observed in 81 patients (50.6%) in the placebo-linaclotide

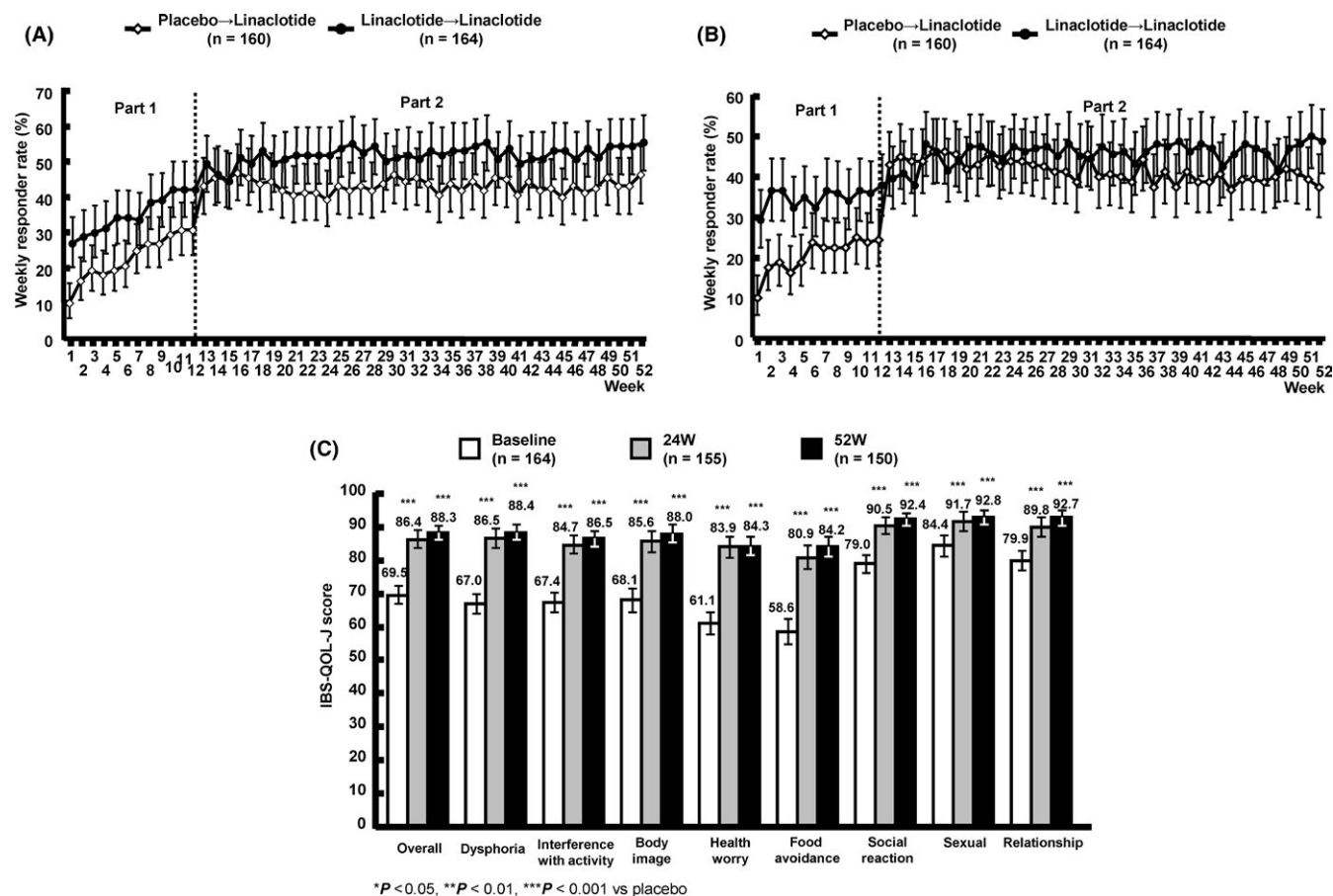


FIGURE 5 Efficacy endpoints to support long-term efficacy of linaclotide. Symbol height: responder rate (%). Error bar: 95% CI. In the Figure 5C, P values derived by paired t test compared to baseline. A, Weekly responder rate of global assessment of relief of IBS symptoms; B, Weekly responder rate of CSBM; C, IBS-QOL-J score in Part 2

group and 98 (59.8%) in the linaclotide-linaclotide group. Incidence of gastrointestinal disorders including diarrhea in the linaclotide-linaclotide group was comparable with that in the placebo-linaclotide group (Table 2). All occurrences of diarrhea in Part 2 were mild or moderate. Drug-related serious adverse event included colitis (one patient) in the placebo-linaclotide group.

4 | DISCUSSION

The results of this study support the hypothesis that the efficacy of linaclotide 0.5 mg is superior to that of placebo with an acceptable safety profile in patients in Japan. In the phase 2 study, which was conducted prior to this study, we identified linaclotide 0.5 mg as the appropriate dose to treat IBS-C patients in Japan.²⁴ Therefore, this study replicated the finding that linaclotide 0.5 mg is effective and tolerable for IBS-C patients in Japan. This dose finding is in contrast with the previous phase 2¹³ and phase 3^{20,21} studies in the US. In those studies, linaclotide 0.29 mg was the best dose for IBS-C patients in the US. For patients with chronic constipation in the US, 0.145 mg linaclotide was proven to be effective.³⁰ The FDA

approved the 0.29 mg dose for IBS-C and both the 0.145 mg dose³¹ and the 0.072 mg dose³² for chronic constipation. Moreover, the NNT using the FDA composite responder in this study was 11 [7, 32], which is higher than that in the phase 3 studies for IBS-C conducted in the US (5.2 [4.0, 7.3]²⁰ and 8.0 [5.4, 15.5]²¹). These data suggest that IBS-C patients in Japan need a higher dose of linaclotide than US IBS-C patients and, therefore, these findings support the hypothesis of this study, underscoring the importance of multicultural/national aspects of IBS, as predicted by Rome IV.²³

Several factors may be responsible for the higher dose requirement for linaclotide in the Japanese population. The GC-C receptor located on the apical membrane of the epithelial cells of the gut is activated by GC-C ligand.^{14,15} This results in an increase in intracellular cGMP in the epithelial cells of the gut which leads to increased secretion of chloride and bicarbonate ions into the gut lumen with a concomitant increase in the secretion of water.^{16–18,33} Differences in genetic polymorphisms of these pathways between Japanese and US citizens, such as a GUCY2C gene (encoding GC-C),³⁴ may be one of these factors. Guanylin and uroguanylin belong to the guanylin-family hormones which are synthesized in the intestine and released both lumenally and into the circulation and work on the endogenous ligand of the GC-C receptor.³⁴ Japanese patients may have more

TABLE 2 Incidence of adverse events ($\geq 2\%$ in each part)

Part 1: System organ class Preferred term	Placebo (n = 251)	Linacotide (n = 249)	Total (n = 500)	P value
All adverse events	65 (25.9%)	78 (31.3%)	143 (28.6%)	0.1986
Gastrointestinal disorders	12 (4.8%)	35 (14.1%)	47 (9.4%)	<0.001
Diarrhea	1 (0.4%)	24 (9.6%)	25 (5.0%)	<0.001
Infections and infestations	45 (17.9%)	38 (15.3%)	83 (16.6%)	0.4713
Nasopharyngitis	24 (9.6%)	25 (10.0%)	49 (9.8%)	0.8814
Part 2: System organ class Preferred term	Placebo→Linacotide (n = 160)	Linacotide→Linacotide (n = 164)	Total (n = 324)	
All adverse events	81 (50.6%)	98 (59.8%)	179 (55.2%)	
Gastrointestinal disorders	33 (20.6%)	45 (27.4%)	78 (24.1%)	
Diarrhea	25 (15.6%)	22 (13.4%)	47 (14.5%)	
General disorders and administration site conditions	8 (5.0%)	7 (4.3%)	15 (4.6%)	
Pyrexia	4 (2.5%)	4 (2.4%)	8 (2.5%)	
Infections and infestations	41 (25.6%)	54 (32.9%)	95 (29.3%)	
Cystitis	2 (1.3%)	4 (2.4%)	6 (1.9%)	
Influenza	4 (2.5%)	3 (1.8%)	7 (2.2%)	
Nasopharyngitis	23 (14.4%)	40 (24.4%)	63 (19.4%)	
Pharyngitis	2 (1.3%)	4 (2.4%)	6 (1.9%)	
Musculoskeletal and connective tissue disorders	8 (5.0%)	9 (5.5%)	17 (5.2%)	
Back pain	3 (1.9%)	5 (3.0%)	8 (2.5%)	
Nervous system disorders	5 (3.1%)	6 (3.7%)	11 (3.4%)	
Headache	4 (2.5%)	2 (1.2%)	6 (1.9%)	

Data are expressed as "number (%)". Events with an incidence of $\geq 2\%$ in the placebo group or the linacotide group in Part 1, and those in the placebo→linacotide group or the linacotide→linacotide group in Part 2 are all listed. P values were calculated using Fisher's exact test.

intraluminal guanylin which competitively binds to the GC-C receptors than US or European patients. Also, there is a 10- to 100-fold interindividual variability in GC-C mRNA expression in normal intestinal epithelial cells across the population.³⁵ Therefore, individual factors including genetic polymorphism may be the origin of dose effect differences between North America and Japan.

The Japanese have different gut microbiota from those in Western countries.³⁶ Porphyranases and agarases which were from dietary microbiota are common in the Japanese population, and are absent in North American individuals.³⁷ Linacotide is converted to the metabolite MM-419447 in the small intestine.³⁴ The disulfide bonds of both peptides are cleaved, proteolyzed, and degraded in the small intestine.³⁴ When compared with other nations,³⁶ the Japanese also have more abundant Bifidobacteria which have exopeptidases.³⁸ A difference in endogenous or bacterial proteases may thus explain why a dose of 0.5 mg/d is more appropriate for IBS-C patients in Japan.

The Japanese have a different diet from people in Western countries.²³ They consume less dietary fat (http://www.mhlw.go.jp/bunya/kenkou/kenkou_eiyou_chousa.html) than Americans (<https://www.ars.usda.gov/northeast-area/beltsville-md/beltsville-human-nutrition-research-center/food-surveys-research-group/>

[docs/wwaia-data-tables/](https://www.ars.usda.gov/northeast-area/beltsville-md/beltsville-human-nutrition-research-center/food-surveys-research-group/docs/wwaia-data-tables/)). Obesity due to overeating produces less guanylin expression in the colon with subsequent GUCY2C silencing.³⁹ The Japanese diet may induce more expression of intraluminal guanylin than a Western diet, which may dampen the effect of linacotide.³⁴

In this study, the responder rates of global improvement and CSBM were the primary endpoints. In addition, the responder rate of abdominal pain/discomfort severity score during 12 weeks was an important endpoint. This endpoint along with the responder rate of CSBM + 1 are coprimary endpoints for IBS-C clinical trials recommended by the FDA guidelines.⁸ In contrast, the responder rate of global assessment of relief of IBS symptoms during 12 weeks has been approved as a primary endpoint for clinical trials by the Japanese PMDA,^{10,11,24} and is in accordance with the Rome IV recommendations.²³ Therefore, although the primary endpoints in this study are not identical to those in recent studies in the US,^{13,20,21} the primary outcome measures in this study do incorporate elements of the FDA guidelines.⁸

We also found that linacotide induced CSBM and SBM within 6 hours after initial administration in 14.9% and 38.2% of patients, respectively, followed by gradual onset of first CSBM/SBM across the rest of the study population. Interestingly, this pattern of

response was also seen in the placebo-treated patients (2.4% and 15.5% in the first 6 hours), albeit at lower incidences compared to linaclotide-treated patients. To our knowledge, this study is the first to report on a differential time course to first CSBM and SBM after the administration of agents for IBS-C.^{13,20–22,30–32}

Long-term administration of linaclotide in Part 2 of this study (both continued administration to patients who received linaclotide in Part 1 and a switch to linaclotide for those who received placebo in Part 1) demonstrated sustained efficacy in IBS-C for up to 52 weeks. As revealed in an earlier study,²⁰ linaclotide did not show any tachyphylaxis. The safety profile demonstrated for up to 52 weeks of treatment with linaclotide was acceptable and consistent with other phase 3 trials: there were adverse events in 55.2%, GI adverse events in 24.1%, and diarrhea in 14.5% of linaclotide-treated patients. These rates are comparable to those seen in a 26-week study in the US with 65.4% treatment-emergent adverse events, 33.8% cumulative GI events, and 19.7% with diarrhea.²⁰ It is noteworthy that 0.5 mg linaclotide did not show any remarkable increase in adverse events in the Japanese population compared to the 0.29 mg dose in the US population.

This study has some limitations. Firstly, linaclotide did not significantly improve the overall IBS-QOL score compared with placebo, except at week 4 in Part 1 of this study. Improvement of IBS-QOL in the linaclotide group compared with the placebo group may be detected with a larger sample size. Nonetheless, the body image and social reaction subscales of the IBS-QOL were significantly improved at the last evaluation in the linaclotide group compared to placebo. Additionally, despite lacking a placebo-control group, improvement in the IBS-QOL was seen at the end of long-term treatment with linaclotide. QOL in IBS can be improved in patients by pharmacotherapy using a longer duration of therapy and/or a larger sample size.³ Secondly, the primary endpoint of this study was not exactly the same as that in the FDA guidelines⁸ or the EMA guidelines for IBS treatment,⁹ but these endpoints were included as secondary and ad hoc additional endpoints in the Japanese trial. In addition, the primary endpoints in this trial were approved by the PMDA in Japan. Given that regional guidelines for IBS endpoints differ, our primary endpoints are not necessarily a limitation of the study. In fact, this study is a good example of pharmacotherapy development being based on consideration of multicultural differences among countries.²³

In conclusion, this study clearly showed evidence that linaclotide can be clinically applicable outside the US. Results of this phase 3 study suggest that 0.5 mg of linaclotide is effective and safe for IBS-C patients in Japan.

ACKNOWLEDGMENTS

The authors thank the investigators for participating in the study. Takashi Ando, Tetsu Aoki, Nobuo Aoyama, Takehiro Arai, Masaaki Arima, Masae Banno, Kazutada Egawa, Shin Fukui, Yukihiro Hamahata, Koichi Hirahata, Hitoshi Hongo, Hiroshi Iida, Atsushi Isono, Yoshifumi Jinnouchi, Shigeyasu Kamata, Hitoshi Kaneko,

Daijo Kasahara, Hyeteok Kim, Naoya Kimoto, Hiroyuki Kimura, Kensuke Kitamura, Shunichi Kobayashi, Toshio Komazaki, Kenji Kondo, Yoshiya Kumagai, Hidenori Kurakata, Kenji Maenou, Yoshio Matsuda, Yasuhiro Matsumoto, Kenzo Matsumura, Mitsuki Miyata, Shinichi Miyazaki, Mari Mizuno, Koji Mori, Hiroshi Morikawa, Kouetsu Morita, Yasuo Nakajima, Toshihide Ohmori, Naomi Ono, Hitoshi Sakai, Hideo Sawada, Koji Sawada, Shigeru Shirota, Masato Shitara, Masashi Sotokawa, Tomohiro Tada, Masahiro Takada, Hiroyuki Takahashi, Tokuma Tanuma, Toshiaki Terada, Kazunari Tominaga, Kentaro Tsuji, Mitsuhiro Tsukui, Osamu Ueda, Nobutoshi Watanabe, Asako Yamada, Norimichi Yamada, and Hideki Yamakoshi. The authors thank the following personnel for assisting with the study: Masataka Morita, Kenta Hayashi, Michie Yagi, Ayano Higa, and Takuma Ito. Statistical analyses of the entire dataset were performed in accordance with the standard procedures of Astellas Pharma Inc. Writing Assistance: was provided by SunFlare Co., Ltd., Tokyo, Japan.

DISCLOSURE

No competing interests declared.

AUTHORS' DECLARATION OF PERSONAL INTERESTS

Shin Fukudo, Hiroto Miwa, Atsushi Nakajima, Ken Haruma, and Yoshikazu Kinoshita are contracted medical consultants to Astellas Pharma Inc. Masanori Kosako, Ayako Nakagawa, Hiraku Akiho, and Yusuke Yamaguchi are employees of Astellas Pharma Inc. Jeffrey M Johnston and Mark Currie are employees of Ironwood Pharmaceuticals Inc.

AUTHOR CONTRIBUTIONS

SF, MK, AN, and HA designed the study, assessed the data, and wrote the manuscript. YY performed statistical analyses. HM, Atsushi Nakajima, KH, MJM, MC, and YK provided important scientific comments on study design, data analysis, and manuscript content. All authors have approved the final version of the article, including the authorship list.

ORCID

Shin Fukudo  <http://orcid.org/0000-0003-2265-0349>

REFERENCES

1. Sperber AD, Dumitrascu D, Fukudo S, et al. The global prevalence of IBS in adults remains elusive due to the heterogeneity of studies. A Rome Foundation working team literature review. *Gut*. 2017;66:1075-1082.
2. Lacy BE, Mearin F, Chang L, et al. Bowel disorders. *Gastroenterology*. 2016;150:1393-1407.
3. Enck P, Aziz Q, Barbara G, et al. Irritable bowel syndrome (IBS). *Nat Rev Dis Primers*. 2016;2:16014.

4. Leong SA, Barghout V, Birnbaum HG, et al. The economic consequences of irritable bowel syndrome: a US employer perspective. *Arch Intern Med*. 2003;163:929-935.
5. Canavan C, West J, Card T. Review article: the economic impact of the irritable bowel syndrome. *Aliment Pharmacol Ther*. 2014;40:1023-1034.
6. Herrick LM, Spalding WM, Saito YA, Moriarty J, Schleck C. A case-control comparison of direct healthcare-provider medical costs of chronic idiopathic constipation and irritable bowel syndrome with constipation in a community-based cohort. *J Med Econ*. 2017;20:273-279.
7. Fukudo S, Kaneko H, Akiho H, et al. Evidence-based clinical practice guidelines for irritable bowel syndrome. *J Gastroenterol*. 2015;50:11-30.
8. Department of Health and Human Services. FDA (US). Guidance for industry on irritable bowel syndrome—clinical evaluation of drugs for treatment. *Fed Regist*. 2012;77:32124-32125.
9. European Medicines Agency. Guideline on the evaluation of medicinal products for the treatment of irritable bowel syndrome. CPMP/EWP/785/97 Rev. 1 2014; EMA/CHMP/60337/2013:1-18.
10. Fukudo S, Ida M, Akiho H, et al. Effect of ramosetron on stool consistency in male patients with irritable bowel syndrome with diarrhea. *Clin Gastroenterol Hepatol*. 2014;12(953-959):e4.
11. Fukudo S, Kinoshita Y, Okumura T, et al. Ramosetron reduces symptoms of irritable bowel syndrome with diarrhea and improves quality of life in women. *Gastroenterology*. 2016;150(358-366):e8.
12. Andresen V, Camilleri M, Busciglio IA, et al. Effect of 5 days linaclotide on transit and bowel function in females with constipation-predominant irritable bowel syndrome. *Gastroenterology*. 2007;133:761-768.
13. Johnston JM, Kurtz CB, Macdougall JE, et al. Linaclotide improves abdominal pain and bowel habits in a phase IIb study of patients with irritable bowel syndrome with constipation. *Gastroenterology*. 2010;139(6):1877-1886.e2.
14. Currie MG, Fok KF, Kato J, et al. Guanylin: an endogenous activator of intestinal guanylate cyclase. *Proc Natl Acad Sci U S A*. 1992;89:947-951.
15. Kita T, Smith CE, Fok KF, et al. Characterization of human uroguanylin: a member of the guanylin peptide family. *Am J Physiol*. 1994;266:F342-F348.
16. Hamra FK, Forte LR, Eber SL, et al. Uroguanylin: structure and activity of a second endogenous peptide that stimulates intestinal guanylate cyclase. *Proc Natl Acad Sci U S A*. 1993;90:10464-10468.
17. Giannella RA. Escherichia coli heat-stable enterotoxins, guanylin, and their receptors: what are they and what do they do? *J Lab Clin Med*. 1995;125:173-181.
18. Forte LR. Guanylin regulatory peptides: structures, biological activities mediated by cyclic GMP and pathobiology. *Regul Pept*. 1999;81:25-39.
19. Castro J, Harrington AM, Hughes PA, et al. Linaclotide inhibits colonic nociceptors and relieves abdominal pain via guanylate cyclase-C and extracellular cyclic guanosine 3',5'-monophosphate. *Gastroenterology*. 2013;145:1334-1346. e1-11.
20. Chey WD, Lembo AJ, Lavins BJ, et al. Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. *Am J Gastroenterol*. 2012;107:1702-1712.
21. Rao S, Lembo AJ, Shiff SJ, et al. A 12-week, randomized, controlled trial with a 4-week randomized withdrawal period to evaluate the efficacy and safety of linaclotide in irritable bowel syndrome with constipation. *Am J Gastroenterol*. 2012;107:1714-1724.
22. Quigley EM, Tack J, Chey WD, et al. Randomised clinical trials: linaclotide phase 3 studies in IBS-C - a prespecified further analysis based on European Medicines Agency-specified endpoints. *Aliment Pharmacol Ther*. 2013;37:49-61.
23. Francisconi CF, Sperber AD, Fang X, et al. Multicultural aspects in functional gastrointestinal disorders (FGIDs). *Gastroenterology*. 2016;150:1344-1354.
24. Fukudo S, Nakajima A, Fujiyama Y, et al. Determining an optimal dose of linaclotide in use in Japanese patients with irritable bowel syndrome with constipation: a phase II randomized, double-blind, placebo-controlled study. *Neurogastroenterol Motil*. 2018;30:e13275.
25. Longstreth GF, Thompson WG, Chey WD, et al. Functional bowel disorders. *Gastroenterology*. 2006;130:1480-1491.
26. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. *Scand J Gastroenterol*. 1997;32:920-924.
27. Patrick DL, Drossman DA, Frederick IO, et al. Quality of life in persons with irritable bowel syndrome: development and validation of a new measure. *Dig Dis Sci*. 1998;43:400-411.
28. Kanazawa M, Drossman DA, Shinozaki M, et al. Translation and validation of a Japanese version of the irritable bowel syndrome-quality of life measure (IBS-QOL-J). *Biopsychosoc Med*. 2007;1:6.
29. International Conference on Harmonisation; guidance on statistical principles for clinical trials—availability: FDA. Notice. *Fed Regist*. 1998;63:49583-49598.
30. Lembo AJ, Schneier HA, Shiff SJ, et al. Two randomized trials of linaclotide for chronic constipation. *N Engl J Med*. 2011;365:527-536.
31. Layer P, Stanghellini V. Review article: linaclotide for the management of irritable bowel syndrome with constipation. *Aliment Pharmacol Ther*. 2014;39:371-384.
32. Brooks M. FDA okays new linaclotide (Linzess) dose for constipation. *Medscape*. 2017. <https://www.medscape.com/viewarticle/875013>
33. Busby RW, Bryant AP, Bartolini WP, et al. Linaclotide, through activation of guanylate cyclase C, acts locally in the gastrointestinal tract to elicit enhanced intestinal secretion and transit. *Eur J Pharmacol*. 2010;649:328-335.
34. Fiskerstrand T, Arshad N, Haukanes BI, et al. Familial diarrhea syndrome caused by an activating GUCY2C mutation. *N Engl J Med*. 2012;366:1586-1595.
35. Bharucha AE, Waldman SA. Taking a lesson from microbial diarrheagenesis in the management of chronic constipation. *Gastroenterology*. 2010;138:813-817.
36. Nishijima S, Suda W, Oshima K, et al. The gut microbiome of healthy Japanese and its microbial and functional uniqueness. *DNA Res*. 2016;23:125-133.
37. Hehemann JH, Correc G, Barbeyron T, et al. Transfer of carbohydrate-active enzymes from marine bacteria to Japanese gut microbiota. *Nature*. 2010;464:908-912.
38. Minagawa E, Kaminogawa S, Tsukasaki F, et al. Exopeptidase profiles of bifidobacteria. *J Nutr Sci Vitaminol (Tokyo)*. 1985;31:599-606.
39. Lin JE, Colon-Gonzalez F, Blomain E, et al. Obesity-induced colorectal cancer is driven by caloric silencing of the guanylin-GUCY2C paracrine signaling axis. *Cancer Res*. 2016;76:339-346.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Fukudo S, Miwa H, Nakajima A, et al. A randomized controlled and long-term linaclotide study of irritable bowel syndrome with constipation patients in Japan. *Neurogastroenterol Motil*. 2018;30:e13444. <https://doi.org/10.1111/nmo.13444>