Dose-finding study of linaclotide in Japanese patients with chronic constipation: A phase II randomized, double-blind, and placebo-controlled study

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Abstract

Background: Based on the previous phase II/III studies of irritable bowel syndrome with constipation (IBS-C) in Japan that demonstrated the efficacy and safety of linaclotide 0.5 mg/d, we evaluated linaclotide at doses of 0.5 mg/d and lower in the treatment of Japanese patients with chronic constipation (CC).

Methods: This was a phase II randomized, double-blind, placebo-controlled, dose-finding study of linaclotide for Japanese patients with CC (n = 382, 64 men, 318 women, age 20-75). After a baseline period of two weeks, patients were randomized to receive placebo (n = 80), or 0.0625 mg (n = 82), 0.125 mg (n = 71), 0.25 mg (n = 73) or 0.5 mg (n = 76) of linaclotide during a two-week treatment period. The primary efficacy endpoint was change from baseline in weekly spontaneous bowel movement (SBM) frequency during the first week. Secondary endpoints included complete SBM (CSBM) responder rates and IBS-QOL. Safety and adverse events were also evaluated.

Key Results: The change in SBM frequency during the first week (mean) was 3.89, 3.11, 3.87, and 3.85 for 0.0625 mg, 0.125 mg, 0.25 mg, and 0.5 mg for linaclotide, significantly higher than for placebo (1.91, P < 0.05). The CSBM responder, which is an important parameter, showed the greatest improvement at the 0.5 mg during the 2 week. The most frequent adverse event in the linaclotide groups was diarrhea.

Conclusions & Inferences: Our results suggest that 0.0625, 0.125, 0.25, and 0.5 mg/d are effective doses of linaclotide for treating CC in Japanese patients. ClinicalTrials.gov: NCT02425722, supported by Astellas Pharma, Inc.

Keywords: abdominal pain, constipation, guanylate cyclase C activator, linaclotide, stool consistency
1 | INTRODUCTION

Chronic gastrointestinal (GI) symptoms have multicultural aspects because culture, race, ethnicity, sex/gender, genetics, the microbiome, environmental hygiene, cytokines, and nervous system may affect the generation of symptoms.¹ Chronic constipation (CC) is a typical GI disorder with prevalence reported to be from 1.9% to 27.2%, with most estimates from 12% to 19% in North America.² In Japan, a population weighted random sample of households selected by controlling for the size of cities, towns and villages showed a 2.08% incidence of constipation in a total of 3356 individuals. Moreover, multivariable regression analyses showed that female gender, older age, number of comorbidities, and a poor mental health component of a general quality of life (QOL) instrument were associated with constipation.³

Linaclotide, a nonabsorbable peptide, is a novel guanylate cyclase-C (GC-C) receptor agonist.⁴ Linaclotide activates GC-C and increases intracellular cyclic guanosine monophosphate (cGMP).⁴ This causes secretion of chloride and bicarbonate ions with molecules of water into the intestinal lumen.⁴,⁵ Earlier studies reported that the optimal dose of linaclotide for North American patients with irritable bowel syndrome with constipation (IBS-C) was 0.29 mg/d.⁶-⁷ and for patients with CC it was 0.145 mg/d.⁸ By contrast, a phase II study of linaclotide in Japan showed that the optimal dose for IBS-C patients was 0.5 mg/d.⁹ This finding was supported by a Japanese phase III study in which linaclotide was administered at 0.5 mg/d to IBS-C patients.¹⁰ Therefore, the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan approved 0.5 mg of linaclotide as the standard clinical dose for IBS-C. However, the optimal dose of linaclotide for Japanese CC patients is unknown.

The scientific importance of performing a dose-finding clinical study of linaclotide in Japanese CC patients is as follows. Studies of a different intestinal secretagogue, lubiprostone, have shown that the optimal doses for CC¹¹,¹² and IBS-C¹³ are different. The clinical dose of lubiprostone for CC is 48 μg/d¹¹,¹² but for IBS-C it is 16 μg/d.¹³ As mentioned above, in the US, the standard doses for IBS-C⁵,⁷ and CC⁸ are also different. However, more recent concepts of IBS-C and functional constipation, based on the Rome IV criteria, suggest that these disorders form a spectrum along a continuum, as opposed to being distinct entities.¹⁴ Therefore, we hypothesized that the most likely optimal dose of linaclotide for Japanese patients with CC is the same as that for IBS-C patients (0.5 mg).

2 | METHODS

2.1 | Patient population

This study was conducted from April 2015 to October 2015 at 50 departments of gastroenterology in Japan hospitals and clinics. Male and female outpatients aged 20-79 years with CC according to the Rome III functional constipation criteria¹⁵ were eligible. In brief, patients who experienced fewer than three defecations per week and met at least one of three other criteria of functional constipation¹⁵ (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 six 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. The study protocol was designed in accordance with principles of the Declaration of Helsinki and was approved by institutional review boards at all sites. General Incorporated Association ICR Clinical Research Hospital Tokyo IRB, a representative ethic committee approved this clinical trial (Reference number: 0456-CL-1021) on April 10, 2015. All patients provided written informed consent prior to participating in the study.

Organic diseases were excluded by colonoscopy or double-contrast barium enema if these examinations had not been performed within the previous five years. Patients satisfying the inclusion and exclusion criteria for typical CC symptoms during a two-week bowel habit observation period were enrolled. Weekly mean spontaneous bowel movement (SBM) frequency had to be less than three. Stool consistency was classified using the Bristol Stool Form Scale (BSFS). Patients who had stool consistency of type 7 (watery, no solid pieces) for one or more SBMs or type 6 (fluffy pieces with ragged edges [mushy stool]) for two or more SBMs using the BSFS¹⁵ 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 five days or more during each week of the bowel habit observation period, and who were determined to be eligible for inclusion in the study according to the clinical laboratory test results during the pretreatment period were randomized into the study.

2.2 | Study design

This randomized, double-blind, placebo-controlled, parallel-group, comparative study comprised a screening period, a two-week bowel habit observation period, and a two-week treatment period. Following the bowel habit observation period, eligible patients were

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Key Points

- Linaclotide has been approved in western countries for IBS with constipation (IBS-C) at a dose of 0.29 mg/d and for chronic constipation (CC) at a dose of 0.145 mg/d.
- Previous phase II/III trials in Japan revealed that 0.5 mg/d of linaclotide was the most effective dose in IBS-C patients.
- The findings of this study replicated those of the US studies in CC patients and Japanese studies in IBS-C patients.
randomly assigned to two-week oral treatments with placebo or linaclotide (0.0625 mg, 0.125 mg, 0.25 mg, or 0.5 mg once daily) before breakfast. Randomization was performed in a 1:1:1:1:1 ratio using a web-based randomization system with a block size of five. All patients, investigators, and sponsors were kept blinded until all observations and evaluations were completed; statistical analysis plans were finalized; and all the data had been entered into the database. Visits were scheduled for week 2 (or at discontinuation) to assess treatment efficacy, drug compliance, and occurrence of adverse events. All the authors had access to the study data and reviewed and approved the final manuscript.

2.3 | Data collection

During the bowel habit observation and treatment periods, patients recorded their chronic constipation symptoms every day in a paper diary at bedtime and at each bowel movement, and electronically entered some of these data into the database daily using an interactive voice response system. This system of evaluating symptoms has been shown to be reliable and valid for IBS-C patient studies. In the paper diary, patients recorded stool frequency and BSFS types for each stool. Patients also scored the severity of their abdominal bloating and abdominal pain/discomfort on a 5-point ordinal scale (1, none; 2, mild; 3, moderate; 4, severe; and 5, very severe). Straining was also 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). Every 7 days during the treatment period, patients also graded current CC symptoms compared with the same symptoms during the bowel habit observation period on a 7-point ordinal scale for global assessment of relief of CC symptoms, improvement in abnormal bowel habits, and relief of abdominal symptoms (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). Disease-specific health-related quality of life was assessed using the IBS-QOL (Japanese version).

2.4 | Efficacy and safety endpoints

The primary endpoint was change in weekly SBM frequency during the first week of the treatment period. Secondary endpoints included SBM responder and complete SBM (CSBM) stool frequency responder, stool consistency (BSFS), severity of abdominal bloating and abdominal pain/discomfort, severity of straining, relief of chronic constipation symptoms, improvement in abnormal bowel habits and abdominal symptoms relief, and improved quality of life (IBS-QOL). Weekly SBM and CSBM responders were defined as patients with SBM or CSBM of three or more and an increase of one or more from baseline at each weekly evaluation point. Weekly responders for global assessment of relief of CC symptoms, abnormal bowel habits improvement, and abdominal symptoms relief were defined as patients with a score of 1 or 2 at each weekly evaluation point. All adverse events (AEs) 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) (SAS Institute Inc., Cary, NC, USA). Sample sizes were estimated to provide more than 80% power to detect a difference in the change from baseline in weekly SBM frequency during the first week of the treatment period between placebo and linaclotide (1.309, 2.76, 3.959, 4.007 and 4.61 for the placebo, linaclotide 0.0625 mg, 0.125 mg, 0.25 mg and 0.5 mg, respectively) based on the phase II18 and phase III8 clinical studies conducted in North America, using analysis of covariance; multiplicity was adjusted using a closed testing procedure: the higher dose was first compared with placebo and if the difference vs placebo was significant and then lower dose was compared with placebo. The procedure was repeated from high dose to low dose.

In total, 350 patients (70 patients/group) were scheduled for randomization. Efficacy analysis populations included the full analysis set comprising all patients who received at least one dose of the study drug during the treatment period and in whom one or more efficacy endpoints could be evaluated, and the safety analysis set, which consisted of all patients who received at least one dose of the study drug during the treatment period.

To compare the linaclotide groups with placebo, an analysis of covariance was performed with treatment groups as a factor and baseline scores as covariates to measure changes from baseline in weekly mean SBM frequency, CSBM frequency, stool form score, abdominal bloating severity score, abdominal pain/discomfort severity score, straining severity score, the overall IBS-QOL and IBS-QOL subscale scores at each evaluation point during the treatment period. SBM responder, CSBM responder, global assessment of relief responder, abnormal bowel habits improvement responder, and abdominal symptom relief responder were expressed as a percentage of randomized patients with 95% confidence intervals (95% CIs). The treatment groups were compared using Fisher’s exact test with a 2-sided significance level of 0.05.

3 | RESULTS

3.1 | Overall study population

Of the 817 patients who provided written informed consent, 435 failed the screening and 382 were randomly assigned to receive placebo (n = 80), or 0.0625 mg (n = 82), 0.125 mg (n = 71), 0.25 mg (n = 73) or 0.5 mg (n = 76) of linaclotide (Figure 1). Of those randomized, 79 patients in the placebo group and 78 (0.0625 mg), 69 (0.125 mg), 72 (0.25 mg) and 74 (0.5 mg) patients in linaclotide groups completed the study. The reasons for discontinuation are shown in Figure 1.

The demographics and baseline characteristics were similar among all the groups with no statistically significant differences (Table 1). The medication compliance rate was 99.91% in placebo group, and 98.54%, 99.40%, 98.43% and 98.97% in the 0.0625 mg, 0.125 mg, 0.25 mg, and 0.5 mg linaclotide groups, respectively.

Efficacy and safety were evaluated in 382 patients.
3.2 | Evaluation of the primary endpoint

Change in weekly mean SBM frequency during the first week of the treatment period was 1.91 in the placebo group, and 3.89, 3.11, 3.87 and 3.85 in the 0.0625 mg, 0.125 mg, 0.25 mg, and 0.5 mg linaclotide groups, respectively (Figure 2). The primary endpoint in each linaclotide group showed a statistically significant improvement compared to the placebo group by analysis of covariance adjusted using a closed testing procedure.

3.3 | Evaluation of secondary endpoints

Change in weekly mean CSBM frequency (Figure 3A), stool form score (Figure 3B), and straining severity score (Figure 3C) during Week 1 showed a statistically significant improvement for linaclotide compared to placebo. At Week 2, the change in mean weekly SBM frequency (Figure 3D), CSBM frequency (Figure 3A), stool form score (Figure 3B), and straining severity score (Figure 3C) in every linaclotide group was significantly greater than that in the placebo group. Weekly mean SBM frequency (Figure S1), CSBM frequency (Figure S2), stool form score (Figure S3), and straining severity score (Figure S4) in every linaclotide group during Week 1 and 2 were also significantly greater than that in the placebo group.

In the 0.5 mg linaclotide group, the CSBM responder rates at Week 1 and 2 were statistically significantly higher than that in the placebo group (Figure 4A). Also in the 0.5 mg linaclotide group, all other responder rates, including SBM (Figure 4B), the global assessment of relief of chronic constipation symptoms (Figure 4C), improvement of abnormal bowel habits for CC symptoms (Figure 4D), and relief of abdominal symptoms for CC symptoms (Figure 4E) at Week 1 and 2, were significantly greater than that in the placebo group.

Linaclotide did not significantly improve abdominal bloating, abdominal pain/discomfort or overall IBS-QOL compared with placebo (ANCOVA change from baseline).

3.4 | Safety

Adverse events were observed in three (3.8%) patients in the placebo group, and 11 (13.4%), six (8.5%), nine (12.3%), and nine patients (11.8%) in the 0.0625 mg, 0.125 mg, 0.25 mg, and 0.5 mg linaclotide groups, respectively. The incidence of diarrhea, the most commonly reported AE which was expected given the pharmacological action of linaclotide, was significantly higher in the 0.0625 mg (7.3%) and 0.25 mg (8.2%) linaclotide groups compared to the placebo (0.0%) group. There was no significant difference in the incidence of diarrhea in the 0.125 mg (4.2%) or the 0.5 mg (3.9%) linaclotide groups compared to the placebo group (Table 2). All the events of diarrhea in this study were rated of mild or moderate severity; there were no cases of severe diarrhea. One patient treated with linaclotide 0.0125 mg reported a linaclotide-related...
4 | DISCUSSION

Positive results for the primary endpoint, change from baseline in SBM frequency in the first week of treatment, support the hypothesis of this study. This study confirms our previous findings that linaclotide 0.5 mg/d is an effective and well-tolerated dose for constipated patients in Japan. This dose also produced statistically significant outcomes for change in weekly mean SBM frequency, weekly SBM responder rate, change in weekly mean CSBM frequency, weekly CSBM responder rate, change in weekly mean stool form score, and change in weekly mean straining severity score. These effects began in the first week and they continued through the second week of dosing.
treatment. Although all doses of linaclotide were equally effective in terms of the primary endpoint, the CSBM responder which is considered to be an important parameter for assessing the efficacy of drugs for CC in a European Medicines Agency (EMA) guideline, showed the greatest improvement at the 0.5 mg dose during Week 2. In addition, change in stool form score, which we observed a great example of dose response in previous phase II trial for Japanese IBS-C patients, showed the greatest improvement at the 0.5 mg dose during Week 1 and 2 in this trial.

A number of factors support the assumption that 0.5 mg is the most appropriate for the treatment of patients with CC in Japan. From a GI motility standpoint, all evaluated doses (from 0.0625 to 0.5 mg) of linaclotide appeared to have stimulatory secretory effects as SBM frequency increased after the administration of all doses of linaclotide. However, efficacy and safety might differ among the treatment groups due to the action of fluid secretion together with visceral perception. Linaclotide is an intestinal secretagogue and has a distinct action that would influence visceral perception. Concerning its action as an intestinal secretagogue, the linaclotide 0.5 mg group showed the greatest changes in BSFS in this study. Linaclotide activates GC-C expressed on mucosal epithelial cells, resulting in the production and release of cGMP. This extracellular cGMP acted on and inhibited nociceptors and reduced the excitability of neurons in the superficial laminae of the dorsal horn, thereby reducing visceral perception. Evaluation of CSBM, straining, and reported adverse events of diarrhea are all related to visceral perception during defecation. Thus, the results in this study suggest that CC patients who received 0.5 mg of linaclotide felt that defecation was made easier.

The most important scientific finding of this study is that linaclotide 0.5 mg, the highest dose studied, showed the greatest efficacy in Japanese CC patients, which is in contrast with the earlier US studies in CC patients. The approved doses in the US are 0.145 and 0.072 mg/d. The reason a higher dose of linaclotide may be required for Japanese CC patients compared to US CC patients would likely be the same as that for previous studies in IBS-C patients. In brief, the following factors, which differ between Japan and US, may partially explain the different dose requirements.

Diet may interfere with digestion of the polypeptide linaclotide. Gut microbiota, especially Bifidobacterium, produce peptidases that may metabolize linaclotide. There are known differences in genetic polymorphism among different populations. The endogenous GC-C receptor ligands guanylin and uroguanylin, which could interfere with linaclotide binding, have also been shown to display genetic polymorphism in the Japanese compared to North Americans. Indeed, polymorphism of the guanylin-uroguanylin gene GUCA2A has been shown to result in functional differences. Another possibility is that pathophysiological features in CC and IBS-C in Japan are closer to each other than those in the US. Some studies have suggested that...
FIGURE 4  Secondary endpoints to support efficacy of linaclotide. (A) Weekly responder rate of CSBM (%). (B) Weekly responder rate of SBM (%). (C) Weekly responder rate of global assessment of relief of CC symptoms (%). (D) Weekly responder rate of abnormal bowel habits improvement in CC symptoms (%). (E) Weekly responder rate of abdominal symptoms relief of CC symptoms (%). Column height: responder rate (%). Error bar: 95% CI. P values were calculated using Fisher’s exact test.

TABLE 2  Incidence of adverse events

| System organ class preferred term | Placebo (N = 80) | Linaclotide 0.0625 mg (N = 82) | Linaclotide 0.125 mg (N = 71) | Linaclotide 0.25 mg (N = 73) | Linaclotide 0.5 mg (N = 76) |
|----------------------------------|-----------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|
| Overall                          | 3 (3.8%)        | 11 (13.4%)*                  | 6 (8.5%)                     | 9 (12.3%)                    | 9 (11.8%)                    |
| Gastrointestinal disorders       | 1 (1.3%)        | 8 (9.8%)*                    | 4 (5.6%)                     | 8 (11.0%)*                   | 3 (3.9%)                     |
| Diarrhoea                        | 0 (0.0%)        | 6 (7.3%)                      | 3 (4.2%)                     | 6 (8.2%)                     | 3 (3.9%)                     |
| Infections and infestations      | 0 (0.0%)        | 0 (0.0%)                      | 2 (2.8%)                     | 1 (1.4%)                     | 2 (2.6%)                     |
| Nasopharyngitis                  | 0 (0.0%)        | 0 (0.0%)                      | 2 (2.8%)                     | 1 (1.4%)                     | 2 (2.6%)                     |

Data were expressed as numbers (%). Events with an incidence of >2% in any group are listed. *P < 0.05, vs placebo.
suggested that CC and IBS-C constitute a single syndrome with a spectrum of symptoms, rather than being distinct disease entities. Whatever the reason, the appropriate therapeutic dose of linaclotide for patients in Japan is correspondingly higher than that in the US.

This study has some limitations. Foremost, the duration of treatment in this study was shorter (2 weeks) than that (4 weeks) in the phase II dose-ranging study in the US. The design of the current study is similar to that of a previous study of the intestinal secretagogue lubiprostone, also conducted in Japan. Because the duration of treatment of 12 weeks in our IBS-C study demonstrated ongoing improvement of symptoms in the latter phase, a longer duration of treatment in CC patients may show greater benefit. However, the efficacy of linaclotide appeared quickly and sustained throughout the treatment period in the phase II study and phase III studies in North America. As the symptom of CC is relatively constant, we set 2 weeks as treatment duration in this study.

In conclusion, this study’s findings suggest that 0.0625, 0.125, 0.25, and 0.5 mg/d are effective doses of linaclotide for CC patients in Japan. The best results for CC were seen at 0.5 mg/d, the same dose that elicited the best results for IBS-C. No new safety trends or concerns were identified. Further studies in patients with CC are warranted.

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DISCLOSURE

No conflicts of interests declared.

AUTHOR CONTRIBUTIONS

SF, MK, AN, HA designed the study, assessed the data, and wrote the manuscript. Kentaro Kuroishi performed statistical analyses. HM, AN, YK, JM, 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.

AUTHORS’ DECLARATION OF PERSONAL INTERESTS

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

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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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