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High-dose linaclotide is effective and safe in patients with chronic constipation: A phase III randomized, double-blind, placebo-controlled study with a long-term open-label extension study in Japan

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Abstract

Background: A previous phase II dose-ranging study of linaclotide in a Japanese chronic constipation (CC) population showed that 0.5 mg was the most effective dose. This study aimed to verify the hypothesis that 0.5 mg of linaclotide is effective and safe in Japanese CC patients.

Methods: This was a Japanese phase III randomized, double-blind, placebo-controlled (part 1), and long-term, open-label extension (part 2) study of linaclotide. CC patients (n = 186) diagnosed using the Rome III criteria were randomly assigned to linaclotide 0.5 mg (n = 95) or placebo (n = 91) for a 4-week double-blind treatment period in part 1, followed by an additional 52 weeks of open-label treatment with linaclotide in part 2. The primary efficacy endpoint was the change from baseline in weekly spontaneous bowel movement (SBM) frequency at the first week. Secondary

Abbreviations: 95% CI, 95% confidence interval; BSFS, Bristol Stool Form Scale; CC, chronic constipation; cGMP, cyclic guanosine monophosphate; 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.

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endpoints included responder rate for complete SBM (CSBM), changes in stool consistency, and severity of straining.

Key Results: Part 1: Change in weekly mean SBM frequency in the first week of treatment with linaclotide (4.02) was significantly greater than that with placebo (1.48, $P < 0.001$). Linaclotide produced a higher CSBM responder rate (52.7%) compared to placebo (26.1%, $P < 0.001$). Part 2: Patients continued to show improved SBM frequency with linaclotide. Through parts 1 and 2, the most common drug-related adverse event was mild and occasionally moderate diarrhea.

Conclusions and Inferences: The results of this study indicate that a linaclotide dose of 0.5 mg/day is effective and safe in Japanese CC patients.

KEYWORDS

chronic constipation, diarrhea, guanylate cyclase C activator, linaclotide, stool consistency

1 | INTRODUCTION

Chronic constipation (CC) is a common disorder with an estimated prevalence in developed countries of 12%-19% in the general population.[1] Japanese data also show an incidence of 2.08% in the general population.[2] CC is known to negatively affect quality of life (QOL), and poor QOL is associated with worsening of CC symptoms.[3] Chronic constipation represents an economic burden for the patient and health care provider.[4] Resource utilization associated with the diagnosis and management of CC is a significant cost driver, whereas constipation prevention programs have demonstrated cost savings.[4] Diagnosing CC using the Rome III[5] (or recently Rome IV[6]) criteria is useful because these criteria can identify subjects with a greater clinical need.[7] Developing appropriate management for CC is therefore clinically valuable.

We previously performed randomized placebo-controlled trials of linaclotide in Japanese patients with CC[8] or irritable bowel syndrome with constipation (IBS-C).[9,10] Linaclotide is a 14-amino acid peptide which acts as a novel guanylate cyclase C (GC-C) activator.[11] GC-C is localized on the luminal surface of the epithelial cells of the gastrointestinal tract.[11] Linaclotide activates GC-C from the lumen, and it causes cyclic guanosine monophosphate (cGMP) to accumulate in the epithelial cells.[11] Increased cGMP in the epithelial cells eventually stimulates cystic fibrosis transmembrane conductance regulator (CFTR), which acts as a chloride ion channel and causes secretion of chloride ions with water molecules.[12] Earlier clinical studies of linaclotide in North America, Oceania and China have demonstrated efficacy and safety in patients with IBS-C[12-15] as well as CC.[16] The recommended doses of linaclotide from these studies are 0.29 mg for IBS-C and 0.145 mg for CC.[12-16] By contrast, results[8-10] obtained in Japan have been somewhat different. A phase II study of IBS-C patients showed 0.5 mg per day of linaclotide to be the optimal dose.[9] A subsequent phase III study of IBS-C patients confirmed 0.5 mg per day of linaclotide to be effective and safe.[10] Additionally, a phase II study of CC patients also showed that 0.5 mg per day of linaclotide is the optimal dose in this patient population.[8]

Key Points

- A previous phase II trial demonstrated that 0.5 mg of linaclotide per day was the most effective dose in Japanese CC patients.
- This phase III randomized, double-blind, placebo-controlled, and long-term, open-label extension study of linaclotide in Japanese CC patients clearly indicated that 0.5 mg of linaclotide is effective and safe.
- This is the fourth replicate study showing that 0.5 mg of linaclotide per day is suitable for constipated Japanese patients.

Therefore, we sought to confirm our hypothesis that 0.5 mg of linaclotide in CC patients is effective and safe by conducting a phase III study in Japan.

2 | METHODS

2.1 | Study oversight

The study was designed and conducted by the sponsor (Astellas Pharma Inc.) in collaboration with the principal investigators in accordance with the principles of the Declaration of Helsinki and a protocol, which was approved by the institutional review boards at all sites. Shinagawa East one Medical Clinic Institution Review Board, a representative ethics committee, approved this clinical trial (Reference number: 0456-CL-1031) on June 24, 2016. All the patients provided voluntary written informed consent prior to participating in the study. The sponsor collected the data, monitored study conduct, and performed the statistical analyses. The initial draft of the manuscript was prepared by a medical writer employed by the sponsor with input from all authors. All authors

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

2.2 | Patient population

We enrolled outpatients aged 20-79 years diagnosed with CC according to the Rome III functional constipation criteria.[5] In brief, patients who experienced fewer than three defecations per week and met at least one of three other criteria of functional constipation[5] (lumpy or hard stools in at least 25% of defecations, sensation of incomplete evacuation for at least 25% of defecations, straining during at least 25% of defecations) for more than 6 months met the Rome criteria for CC. Because the Rome III criteria exclude IBS-C from functional constipation, no patients with IBS-C were enrolled in this study. Enrolled patients were included if their average frequency of spontaneous bowel movements (SBM, 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) per week was less than 3 and they experienced no more than one type 6 stool and no type 7 stool over a 2-week pre-treatment observation period before randomization. Stool type was determined using the Bristol Stool Form Scale (BSFS):[5] type 1, separate hard lumps like nuts (difficult to pass); type 2, sausage shaped but lumpy; type 3, like sausage but with cracks on its surface; type 4, like sausage or snake, smooth, and soft; type 5, soft blobs with clear-cut edges (passed easily); type 6, fluffy pieces with ragged edges (mushy stool); and type 7, watery, no solid pieces, and entirely liquid. Patients were excluded if they had a history of inflammatory bowel disease or celiac disease or had concurrent organic diseases confirmed by colonoscopy or double-contrast barium enema, which was done only if these examinations had not been performed within the preceding 5 years.

2.3 | Study design

The phase III study was conducted in Japan from June 2016 to November 2017 at 39 hospitals and clinics with departments of gastroenterology. The study included a pre-treatment period (a screening period of up to 4 weeks and a 2-week bowel habit observation period) and a 56-week treatment period. The treatment period included a 4-week double-blind, placebo-controlled, parallel-group, comparative study period (part 1) and a 52-week open-label, uncontrolled study period (part 2).

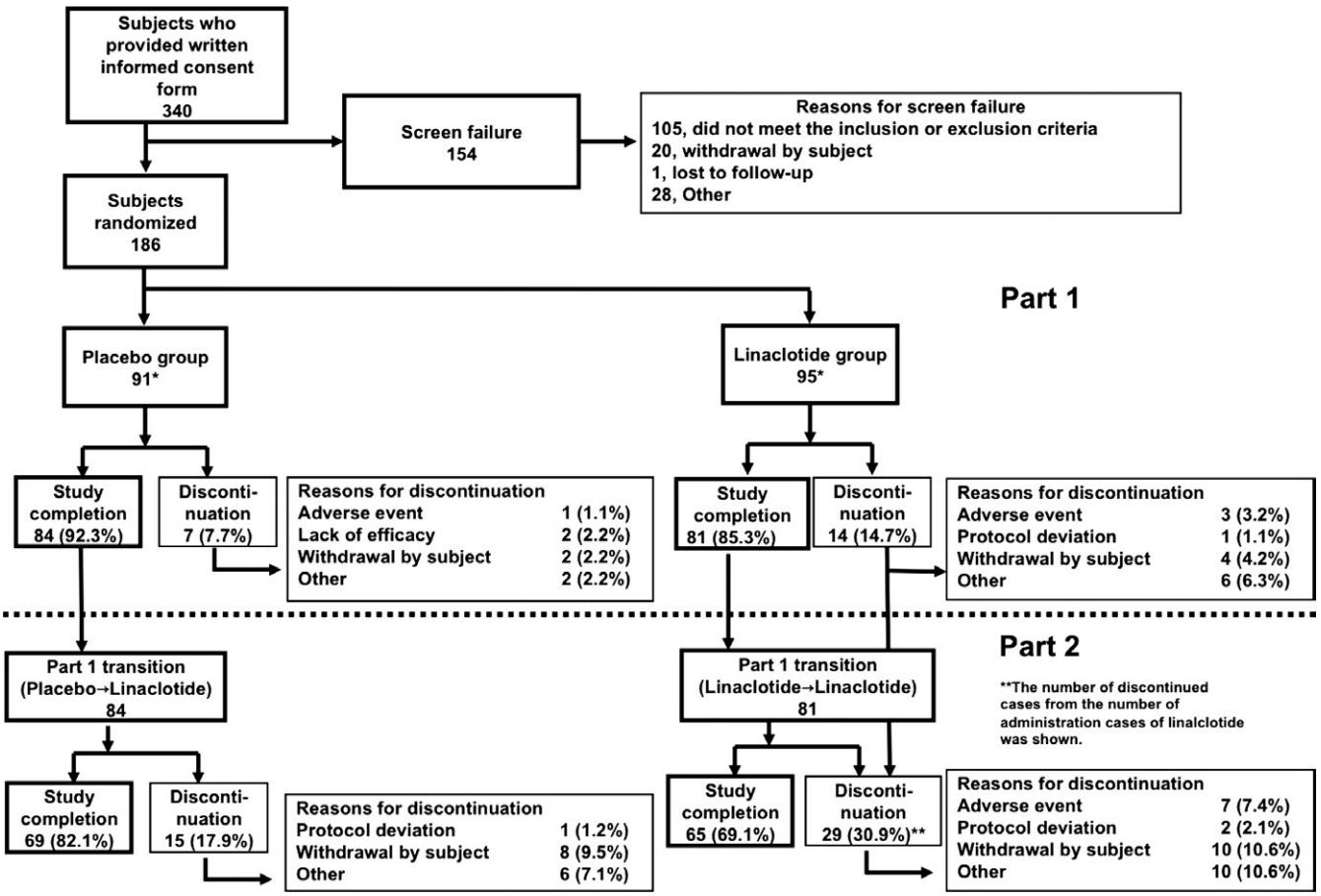

FIGURE 1 Flow diagram. Note that one patient in the placebo group with no data after administration of the study drug was excluded from the full analysis set as was defined in the protocol. One patient who was allocated to the linaclotide group at first but withdrew consent was excluded from the full analysis set and safety analyses. Three patients (one patient in the placebo group and two patients in the linaclotide group) from whom a written consent to data collection could not obtain due to the death of the investigator were excluded from full analysis set and safety analyses (*). From the protocol requirement, full analysis set and safety analyses are shown

TABLE 1 Demographics and baseline characteristics of the treatment groups

Characteristic	Part 1			Part 2		
	Placebo (N = 89)	Linaclotide (N = 92)	*P* value[a]	Placebo→Linaclotide (N = 84)	Linaclotide→Linaclotide (N = 92)	Total (N = 176)
Age – y	43.5 ± 11.5	42.0 ± 12.2		43.3 ± 11.1	42.0 ± 12.2	42.7 ± 11.7
Age ≥ 65 y—no. of patients (%)	3 (3.4%)	4 (4.3%)	0.415	2 (2.4%)	4 (4.3%)	6 (3.4%)
Sex—no. of patients (%)						
Female	75 (84.3%)	74 (80.4%)	0.561	71 (84.5%)	74 (80.4%)	145 (82.4%)
Male	14 (15.7%)	18 (19.6%)		13 (15.5%)	18 (19.6%)	31 (17.6%)
Duration of disease—mo	240.0 ± 153.3	213.2 ± 141.8	0.222	238.6 ± 148.8	213.2 ± 141.8	225.3 ± 145.4
CSBM—no./wk	0.63 ± 0.76	0.60 ± 0.68	0.808	0.65 ± 0.76	0.60 ± 0.68	0.63 ± 0.72
SBM—no./wk	1.74 ± 0.64	1.68 ± 0.74	0.555	1.76 ± 0.62	1.68 ± 0.74	1.72 ± 0.69
Stool form score (1-7)[b]	2.40 ± 1.09	2.74 ± 1.08	0.042	2.44 ± 1.08	2.74 ± 1.08	2.59 ± 1.09
Abdominal pain/discomfort severity score (1-5)	1.97 ± 0.85	1.88 ± 0.79	0.450	1.95 ± 0.83	1.88 ± 0.79	1.91 ± 0.81
Abdominal bloating severity score (1-5)	2.25 ± 0.84	2.10 ± 0.81	0.214	2.24 ± 0.83	2.10 ± 0.81	2.17 ± 0.82
Straining severity score (1-5)[b]	3.25 ± 0.93	3.01 ± 0.83	0.070	3.22 ± 0.93	3.01 ± 0.83	3.11 ± 0.88
IBS-QOL-J overall score (1-100)	80.7 ± 14.9	83.4 ± 13.5	0.194	80.3 ± 15.1	83.4 ± 13.5	81.9 ± 14.4

CSBM (complete spontaneous bowel movement); SBM without 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.

Data were expressed as mean ± SD, actual numbers, or %.

[a]ANOVA (sex was evaluated by Fisher's exact test).

[b]Number of subjects in the placebo, linaclotide, placebo→linaclotide, and linaclotide→linaclotide groups is 86, 85, 82, and 85, respectively, because data were unknown in some subjects.

Eligible patients were randomly assigned in a 1:1 ratio, using a web-based system, to receive either linaclotide tablets at a dose of 0.5 mg or placebo tablets, administered orally once daily before breakfast for 4 weeks. After a completion of 4 weeks of treatment, patients meeting the transfer criteria (Table S1) were assigned to an additional 52 weeks of treatment with linaclotide 0.5 mg once daily before breakfast. Visits 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 were allowed by the investigators following the week 4 visit in part 1 through the week 12 visit of the treatment period in part 2 (See the details in Table S1). All patients, investigators, and sponsors were kept blinded until all observations and evaluations in part 1 were completed, statistical analysis plans were finalized, and all the data had been entered into the database.

2.4 | Assessments

During the bowel habit observation period and treatment period, using a paper diary, patients recorded their CC symptoms. Subsequently, some of these data were entered daily into an electronic database using an interactive voice response system.[9] In the paper diary, patients recorded the following assessments for each bowel movement (BM): stool consistency (scored using the 7-point BSFS); severity of straining, abdominal bloating, and abdominal pain/discomfort (all scored on a 5-point ordinate scale: 1, none; 2, mild; 3, moderate; 4, severe; and 5, very severe); and sensation of incomplete evacuation assessed on a binary scale (0, absent or 1, present). Every 7 days during the treatment period, patients also recorded their global assessment of relief of constipation symptoms, abnormal bowel habit improvement, and relief of abdominal symptoms compared to baseline (bowel habit observation period) using a 7-point ordinate 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). The site investigators assessed all patient-reported adverse events and serious adverse events. Other safety evaluations included physical examinations, vital sign measurements, and standard laboratory tests.

2.5 | Study endpoints

The primary efficacy endpoint was the change from baseline in SBM frequency in the first week of treatment, as previously approved for other constipation trials[17] by Japanese Pharmaceuticals and Medical Devices Agency (PMDA).[8] The secondary endpoints

included the following: complete SBM (CSBM, defined as an SBM for which the patient reported a feeling of complete evacuation), 50% responder rate (to be a CSBM 50% responder, a patient had to be a weekly responder for at least 2 of the 4 double-blind treatment period weeks; to be a weekly CSBM responder, a patient had to report in the same week at least three CSBMs and an increase in at least one CSBM from baseline), stool consistency, straining, abdominal bloating, abdominal pain/discomfort, responder rates for relief of CC-related parameters (global assessment of relief of CC symptoms, improvement in abnormal bowel habits, and relief of abdominal symptoms; weekly responders of relief for each parameter were defined as patients with a score of 1 or 2 at each weekly evaluation point, and patients who were weekly responders for at least 2 of the 4 weeks of the double-blind treatment period were considered to be overall responders), proportion of patients who had an SBM/CSBM within 24 hours after the start of the initial administration of the study drug, time to first SBM, and IBS-QOL.[18,19] Ad hoc additional endpoints were assessed, including the CSBM 75% responder rate (to be a CSBM 75% responder, a patient had to be a weekly responder for at least 3 of the 4 weeks of the double-blind treatment period) based on the European Medicines Agency (EMA) guideline.[20] All adverse events were recorded during the treatment period.

2.6 | Statistical analysis

Statistical analysis was performed using SAS Drug Development (ver. 4.5) and PC-SAS (ver. 9.4) (SAS Institute Inc., Cary, NC, USA). Sample sizes estimated to provide more than 90% power to detect a difference in the primary endpoint between placebo and linaclotide 0.5 mg were based on the phase II clinical study data,[8] using asymptotic normal approximation with a two-sided significance level of 0.05. In total, 170 patients (85 patients for 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.[21] The full analysis set included all patients who received at least one dose of the study drug during the treatment period and in whom at least one endpoint could be evaluated. Safety analyses were performed for all patients who received at least one dose of the study drug during the treatment period.

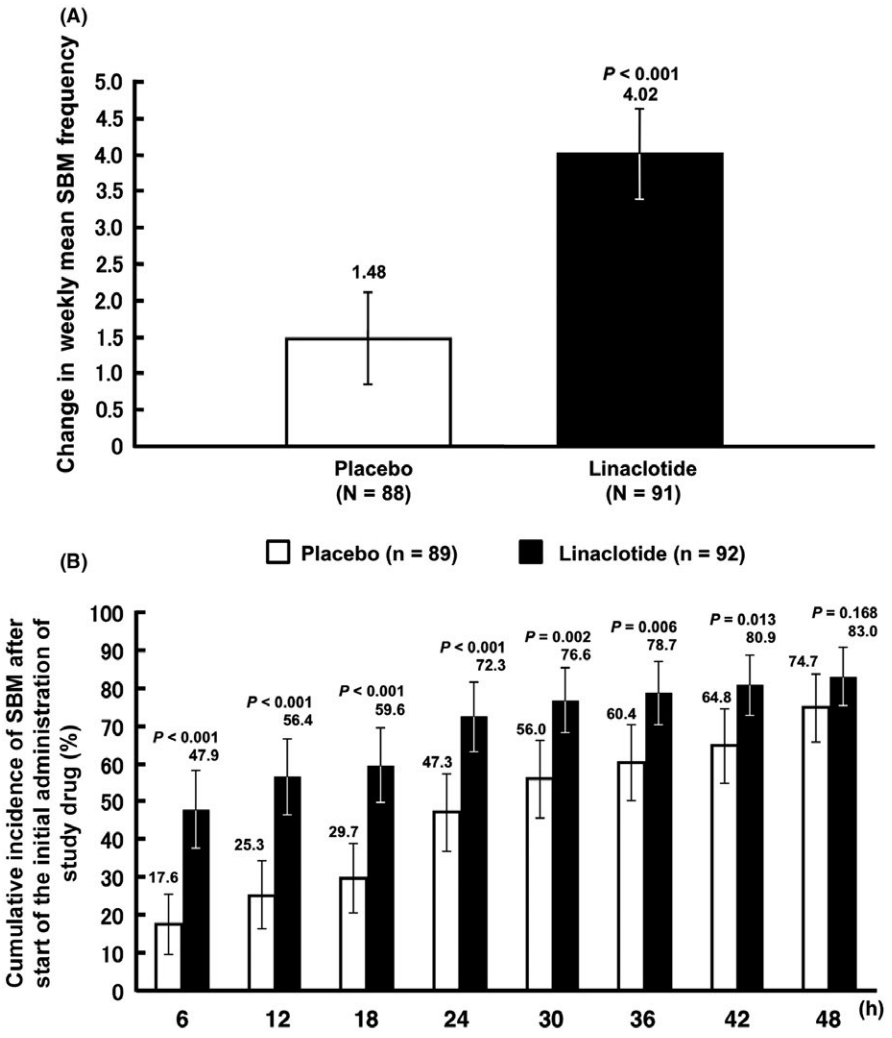

FIGURE 2 Primary and additional efficacy endpoints for Part 1. A, Change from baseline in weekly mean SBM frequency in the first week of treatment. Error bar: 95% CI. *P* values derived by analysis of covariance; B, Cumulative incidence of SBM after start of the initial administration of study drug. Error bar: 95% CI. *P* values derived by Wald test of difference of Kaplan-Meier estimates compared to placebo

TABLE 2 Secondary and Additional Efficacy Endpoints at part 1

Endpoints	Placebo (N = 89[a])	Linaclotide (N = 92[a])	*P* value
SBMs			
Mean no./wk[c]	3.19 [2.55, 3.82]	5.72 [5.10, 6.35]	< 0.001
Change from baseline no./wk[c]	1.48 [0.85, 2.12]	4.02 [3.39, 4.64]	< 0.001
SBM ≤24 hr after first dose (% of patients)	48.3 [37.6, 59.2]	72.8 [62.6, 81.6]	< 0.001
Median time to first SBM (hr)	24.67 [22.00, 34.58]	6.71 [4.67, 18.08]	0.013[b]
Responder[e] at the first week (% of patients)	56.8 [45.8, 67.3]	83.5 [74.3, 90.5]	< 0.001
Responder[e] for 2 of 4 wk (% of patients)	64.8 [53.9, 74.7]	83.5 [74.3, 90.5]	0.006
Responder[e] for 3 of 4 wk (% of patients)	42.0 [31.6, 53.0]	71.4 [61.0, 80.4]	< 0.001
CSBMs			
Mean no./wk[c]	1.40 [0.93, 1.86]	3.07 [2.61, 3.52]	< 0.001
Change from baseline[c]	0.78 [0.32, 1.24]	2.46 [2.00, 2.91]	< 0.001
CSBM ≤24 hr after first dose (% of patients)	24.7 [16.2, 35.0]	45.7 [35.2, 56.4]	0.005
Responder[e] at the first week (% of patients)	26.1 [17.3, 36.6]	52.7 [42.0, 63.3]	< 0.001
Responder[e] for 2 of 4 wk (% of patients)	27.3 [18.3, 37.8]	56.0 [45.2, 66.4]	< 0.001
Responder[e] for 3 of 4 wk (% of patients)	12.5 [6.4, 21.3]	45.1 [34.6, 55.8]	< 0.001
Stool consistency			
Mean BSFS score[c]	2.87 [2.59, 3.14]	4.12 [3.85, 4.39]	< 0.001
Change from baseline score[c]	0.29 [0.02, 0.56]	1.54 [1.27, 1.82]	< 0.001
Straining severity			
Mean straining severity score[c]	2.81 [2.63, 2.99]	2.30 [2.12, 2.48]	< 0.001
Change from baseline score[c]	-0.33 [-0.51, -0.15]	-0.84 [-1.02, -0.66]	< 0.001
Abdominal bloating			
Mean bloating score[c]	2.02 [1.91, 2.13]	2.00 [1.89, 2.11]	0.835
Change from baseline score[c]	-0.15 [-0.26, -0.04]	-0.17 [-0.28, -0.06]	0.835
Abdominal pain/discomfort			
Mean pain/discomfort score[c]	1.81 [1.70–1.92]	1.98 [1.87, 2.09]	0.031
Change from baseline score[c]	−0.11 [−0.22, 0.00]	0.07 [−0.05, 0.18]	0.031
Relief of chronic constipation symptoms			
Responder[f] of global assessment of relief for 2 of 4 wk (% of patients)	9.1 [4.0, 17.1]	48.4 [37.7, 59.1]	< 0.001
Responder[f] of abnormal bowel habits improvement for 2 of 4 wk (% of patients)	11.4 [5.6, 19.9]	47.3 [36.7, 58.0]	< 0.001
Responder[f] of abdominal symptoms relief for 2 of 4 wk (% of patients)	5.7 [1.9, 12.8]	33.0 [23.5, 43.6]	< 0.001
IBS-QOL (overall)			
Mean QOL score[d]	87.4 [85.6, 89.1]	89.0 [87.2, 90.8]	0.204
Change from baseline[d]	5.6 [3.8, 7.3]	7.2 [5.4, 9.0]	0.204
IBS-QOL (sub-scales)			
Change from baseline[d] dysphoria	6.0 [3.6, 8.3]	7.8 [5.4, 10.2]	0.277
Change from baseline[d] interference with activity	5.8 [3.7, 7.9]	6.1 [4.0, 8.2]	0.838
Change from baseline[d] body image	7.0 [4.7, 9.4]	10.0 [7.7, 12.3]	0.081

(Continues)

TABLE 2 (Continued)

Endpoints	Placebo (N = 89[a])	Linaclotide (N = 92[a])	*P* value
Change from baseline[d] health worry	8.3 [5.7, 11.0]	12.4 [9.8, 15.0]	0.031
Change from baseline[d] food avoidance	6.7 [3.5, 10.0]	11.4 [8.2, 14.7]	0.047
Change from baseline[d] social reaction	3.6 [1.8, 5.3]	3.5 [1.8, 5.3]	0.973
Change from baseline[d] sexual	1.5 [−0.8, 3.8]	3.0 [0.7, 5.3]	0.371
Change from baseline[d] relationship	2.4 [0.6, 4.2]	3.7 [1.9, 5.5]	0.327

[a]Full analysis set number.
[b]P-value comparing incidence curve between placebo and Linaclotide.
[c]No./wk or score at the first week of treatment.
[d]Score at the last evaluation point of part 1.
[e]Patients reported ≥3 SBMs/CSBMs per week with an increase of ≥1 SBMs/CSBMs from baseline.
[f]Patients reported score of 1 (complete relief) or 2 (considerable relief) at each weekly evaluation point.

Analysis of covariance for the change from baseline endpoints was performed with treatment group as a factor and baseline as the covariate. Responder rates and percentage of patients with SBM/CSBM within 24 hours after start of the initial administration of the study drug 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. The median time to first SBM was estimated using the Kaplan-Meier method, and the estimated incidence curves were compared by log-rank test. In part 2, overall IBS-QOL and subscale scores obtained at weeks 24 and 56 were compared to baseline using paired *t* test. Cumulative incidences of SBM at specified time points after start of the initial administration were estimated by the Kaplan-Meier method. For the imputation of the missing data of change from baseline endpoints and responder rate parameters, an observed case approach was applied. All reported *P* values are based on two-sided tests at the 0.05 significance level.

3 | RESULTS

3.1 | Patients

Of 340 patients who provided written informed consent, 186 patients were randomized into the placebo group (n = 91) or the linaclotide group (n = 95) in part 1. Of these 186 patients, a total of 165 patients completed the 4-week treatment in part 1 and all of them received linaclotide (Figure 1). The demographics and baseline characteristics were similar across the groups (Table 1). As for linaclotide dosage, 15 (8.5%) patients had their dose reduced to 0.25 mg based on the investigators' judgment; no cases were subsequently escalated back to the 0.5 mg dose.

3.2 | Efficacy

The change from baseline in SBM frequency during the first week of treatment (primary endpoint) in the linaclotide group was significantly greater than that in the placebo group (4.02, 95% confidence interval [CI], 3.39-4.64 with linaclotide vs 1.48, 95% CI, 0.85-2.12 with placebo; $P < 0.001$) (Figure 2A). The CSBM responder rate at the first week was significantly higher for linaclotide than for placebo (52.7%, 95% CI, 42.0%-63.3% with linaclotide vs 26.1%, 95% CI, 17.3%-36.6% with placebo; $P < 0.001$) (Table 2), with a difference between linaclotide and placebo of 26.6% (95% CI, 11.7-41.5%), relative risk (RR) of 2.02 (95% CI, 1.35-3.02), and number needed to treat (NNT) of 4 (95% CI, 3-9). The CSBM 75% (for 3 of 4 weeks) responder rate was also significantly higher for linaclotide than for placebo (45.1%, 95% CI, 34.6-55.8% with linaclotide vs 12.5%, 95% CI, 6.4-21.3% with placebo; $P < 0.001$), with a difference between linaclotide and placebo of 32.6% (95% CI, 19.1-46.0%), RR of 3.60 (95% CI, 1.98-6.55), and NNT of 4 (95% CI 3-6). The percentage of patients who had an SBM within 24 hours of the initial administration of the study drug was significantly higher in the linaclotide group than it was in the placebo group ($P < 0.001$), and the incidence curve for the first SBM was also significantly different ($P = 0.013$). Cumulative incidences of SBM after the start of the initial administration of the study drug were significantly higher in the linaclotide group than those in the placebo group at every time point except for 48 hours (Wald test of differences on Kaplan-Meier estimates, $P < 0.05$) (Figure 2B).

The number of 50% (for 2 of 4 weeks) responders who were considered to have relief from CC-related parameters (global assessment of relief of CC symptoms, improvement in abnormal bowel habits, and relief of abdominal symptoms) was significantly higher in the linaclotide group than in the placebo group($P < 0.001$). At the last evaluation time point in part 1, linaclotide performed significantly better on the IBS-QOL-J subscale for health worry ($P = 0.031$) and food avoidance ($P = 0.047$) compared to placebo, but not for the overall IBS-QOL-J or the other subscales (Table 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 SBM frequency, weekly CSBM responder rate, stool consistency, and straining. Gradually increasing effects were seen for changes in abdominal bloating and abdominal pain/discomfort, and the other efficacy endpoints assessed in part 2 also showed improvement. Long-term treatment with linaclotide was associated with a significant improvement in the overall and all subscale scores of IBS-QOL-J at weeks 24 and 56 compared with scores at baseline ($P < 0.01$) (Figures 3 and 4A-D). For the 15 patients whose dose was reduced in part 2 to 0.25 mg based on the investigators' judgment, each patient's weekly SBM frequency after dose reduction is shown in Figure 4E.

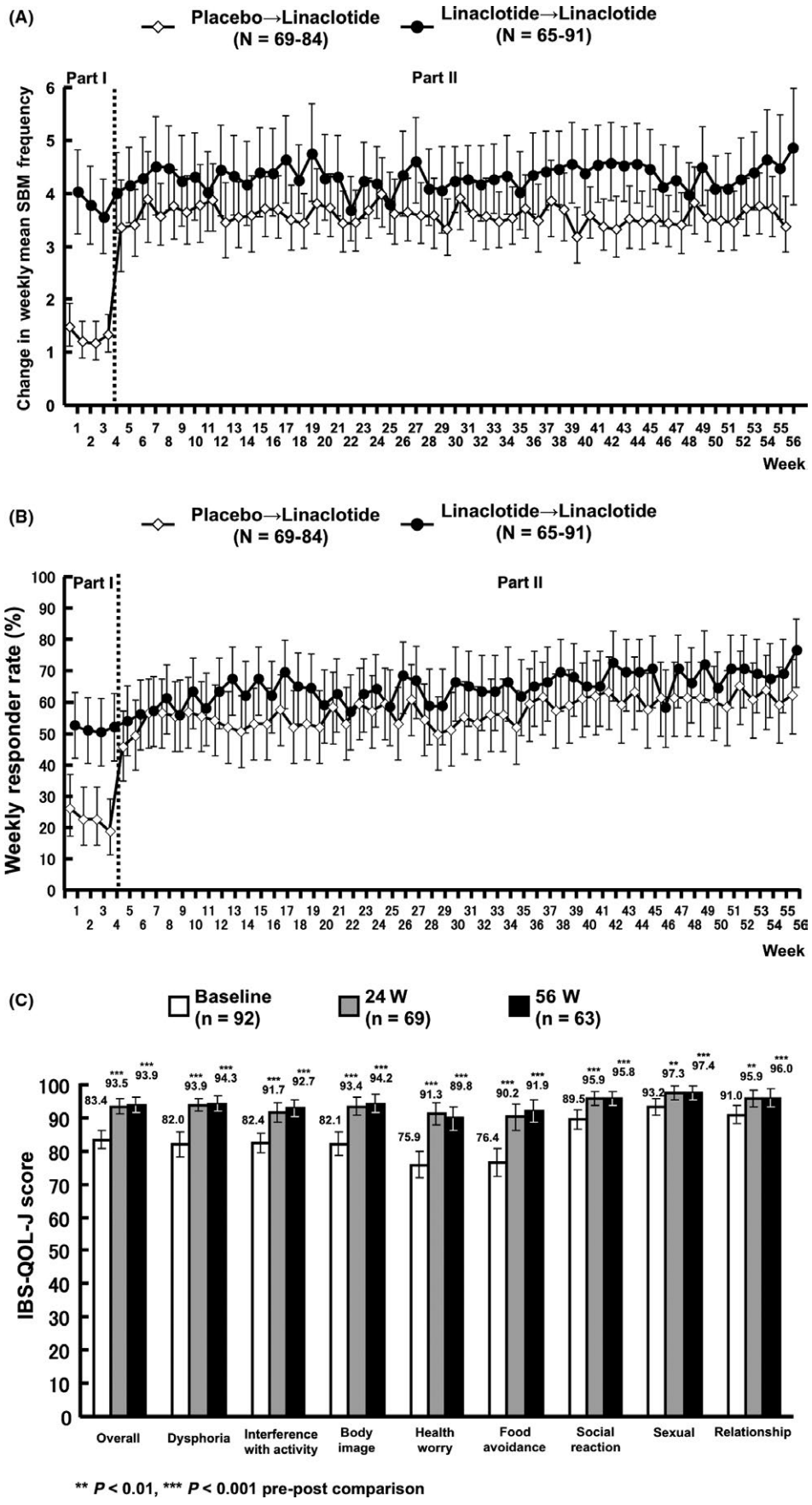

FIGURE 3 Main long-term efficacy endpoint. A, Change in weekly mean SBM frequency; B, Weekly responder rate of CSBM; C, IBS-QOL-J score. Error bar: 95% CI

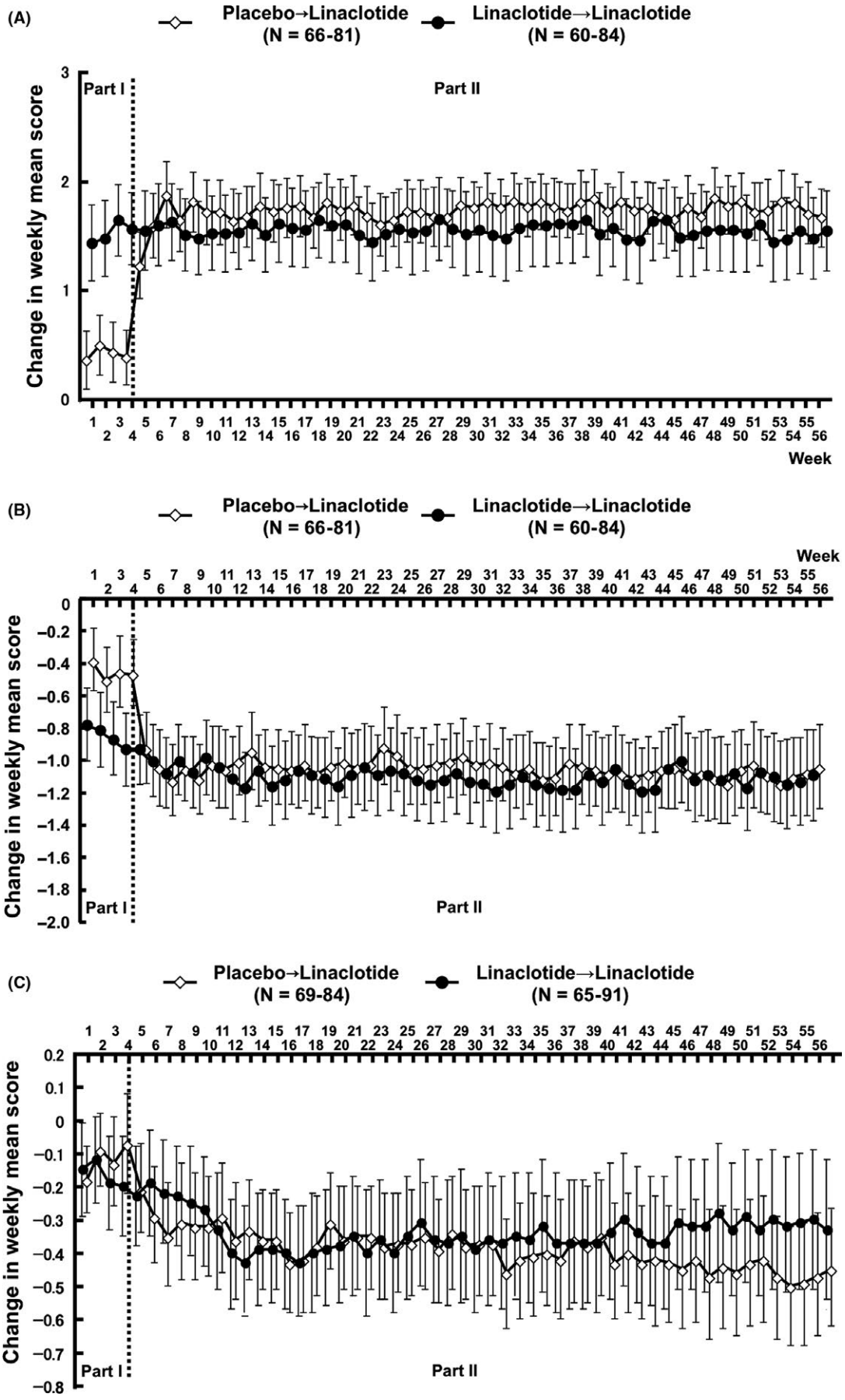

FIGURE 4

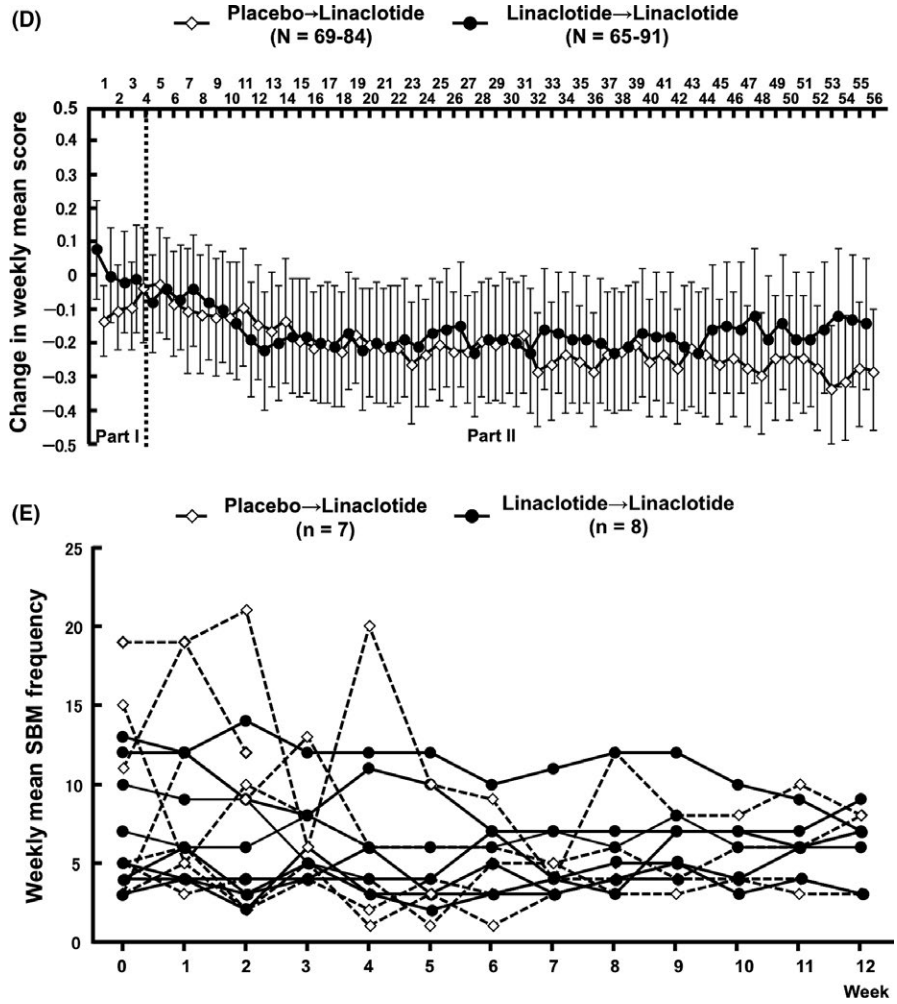

FIGURE 4 Other long-term efficacy endpoints. A, Change in weekly mean stool form score; B, Change in weekly mean straining severity score; C, Change in weekly mean abdominal bloating severity score; D, Change in weekly mean abdominal pain/discomfort severity score; E, Weekly mean SBM frequency after dose reduction (0.5 mg→0.25 mg). Error bar: 95% CI

3.3 | Safety

The most frequently reported adverse event was diarrhea. During the 4-week double-blind treatment period, the incidence of diarrhea was significantly higher in the linaclotide group compared to the placebo group (13.0% vs 1.1%, $P = 0.002$). During the long-term open-label treatment period, the incidence of overall adverse events in the linaclotide-linaclotide group was comparable to that in the placebo-linaclotide group (Table 3). For all the patients who reported diarrhea, the maximum severity was mild or moderate; discontinuation due to diarrhea was 3.3% and 0%, respectively, in the linaclotide and placebo groups in part 1 and 3.3% and 0%, respectively, in the linaclotide-linaclotide and placebo-linaclotide group in part 2. The difference between the linaclotide and placebo groups for incidence of diarrhea in part 1 was 11.9% (95% CI, 3.6-20.2%) with RR of 11.74 (95% CI, 1.56-88.42) and number needed to harm (NNH) of 9 (95% CI, 5-28). Of the 15 patients whose dose was reduced to 0.25 mg based on the investigators' judgment, four patients had diarrhea after dose reduction and 10 patients completed the 52 weeks of treatment in part 2. A total of two serious adverse events (breast cancer and abdominal pain) occurred in two patients who received linaclotide-linaclotide; however, neither event was considered to be treatment-related. No deaths were reported during the study. There were no clinically significant differences in hematologic or blood chemical results, findings on urinalysis, or vital signs among the treatment groups.

4 | DISCUSSION

Positive results for the primary and secondary endpoints of this study support the hypothesis that 0.5 mg of linaclotide in Japanese CC patients is effective and safe. Not only the double-blind part of the study (part 1), but also the long-term part of the study (part 2), demonstrated the rapid and sustained effect of 0.5 mg of linaclotide without treatment-related serious adverse events. The first Japanese study of linaclotide was a phase II study in IBS-C patients.[9] In the study, the most effective dose of linaclotide was 0.5 mg per day.[9] The subsequent Japanese phase III trial of linaclotide in IBS-C patients confirmed that 0.5 mg per day of linaclotide was effective and safe.[10] A more recent phase II Japanese study of linaclotide in CC patients

TABLE 3 Incidence of adverse events (≥2% in each part)

Part 1: system organ class Preferred term	Placebo (N = 90)	Linaclotide (N = 92)	*P* value
Overall	13 (14.4%)	26 (28.3%)	0.030
Gastrointestinal disorders	4 (4.4%)	16 (17.4%)	0.008
Diarrhea	1 (1.1%)	12 (13.0%)	0.002
Infections and infestations	6 (6.7%)	6 (6.5%)	1.000
Nasopharyngitis	5 (5.6%)	4 (4.3%)	0.746
Investigations	1 (1.1%)	3 (3.3%)	0.621
Blood potassium increased	1 (1.1%)	2 (2.2%)	1.000
Part 2: system organ class Preferred term	**Placebo→Linaclotide (n = 84)**	**Linaclotide→Linaclotide (n = 92)**	**Total (n = 176)**
Overall	53 (63.1%)	61 (66.3%)	114 (64.8%)
Gastrointestinal disorders	14 (16.7%)	30 (32.6%)	44 (25.0%)
Diarrhea	11 (13.1%)	17 (18.5%)	28 (15.9%)
Feces soft	3 (3.6%)	4 (4.3%)	7 (4.0%)
Abdominal pain	0 (0.0%)	3 (3.3%)	3 (1.7%)
Abdominal discomfort	0 (0.0%)	2 (2.2%)	2 (1.1%)
Dental caries	0 (0.0%)	3 (3.3%)	3 (1.7%)
Toothache	0 (0.0%)	2 (2.2%)	2 (1.1%)
General disorders and administration site conditions	1 (1.2%)	3 (3.3%)	4 (2.3%)
Chest pain	0 (0.0%)	2 (2.2%)	2 (1.1%)
Immune system disorders	2 (2.4%)	4 (4.3%)	6 (3.4%)
Seasonal allergy	2 (2.4%)	4 (4.3%)	6 (3.4%)
Infections and infestations	32 (38.1%)	30 (32.6%)	62 (35.2%)
Bronchitis	2 (2.4%)	1 (1.1%)	3 (1.7%)
Gastroenteritis	2 (2.4%)	7 (7.6%)	9 (5.1%)
Influenza	2 (2.4%)	2 (2.2%)	4 (2.3%)
Nasopharyngitis	21 (25.0%)	21 (22.8%)	42 (23.9%)
Pharyngitis	1 (1.2%)	3 (3.3%)	4 (2.3%)
Oral herpes	2 (2.4%)	0 (0.0%)	2 (1.1%)
Injury, poisoning, and procedural complications	6 (7.1%)	4 (4.3%)	10 (5.7%)
Wound	2 (2.4%)	0 (0.0%)	2 (1.1%)
Investigations	5 (6.0%)	7 (7.6%)	12 (6.8%)
Blood potassium increased	1 (1.2%)	3 (3.3%)	4 (2.3%)
Glucose urine present	0 (0.0%)	2 (2.2%)	2 (1.1%)
Musculoskeletal and connective tissue disorders	6 (7.1%)	11 (12.0%)	17 (9.7%)
Back pain	2 (2.4%)	2 (2.2%)	4 (2.3%)
Neck pain	1 (1.2%)	2 (2.2%)	3 (1.7%)
Musculoskeletal stiffness	1 (1.2%)	3 (3.3%)	4 (2.3%)
Nervous system disorders	2 (2.4%)	4 (4.3%)	6 (3.4%)
Headache	2 (2.4%)	3 (3.3%)	5 (2.8%)
Respiratory, thoracic, and mediastinal disorders	3 (3.6%)	6 (6.5%)	9 (5.1%)
Upper respiratory tract inflammation	3 (3.6%)	1 (1.1%)	4 (2.3%)
Cough	0 (0.0%)	2 (2.2%)	2 (1.1%)
Asthma	0 (0.0%)	3 (3.3%)	3 (1.7%)
Skin and subcutaneous tissue disorders	3 (3.6%)	8 (8.7%)	11 (6.3%)
Urticaria	0 (0.0%)	2 (2.2%)	2 (1.1%)
Dermatitis atopic	2 (2.4%)	0 (0.0%)	2 (1.1%)
Eczema	1 (1.2%)	2 (2.2%)	3 (1.7%)

Data are expressed as numbers (%). Events with an incidence of ≥2% in either treatment group (linaclotide or placebo in part 1, and placebo→linaclotide group or the linaclotide→linaclotide in part 2) are listed. *P* values were calculated using Fisher exact test.

indicated that the optimal dose of linaclotide for this population was also 0.5 mg per day.[8] The current phase III trial, the fourth study of linaclotide conducted in Japan, has confirmed that 0.5 mg linaclotide is effective and safe in Japanese patients with constipation.

It is of interest that North America approved a lower dose of linaclotide for constipated patients than has been approved in Japan. In these countries, 0.29 mg per day of linaclotide is indicated for IBS-C.[12-15] Even lower doses of linaclotide, 0.145 mg per day[16] and 0.072 mg per day,[22] have been shown to be effective and safe and have been approved in the United States for the treatment of CC patients.[22] Thus, the optimal dose of linaclotide for Western patients with constipation is lower than that used in Japan.

The GC-C-cGMP signaling axis is selectively regulated by the changing pH environments across the rostral-caudal axis of the intestine.[23] The natural ligands of GC-C are uroguanylin and guanylin. Uroguanylin is a 16-amino acid peptide that activates GC-C with maximum potency in pH 5-6 environments of the duodenum and proximal jejunum,[24] while guanylin is a 15-amino acid peptide that activates GC-C in neutral to slightly basic pH environments expressed principally in the colorectum by goblet cells.[24] Uroguanylin and guanylin have globular conformations defined by two disulfide bonds.[23] Linaclotide is a synthetic 14-amino acid peptide with three disulfide bonds[11] which confers a more rigid and acid-independent structure. Given these background factors, individual differences in the efficacy of linaclotide may be dependent on catabolism of linaclotide, GC-C gene polymorphism, GUCA2A gene polymorphism, and/or dietary factors. Gut microbiota, especially Bifidobacterium, produce peptidases that may metabolize linaclotide.[25] GC-C gene polymorphism[26] and GUCA2A gene polymorphism[27] are actually present. Therefore, a differential combination of these factors may explain the difference.

This study has some notable strengths. Firstly, in addition to the positive findings for the primary endpoint, the CSBM responder rate, an important parameter in the EMA guideline,[20] supported efficacy in our study with RR of 2.02 [1.35-3.02] and NNT of 4 [3-9] in the first week; in addition, the CSBM 75% responder rate also reflected robust efficacy, RR of 3.60 [1.98-6.55], and NNT of 4 [3-6]. Although the evaluation duration in this study was shorter than that in the earlier study, these numbers, especially NNT, were better than the numbers obtained in the earlier study (5.6-10.1).[16] Secondly, Figure 2 shows that bowel movement was rapidly induced by linaclotide within 1.5 days after administration initiation. At 48 hours, the placebo group had caught up and some defecation occurred, but the findings for stool consistency and straining in the linaclotide group were better than those in the placebo group. Thirdly, the dose reduction from 0.5 mg to 0.25 mg in some patients during the long-term administration of linaclotide resulted in a near normal state of BM frequency.

There are some limitations to this study. Firstly, abdominal pain/discomfort in the first week of administration increased in the linaclotide group compared to the placebo group. This result seems to be in contradiction to the visceral analgesic effect attributed to linaclotide,[28] and we suspect that it may be explained by the early stimulatory effect of linaclotide on colonic motility.[11] Secondly, the duration of treatment in this study was shorter (4 weeks) than that (12 weeks) in the phase III study in the United States.[16] The design of this study was approved by the Japanese PMDA and was concordant with that of a previous phase III study of the intestinal secretagogue lubiprostone, also conducted in Japan.[17] The shorter duration of evaluation meets the standards for clinical practice and the requirements of the medical system in Japan.[29] Multicultural aspects should be considered in this paradigm.[30] Thirdly, in the double-blind phase of the study (part 1), linaclotide produced better IBS-QOL only in the two subscales of health worry and food avoidance. This finding is not surprising as prolonged treatment is generally required to improve health-related QOL.[17] Actually, in the open-label phase of this study (part 2), long-term treatment with linaclotide showed continued improvement in QOL as demonstrated by the total score and all subscales of IBS-QOL at 24 weeks and 56 weeks.

In conclusion, the results of this study indicate that a linaclotide dose of 0.5 mg/day is effective and safe in Japanese CC patients. These data augment the positive results already obtained for linaclotide treatment in IBS patients with constipation and support the use of GC-C agonists in Japan for constipation without a known organic cause.

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DISCLOSURE

No competing interests declared.

AUTHORS' DECLARATION OF PERSONAL INTERESTS

Shin Fukudo, Hiroto Miwa, Atsushi Nakajima, Yoshikazu Kinoshita, and Toshifumi Ohkusa are contracted medical consultants to Astellas Pharma Inc. Masanori Kosako, Ayako Nakagawa, Hiraku Akiho, and Kentaro Kuroishi are/were employees of Astellas Pharma Inc. Jeffrey M Johnston and Mark Currie were employees of Ironwood when this study was designed and conducted.

AUTHOR CONTRIBUTIONS

SF, MK, KH, and HA designed the study, assessed the data, and wrote the manuscript. KK performed statistical analyses. HM, AN, YK, JMJ, MC, and TO contributed 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.

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SUPPORTING INFORMATION

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

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